

STUDY TITLE

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors
in Female B6D2F1/Crl Mice

Test Guidelines

Not Applicable

Author(s)

M. J. LeBaron, Ph.D.
R. M. Golden, B.S.
F. Zhang, Ph.D.

Study Completion Date

30 August 2019

Sponsor

Foundation for Chemistry Research & Initiatives
American Chemistry Council (ACC)
700 Second St. NE
Washington, DC 20002

Performing Laboratory

Toxicology and Environmental Research and Consulting
The Dow Chemical Company
Midland, Michigan 48674

Laboratory Project Study ID

181012

This page is intentionally left blank

COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

Compound: 1,4-Dioxane

Title: 1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

All phases of this study were conducted in compliance with the following Good Laboratory Practice Standards:

US Environmental Protection Agency -- TSCA GLPs Title 40 CFR, Part 792- Federal Toxic Substances Control Act (TSCA); Good Laboratory Practice Standards, Final Rule

Exceptions: 1) Municipal drinking water was analyzed for chemical parameters and biological/chemical contaminants in non-GLP facilities; however, both facilities are either certified to conduct drinking water microbiology testing through the Indiana State Department of Health Laboratories or a certified drinking water laboratory through the Michigan Department of Environmental Quality. 2) Feed was prepared and analyzed in non-GLP facilities; however, the production plant is GMP-compliant and is a FSSC 22000 Certified Laboratory animal diet production facility and the laboratory that completed the composition analysis is ISO 17025:2005 certified. Therefore, this exception had no impact on the study. 3) The test material purity was provided by the non-GLP supplier, and found to be suitable for study purposes; therefore, there was no negative impact on the study. 4) The test material 1,4-dioxane, lot SHBJ7415, was not tested for neat test material stability. The test material was appropriately characterized and tested for stability in vehicle; therefore, there was no negative impact on the study. 5) There is not a governing SOP for the archiving of Provantis data; however, the Provantis data for the study has been placed into a secure status in which data cannot be changed, therefore this exception had no impact on the study.

SIGNATURES
REDACTED

QUALITY ASSURANCE STATEMENT

Compound: 1,4-Dioxane

Title: 1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

This study was examined for conformance with Good Laboratory Practices as published by the USEPA TSCA. The final report was determined to be an accurate reflection of the data obtained. The dates of Quality Assurance activities on this study are listed below.

Study Initiation Date: 28 August 2018

<u>TYPE OF AUDIT:</u>	<u>DATE OF AUDIT:</u>	<u>DATE FINDINGS REPORTED TO STUDY DIRECTOR/MANAGEMENT:</u>
Final protocol	29 August 2018	29 August 2018
Observed body weights, feed weights, and clinical observations	03 October 2018	03 October 2018
Observed slide preparation	12 December 2018	12 December 2018
Protocol, data, and draft report	26 July 2019 – 20 August 2019	20 August 2019
Final report	30 August 2019	30 August 2019

The final report accurately reflects the raw data of the study. For a multisite study, test site QA Statements are located in the corresponding contributing scientist report.

SIGNATURE
REDACTED

SIGNATURE PAGE

Compound: 1,4-Dioxane

Title: 1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced
Liver Tumors in Female B6D2F1/Crl Mice

**SIGNATURES
REDACTED**

TABLE OF CONTENTS

	Page
STUDY TITLE	1
COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS	3
QUALITY ASSURANCE STATEMENT	4
SIGNATURE PAGE	5
SUMMARY	11
INTRODUCTION	13
Purpose	13
Test Guidelines	13
GLP Standards	13
Quality Assurance	13
Animal Welfare Standards	13
Animal Welfare Compliance	13
Archiving	14
Safety	14
TEST MATERIAL INFORMATION	14
Test Material Name	14
Chemical Name	14
Synonyms	14
Supplier (City, State) and Lot/Reference/Batch Number	14
Purity/Characterization (Method of Analysis and Reference)	14
Test Material Stability Under Storage Conditions	14
Characteristics	14
Molecular Formula	14
Molecular Weight	15
Chemical Structure	15
CAS Number	15
Vehicle	15
Previous Toxicity Information	15
Two-Year Cancer Bioassay	15
13-Week Drinking Water Studies	15
STUDY DESIGN	17
Experimental Design and Critical Dates	17
Route and Justification, Method of Administration, Frequency and Duration	18
Dose Levels and Justification	18
Text Table 1. Dose Levels	18
Dose Preparation	18
Solubility	19
Analysis	19

TABLE OF CONTENTS

	Page
Dose Confirmation and Homogeneity.....	19
Stability.....	19
Retainer Samples	19
TEST SYSTEM	19
Species and Sex.....	19
Strain and Justification.....	19
Supplier and Location	19
Age at Study Start and Weight Range.....	20
Health Status and Acclimation.....	20
Housing	20
Enrichment	21
Randomization and Identification	21
Text Table 2. Animal Identification Numbers.....	21
Feed and Water	21
STUDY SPECIFIC PARAMETERS.....	22
Daily Observations.....	22
Clinical Observations.....	22
Body Weights/Body Weight Gains.....	22
Feed Consumption	22
Water Consumption	23
Test Material Intake	23
Implantation of Alzet Osmotic Pumps.....	23
Clinical Chemistry	24
Sample Preparation.....	24
Enzyme Activities of:	24
Anatomic Pathology.....	24
Necropsy.....	24
Tissue Processing.....	25
Kidney	25
Liver	25
Nasal tissue.....	25
Histopathology	26
Examination of Hepatocellular Proliferation	26
BrdU Slide Preparation.....	26
Manual counts of BrdU stained slides.....	26
Examination of Hepatocellular Apoptosis	26
Caspase-3 and GST-P Slide Preparation	26
Image Analysis of Caspase-3 Stained Slides.....	27
GST-P	27
Toxicokinetic Analysis of Whole Blood.....	27

TABLE OF CONTENTS

	Page
Liver Transcriptomics	28
STATISTICS AND CALCULATIONS	28
RESULTS	29
Analytical Chemistry	29
Mortality.....	29
Clinical and Cage-side Observations	29
Body Weights/Body Weight Gain	29
Feed Consumption	30
Water Consumption	30
Test Material Intake	30
Text Table 3. Time Weighted Average Doses of 1,4-Dioxane	30
Clinical Chemistry	31
Organ Weight	31
Histopathology	31
Examination of Hepatocellular Proliferation	32
Text Table 4. Summary of Hepatocellular Proliferation	33
Apoptosis Quantification as Measured by Caspase-3.....	33
Text Table 5. Caspase-3 Positive Cells per 10,000	33
Toxicokinetics	34
CONCLUSIONS.....	35
ACKNOWLEDGEMENTS	36
REFERENCES	37
FIGURES	37
FIGURE 1. 7-day BrdU data.....	39
FIGURE 2. 28-day BrdU data.....	40
FIGURE 3. 90-day BrdU data.....	41
FIGURE 4. Blood Concentrations of HEAA at 7 Days.....	42
FIGURE 5. Blood Concentrations of HEAA at 28 Days.....	43
FIGURE 6. Blood Concentrations of HEAA at 90 Days.....	44
FIGURE 7. Blood Concentrations of 1,4-dioxane at 90 Days (all dose levels)	45
FIGURE 8. Blood Concentrations of 1,4-dioxane at 90 Days (high dose level removed)	46
TABLES	46
TABLE 1. Study Design	47
TABLE 2. Clinical Observations Summary – 7-day	48
TABLE 3. Clinical Observations Summary – 28-day	49
TABLE 4. Clinical Observations Summary – 90-day	50

TABLE OF CONTENTS

	Page
TABLE 5. Body Weights/Body Weight Gains Summary (g) – 7-Day.....	52
TABLE 6. Body Weights/Body Weight Gains Summary (g) – 28-Day.....	53
TABLE 7. Body Weights/Body Weight Gains Summary (g) – 90-Day.....	54
TABLE 8. Feed Consumption (g/day) Summary – 7-Day	57
TABLE 9. Feed Consumption (g/day) Summary – 28-Day	58
TABLE 10. Feed Consumption (g/day) Summary – 90-Day	59
TABLE 11. Water Consumption Summary (g) – 7-day	60
TABLE 12. Water Consumption Summary (g) – 28-day	61
TABLE 13. Water Consumption Summary (g) – 90-day	62
TABLE 14. Test Material Intake Summary – 7-Day.....	64
TABLE 15. Test Material Intake Summary – 28-Day.....	65
TABLE 16. Test Material Intake Summary – 90-Day.....	66
TABLE 17. Clinical Chemistry Summary – 7-Day.....	67
TABLE 18. Clinical Chemistry Summary – 28-Day	68
TABLE 19. Clinical Chemistry Summary – 90-Day.....	69
TABLE 20. Organ and Organ/Body Weights Summary – 7-day	70
TABLE 21. Organ and Organ/Body Weights Summary – 28-day	71
TABLE 22. Organ and Organ/Body Weights Summary – 90-day	72
TABLE 23. Hepatocellular Proliferation as Measured by BrdU – 7-Day	73
TABLE 24. Hepatocellular Proliferation as Measured by BrdU – 28-Day	74
TABLE 25. Hepatocellular Proliferation as Measured by BrdU – 90-Day	75
TABLE 26. Apoptosis Quantification as Measured by Caspase-3 – 28-Day	76
TABLE 27. Apoptosis Quantification as Measured by Caspase-3 – 90-Day	77
TABLE 28. Final TMI and blood levels of 1,4-dioxane and HEAA	78
TABLE 29. Summary of Dose, Blood Concentrations, and TK Analysis Results for 1,4-dioxane and HEAA	79
APPENDICES	79
APPENDIX TABLE 1. Individual Clinical Observations – 7-Day.....	80
APPENDIX TABLE 2. Individual Clinical Observations – 28-Day.....	86
APPENDIX TABLE 3. Individual Clinical Observations – 90-Day.....	91
APPENDIX TABLE 4. Individual Body Weights/Body Weight Gains (g) – 7- Day	97
APPENDIX TABLE 5. Individual Body Weights/Body Weight Gains (g) – 28- Day	100
APPENDIX TABLE 6. Individual Body Weights/Body Weight Gains (g) – 90- Day	103
APPENDIX TABLE 7. Individual Feed Consumption (g/day) – 7-Day.....	112

TABLE OF CONTENTS

	Page
APPENDIX TABLE 8. Individual Feed Consumption (g/day) – 28-Day.....	115
APPENDIX TABLE 9. Individual Feed Consumption (g/day) – 90-Day.....	118
APPENDIX TABLE 10. Individual Water Consumption (g/day) – 7-Day.....	121
APPENDIX TABLE 11. Individual Water Consumption (g/day) – 28-Day.....	124
APPENDIX TABLE 12. Individual Water Consumption (g/day) – 90-Day.....	127
APPENDIX TABLE 13. Individual Clinical Chemistry – 7-Day	133
APPENDIX TABLE 14. Individual Clinical Chemistry – 28-Day	136
APPENDIX TABLE 15. Individual Clinical Chemistry – 90-Day	139
APPENDIX TABLE 16. Individual Organ Weights – 7-Day	142
APPENDIX TABLE 17. Individual Organ Weights – 28-Day	145
APPENDIX TABLE 18. Individual Organ Weights – 90-Day	148
APPENDIX TABLE 19. Individual Hepatocellular Proliferation – 7-Day.....	151
APPENDIX TABLE 20. Individual Hepatocellular Proliferation – 28-Day.....	154
APPENDIX TABLE 21. Individual Hepatocellular Proliferation – 90-Day.....	157
APPENDIX TABLE 22. Individual Apoptosis Quantification as Measured by Caspase-3 – 28-Day	160
APPENDIX TABLE 23. Individual Apoptosis Quantification as Measured by Caspase-3 – 90-Day	163
APPENDIX A. Osmotic Pump Implant Procedure.....	166
APPENDIX B. Immunohistochemical Staining Procedures	168
APPENDIX C. Dose Confirmation, Homogeneity, and Stability Report	170
APPENDIX D. Histopathology Report	189
APPENDIX E. Toxicokinetic Analytical Report.....	387
APPENDIX F. Transcriptomics Report.....	421

SUMMARY

The objectives of this study were to investigate potential key events and responses related to the Mode-of-Action (MOA) for mouse liver tumors following 1,4-dioxane drinking water administration. This study was designed to examine biological responses at specified, interim time points within the overall 90-day exposure period. Groups of ten female B6D2F1 mice were given drinking water at concentrations of 0, 40, 200, 600, 2000 or 6000 ppm 1,4-dioxane for a duration of at least 7, 28, or 90 days (10 animals per exposure group and exposure duration = 180 animals). The targeted mg/kg/day dose levels were 0, 10, 50, 150, 500, and 1500 mg/kg/day. Parameters evaluated were daily cage-side observations, weekly clinical observations, body weights, feed consumption, water consumption, select clinical chemistry, liver weights and histopathology of the liver, blood levels of 1,4-dioxane and primary metabolite (β -hydroxyethoxyacetic acid (HEAA)), assessments of hepatocellular proliferation (BrdU) and apoptosis (Caspase-3), and liver transcriptomics. Liver transcriptomics were analyzed by ToxStrategies, Inc., and its contractor (BioSpyder Technologies) and the genomics results are reported separately and appended to this report.

There were no treatment-related effects in clinical signs, body weights, or clinical chemistry parameters in any of the 7-day, 28-day, or 90-day 1,4-dioxane treated groups compared to their respective controls.

During the 7-day treatment period, animals given 6000 ppm had a slight transient decrease in water consumption from test day 1-4 (14%), but was not statistically different from test day 4-8, when compared to their respective control group. There were no treatment-related differences in water consumption in any 1,4-dioxane treated animals during the 28-day treatment period when compared to their respective control group. During most intervals in the 90-day treatment period, animals given 6000 ppm had treatment-related decreases in water consumption ranging from 12-29% compared to their respective control.

At necropsy, 7-day animals given 6000 ppm had a statistically significant increase in mean relative liver weight compared to controls. Similarly, 28-day and 90-day animals given 6000 ppm had statistically significant increases in absolute and relative liver weight compared to their respective controls. Additionally, 28-day and 90-day animals given 2000 ppm had a statistically significant increase in relative weight compared to their respective controls.

Histopathologically, there were no exposure-related findings at dosages ≤ 200 ppm at any exposure duration. After 7 days of exposure, dose-related vacuolation, centrilobular, minimal or mild, was observed at ≥ 600 ppm; this finding was also observed in 28-day and 90-day cohorts. After 28 days of exposure, additional liver findings at the 6000 ppm exposure level included minimal to mild centrilobular hepatocyte hypertrophy in all mice and minimal to mild increased centrilobular apoptosis in most. After 90 days of exposure, hepatocyte hypertrophy was slightly more severe in 6000 ppm mice, and there was one mouse at 2000 ppm with the finding. Also after 90 days of exposure, minimal to mild centrilobular apoptosis of hepatocytes affected all mice at 6000 ppm and one mouse at 2000 ppm. Increased centrilobular apoptosis is considered adverse.

There was a treatment-related and statistically identified increase in hepatocellular proliferation as measured by BrdU incorporation (panlobular: 4.3 and 20.8% labeling index in control and high dose, respectively) in the 90-day animals given 6000 ppm 1,4-dioxane. There were no treatment-related changes in hepatocellular proliferation in any other dose group or treatment duration.

Consistent with the histopathological assessment, the 28-day and 90-day animals given 6000 ppm had statistically significant increases in apoptosis as measured by caspase-3 positive cells compared to controls (0.08 and 0.46 for 28-day animals, and 0.04 and 1.08 for 90-day animals per 10,000 cells in control and high dose, respectively). There were no statistical or treatment-related differences in any other treatment group of the 28-day or 90-day 1,4-dioxane treated animals when compared to their respective controls.

Toxicokinetic analysis indicated that blood levels of HEAA exhibited linear, dose-proportional kinetics across all dose groups at all treatment durations. Further toxicokinetic analysis on the limited quantifiable blood levels indicated that 1,4-dioxane was supralinear at 6000 ppm and was sublinear at 2000 ppm in the 90-day animals, indicating the potential saturation of absorption and/or metabolic pathways of 1,4-dioxane in the highest dose group (6000 ppm) after the 90-day exposure.

In summary, when administered via the drinking water, the data collected for 1,4-dioxane indicate a clear time- and dose-dependent threshold for hepatic effects. The molecular and apical treatment-induced biological changes correlate with increased quantifiable concentrations of 1,4-dioxane in the blood and a potential shift in metabolism over time.

INTRODUCTION

Purpose

The objectives of this study were to investigate potential key events and responses related to the Mode-of-Action (MOA) for mouse liver tumors following 1,4-dioxane drinking water administration. This study was designed to examine biological responses at specified, interim time points within the overall 90-day exposure period.

Test Guidelines

Not applicable

GLP Standards

US Environmental Protection Agency -- TSCA GLPs Title 40 CFR, Part 792- Federal Toxic Substances Control Act (TSCA); Good Laboratory Practice Standards, Final Rule

Quality Assurance

The study conduct, data, protocol, protocol deviation(s)/amendment(s) if applicable, and final report will be inspected by the Quality Assurance Unit, Toxicology and Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan.

Animal Welfare Standards

U.S. Department of Agriculture's Animal Welfare Act (9) Code of Federal Regulations (CFR) Parts 1, 2 and 3.

NRC [National Research Council]. 2011. Guide for the Care and Use of Laboratory Animals. Washington, DC: The National Academies Press.

American Veterinary Medical Association (AVMA). 2013. AVMA Guidelines for the Euthanasia of Animals: 2013 Edition.

Animal Welfare Compliance

In accordance with the animal welfare standards above, the TERC Institutional Animal Care and Use Committee (IACUC) determined that the activities within this study were in full accordance with all applicable animal welfare standards. All animal use activities were conducted as described within the approved protocol or within laboratory standard operating procedures and IACUC policies.

Archiving

The data, specimens (if applicable), protocol, protocol deviation(s)/amendment(s) if applicable, and final report were archived and stored by Toxicology and Environmental Research and Consulting and stored in the satellite location at The Dow Chemical Company, Midland, Michigan.

Safety

All personnel involved in the study were advised of the safety precautions to follow when handling the test material and treated animals prior to study initiation. Chemical safety information was made available.

TEST MATERIAL INFORMATION

Test Material Name

1,4-Dioxane

Chemical Name

1,4-Dioxane

Synonyms

p-Dioxane

Supplier (City, State) and Lot/Reference/Batch Number

Sigma-Aldrich, St. Louis MO; SHBJ7415

Purity/Characterization (Method of Analysis and Reference)

The non-GLP purity of the test material was determined to be 99.98% by gas chromatography with identification by Infrared spectroscopy (Grady, 2018).

Test Material Stability Under Storage Conditions

The test material 1,4-dioxane, Lot SHBJ7415, was not tested for neat test material stability.

Characteristics

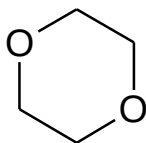
Molecular Formula

C₄H₈O₂

Molecular Weight

88.1

Chemical Structure



CAS Number

123-91-1

Vehicle

Ultrapure water (ELGA PURELAB Ultrapure Water System, The Dow Chemical Company, Midland, Michigan)

Previous Toxicity Information

Two-Year Cancer Bioassay

The carcinogenicity of 1,4-dioxane was examined by giving groups of 50 Crj:BDF₁ mice of each sex 1,4-dioxane in the drinking-water for 2 years (Kano *et al.*, 2009). The concentrations of 1,4-dioxane were 0, 500, 2000 and 8000 ppm (wt./wt.) which corresponded to test material intake values of 0, 49, 191, and 667 mg/kg/day respectively in male mice, and 0, 66, 278, and 964 mg/kg/day, respectively in female mice. Both food and water consumption were significantly decreased in the 8000 ppm-dosed males and females. Two nasal tumors occurring in the 8000 ppm-dosed groups were spontaneously rare and, thus, were attributed to 1,4-dioxane exposure by the investigators. Hepatocellular carcinomas occurred dose-dependently, and their incidences were significantly increased in the 8000 ppm dosed males and in all 1,4-dioxane-dosed female groups. A significant induction of hepatocellular adenomas occurred in the 2000 ppm-dosed males and in the 500 ppm and 2000 ppm-dosed females. Limited histopathological information was provided by the Japanese investigators in the published study, hence limited key event information could be extracted and no interim time point data were obtained.

13-Week Drinking Water Studies

Subchronic oral toxicity of 1,4-dioxane was examined by administering 1,4-dioxane in drinking water at 6 different concentrations of 0, 640, 1600, 4000, 10000, or 25000 ppm (wt/wt) to F344 rats and BDF₁ mice of both sexes for 13 weeks (Kano

et al., 2008). The corresponding test material intake values for 640, 1600, 4000, 10000, or 25000 ppm were 86, 231, 585, 882, and 1570 mg/kg/day respectively in male mice, and 170, 387, 898, 1620, and 2669 mg/kg/day respectively in female mice. Food and water consumption and terminal body weight were decreased dose-dependently in rats and mice. A dose-dependent increase in the relative weights of kidney and lung was noted in rats and mice, while the relative liver weight was increased only in rats. Increases in plasma levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and a decrease in plasma glucose were noted primarily in the rats and mice dosed at 25,000 ppm. Histopathological examination revealed that 1,4-dioxane affected the upper and lower respiratory tracts, liver, kidneys and brain in rats, while only the former two organs were affected in mice. Nuclear enlargement occurred in the respiratory, olfactory, tracheal, and bronchial epithelia of the 1,4-dioxane-dose rats and mice. The 1,4-dioxane-induced hepatic lesions were characterized by focal inflammation along with centrilobular swelling and necrosis in rats and mice and glutathione S-transferase placental form (GST-P)-positive altered hepatocellular foci in rats. A no-observed-adverse-effect-level (NOAEL) was determined at 640 ppm for both rats and mice, since the nuclear enlargement in the nasal respiratory epithelium and the centrilobular swelling of hepatocytes in rats and the nuclear enlargement in the bronchial epithelium in mice were observed at 1600 ppm. The NOAEL value corresponded to the estimated 1,4-dioxane intake of 52 mg/kg/day in rats and 170 mg/kg/day in mice.

In another thirteen-week study, six study groups were created, with each group consisting of 10 male and 10 female rats and 10 male and 10 female of mice, totaling 120 rats and 120 mice. Drinking water containing 25,000, 10,000, 4,000, 1,600, 640 ppm of 1,4-dioxane was administered to rats and mice, or 0 ppm (for the control groups) (Yamamoto *et al.*, 1990). Rats in the $\geq 10,000$ ppm groups had a decrease in body weight and water consumption and showed intense changes in the nasal cavity, trachea, liver, kidney, and brain during histopathological examinations, such as nuclear enlargement of the olfactory, respiratory, and tracheal epithelium, centrilobular hepatic vacuolar degeneration, increased incidence of granulation formation in liver, increased incidences of nuclear enlargement of the proximal renal tubule epithelium, and cerebral vacuolar degeneration. Rats in the 4,000 ppm groups had a decrease in water consumption and showed changes in the nasal cavity (nuclear enlargement of the olfactory epithelium), trachea (nuclear enlargement of the tracheal epithelium), and liver (increased incidence of

centrilobular hepatic cellular swelling and granulation formation). Rats in the 1,600 ppm groups had changes in the nasal cavity and liver. These findings were considered to be effects of the 1,4-dioxane administration. There were no significant changes in rats in the 640 ppm groups. Mice in the 25,000 ppm group had the same findings as the rats in the $\geq 10,000$ ppm groups. The mice in the 10,000 and 4,000 ppm groups had a decrease in water consumption and showed changes in the nasal cavity, trachea, lungs, and liver. Male mice demonstrated nasal olfactory and respiratory mucosa nuclear enlargement at concentrations of 4000 ppm and higher and eosinophilic changes at 25,000 ppm. Female mice were more sensitive to eosinophilic development in the respiratory and olfactory epithelium (around 10,000 ppm and higher). Nuclear enlargement in female mice was observed in both the respiratory and olfactory epithelium at concentrations of 4000 ppm and higher. Single cell hepatocellular necrosis accompanied by centrilobular swelling was observed at 4000 ppm and higher in both male and female mice. These findings were considered to be effects of the 1,4-dioxane administration. The mice in the 1,600 ppm groups showed changes in the lungs only. There were no significant changes in mice in the 640 ppm groups.

These previous studies influenced the current study design including dose levels, test system, route of test material administration, and study endpoints to further investigate the MOA for mouse liver tumors following 1,4-dioxane administration.

STUDY DESIGN

Experimental Design and Critical Dates

Groups of ten female B6D2F1 mice were given drinking water at concentrations of 0, 40, 200, 600, 2000 or 6000 ppm 1,4-dioxane for a duration of 7, 28, or 90 days. The targeted mg/kg/day dose levels were 0, 10, 50, 150, 500, and 1500 mg/kg/day. The parameters summarized in Table 1 were measured. Specific details of collected parameters are outlined below in the appropriate sections. Test material administration for the 90-day animals began September 7, 2018, with necropsy following on December 6th and 7th, 2018 (test days 91 and 92). Test material administration for the 28-day animals began October 9, 2018 followed by necropsy on November 6 and 7, 2018 (test days 29 and 30). Test material administration for the 7-day animals began October 2 and 3, 2018 followed by necropsy on October 9 and 10, 2018 (test day 8).

Route and Justification, Method of Administration, Frequency and Duration

Drinking water was the chosen route of exposure because it was previously used in the cancer bioassays, and this study was designed to generate data to help with mechanistic understanding of those bioassays. Animals were provided with drinking water containing five different concentrations of 1,4-dioxane for seven days/week and sacrificed following at least 7, 28, or 90-days of exposure.

Dose Levels and Justification

The dose levels selected (Text Table 1) were based on previous studies and were selected to bracket the biological effect (tumors) dose level, as well as the toxicokinetic transition points, *e.g.*, saturation metabolism of 1,4-dioxane where the parent compound is expected to increase in a non-linear fashion relative to dose and contribute to the key events leading to mouse liver tumors. The lower dose levels were expected to provide dose response data for anchoring points of departure to support dose-response modeling, such as benchmark dose modeling of key events observed in the study.

Text Table 1. Dose Levels

Targeted Dose Levels (mg/kg/day)	Concentration (ppm)	No. of Mice/Sex/Dose/ time point
0	0	10
10	40	10
50	200	10
150	600	10
500	2000	10
1500	6000	10
TOTAL		180

Dose Preparation

All drinking water solutions were prepared by mixing test material with Ultrapure water (w/w %). Drinking water solutions were prepared approximately weekly or more frequently (based on known stability data).

Solubility

The MSDS indicated 1,4-dioxane is completely miscible in drinking water. Additional solubility testing was not conducted and the analytical dose confirmation analysis established solubility to achieve the higher drinking water concentrations.

Analysis

Dose Confirmation and Homogeneity

Dose confirmation analyses of all dose levels, plus control were determined near the beginning of the study and at approximately the middle of the study (test day 42). The homogeneity of the low-dose and the high-dose drinking water solutions was determined concurrently with dose confirmation. The test material in the water was quantitatively analyzed by gas chromatography with mass spectrometry detection (GC/MS). Validation of the analytical methodology was conducted concurrently with the study per standard operating procedure (SOP) MTH-ACL-2 (2014).

Stability

The stability of the drinking water solutions was determined concurrently with the study for 11 days (Appendix C).

Retainer Samples

A sample of the bulk test material was retained. Samples of the dose solutions were not retained.

TEST SYSTEM

Species and Sex

Mice, female (nulliparous and non-pregnant)

Strain and Justification

B6D2F1/Crl mice were selected because of their general acceptance and suitability for toxicity testing, previous use in toxicity studies with 1,4-dioxane, and the reliability of the commercial supplier.

Supplier and Location

Charles River Laboratories (Raleigh, North Carolina)

Age at Study Start and Weight Range

Approximately 6 - 11 weeks old.

Health Status and Acclimation

Upon arrival, all animals were acclimated to the laboratory for at least one week prior to the study. During the acclimation period, each animal was evaluated by a veterinarian trained in the field of Laboratory Animal Medicine, or a trained animal/toxicology technician, to determine the general health status and acceptability for study purposes. The Toxicology and Environmental Research and Consulting Laboratory is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International).

Housing

Upon arrival animals were housed two-three per cage in plastic tubs. Cages contained corncob bedding and a feed crock. Water was supplied via a water bottle with a sipper tube.

After assignment, animals were housed two per cage in plastic tubs or housed singly in similar cages at the time of osmotic pump surgery until necropsy. Cages contained corncob bedding and a feed crock(s). Water was supplied via a water bottle with a sipper tube.

The following environmental conditions were targeted in the animal room from the day of arrival until necropsy, however temporary excursions from these environmental conditions may have occurred on an infrequent basis. All observed ranges are documented in the study file.

Temperature: 22°C with a range of 20°C-26°C

Humidity: 50% with a range of 30-70%

Air Changes: 10-15 times/hour (average)

Photoperiod: 12-hour light/dark (on at 6:00 a.m. and off at 6:00 p.m.)

Note: If photoperiod times changed due to study-related activities, it was documented in the study file.

Enrichment

Enrichment for animals was given from the day of arrival until necropsy. Enrichment included Shepherd Shacks and pair housing (except when singly housed due to surgery).

Randomization and Identification

Before administration of test material began, sets of animals were stratified by body weight and then randomly assigned to treatment groups using a computer program designed to increase the probability of uniform group mean weights and standard deviations at the start of the study. Animals placed on study were uniquely identified via subcutaneously implanted transponders (BioMedic Data Systems, Seaford, Delaware) that are correlated to unique alphanumeric identification numbers (Text Table 2). If a transponder stopped functioning or was lost, it was replaced with a new transponder that was correlated with the unique animal number. In addition, the first animal in the cage of pair-housed animals was ear punched to distinguish between cage mates.

Text Table 2. Animal Identification Numbers

Dose Level ppm	7-day Animals	28-day Animals	90-day Animals
0	18A0849 – 18A0858	18A0839 – 18A0848	18A0829 – 18A0838
40	18A0879 – 18A0888	18A0869 – 18A0878	18A0859 – 18A0868
200	18A0909 – 18A0918	18A0899 – 18A0908	18A0889 – 18A0898
600	18A0939 – 18A0948	18A0929 – 18A0938	18A0919 – 18A0928
2000	18A0969 – 18A0978	18A0959 – 18A0968	18A0949 – 18A0958
6000	18A0999 – 18A1008	18A0989 – 18A0998	18A0979 – 18A0988

Feed and Water

Feed and Ultrapure water were provided *ad libitum*. Animals were provided LabDiet Certified Rodent Diet #5002 (PMI Nutrition International, St. Louis, Missouri) in meal form and Ultrapure water (The Dow Chemical Company, Midland, Michigan). Analyses of the feed were performed by PMI Nutrition International to confirm the diet provides adequate nutrition and to quantify the levels of selected contaminants. There were no contaminants in the feed at levels that would have adversely impacted the results or interpretation of this study. Copies of these analyses are maintained in the study file.

STUDY SPECIFIC PARAMETERS

Daily Observations

A cage-side examination was conducted at least once a day, usually at the same time each day. This examination was typically performed with the animals in their cages and was designed to detect significant clinical abnormalities that were clearly visible upon a limited examination and to monitor the general health of the animals. The animals were not hand-held for these observations unless deemed necessary. Significant abnormalities that would be observed include, but were not limited to: decreased/increased activity, repetitive behavior, vocalization, incoordination/limping, injury, neuromuscular function (convulsion, fasciculation, tremor, twitches), altered respiration, blue/pale skin and mucous membranes, severe eye injury (rupture), alterations in fecal consistency, and fecal/urine quantity. In addition, all animals were observed for morbidity, mortality, and the availability of feed and water at least twice daily. Cage-side observations, in which only positive findings were documented, are summarized with clinical observations.

Clinical Observations

Animals were observed at least weekly. Clinical observations included a careful evaluation of abnormalities in the eyes, urine, feces, gastrointestinal tract, extremities, movement, posture, reproductive system, respiration, skin/hair-coat, and mucous membranes, as well as an assessment of general behavior, injuries, or palpable mass/swellings.

Body Weights/Body Weight Gains

All mice were weighed during the pre-exposure period and at least weekly during the study. Body weight gains were calculated relative to day 1.

Feed Consumption

The amount of feed consumed was determined at least weekly for all animals by weighing feed containers at the start and end of a measurement cycle. Feed consumption was calculated using the following equation:

$$\text{Feed consumption (g/day)} = \frac{(\text{initial weight of feed container} - \text{final weight of feed container})}{(\text{\# of days in measurement cycle}) (\text{\# of animals per cage})}$$

Water Consumption

Water consumption was determined twice weekly for all animals by weighing water bottles at the start and end of a measurement cycle. Water consumption was calculated using the following equation:

$$\text{Water consumption (g/day)} = \frac{(\text{initial weight of water bottle} - \text{final weight of water bottle})}{(\# \text{ of days in measurement cycle}) (\# \text{ of animals per cage})}$$

Test Material Intake

Test material intake (TMI) was calculated upon completion of the study using test material concentrations in the water, and mean body weights and water consumption data for each group per exposure duration. The following equation is used:

$$TMI = \frac{(\text{Water consumption} \left(\frac{\text{g}}{\text{day}} \right) * (1000 \text{ mg/g}) * (\% \text{ of test material in Water})}{100} \div \frac{(\text{current BW [g]} + \text{previous BW [g]})}{2} \div 1000 \text{ g/kg}$$

Implantation of Alzet Osmotic Pumps

All study animals were implanted with mini-osmotic pumps model 2ML1 (Alzet Corporation, Palo Alto, California) eight days prior to scheduled necropsy (Appendix A). The 7-day animals had the pumps implanted on test day -1 and were necropsied on test day 8. The 28-day animals were implanted with the pump on test day 21 or 22 and were necropsied on test day 29 or 30. The 90-day animals were implanted on test day 83 or 84, and were necropsied on test day 91 or 92. Two extra mice not placed onto study were used for surgical procedure proficiency purposes, and data for these mice are included in the study file only.

Incorporation of 5-bromo-2'-deoxyuridine (BrdU (CAS#59-14-2)) into nuclear DNA (a structural analog of thymidine) was used as a surrogate marker of cell proliferation. Animals were continuously infused with BrdU via the implanted osmotic pumps filled with a 20 mg/ml solution of BrdU in phosphate buffered saline (pH 7.6), at a delivery rate of 1.0 µl/hour. The osmotic pumps were implanted subcutaneously into the lumbar region or intrascapular region on the dorsum of each mouse. This implantation method assured a constant, uniform, systemic delivery of BrdU.

Clinical Chemistry

Sample Preparation

Blood samples were collected and serum was separated from cells as soon as possible. The following serum parameters were measured using the cobas c311 Clinical Chemistry Analyzer (Roche Diagnostics, Indianapolis, Indiana).

Enzyme Activities of:

Alkaline phosphatase (ALP)

Alanine aminotransferase (ALT)

Aspartate aminotransferase (AST)

Gamma glutamyl transpeptidase (GGT)

Anatomic Pathology

Necropsy

Non-fasted animals were submitted alive for necropsy after 7, 28, or 90 days of treatment (overall TD 8, 29/30, or 91/92). Animals were weighed in the animal room and transported to necropsy. Animals were anesthetized via inhalation of isoflurane vapors mixed with medical oxygen, and blood samples were obtained from the orbital sinus. The animals were then placed in a CO₂ chamber to continue anesthesia. Under a deep plane of anesthesia, their tracheas were exposed and clamped, and the animals were euthanized by decapitation.

After the animal was euthanized, the osmotic pump was removed and weighed individually so the osmotic pump weight could be subtracted from the animal weight recorded to get accurate body weights. The skin was reflected from the carcass, the thoracic and abdominal cavities were opened and the liver and kidneys were excised. Additionally, a 2-3 cm segment of the proximal duodenum were excised, flushed with 10% neutral buffered formalin, and was placed in the same fixative along with the liver tissue for analysis of BrdU incorporation. This tissue served as a positive control for BrdU uptake.

Transponders were removed and placed in formalin with the saved tissues. The ratios of liver weight to terminal body weight were calculated.

Tissue Processing

Kidney

Five animals/group/study duration (7-day, 28-day and 90-day) had both kidneys saved in formalin, processed by standard histological procedures within 48 hours of fixation, and embedded for possible future analysis.

From the remaining five animals/group/study duration, the left kidney was flash frozen and stored in a -80°C freezer for potential future analysis, the right kidney was discarded.

Liver

The liver from all study animals was processed and evaluated by standard histologic procedures. The formalin fixed liver, embedded with duodenum, was processed for light microscopy which included histochemical (hematoxylin and eosin; H &E) and immunohistochemical (BrdU-labeled cells, caspase-3, or GST-P (90-day animals only)) staining.

An unstained slide of liver tissue from the routine sectioning of the liver was sent to BioSpyder Technologies, Inc. (Carlsbad, CA) for TempO-Seq analysis from 5 animals/group/study duration. The slide had the left lateral lobe identified for BioSpyder.

A small portion of liver from the first 6 animals per group of the 28-day and 90-day duration animals was flash frozen and stored in a -80°C freezer for possible future analysis.

Nasal tissue

Five animals/group/study duration (7-day, 28-day and 90-day) had the lower jaw, skin and musculature removed, the nasal airways were flushed, retrograde, via the nasopharyngeal orifice with 10% neutral buffered formalin, and the nasal cavity was placed in a container with formalin. Approximately 24-hours post-fixation, nasal tissue was processed and embedded in paraffin and saved for possible future analyses. Nasal tissues were not sectioned or examined.

From the remaining five animals/group/study duration, the lower jaw, skin and musculature was removed, the nasal airways were flushed, retrograde, via the nasopharyngeal orifice with RNAlater, and the nasal cavity was stored in RNAlater. The heads were removed from RNAlater storage within a week, blotted to remove residual RNAlater, and stored in -80°C freezer for possible future analyses.

Histopathology

Histopathological evaluation of the H & E stained liver slides was contracted to Vet Path Services, Inc. (Mason, Ohio). A board-certified (ACVP) veterinary pathologist evaluated the tissues described above from all animals on study (n=180 animals) using standard criteria, and the pathology data was tabulated using Vet Path Services' Provantis system (Appendix D).

Examination of Hepatocellular Proliferation

BrdU Slide Preparation

Liver S-phase DNA synthesis was determined using 5-bromo-2'-deoxyuridine (BrdU) immunohistochemistry for identification of BrdU incorporation into nuclear DNA using the method outlined by Eldridge and Goldsworthy (1996). Following fixation, a section of liver was processed by standard techniques and mounted on glass slides. Tissue was stained for BrdU using the manufacturers' protocol (BD Biosciences, San Diego, California) and modified heat-induced antigen retrieval. As described, a small section of duodenum from each animal was also processed to serve as a control for confirming systemic availability of the BrdU.

Manual counts of BrdU stained slides

Using light microscopy, from each slide approximately 1000 BrdU labeled and unlabeled hepatocellular nuclei from each of the hepatolobular zones: centrilobular, periportal and mid-zonal region were counted. Representative fields consisting of a classic hepatic lobule with a central vein and peripherally located portal triads were selected for scoring. Central veins and portal triads were selected to be generally of similar size and distance between the lobular features to minimize variability. The lobule was divided into approximately thirds, consisting of the centrilobular zone, the periportal zone, and the midzonal region and 1000 hepatocytes were counted from each of the three zones for each animal (for a total of 3000 hepatocytes per slide).

Examination of Hepatocellular Apoptosis

Caspase-3 and GST-P Slide Preparation

See Appendix B for method details of the slide preparation.

Image Analysis of Caspase-3 Stained Slides

Stained slides were scanned and digitized using a Versa whole-slide imaging system (Leica Biosystems, Buffalo Grove, IL) and the digitized images stored using a GLP compliant data management system (E-Slide Manager; Leica Biosystems).

The number of caspase-3 positive hepatocytes was determined by quantitative image analysis from all analyzable liver tissue on the caspase-3 stained slides from all 28-day and 90-day animals. Caspase-3 positive hepatocytes, as determined by quantitative image analysis software, were reviewed manually to confirm true positives. The data were presented and analyzed as a positive count per 10,000 cells.

The annotated digital images showing the regions analyzed and the identification and enumeration of labeled and unlabeled cells within each region was stored with the original unmodified images on E-Slide Manager per SOP EQP-097.

GST-P

One of the selected ways to characterize the liver status in this mode of action study was to evaluate preneoplastic hepatic foci using immunohistochemical GST-P staining. Because there were no foci identified through histopathological examination (see Appendix D), glutathione S-transferase – pi isoform GST-P quantitation was not conducted.

Toxicokinetic Analysis of Whole Blood

To evaluate the dose response of test material metabolism, blood samples were collected from five non-fasted mice/dose/exposure duration at necropsy via the orbital sinus following anesthesia with a mixture of isoflurane and medical oxygen at the time of terminal sacrifice. Each blood sample was divided into two pre-weighed vials containing extraction solvent and vortex mixed. These two sets of samples were stored in a -80°C freezer until analysis. At analysis, one set of samples was quantitatively analyzed for determining the concentration of 1,4-dioxane and major metabolite HEAA via the GC/MS method. The second set were used for contingency analyses. All samples were discarded after study finalization.

Liver Transcriptomics

Formalin fixed, paraffin embedded liver tissue was submitted on glass slides (room temp) to BioSpyder Technologies, Inc. (Carlsbad, CA) from 5 animals/group of the 7-day, 28-day, and 90-day exposure duration animals. BioSpyder performed the data acquisition process non-GLP. ToxStrategies, Inc. (Austin, TX) analyzed and reported the data non-GLP. The provided non-GLP report is presented in Appendix F.

STATISTICS AND CALCULATIONS

Statistics were performed separately for each treatment duration (*i.e.*, 7, 28, or 90-day treatment periods). Means and standard deviations were calculated for all continuous data.

Based on the results of Bartlett's test for homogeneity of variance at $\alpha=0.01$ (Winer, 1971), body weights, feed consumption, water consumption, liver weights (absolute and relative), cell proliferation data (BrdU), and apoptosis quantitation data (caspase-3) were evaluated with a parametric (Steel and Torrie, 1960) or nonparametric (Hollander and Wolfe, 1973) analysis of variance (ANOVA). If significant at $\alpha = 0.05$, the ANOVA was followed respectively by Dunnett's test ($\alpha = 0.05$; Winer, 1971) or the Wilcoxon Rank-Sum test ($\alpha = 0.05$; Hollander and Wolfe, 1973) with a Bonferroni correction (Miller, 1966) for multiple comparisons to the control. The experiment-wise α level was reported for these two tests. Feed and water consumption values were excluded from analysis if the feed/water was spilled, scratched, or leaking.

Descriptive statistics only (means and standard deviations) were reported for body weight gain. Statistical outliers were identified by a sequential test ($\alpha = 0.02$; Grubbs, 1969), and may have been excluded only for documented scientifically sound reasons.

Descriptive statistics (*i.e.*, mean $\pm$ standard deviation) were calculated for the toxicokinetic data using Microsoft Excel (Microsoft Corporation, Redmond, Washington) spreadsheets in full precision mode (15 digits of accuracy). A least squares regression analysis was conducted with the blood concentrations of 1,4-dioxane, and its HEAA metabolite, regressed against dose and the quadratic term (squared value of dose) (Neter *et al.*, 1990). A significant quadratic term ($\alpha \leq 0.025$) meant that the model was encountering nonlinearity in the dose-response curve. The model containing all dose groups was run first and, if there was a significant quadratic term the dataset was reevaluated with successive removal of the highest dose level until the quadratic term became non-significant or there were only three dose levels left (McFadden *et al.*, 2012).

RESULTS

Analytical Chemistry

Dose confirmation analyses of all dose levels, plus control were determined near the beginning of the study and at approximately the middle of the study (test day 42). The homogeneity of the low-dose (40 ppm) and the high-dose (6000 ppm) drinking water solutions was determined concurrently with dose confirmation. Stability of 1,4-dioxane in drinking water was evaluated on stability days 0, 5, and 11 (Appendix C).

Analyses of all 1,4-dioxane drinking water solutions indicated the mean concentration for each dose level ranged from 93.8% to 102% of targeted concentrations, indicating acceptable concentrations of 1,4-dioxane.

The relative standard deviations for all drinking water solutions sampled were between 0.637 and 5.55% indicating that the solutions were homogeneously mixed.

1,4-dioxane was demonstrated to be stable in drinking water for up to 11 days at concentrations ranging from 40 ppm to 6000 ppm based on the acceptance criteria of $\pm 15\%$ of corresponding Day 0 concentrations.

Mortality

All mice survived the treatment period.

Clinical and Cage-side Observations

Clinical observations are summarized in [Tables 2-4](#); individual data are reported in [Appendix Tables 1 -3](#) for the 7-day, 28-day, and 90-day animals.

There were no treatment-related clinical observations noted throughout the study.

Body Weights/Body Weight Gain

Mean body weight and body weight gain data for 7-day, 28-day, and 90-day animals are summarized in [Tables 5-7](#), individual data are reported in [Appendix Tables 4-6](#).

There were no statistical or treatment-related differences in the body weights or body weight gains in any of the 7-day, 28-day, or 90-day 1,4-dioxane treated animals when compared to their respective controls.

Feed Consumption

Mean feed consumption data for the 7-day, 28-day, and 90-day animals are summarized in [Tables 8-10](#); individual data are reported in [Appendix Tables 7-9](#).

There were no treatment-related differences in feed consumption in any of the 7-day, 28-day, or 90-day 1,4-dioxane treated animals when compared to their respective controls.

Water Consumption

Mean water consumption data for the 7-day, 28-day, and 90-day animals are summarized in [Tables 11-13](#); individual data are reported in [Appendix Tables 10-12](#).

During the 7-day treatment period, animals in the 6000 ppm group had a slight decrease in water consumption from test day 1-4 (14%), compared to their respective control.

There were no treatment-related differences in water consumption in any 1,4-dioxane treated animals during the 28-day treatment period when compared to their respective control.

During the 90-day treatment period, animals given 6000 ppm had treatment-related decreases in water consumption ranging from 12-29% compared to their respective control at most intervals.

Test Material Intake

TMI for the 7-day, 28-day, and 90-day animals are summarized in [Tables 14-16](#) and are presented in Text Table 3 below.

Text Table 3. Time Weighted Average Doses of 1,4-Dioxane

Concentration (ppm)	0	40	200	600	2000	6000
	Actual Dose (mg/kg/day) ¹					
7-day	0	9.12 (±0.133)	47.1 (±0.661)	142 (±0.00)	484 (±13.1)	1288 (±80.4)
28-day	0	8.40 (±0.584)	43.4 (±2.88)	124 (±12.0)	419 (±30.5)	1147 (±121)
90-day	0	7.20 (±0.624)	37.3 (±2.59)	116 (±10.2)	364 (±27.0)	979 (±83.8)

¹ Calculated time weighted average dose for the duration of each exposure period (7, 28, or 90-days) based on mean water consumption, body weights, and 1,4-dioxane concentrations.

Clinical Chemistry

Clinical chemistry data (*i.e.* ALP, ALT, AST, and GGT) for the 7-day, 28-day, and 90-day animals are summarized in [Tables 17-19](#); individual data are reported in [Appendix Tables 13-15](#).

There were no statistical or treatment-related differences in the liver enzymes in any of the 7-day, 28-day, or 90-day 1,4-dioxane treated animals when compared to their respective controls.

Organ Weight

Terminal body and liver weight data for the 7-day, 28-day, and 90-day animals are summarized in [Tables 20-22](#); individual data are reported in [Appendix Tables 16-18](#). Unless noted below, there was not a statistically identified change when compared to the respective control group.

7-day animals given 6000 ppm had a statistically significant 9.1% increase in mean relative liver weight compared to controls.

28-day animals given 6000 ppm had statistically significant increases in absolute (9.1%) and relative (10.7%) liver weight compared to controls. Additionally, animals given 2000 ppm had a statistically significant 4.9% increase in relative weight compared to controls.

Similar to the 28-day animals, 90-day animals given 6000 ppm had statistically significant increases in absolute (7.6%) and relative (9.3%) liver weight compared to controls. Additionally, animals given 2000 ppm had a statistically significant 6.3% increase in relative weight compared to controls.

Histopathology

Histopathology data and interpretation are located in histopathology report in Appendix D. The conclusions of the histopathology report are added here.

There were no exposure-related findings at dosages ≤ 200 ppm at any exposure duration. After 7 days of exposure, dose-related vacuolation, centrilobular, minimal or mild, was observed at ≥ 600 ppm; this finding was also observed in 28-day and 90-day cohorts. After 28 days of exposure, additional liver findings at the 6000 ppm exposure level included minimal to mild centrilobular hepatocyte hypertrophy in all mice and minimal to mild increased centrilobular apoptosis in most. After 90 days of exposure, hepatocyte

hypertrophy was slightly more severe in 6000 ppm mice, and there was one mouse at 2000 ppm with the finding. Also after 90 days of exposure, minimal to mild centrilobular apoptosis of hepatocytes affected all mice at 6000 ppm and one mouse at 2000 ppm. Increased centrilobular apoptosis is considered adverse.

For female B6D2F1/Crl mice exposed to 1,4-dioxane in drinking water for 7, 28, or 90 days, the No Observed Effect Level (NOEL) for microscopic findings was 200 ppm. The No Observed Adverse Effect Level for microscopic findings was 600 ppm.

Examination of Hepatocellular Proliferation

Hepatocellular proliferation data for the 7-day, 28-day, and 90-day animals are summarized in [Tables 23-25](#); individual data are reported in Figures 1-3 and in [Appendix Tables 19-21](#). As previously described in the Study-Specific Parameters section, immunohistochemical staining for BrdU-labeled nuclei as a measure of hepatocellular proliferation was assessed in at least 1000 hepatocytes in each of three hepatic zones per animal. As there were no treatment-related, zonal-specific effects on hepatocellular proliferation, the data were summed per animal and presented as panlobular in Figures 1-3 and for fold-change differences in Text Table 4 below.

The only treatment-related and statistically identified change in hepatocellular proliferation was an increase in the labeling index in the 90-day animals given 6000 ppm 1,4-dioxane (panlobular: 4.3 and 20.8% in control and high dose, respectively). In this study and in all treatment durations, the background labeling index was increased when compared to other mouse strains (Geter *et al.*, 2014, unpublished internal laboratory observations), presumably due to altered growth kinetics and strain-specific differences. Note, the 7-day and 28-day animals were coordinated to be a similar age at pump implantation and necropsy to minimize that potential source of variation. Furthermore, the expected variation in hepatocellular labeling index due to estrous cycling (Umeda *et al.*, 2015) may have contributed to, but was not sufficient to fully account for, the variation in labeling index identified within a specific treatment group.

Text Table 4. Summary of Hepatocellular Proliferation

Dose Level (ppm)	7-Day	28-Day	90-Day
0	-	-	-
40	0.9	0.9	1.7
200	1.0	1.6	1.2
600	1.4	1.4	1.1
2000	1.0	1.6	1.5
6000	1.0	1.0	4.8
Data expressed as fold-change (mean, all zones) compared to respective control. Bold indicates treatment-related effects.			

Apoptosis Quantification as Measured by Caspase-3

Apoptosis quantification data for the 28-day and 90-day animals are summarized in [Tables 26 and 27](#); individual data are reported in [Appendix Tables 22 and 23](#).

The 28-day and 90-day animals given 6000 ppm had statistically significant increases in caspase-3 positive cells compared to controls (Text Table 5).

There were no statistical or treatment-related differences in any other treatment group of the 28-day or 90-day 1,4-dioxane treated animals when compared to their respective controls.

Collectively, these data indicate that, under these experimental conditions, the inhibition of apoptosis MoA (*i.e.*, a decrease in the basal rate of caspase-positive staining) can be ruled-out as a contributing factor in 1,4-dioxane-mediated murine hepatocarcinogenesis. Furthermore, the small magnitude of caspase induction coupled with the minimal histopathological findings, indicate that a cytotoxicity/regenerative proliferation MoA may not adequately account for the increased hepatocellular proliferation (and eventual tumors) during this limited exposure paradigm.

Text Table 5. Caspase-3 Positive Cells per 10,000

Dose Level (ppm)	28-Day	90-Day
0	0.08	0.04
40	0.03	0.18
200	0.00	0.04
600	0.02	0.07
2000	0.07	0.12
6000	0.46*	1.08*
* Statistically different from control mean by Wilcoxon's test, alpha=0.05 Bold indicates treatment-related effects.		

Toxicokinetics

Blood samples collected at the end of treatment for the 7-day, 28-day, and 90-day animals, were quantitatively analyzed by GC/MS-MS to determine the blood levels of 1,4-dioxane and the corresponding HEAA metabolite. The final blood levels of both 1,4-dioxane and HEAA were summarized in the TERC-ACL report (Appendix E). A summary of analytical results, animal number, TMI, and measured blood levels of 1,4-dioxane and HEAA is presented in [Table 28](#).

No 1,4-dioxane or HEAA were detected in any control animals across all three time points (7-day, 28-day or 90-day).

At 7 days, 1,4-dioxane was not detected in animals across any dose groups; however, HEAA was quantifiable in all treated animals except the 40 ppm-treated animals and two of five 200 ppm-treated animals. The quantifiable levels of HEAA ranged from 0.198 to 80.7 µg/mL blood with average values ranging from 1.21 to 43.5 µg/mL blood ([Table 28](#)). Toxicokinetic analysis showed that the blood level of HEAA was linear across 0, 200, 600, 2000, and 6000 ppm groups ([Figure 4](#) and [Table 29](#)).

At 28 days, 1,4-dioxane was only detectable and quantifiable in few animals (one of five 200 ppm-treated animals, two of five 2000 ppm-treated animals, and one of five 6000 ppm-treated animals) and the blood levels of 1,4-dioxane ranged from 0.462 to 44.8 µg/mL ([Table 28](#)). Due to the very limited number of samples containing quantifiable 1,4-dioxane, kinetic linearity or non-linearity could not be determined ([Table 29](#)). In contrast to 1,4-dioxane, HEAA was quantifiable in all treated animals. The quantifiable levels of HEAA ranged from 0.125 to 6.37 µg/mL blood with average values ranging from 0.359 to 3.49 µg µg/mL blood ([Table 28](#)). Kinetically, the blood level of HEAA was linear across all treatment groups ([Figure 5](#) and [Table 29](#)).

At 90 days, 1,4-dioxane was quantifiable in most animals across all dose groups with a few exceptions (*i.e.* five of five 40 ppm-treated animals, two of five 200 ppm-treated animals and two of five 600 ppm-treated animals). The quantifiable levels of 1,4-dioxane ranged from 0.274 to 210 µg/mL blood samples with average values ranging from 0.338 to 80.8 µg µg/mL blood ([Table 28](#)). Toxicokinetic analysis showed that the blood level of 1,4-dioxane was non-linear at 2000 ppm and 6000 ppm exposure concentrations (supralinear at 6000 ppm ([Figure 7](#), [Table 29](#)) and sublinear at 2000 ppm ([Figure 8](#), [Table 29](#))). HEAA was quantifiable in all animals across all dose groups. The quantifiable levels of HEAA ranged from 0.0799 to 9.81 µg/mL blood with average values ranging from 0.186 to 5.91 µg µg/mL blood ([Table 28](#)). Kinetically, the blood level of HEAA was linear across all treatment groups ([Figure 6](#) and [Table 29](#)).

Overall, the toxicokinetic analysis results from the blood levels of 1,4-dioxane and HEAA are suggestive of potential saturation of some absorption and/or metabolic pathways of 1,4-dioxane in the highest dose group (6000 ppm) after 90 days of exposure.

CONCLUSIONS

When administered via the drinking water, the data collected for 1,4-dioxane indicate a clear time- and dose-dependent threshold for hepatic effects. The molecular and apical treatment-induced biological changes correlate with increased quantifiable concentrations of 1,4-dioxane in the blood and a potential shift in metabolism over time. After 7 days of treatment, liver weight increases in the 6000 ppm group correlated to increased centrilobular vacuolation characteristic of glycogen storage. After 28 and/or 90 days, liver weight increases in the 6000 ppm groups were correlated to histopathological findings of increased centrilobular vacuolation, hypertrophy, and apoptosis. Notably, the magnitude of hepatocellular proliferative induction (~5-fold) at the highest dose is comparable to other mitogenic, non-genotoxic hepatocarcinogens. Furthermore, under these experimental conditions, the inhibition of apoptosis MoA (*i.e.*, a decrease in the basal rate of caspase-positive staining) can be ruled-out as a contributing factor in 1,4-dioxane-mediated murine hepatocarcinogenesis. Within the first 90 days of drinking water exposure, the small magnitude of caspase induction coupled with the minimal histopathological findings, indicate that a cytotoxicity/ regenerative proliferation MoA cannot adequately account for the increased hepatocellular proliferation (and eventual tumors). Collectively, these data indicate that after an extended period of administration at metabolically saturating doses of 1,4-dioxane, a mitogenic response is triggered in the liver of female mice.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the contributions of the following individuals to the conduct of the study and report preparation:

E. J. Nelson	Analytical and TK Analyses
M. E. Gum	Animal Technician
M. A. Lawson	Clinical Pathology
K. A. Vasold	Document Management
L. A. Stilgenbauer	Quality Assurance
S. K. Lidke	Technologist
K. M. Kleinert	BrdU and Caspase-3 Scoring
E. J. Collins	Caspase-3 Image Analysis
K. S. Bell	Immunohistochemical Staining
Histology Group Support, Necropsy Team, and Animal Care Staff	

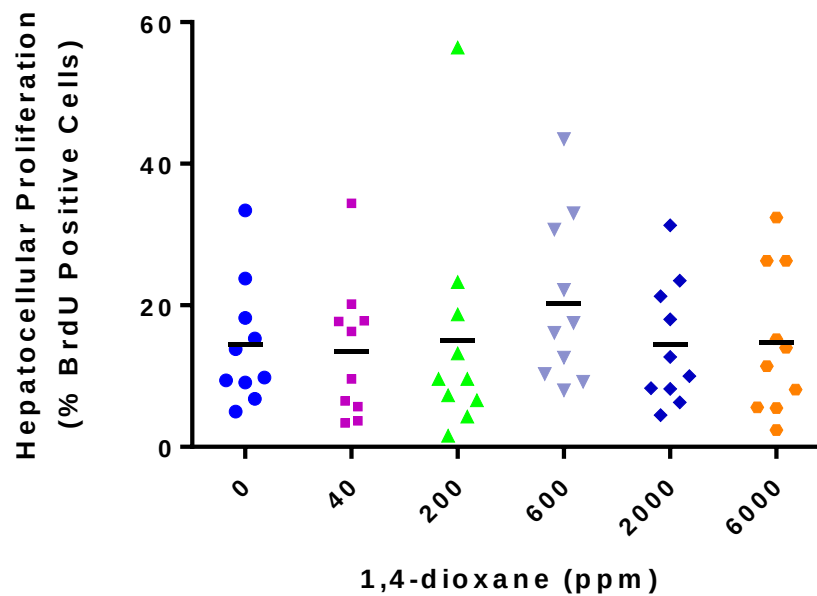
REFERENCES

- Eldridge, S. R. and Goldsworthy, S. M. (1996). Cell Proliferation Rates in Common Cancer Target Tissues of B6C3F1 Mice and F344 Rats: Effect of Age, Gender, and Choice of Marker. *Fundam Appl Toxicol* **32**, 159-167.
- EQP-097-1 (2017). Operation, Use, and Maintenance of Leica Imaging System. Standard Operating Procedure (SOP). Toxicology and Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan.
- Grady, M. (2018). Certificate of Analysis of 1,4-Dioxane, Lot # SHBJ7415. Sigma-Aldrich, Sheboygan Falls, Wisconsin.
- Grubbs, F. E. (1969). Procedures for detecting outlying observations in samples. *Technometrics* 11:1-21.
- Hollander, M. and Wolfe, D. A. (1973). *Nonparametric Statistical Methods*. John Wiley & Sons, New York.
- Kano, H., Umeda Y, Saito, M., Hideki S., Ohbayashi, H., Aiso, S., Yamazaki, K., Nagano, K., Fukushima S. (2008). Thirteen-week oral toxicity of 1,4-dioxane in rats and mice. *The Journal of Toxicological Sciences* **33-2**: 141-153.
- Kano, H., Umeda Y., Kasai, T., Sasaki, T., Matsumoto, M., Yamazaki, K., Nagano, K., Arito, H. Fukushima S. (2009). Carcinogenicity studies of 1,4-dioxane administered in drinking-water to rats and mice for 2 years. *Food and Chemical Toxicology* **47**: 2776-2784.
- McFadden, L. G., Bartels, M. J., Rick, D. L., Price, P. S., Fontaine, D. D., and Saghir, S. S. (2012). Statistical methodology to determine kinetically derived maximum tolerated dose in repeat dose toxicity studies. *Reg. Toxicol. Pharmacol.* **63**, 344- 351.
- Miller, R. G., Jr., (1966). *Simultaneous Statistical Inference*. McGraw-Hill, New York, pp. 67-70, 101-102.
- MTH-ACL-2 (2014). Development and Validation of Quantitative Analytical Procedures to Determine Concentration of Test Material in Test Matrix. Standard Operating Procedure (SOP). Toxicology and Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan.
- Neter, J., Wasserman, W., and Kutner, M. H. (1990). Applied Linear Statistical Models: Regression, Analysis of Variance, and Experimental Designs (Third Edition). McGraw Hill/Irwin Series Operation and Decision Sciences, New York.

- Steel, R. G. D. and Torrie, J. H. (1960). *Principles and Procedures of Statistics*. McGraw-Hill, New York.
- Umeda, M., Hiramoto, M., and Imai, T. Partial hepatectomy induces delayed hepatocyte Prolifereation and Normal Liver Regeneration in Ovariectomized Mice. *Clinical and Experimental Gastroenterology*. 2 July 2015 Volume 2015:8 Pages 175-182.
- Winer, B. J. (1971). *Statistical Principles in Experimental Design* (2nd Edition). McGraw-Hill, New York.
- Yamamoto, S., Aiso S., Ikawa, N., Enomoto, S., Onishi, M., Obayashi H., Katagiri, T., Kaneno, O., Sato, T., Nagano, K., Narumi A., Noguchi T., Matsumoto, M. (1990). Report of Preliminary Carcinogenicity Studies (Acute, Two-Week, and Thirteen-Week Studies) by Oral Administration of 1,4-Dioxane (Mixed with Water) to Rats and Mice. Japan Industrial Safety and Health Association, Japan Bioassay Research Center, Hadano, Kanagawa, Japan.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/CrI Mice

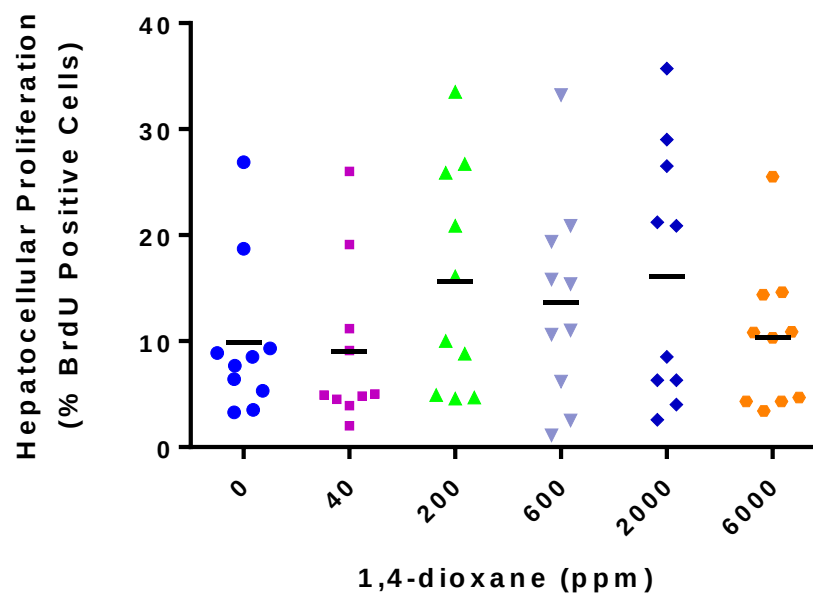
FIGURE 1. 7-day BrdU data



See Text Table 1 for the approximate estimation of dose based on exposure concentration.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

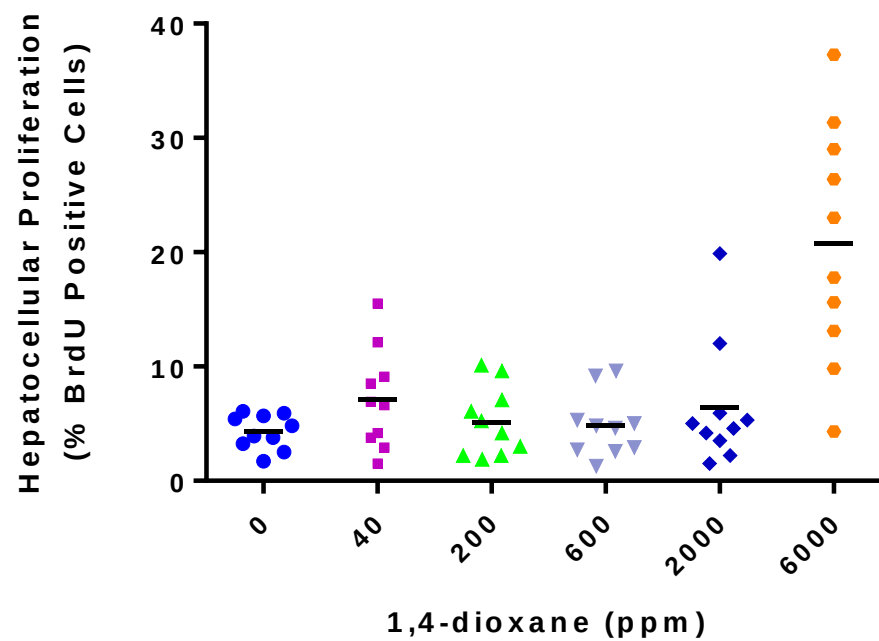
FIGURE 2. 28-day BrdU data



See Text Table 1 for the approximate estimation of dose based on exposure concentration.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/CrI Mice

FIGURE 3. 90-day BrdU data



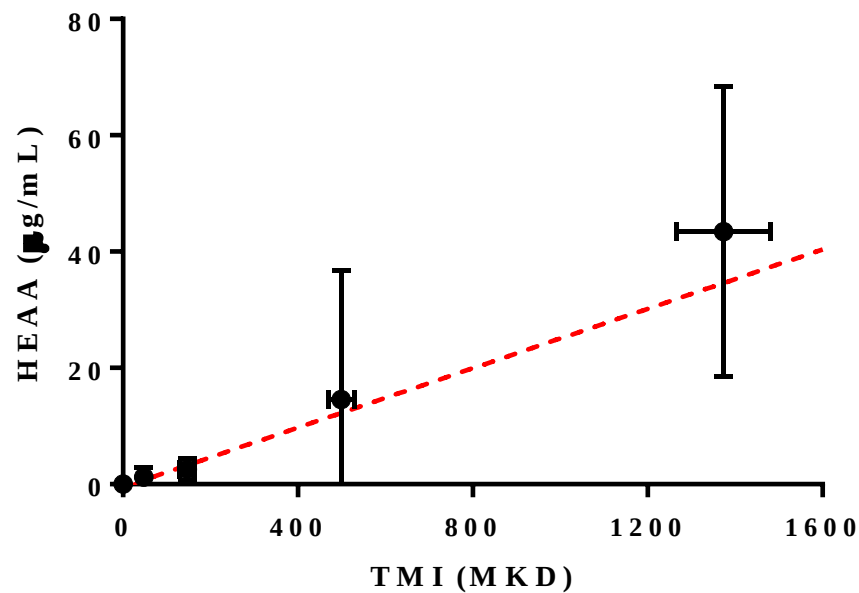
See Text Table 1 for the approximate estimation of dose based on exposure concentration.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/CrI Mice

FIGURE 4. Blood Concentrations of HEAA at 7 Days

Data are presented for blood levels of HEAA and calculated dose (TMI) specific to analyzed animals.

Dotted line indicates projection for linear kinetics of HEAA.



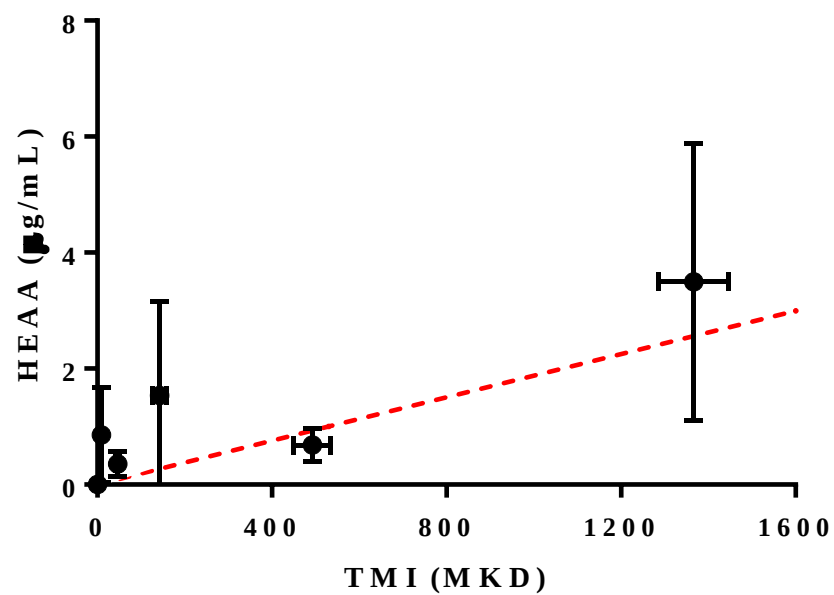
See Text Table 1 for exposure concentrations correlated to the approximate estimation of dose.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

FIGURE 5. Blood Concentrations of HEAA at 28 Days

Data are presented for blood levels of HEAA and calculated dose (TMI) specific to analyzed animals.

Dotted line indicates projection for linear kinetics of HEAA.



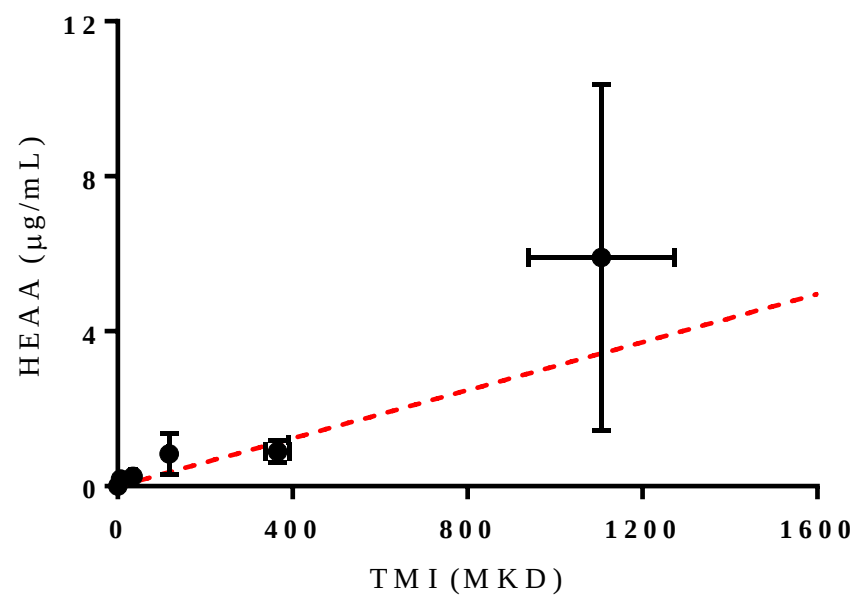
See Text Table 1 for exposure concentrations correlated to the approximate estimation of dose.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

FIGURE 6. Blood Concentrations of HEAA at 90 Days

Data are presented for blood levels of HEAA and calculated dose (TMI) specific to analyzed animals.

Dotted line indicates projection for linear kinetics of HEAA



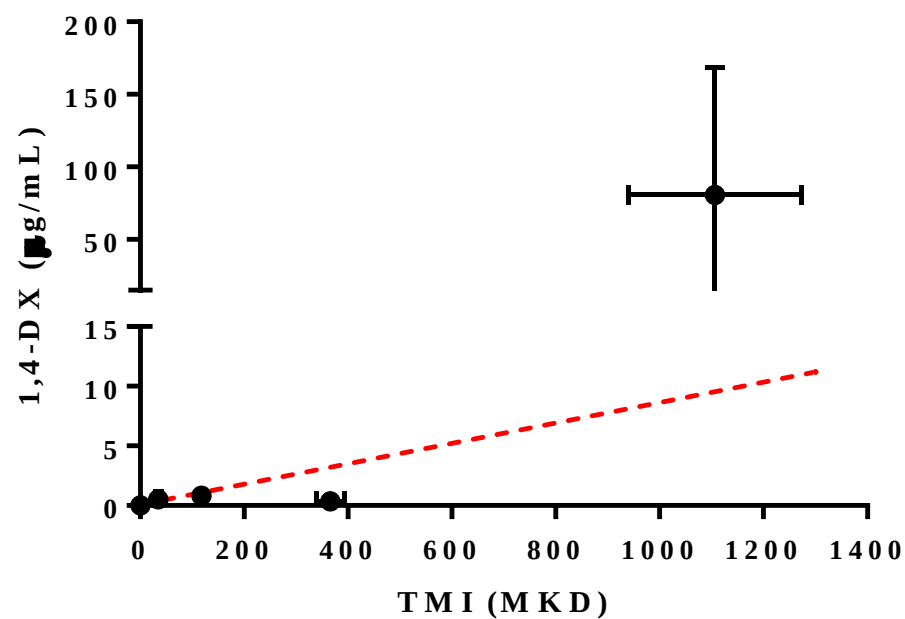
See Text Table 1 for exposure concentrations correlated to the approximate estimation of dose.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/CrI Mice

FIGURE 7. Blood Concentrations of 1,4-dioxane at 90 Days (all dose levels)

Data are presented for blood levels of 1,4-dioxane and calculated dose (TMI) specific to analyzed animals.

Dotted line indicates projection for linear kinetics of 1,4-dioxane.

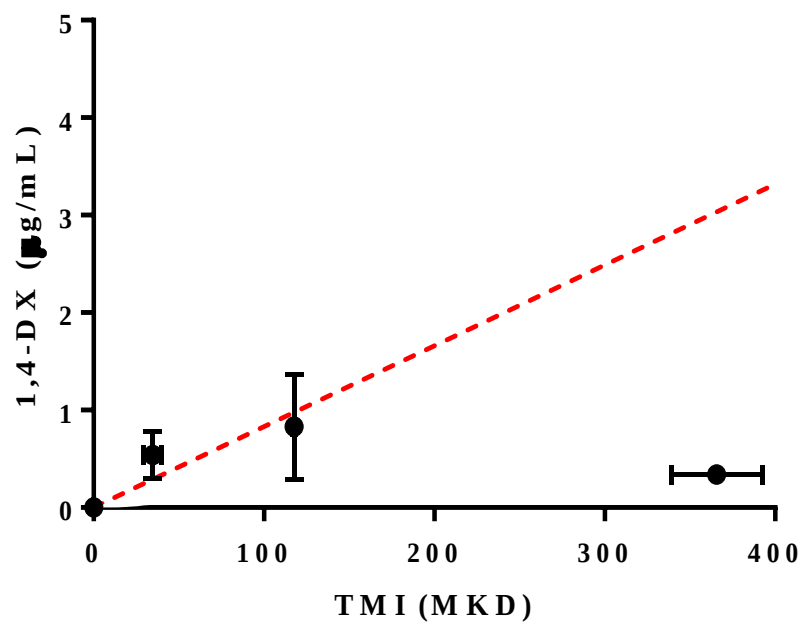


See Text Table 1 for exposure concentrations correlated to the approximate estimation of dose.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/CrI Mice

FIGURE 8. Blood Concentrations of 1,4-dioxane at 90 Days (high dose level removed)

Data are presented for blood levels of 1,4-dioxane and calculated dose (TMI) specific to analyzed animals.



Dotted line indicates projection for linear kinetics of 1,4-dioxane using all dose levels. The high dose level data point was removed in this figure for better visualization of the sublinearity at 2000 ppm (366 mkd). See Text Table 1 for exposure concentrations correlated to the approximate estimation of dose.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 1. Study Design

Study Parameters	7-Day Sacrifice No. of Animals/Sex/Dose	28-Day Sacrifice No. of Animals/Sex/Dose	90-Day Sacrifice No. of Animals/Sex/Dose
Daily Cageside Observations	10	10	10
Clinical Observations	10	10	10
Body Weights	10	10	10
Feed Consumption	10	10	10
Water Consumption	10	10	10
Osmotic Pump Implantation	10	10	10
Select Clinical Chemistry	10	10	10
Toxicokinetics in Terminal Blood	5	5	5
Necropsy	10	10	10
Liver Weights	10	10	10
Liver Histopathology			
H &E	10	10	10
Caspase-3	10	10	10
BrdU	10	10	10
GST-P (prep to slide)	0	0	10
Examination of Liver Proliferation (BrdU)	10	10	10
Quantitation of Liver Apoptosis (Caspase-3)	0	10	10
Contingency Specimen Collection			
Noses ¹	10	10	10
Liver ²	5	5	5
Kidney ³	10	10	10
Transcriptomics	5	5	5

¹ Following approximately 24-hours of fixation, noses were processed and embedded in paraffin to preserve tissue for subsequent sectioning, histopathological assessment, and measurement of BrdU upon Sponsor request.

² Livers were additionally processed and preserved for future RNA sequencing analysis.

³ Sections of kidneys were processed and embedded in paraffin to preserve tissue for possible future histopathological assessment, measurement of BrdU, and other biomarkers of potential key events, and also preserved for future gene expression analysis.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 2. Clinical Observations Summary – 7-day

SEX		FEMALES					
DOSE (PPM)		0	40	200	600	2000	6000
Number of Animals Examined							
DAY	1	10	10	10	10	10	10
DAY	8	10	10	10	10	10	10
All Categories, Within Normal Limits							
DAY	1	10	10	10	10	10	10
DAY	8	10	10	10	9	8	9
Skin/Fur/Mucous Membranes, Skin, Scab, Focal							
DAY	8	0	0	0	1	2	1

- No Data

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 3. Clinical Observations Summary – 28-day

SEX		FEMALES					
DOSE (PPM)		0	40	200	600	2000	6000

Number of Animals Examined							
DAY	1	10	10	10	10	10	10
DAY	8	10	10	10	10	10	10
DAY	15	10	10	10	10	10	10
DAY	21	10	10	10	10	10	10
DAY	29	10	10	10	10	10	10
All Categories, Within Normal Limits							
DAY	1	10	10	10	10	10	10
DAY	8	10	10	10	10	10	10
DAY	15	10	10	10	10	10	10
DAY	21	10	10	10	10	10	10
DAY	29	10	10	10	10	10	10

- No Data

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/CrI Mice

TABLE 4. Clinical Observations Summary – 90-day

SEX		FEMALES					
DOSE (PPM)		0	40	200	600	2000	6000
Number of Animals Examined							
DAY	1	10	10	10	10	10	10
DAY	8	10	10	10	10	10	10
DAY	15	10	10	10	10	10	10
DAY	22	10	10	10	10	10	10
DAY	29	10	10	10	10	10	10
DAY	36	10	10	10	10	10	10
DAY	43	10	10	10	10	10	10
DAY	50	10	10	10	10	10	10
DAY	57	10	10	10	10	10	10
DAY	64	10	10	10	10	10	10
DAY	71	10	10	10	10	10	10
DAY	78	10	10	10	10	10	10
DAY	83	10	10	10	10	10	10
DAY	91	10	10	10	10	10	10
All Categories, Within Normal Limits							
DAY	1	10	10	10	10	10	10
DAY	8	10	10	10	10	10	10
DAY	15	10	10	10	10	10	10
DAY	22	10	10	10	10	10	10
DAY	29	10	10	9	10	10	10
DAY	36	10	10	9	10	10	10
DAY	43	10	10	9	10	10	10
DAY	50	10	10	9	10	10	10
DAY	57	10	10	9	10	10	10
DAY	64	10	10	9	10	10	10
DAY	71	10	10	9	10	10	10
DAY	78	10	10	9	10	10	10
DAY	83	10	10	9	10	10	10
DAY	91	10	10	9	9	9	10
Injury, Apparent Mechanical							
DAY	29	0	0	1	0	0	0
Miscellaneous, Missing Part of Tail, Sloughed							
DAY	36	0	0	1	0	0	0
DAY	43	0	0	1	0	0	0
DAY	50	0	0	1	0	0	0

- No Data

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 4. Clinical Observations Summary – 90-day (continued)

SEX		FEMALES					
DOSE (PPM)		0	40	200	600	2000	6000

Miscellaneous, Missing Part of Tail, Sloughed							
DAY	57	0	0	1	0	0	0
DAY	64	0	0	1	0	0	0
DAY	71	0	0	1	0	0	0
DAY	78	0	0	1	0	0	0
DAY	83	0	0	1	0	0	0
DAY	91	0	0	1	0	0	0
Skin/Fur/Mucous Membranes, Skin, Scab, Focal							
DAY	91	0	0	0	1	1	0

- No Data

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 5. Body Weights/Body Weight Gains Summary (g) – 7-Day

DOSE PPM		DAYS ON TEST		
		1	8	GAIN
=====				
0	MEAN	20.3	22.0	1.6&
	S.D.	1.2	1.2	0.5
	N=	10	10	10
40	MEAN	20.5	22.0	1.5&
	S.D.	1.2	1.3	0.5
	N=	10	10	10
200	MEAN	20.4	22.4	1.9&
	S.D.	1.3	1.5	0.4
	N=	10	10	10
600	MEAN	20.5	21.9	1.4&
	S.D.	1.1	1.2	0.4
	N=	10	10	10
2000	MEAN	20.8	22.3	1.6&
	S.D.	1.2	1.6	0.7
	N=	10	10	10
6000	MEAN	20.2	22.0	1.8&
	S.D.	1.0	1.1	0.4
	N=	10	10	10
=====				

& INDICATES NO STATISTICAL COMPARISON OF MEANS.
 THERE WERE NO STATISTICAL DIFFERENCES FROM CONTROL AT ALPHA=0.05.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 6. Body Weights/Body Weight Gains Summary (g) – 28-Day

DOSE PPM		DAYS ON TEST										
		1	8	GAIN	15	GAIN	21	GAIN	25	GAIN	29	GAIN
0	MEAN	19.7	20.3	0.6&	21.4	1.7&	21.3	1.6&	21.4	1.7&	22.0	2.3&
	S.D.	1.0	1.3	0.7	1.5	0.7	0.8	0.8	1.1	0.6	1.1	0.8
	N=	10	10	10	10	10	10	10	10	10	10	10
40	MEAN	19.7	20.3	0.6&	21.4	1.7&	21.6	1.9&	21.6	1.9&	22.1	2.4&
	S.D.	1.2	1.3	0.7	1.2	0.3	1.8	1.1	1.0	0.5	1.0	0.4
	N=	10	10	10	10	10	10	10	10	10	10	10
200	MEAN	19.4	20.3	0.9&	21.1	1.6&	21.7	2.3&	21.7	2.3&	22.1	2.7&
	S.D.	1.0	1.1	0.9	1.4	0.9	1.6	1.1	1.6	1.2	1.2	0.8
	N=	10	10	10	10	10	10	10	10	10	10	10
600	MEAN	19.4	19.6	0.1&	20.7	1.3&	21.1	1.7&	21.2	1.7&	21.7	2.3&
	S.D.	1.2	0.6	0.8	1.2	0.7	0.9	0.9	0.6	0.9	0.6	0.8
	N=	10	10	10	10	10	10	10	10	10	10	10
2000	MEAN	19.4	19.9	0.5&	20.9	1.5&	21.3	1.9&	21.4	1.9&	21.8	2.4&
	S.D.	1.1	1.0	0.6	1.3	0.6	0.9	0.9	0.9	0.8	0.8	0.8
	N=	10	10	10	10	10	10	10	10	10	10	10
6000	MEAN	19.8	20.0	0.2&	21.0	1.1&	21.3	1.5&	21.2	1.4&	21.8	1.9&
	S.D.	1.2	1.4	0.9	1.0	0.6	1.4	1.1	1.0	0.8	1.0	0.7
	N=	10	10	10	10	10	10	10	10	10	10	10

& INDICATES NO STATISTICAL COMPARISON OF MEANS.
THERE WERE NO STATISTICAL DIFFERENCES FROM CONTROL AT ALPHA=0.05.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 7. Body Weights/Body Weight Gains Summary (g) – 90-Day

DOSE PPM		DAYS ON TEST												
		1	8	GAIN	15	GAIN	22	GAIN	29	GAIN	36	GAIN	43	GAIN
0	MEAN	18.5	19.1	0.6&	19.9	1.3&	20.8	2.3&	21.3	2.7&	22.1	3.5&	22.6	4.1&
	S.D.	1.1	1.4	0.8	0.9	0.8	1.4	0.9	1.4	1.0	1.4	1.2	1.9	1.2
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
40	MEAN	18.5	19.3	0.7&	19.9	1.3&	20.6	2.1&	21.6	3.1&	21.5	3.0&	22.4	3.9&
	S.D.	1.2	1.6	0.9	1.2	0.7	1.5	1.2	1.2	0.7	1.9	1.5	1.6	1.6
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
200	MEAN	18.5	19.1	0.6&	20.1	1.5&	20.6	2.1&	21.2	2.7&	22.0	3.4&	22.1	3.5&
	S.D.	1.2	1.1	1.0	1.4	1.1	1.1	0.8	1.2	0.9	1.7	0.9	1.7	1.2
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
600	MEAN	18.4	19.5	1.1&	20.1	1.7&	20.9	2.5&	22.2	3.8&	22.3	4.0&	23.2	4.8&
	S.D.	1.1	1.4	0.8	1.1	0.9	0.8	1.0	1.4	0.9	1.4	1.3	1.1	1.4
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
2000	MEAN	18.5	19.4	0.9&	19.9	1.4&	20.5	2.0&	21.2	2.7&	22.0	3.5&	22.4	3.9&
	S.D.	1.2	1.1	0.6	1.3	0.9	1.1	0.8	1.3	0.8	1.2	0.8	1.8	1.5
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
6000	MEAN	18.5	18.8	0.3&	19.8	1.3&	20.4	2.0&	21.3	2.8&	22.3	3.8&	22.1	3.7&
	S.D.	1.5	1.3	0.7	1.5	1.0	1.5	0.6	1.9	1.3	1.9	1.3	1.7	0.8
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10

& INDICATES NO STATISTICAL COMPARISON OF MEANS.
THERE WERE NO STATISTICAL DIFFERENCES FROM CONTROL AT ALPHA=0.05.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 7. Body Weights/Body Weight Gains Summary (g) – 90-Day (continued)

DOSE PPM		DAYS ON TEST												
		1	50	GAIN	57	GAIN	64	GAIN	71	GAIN	78	GAIN	83	GAIN
0	MEAN	18.5	23.3	4.8&	23.1	4.5&	23.9	5.3&	24.8	6.2&	25.2	6.7&	24.8	6.3&
	S.D.	1.1	2.1	1.7	1.9	1.6	2.1	1.5	2.6	2.2	3.3	2.9	3.1	2.7
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
40	MEAN	18.5	22.5	4.0&	23.4	4.9&	24.0	5.5&	23.6	5.1&	25.5	7.0&	24.6	6.1&
	S.D.	1.2	1.9	1.3	1.9	1.4	2.3	1.9	1.8	1.1	2.9	2.4	2.0	1.5
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
200	MEAN	18.5	23.0	4.4&	23.4	4.9&	23.9	5.4&	24.6	6.1&	24.5	6.0&	25.5	6.9&
	S.D.	1.2	1.3	1.2	1.6	1.4	1.8	1.3	2.3	1.5	1.8	1.8	2.7	2.2
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
600	MEAN	18.4	23.4	5.0&	24.8	6.4&	24.7	6.4&	25.0	6.6&	25.9	7.5&	25.6	7.2&
	S.D.	1.1	2.3	1.7	1.4	1.2	2.4	1.8	1.7	1.4	2.1	1.8	3.0	2.3
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
2000	MEAN	18.5	22.7	4.2&	22.8	4.3&	24.1	5.6&	23.7	5.2&	25.0	6.5&	24.4	5.9&
	S.D.	1.2	1.6	0.8	1.2	0.8	1.9	1.2	1.3	0.8	1.8	1.6	1.9	1.6
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
6000	MEAN	18.5	22.8	4.4&	23.8	5.3&	23.4	4.9&	23.7	5.3&	24.0	5.6&	23.8	5.3&
	S.D.	1.5	1.8	1.5	2.2	1.6	1.4	1.0	1.6	0.7	1.7	1.8	2.3	1.9
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10

& INDICATES NO STATISTICAL COMPARISON OF MEANS.
THERE WERE NO STATISTICAL DIFFERENCES FROM CONTROL AT ALPHA=0.05.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 7. Body Weights/Body Weight Gains Summary (g) – 90-Day (continued)

DOSE PPM		DAYS ON TEST		
		1	91/92	GAIN
=====				
0	MEAN	18.5	24.4	5.9&
	S.D.	1.1	2.0	1.7
	N=	10	10	10
40	MEAN	18.5	23.7	5.2&
	S.D.	1.2	1.3	0.9
	N=	10	10	10
200	MEAN	18.5	24.1	5.5&
	S.D.	1.2	1.3	0.7
	N=	10	10	10
600	MEAN	18.4	25.1	6.7&
	S.D.	1.1	1.1	0.9
	N=	10	10	10
2000	MEAN	18.5	24.2	5.7&
	S.D.	1.2	1.2	0.8
	N=	10	10	10
6000	MEAN	18.5	24.0	5.6&
	S.D.	1.5	1.4	1.0
	N=	10	10	10
=====				

& INDICATES NO STATISTICAL COMPARISON OF MEANS.
 THERE WERE NO STATISTICAL DIFFERENCES FROM CONTROL AT ALPHA=0.05.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 8. Feed Consumption (g/day) Summary – 7-Day

DOSE		DAYS ON
PPM		-----
		1-8
=====		
0	MEAN	4.4
	S.D.	0.2
	N=	10
40	MEAN	4.4
	S.D.	0.2
	N=	10
200	MEAN	4.6
	S.D.	0.3
	N=	10
600	MEAN	4.6
	S.D.	0.3
	N=	10
2000	MEAN	4.6
	S.D.	0.1
	N=	10
6000	MEAN	4.5
	S.D.	0.3
	N=	10
=====		

THERE WERE NO STATISTICAL DIFFERENCES FROM CONTROL AT ALPHA=0.05.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 9. Feed Consumption (g/day) Summary – 28-Day

DOSE PPM		DAYS ON TEST			
		1-8	8-15	15-21	21-29
=====					
0	MEAN	3.2	3.3	3.2	4.0
	S.D.	0.2	0.2	0.3	0.2
	N=	10	10	10	10
40	MEAN	3.5*	3.5\$	3.5*	4.2
	S.D.	0.2	0.1	0.2	0.3
	N=	10	10	10	10
200	MEAN	3.4*	3.6	3.6*	4.2
	S.D.	0.2	0.4	0.2	0.3
	N=	10	10	10	10
600	MEAN	3.2	3.3	3.3	4.2
	S.D.	0.2	0.2	0.3	0.2
	N=	10	10	10	10
2000	MEAN	3.4	3.4	3.4	4.1
	S.D.	0.1	0.1	0.1	0.2
	N=	10	10	10	10
6000	MEAN	3.2	3.2	3.3	4.1
	S.D.	0.1	0.1	0.1	0.2
	N=	10	10	10	10
=====					

* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA=0.05.
\$ STATISTICALLY DIFFERENT FROM CONTROL MEAN BY WILCOXON'S TEST, ALPHA=0.05.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 10. Feed Consumption (g/day) Summary – 90-Day

DOSE PPM		DAYS ON TEST												
		1-8	8-15	15-22	22-29	29-36	36-43	43-50	50-57	57-64	64-71	71-78	78-83	83-91
0	MEAN	3.2	3.3	3.5	3.5	3.6	3.5	3.6	3.4	3.6	3.6	3.6	3.5	3.8
	S.D.	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.2	0.3	0.3	0.2	0.4
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
40	MEAN	3.3	3.3	3.5	3.4	3.4	3.4	3.5	3.5	3.5	3.4	3.8	3.2	3.7
	S.D.	0.1	0.1	0.2	0.1	0.3	0.2	0.2	0.5	0.1	0.2	0.3	0.4	0.3
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
200	MEAN	3.2	3.3	3.3	3.6	3.5	3.4	3.5	3.5	3.5	3.6	3.4	3.8	3.7
	S.D.	0.2	0.1	0.1	0.3	0.2	0.1	0.2	0.3	0.1	0.3	0.3	0.5	0.3
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
600	MEAN	3.3	3.4	3.7*	3.8*	3.7	3.8*	3.7	3.9\$	3.6	3.6	3.8	3.7	4.0
	S.D.	0.1	0.1	0.1	0.2	0.2	0.1	0.3	0.1	0.4	0.2	0.5	0.4	0.4
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
2000	MEAN	3.3	3.3	3.4	3.6	3.6	3.4	3.5	3.5	3.7	3.5	3.6	3.7	3.8
	S.D.	0.1	0.2	0.1	0.2	0.2	0.3	0.1	0.2	0.2	0.1	0.3	0.2	0.3
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
6000	MEAN	3.1	3.5	3.4	3.6	3.6	3.4	3.5	3.6	3.5	3.5	3.5	3.5	4.0
	S.D.	0.1	0.5	0.1	0.2	0.2	0.1	0.2	0.2	0.1	0.1	0.2	0.3	0.2
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10

* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA=0.05.

\$ STATISTICALLY DIFFERENT FROM CONTROL MEAN BY WILCOXON'S TEST, ALPHA=0.05.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 11. Water Consumption Summary (g) – 7-day

DOSE PPM		DAYS ON TEST	
		1-4	4-8
=====			
0	MEAN	5.0	5.0
	S.D.	0.6	0.6
	N=	10	10
40	MEAN	4.9	4.8
	S.D.	0.5	0.4
	N=	10	10
200	MEAN	5.1	5.0
	S.D.	0.6	0.5
	N=	10	10
600	MEAN	5.0	5.0
	S.D.	0.6	0.4
	N=	10	10
2000	MEAN	5.1	5.3
	S.D.	0.3	0.3
	N=	10	10
6000	MEAN	4.3*	4.7
	S.D.	0.6	0.6
	N=	10	10
=====			

* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA=0.05.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 12. Water Consumption Summary (g) – 28-day

DOSE PPM		DAYS ON TEST							
		1-4	4-8	8-11	11-15	15-18	18-21	21-25	25-29
0	MEAN	4.0	3.6	4.0	3.9	3.9	4.0	4.6	4.9
	S.D.	0.2	0.4	0.2	0.2	0.4	0.3	1.0	0.4
	N=	10	10	10	10	10	10	10	10
40	MEAN	4.0	3.9	4.3\$	4.3*	4.2	4.5*	4.8	5.2
	S.D.	0.3	0.3	0.1	0.2	0.4	0.3	0.4	0.3
	N=	10	10	10	10	10	10	10	9
200	MEAN	4.0	4.0*	4.5	4.5*	4.4*	4.5*	5.0	5.3
	S.D.	0.3	0.3	0.5	0.3	0.4	0.3	0.7	0.5
	N=	10	10	10	10	10	10	10	10
600	MEAN	3.8	3.6	4.0	4.0	3.9	4.3	4.8	5.2
	S.D.	0.2	0.2	0.3	0.2	0.4	0.2	0.4	0.5
	N=	10	10	10	10	10	10	10	10
2000	MEAN	3.9	3.8	4.2	4.2*	4.2	4.3	4.7	5.2
	S.D.	0.3	0.2	0.1	0.1	0.1	0.3	0.4	0.4
	N=	10	10	10	10	10	10	10	10
6000	MEAN	3.7	3.5	4.0	3.5*	3.8	3.7	4.5	4.9
	S.D.	0.5	0.3	0.4	0.2	0.5	0.4	0.4	0.4
	N=	10	10	10	10	10	10	10	10

* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA=0.05.
\$ STATISTICALLY DIFFERENT FROM CONTROL MEAN BY WILCOXON'S TEST, ALPHA=0.05.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 13. Water Consumption Summary (g) – 90-day

DOSE PPM		DAYS ON TEST												
		1-5	5-8	8-12	12-15	15-19	19-22	22-26	26-29	29-33	33-36	36-40	40-43	43-47
0	MEAN	3.9	3.9	3.8	4.0	4.3	4.2	4.4	4.8	4.3	4.3	4.2	4.3	4.3
	S.D.	0.3	0.2	0.1	0.3	0.4	0.3	0.6	0.3	0.5	0.7	0.4	0.2	0.4
	N=	10	10	10	10	10	10	10	10	8	10	10	10	10
40	MEAN	3.8	3.8	3.5	4.0	4.2	4.1	3.9	4.1\$	3.7	4.1	3.9	4.1	4.1
	S.D.	0.4	0.3	0.5	0.2	0.2	0.4	0.2	0.1	0.5	0.2	0.3	0.4	0.2
	N=	10	10	8	10	10	10	10	10	10	10	10	10	10
200	MEAN	3.6	3.6*	3.6\$	3.9	3.9	4.1	4.8	4.1\$	4.1	4.2	3.9	4.1	4.1
	S.D.	0.2	0.3	0.1	0.2	0.1	0.2	1.7	0.2	0.4	0.3	0.2	0.4	0.3
	N=	10	10	10	10	10	10	10	10	8	10	10	10	8
600	MEAN	3.8	4.2	4.0\$	4.5*	4.3	4.5	4.5	4.4\$	4.4	4.6	4.4	4.2	4.5
	S.D.	0.1	0.2	0.2	0.4	0.1	0.3	0.1	0.1	0.2	0.2	0.2	0.2	0.4
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
2000	MEAN	3.6	3.7	3.6\$	4.0	3.9	4.1	3.9	4.1\$	4.1	4.0	3.8*	4.2	4.1
	S.D.	0.2	0.3	0.2	0.3	0.2	0.4	0.2	0.3	0.1	0.2	0.3	0.4	0.1
	N=	10	10	10	8	10	10	10	10	10	10	10	10	10
6000	MEAN	3.3\$	3.0*	3.0\$	3.4*	3.6\$	3.5*	3.3\$	3.7\$	3.7	3.7	3.3*	3.6*	3.5*
	S.D.	0.3	0.1	0.2	0.2	0.4	0.3	0.3	0.3	0.2	0.3	0.2	0.2	0.3
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10

* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA=0.05.
\$ STATISTICALLY DIFFERENT FROM CONTROL MEAN BY WILCOXON'S TEST, ALPHA=0.05.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 13. Water Consumption Summary (g) – 90-day (continued)

DOSE PPM		DAYS ON TEST											
		47-50	50-54	54-57	57-61	61-64	64-68	68-71	71-75	75-78	78-83	83-88	88-91
0	MEAN	4.6	4.5	4.6	4.7	4.4	4.3	4.4	4.2	4.3	4.2	4.5	5.0
	S.D.	0.5	0.9	0.4	0.7	0.6	0.5	0.2	0.4	0.2	0.4	0.3	0.6
	N=	10	10	10	10	10	10	10	10	10	10	10	10
40	MEAN	3.8*	3.8	4.3	3.9*	4.3	4.0	3.9*	4.1	4.1	3.6*	4.4	4.4*
	S.D.	0.4	0.5	0.4	0.3	0.8	0.2	0.6	0.3	0.4	0.5	0.4	0.6
	N=	10	10	10	10	10	10	10	10	10	10	10	10
200	MEAN	4.4	4.2	4.6	4.3	4.1	4.3	4.4	4.0	4.4	4.4	4.3	4.7
	S.D.	0.2	0.4	0.4	0.3	0.4	0.3	0.3	0.3	0.2	0.5	0.4	0.5
	N=	10	10	10	10	10	10	10	10	10	10	10	10
600	MEAN	4.5	4.7	5.0	4.5	4.0	4.3	4.5	4.4	4.5	4.3	4.7	4.9
	S.D.	0.2	0.5	0.2	0.4	0.4	0.3	0.3	0.6	0.1	0.3	0.4	0.4
	N=	10	10	10	10	10	10	10	10	10	10	10	10
2000	MEAN	4.1*	4.1	4.6	4.3	4.1	3.9	4.0*	3.8	4.0	3.9	4.4	4.6
	S.D.	0.3	0.4	0.4	0.3	0.2	0.1	0.3	0.3	0.5	0.2	0.5	0.4
	N=	10	10	10	10	10	10	10	10	10	10	10	10
6000	MEAN	3.7*	3.2\$	4.5	3.5*	3.6\$	3.9	3.6*	3.5*	3.6\$	3.6*	4.3	4.4*
	S.D.	0.3	0.2	0.4	0.3	0.2	0.8	0.3	0.3	0.3	0.4	0.4	0.4
	N=	10	10	10	10	10	10	10	10	10	10	10	10

* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA=0.05.

\$ STATISTICALLY DIFFERENT FROM CONTROL MEAN BY WILCOXON'S TEST, ALPHA=0.05.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 14. Test Material Intake Summary – 7-Day

DOSE		0 PPM		40 PPM			200 PPM			600 PPM			2000 PPM			6000 PPM		
Administration Period (in Days)	Day(s)	PPM ^a	MKD ^b	% Test Material in Water	PPM ^a	MKD ^b	% Test Material in Water	PPM ^a	MKD ^b	% Test Material in Water	PPM ^a	MKD ^b	% Test Material in Water	PPM ^a	MKD ^b	% Test Material in Water	PPM ^a	MKD ^b
1-4	3	0	0	0.0040	40	9.22	0.0200	200	47.7	0.0600	600	142	0.2000	2000	473	0.6000	6000	1223
4-8	4	0	0	0.0040	40	9.04	0.0200	200	46.7	0.0600	600	142	0.2000	2000	492	0.6000	6000	1336
Time Weighted Avg. ^c		0	0		40	9.12		200	47.1		600	142		2000	484		6000	1288
±SD ^d					0	0.133		0	0.661		0	0.00		0	13.1		0	80.4
7		Sum of Days																

^aPPM = % Test Material in Water * 10000

^bMKD = (PPM * Water consumption (mg/day) for that period) / (Average body weight (kg) for that period)

^cTWA = Time Weighted Average = Sum (PPM or MKD period * number of days for that period) / sum of all days

^dSD = Standard Deviation

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 15. Test Material Intake Summary – 28-Day

DOSE		0 PPM		40 PPM			200 PPM			600 PPM			2000 PPM			6000 PPM		
Administration Period (in Days)	Day (s)	PPM ^a	MKD ^b	% Test Material in Water	PPM ^a	MKD ^b	% Test Material in Water	PPM ^a	MKD ^b	% Test Material in Water	PPM ^a	MKD ^b	% Test Material in Water	PPM ^a	MKD ^b	% Test Material in Water	PPM ^a	MKD ^b
1-4	3	0	0	0.0040	40	8.00	0.0200	200	40.3	0.0600	600	117	0.2000	2000	397	0.6000	6000	1116
4-8	4	0	0	0.0040	40	7.80	0.0200	200	40.3	0.0600	600	111	0.2000	2000	387	0.6000	6000	1055
8-11	3	0	0	0.0040	40	8.25	0.0200	200	43.5	0.0600	600	119	0.2000	2000	412	0.6000	6000	1171
11-15	4	0	0	0.0040	40	8.25	0.0200	200	43.5	0.0600	600	119	0.2000	2000	412	0.6000	6000	1024
15-18	3	0	0	0.0040	40	7.81	0.0200	200	41.1	0.0600	600	112	0.2000	2000	398	0.6000	6000	1078
18-21	3	0	0	0.0040	40	8.37	0.0200	200	42.1	0.0600	600	123	0.2000	2000	408	0.6000	6000	1050
21-25	4	0	0	0.0040	40	8.89	0.0200	200	46.1	0.0600	600	136	0.2000	2000	440	0.6000	6000	1271
25-29	4	0	0	0.0040	40	9.52	0.0200	200	48.4	0.0600	600	145	0.2000	2000	481	0.6000	6000	1367
Time Weighted Avg. ^c		0	0		40	8.40		200	43.4		600	124		2000	419		6000	1147
±SD ^d					0	0.584		0	2.88		0	12.0		0	30.5		0	121
28		Sum of Days																

^aPPM = % Test Material in Water * 10000

^bMKD = (PPM * Water consumption (mg/day) for that period) / (Average body weight (kg) for that period)

^cTWA = Time Weighted Average = Sum (PPM or MKD period * number of days for that period) / sum of all days

^dSD = Standard Deviation

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 16. Test Material Intake Summary – 90-Day

DOSE		0 PPM		40 PPM			200 PPM			600 PPM			2000 PPM			6000 PPM		
Administration Period (in Days)	Day(s)	PPM ^a	MKD ^b	% Test Material in Water	PPM ^a	MKD ^b	% Test Material in Water	PPM ^a	MKD ^b	% Test Material in Water	PPM ^a	MKD ^b	% Test Material in Water	PPM ^a	MKD ^b	% Test Material in Water	PPM ^a	MKD ^b
1-5	4	0	0	0.0040	40	8.04	0.0200	200	38.3	0.0600	600	120	0.2000	2000	380	0.6000	6000	1062
5-8	3	0	0	0.0040	40	8.04	0.0200	200	38.3	0.0600	600	133	0.2000	2000	391	0.6000	6000	965
8-12	4	0	0	0.0040	40	7.14	0.0200	200	36.7	0.0600	600	121	0.2000	2000	366	0.6000	6000	933
12-15	3	0	0	0.0040	40	8.16	0.0200	200	39.8	0.0600	600	136	0.2000	2000	407	0.6000	6000	1057
15-19	4	0	0	0.0040	40	8.30	0.0200	200	38.3	0.0600	600	126	0.2000	2000	386	0.6000	6000	1075
19-22	3	0	0	0.0040	40	8.10	0.0200	200	40.3	0.0600	600	132	0.2000	2000	406	0.6000	6000	1045
22-26	4	0	0	0.0040	40	7.39	0.0200	200	45.9	0.0600	600	125	0.2000	2000	374	0.6000	6000	950
26-29	3	0	0	0.0040	40	7.77	0.0200	200	39.2	0.0600	600	123	0.2000	2000	393	0.6000	6000	1065
29-33	4	0	0	0.0040	40	6.87	0.0200	200	38.0	0.0600	600	119	0.2000	2000	380	0.6000	6000	1018
33-36	3	0	0	0.0040	40	7.61	0.0200	200	38.9	0.0600	600	124	0.2000	2000	370	0.6000	6000	1018
36-40	4	0	0	0.0040	40	7.11	0.0200	200	35.4	0.0600	600	116	0.2000	2000	342	0.6000	6000	892
40-43	3	0	0	0.0040	40	7.47	0.0200	200	37.2	0.0600	600	111	0.2000	2000	378	0.6000	6000	973
43-47	4	0	0	0.0040	40	7.31	0.0200	200	36.4	0.0600	600	116	0.2000	2000	364	0.6000	6000	935
47-50	3	0	0	0.0040	40	6.77	0.0200	200	39.0	0.0600	600	116	0.2000	2000	364	0.6000	6000	989
50-54	4	0	0	0.0040	40	6.62	0.0200	200	36.2	0.0600	600	117	0.2000	2000	360	0.6000	6000	824
54-57	3	0	0	0.0040	40	7.49	0.0200	200	39.7	0.0600	600	124	0.2000	2000	404	0.6000	6000	1159
57-61	4	0	0	0.0040	40	6.58	0.0200	200	36.4	0.0600	600	109	0.2000	2000	367	0.6000	6000	890
61-64	3	0	0	0.0040	40	7.26	0.0200	200	34.7	0.0600	600	97.0	0.2000	2000	350	0.6000	6000	915
64-68	4	0	0	0.0040	40	6.72	0.0200	200	35.5	0.0600	600	104	0.2000	2000	326	0.6000	6000	994
68-71	3	0	0	0.0040	40	6.55	0.0200	200	36.3	0.0600	600	109	0.2000	2000	335	0.6000	6000	917
71-75	4	0	0	0.0040	40	6.68	0.0200	200	32.6	0.0600	600	104	0.2000	2000	312	0.6000	6000	881
75-78	3	0	0	0.0040	40	6.68	0.0200	200	35.8	0.0600	600	106	0.2000	2000	329	0.6000	6000	906
78-83	5	0	0	0.0040	40	5.75	0.0200	200	35.2	0.0600	600	100	0.2000	2000	316	0.6000	6000	904
83-88	5	0	0	0.0040	40	7.29	0.0200	200	34.7	0.0600	600	111	0.2000	2000	362	0.6000	6000	1079
88-91	3	0	0	0.0040	40	7.29	0.0200	200	37.9	0.0600	600	116	0.2000	2000	379	0.6000	6000	1105
Time Weighted Avg. ^c		0	0		40	7.20		200	37.3		600	116		2000	364		6000	979
±SD ^d					0	0.624		0	2.59		0	10.2		0	27.0		0	83.8
90		Sum of Days																

^aPPM = % Test Material in Water * 10000

^bMKD = (PPM * Water consumption (mg/day) for that period) / (Average body weight (kg) for that period)

^cTWA = Time Weighted Average = Sum (PPM or MKD period * number of days for that period) / sum of all days

^dSD = Standard Deviation

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 17. Clinical Chemistry Summary – 7-Day

DOSE PPM		ALP U/L	ALT U/L	AST U/L	GGT U/L
=====					
0	MEAN	113	25	58	1.5
	S.D.	14	5	22	0.0
	N=	10	10	10	10
40	MEAN	111	35	61	1.5
	S.D.	22	17	15	0.0
	N=	10	10	10	10
200	MEAN	105	34	50	1.5
	S.D.	14	34	7	0.0
	N=	10	10	10	10
600	MEAN	117	26	56	1.5
	S.D.	14	9	14	0.0
	N=	10	10	10	10
2000	MEAN	103	28	60	1.5
	S.D.	14	3	13	0.0
	N=	10	10	10	10
6000	MEAN	105	28	55	1.5
	S.D.	16	11	8	0.0
	N=	10	10	10	10

=====

GGT LOWEST DETECTION LIMIT IS 3.0. INDIVIDUAL VALUES <3.0 WERE
 REPORTED AS 1.5 (ONE-HALF THE DETECTION LIMIT) FOR STATISTICAL ANALYSIS.

THERE WERE NO STATISTICAL DIFFERENCES FROM CONTROL AT ALPHA=0.05.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 18. Clinical Chemistry Summary – 28-Day

DOSE PPM		ALP U/L	ALT U/L	AST U/L	GGT U/L
=====					
0	MEAN	109	31	78	1.5
	S.D.	10	18	71	0.0
	N=	10	10	10	10
40	MEAN	106	24	66	1.5
	S.D.	16	4	30	0.0
	N=	10	10	10	10
200	MEAN	105	50	67	1.5
	S.D.	18	80	35	0.0
	N=	10	10	10	10
600	MEAN	110	29	62	1.5
	S.D.	9	11	28	0.0
	N=	10	10	10	10
2000	MEAN	101	34	62	1.5
	S.D.	8	11	12	0.0
	N=	10	10	10	10
6000	MEAN	106	47	69	1.5
	S.D.	9	38	36	0.0
	N=	10	10	10	10

=====

GGT LOWEST DETECTION LIMIT IS 3.0. INDIVIDUAL VALUES <3.0 WERE
REPORTED AS 1.5 (ONE-HALF THE DETECTION LIMIT) FOR STATISTICAL ANALYSIS.

THERE WERE NO STATISTICAL DIFFERENCES FROM CONTROL AT ALPHA=0.05.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 19. Clinical Chemistry Summary – 90-Day

DOSE PPM		ALP U/L	ALT U/L	AST U/L	GGT U/L
=====					
0	MEAN	80	41	78	1.5
	S.D.	7	29	44	0.0
	N=	10	10	10	10
40	MEAN	75	34	70	1.5
	S.D.	10	11	22	0.0
	N=	10	10	10	10
200	MEAN	85	30	64	1.5
	S.D.	8	8	13	0.0
	N=	10	10	10	10
600	MEAN	79	26	61	1.5
	S.D.	6	5	17	0.0
	N=	10	10	10	10
2000	MEAN	80	40	67	1.5
	S.D.	2	27	31	0.0
	N=	10	10	10	10
6000	MEAN	90	35	66	1.5
	S.D.	10	7	10	0.0
	N=	10	10	10	10

=====

GGT LOWEST DETECTION LIMIT IS 3.0. INDIVIDUAL VALUES <3.0 WERE
 REPORTED AS 1.5 (ONE-HALF THE DETECTION LIMIT) FOR STATISTICAL ANALYSIS.

THERE WERE NO STATISTICAL DIFFERENCES FROM CONTROL AT ALPHA=0.05.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 20. Organ and Organ/Body Weights Summary – 7-day

DOSE PPM		FINAL	LIVER	
		BODY	-----	
		WT. (G)	(G)	(G/100)
=====				
0	MEAN	22.0	1.141	5.192
	S.D.	1.2	0.090	0.244
	N=	10	10	10
40	MEAN	22.0	1.134	5.150
	S.D.	1.3	0.072	0.151
	N=	10	10	10
200	MEAN	22.4	1.175	5.259
	S.D.	1.5	0.075	0.193
	N=	10	10	10
600	MEAN	21.9	1.155	5.273
	S.D.	1.2	0.096	0.208
	N=	10	10	10
2000	MEAN	22.3	1.206	5.402
	S.D.	1.6	0.086	0.233
	N=	10	10	10
6000	MEAN	22.0	1.242	5.644*
	S.D.	1.1	0.095	0.178
	N=	10	10	10
=====				

* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA=0.05.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 21. Organ and Organ/Body Weights Summary – 28-day

DOSE PPM		FINAL	LIVER	
		BODY	-----	
		WT. (G)	(G)	(G/100)
=====				
0	MEAN	22.3	1.175	5.276
	S.D.	0.9	0.062	0.119
	N=	10	10	10
40	MEAN	22.2	1.153	5.190
	S.D.	1.0	0.078	0.228
	N=	10	10	10
200	MEAN	22.2	1.173	5.270
	S.D.	1.1	0.085	0.169
	N=	10	10	10
600	MEAN	21.9	1.186	5.418
	S.D.	0.8	0.069	0.188
	N=	10	10	10
2000	MEAN	22.1	1.221	5.534*
	S.D.	0.8	0.074	0.234
	N=	10	10	10
6000	MEAN	22.0	1.282*	5.841*
	S.D.	1.0	0.053	0.117
	N=	10	10	10

* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA=0.05.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 22. Organ and Organ/Body Weights Summary – 90-day

DOSE PPM		FINAL	LIVER	
		BODY WT. (G)	(G)	(G/100)
=====				
0	MEAN	24.4	1.214	4.977
	S.D.	2.0	0.076	0.195
	N=	10	10	10
=====				
40	MEAN	23.7	1.154	4.864
	S.D.	1.3	0.072	0.225
	N=	10	10	10
=====				
200	MEAN	24.1	1.188	4.942
	S.D.	1.3	0.063	0.121
	N=	10	10	10
=====				
600	MEAN	25.1	1.289	5.151
	S.D.	1.1	0.060	0.280
	N=	10	10	10
=====				
2000	MEAN	24.2	1.283	5.293*
	S.D.	1.2	0.085	0.205
	N=	10	10	10
=====				
6000	MEAN	24.0	1.306*	5.442*
	S.D.	1.4	0.090	0.286
	N=	10	10	10
=====				

* STATISTICALLY DIFFERENT FROM CONTROL MEAN BY DUNNETT'S TEST, ALPHA=0.05.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 23. Hepatocellular Proliferation as Measured by BrdU – 7-Day

DOSE PPM		CENTRI- LOBULAR	MIDZONAL	PERI- PORTAL	PAN- LOBULAR
		LI %	LI %	LI %	LI %
=====					
0	MEAN	15.5	17.3	10.6	14.5
	S.D.	9.0	10.6	6.9	8.7
	N=	10	10	10	10
40	MEAN	14.1	16.3	10.2	13.5
	S.D.	10.4	11.5	7.5	9.7
	N=	10	10	10	10
200	MEAN	16.1	18.9	10.2	15.1
	S.D.	17.4	21.3	9.4	15.9
	N=	10	10	10	10
600	MEAN	21.8	23.9	15.3	20.3
	S.D.	13.1	14.4	8.4	11.9
	N=	10	10	10	10
2000	MEAN	14.8	18.2	10.2	14.4
	S.D.	9.4	11.1	6.1	8.8
	N=	10	10	10	10
6000	MEAN	16.0	18.0	10.2	14.7
	S.D.	11.3	13.3	6.8	10.3
	N=	10	10	10	10
=====					

THERE WERE NO STATISTICAL DIFFERENCES FROM CONTROL AT ALPHA=0.05.
 LI - LABELING INDEX

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 24. Hepatocellular Proliferation as Measured by BrdU – 28-Day

DOSE PPM		CENTRI- LOBULAR	MIDZONAL	PERI- PORTAL	PAN- LOBULAR
		LI %	LI %	LI %	LI %
=====					
0	MEAN	10.7	10.9	7.9	9.9
	S.D.	7.9	8.8	5.7	7.4
	N=	10	10	10	10
40	MEAN	9.8	10.5	6.9	9.1
	S.D.	9.0	9.8	4.7	7.8
	N=	10	10	10	10
200	MEAN	17.1	17.4	12.4	15.6
	S.D.	11.9	12.8	7.5	10.6
	N=	10	10	10	10
600	MEAN	14.8	15.4	10.6	13.6
	S.D.	10.4	10.8	7.7	9.6
	N=	10	10	10	10
2000	MEAN	17.4	17.9	13.0	16.1
	S.D.	14.3	12.5	9.5	12.0
	N=	10	10	10	10
6000	MEAN	7.5	12.3	11.2	10.3
	S.D.	5.6	8.3	6.6	6.8
	N=	10	10	10	10
=====					

THERE WERE NO STATISTICAL DIFFERENCES FROM CONTROL AT ALPHA=0.05.
 LI - LABELING INDEX

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 25. Hepatocellular Proliferation as Measured by BrdU – 90-Day

DOSE PPM		CENTRI- LOBULAR	MIDZONAL	PERI- PORTAL	PAN- LOBULAR
		LI %	LI %	LI %	LI %
=====					
0	MEAN	4.2	5.3	3.4	4.3
	S.D.	1.8	2.1	0.8	1.5
	N=	10	10	10	10
40	MEAN	7.4	8.4	5.6	7.1
	S.D.	4.3	5.6	3.5	4.3
	N=	10	10	10	10
200	MEAN	5.5	5.6	4.4	5.2
	S.D.	4.2	2.3	2.8	3.0
	N=	10	10	10	10
600	MEAN	4.5	5.7	4.2	4.8
	S.D.	2.7	3.5	2.4	2.7
	N=	10	10	10	10
2000	MEAN	5.2	7.5	6.5	6.4
	S.D.	5.2	6.0	5.6	5.5
	N=	10	10	10	10
6000	MEAN	15.5\$	24.7\$	22.1\$	20.8\$
	S.D.	8.3	12.3	11.0	10.4
	N=	10	10	10	10
=====					

\$ STATISTICALLY DIFFERENT FROM CONTROL MEAN BY WILCOXON'S TEST, ALPHA=0.05.
 LI - LABELING INDEX

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 26. Apoptosis Quantification as Measured by Caspase-3 – 28-Day

DOSE PPM		CASPASE-3 POSITIVE PER 10000
=====		
0	MEAN	0.08
	S.D.	0.18
	N=	10
40	MEAN	0.03
	S.D.	0.07
	N=	10
200	MEAN	0.00
	S.D.	0.00
	N=	10
600	MEAN	0.02
	S.D.	0.06
	N=	10
2000	MEAN	0.07
	S.D.	0.13
	N=	10
6000	MEAN	0.46\$
	S.D.	0.35
	N=	10
=====		

\$ STATISTICALLY DIFFERENT FROM CONTROL MEAN BY WILCOXON'S TEST, ALPHA=0.05.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 27. Apoptosis Quantification as Measured by Caspase-3 – 90-Day

DOSE PPM		CASPASE-3 POSITIVE PER 10000
=====		
0	MEAN	0.04
	S.D.	0.08
	N=	10
40	MEAN	0.18
	S.D.	0.23
	N=	10
200	MEAN	0.04
	S.D.	0.07
	N=	10
600	MEAN	0.07
	S.D.	0.18
	N=	10
2000	MEAN	0.12
	S.D.	0.18
	N=	10
6000	MEAN	1.08\$
	S.D.	0.91
	N=	10
=====		

\$ STATISTICALLY DIFFERENT FROM CONTROL MEAN BY WILCOXON'S TEST, ALPHA=0.05.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 28. Final TMI and blood levels of 1,4-dioxane and HEAA

Nominal Dose Level (PPM)	Day 7				Day 28				Day 90			
	Animal ID	TMI (MKD)	HEAA (µg/mL)	1,4-DX (µg/mL)	Animal ID	TMI (MKD)	HEAA (µg/mL)	1,4-DX (µg/mL)	Animal ID	TMI (MKD)	HEAA (µg/mL)	1,4-DX (µg/mL)
0	18A0849	0.000	ND	ND	18A0839	0.000	ND	ND	18A0829	0.000	ND	ND
	18A0850	0.000	ND	ND	18A0840	0.000	ND	ND	18A0830	0.000	ND	ND
	18A0851	0.000	ND	ND	18A0841	0.000	ND	ND	18A0831	0.000	ND	ND
	18A0852	0.000	ND	ND	18A0842	0.000	ND	ND	18A0832	0.000	ND	ND
	18A0853	0.000	ND	ND	18A0843	0.000	ND	ND	18A0833	0.000	ND	ND
	Average SD	0.000 0.000	ND	ND	Average SD	0.000 0.000	ND	ND	Average SD	0.000 0.000	ND	ND
40	18A0879	7.86	ND	ND	18A0869	9.91	2.22	ND	18A0859	9.09	0.227	ND
	18A0880	9.54	ND	ND	18A0870	9.14	0.932	ND	18A0860	7.64	0.206	ND
	18A0881	8.69	ND	ND	18A0871	9.86	0.150	ND	18A0861	7.26	0.298	ND
	18A0882	10.1	ND	ND	18A0872	9.62	0.701	ND	18A0862	6.04	0.121	ND
	18A0883	9.77	ND	ND	18A0873	9.86	0.276	ND	18A0863	5.05	0.0809	ND
	Average SD	9.19 0.910	ND	ND	Average SD	9.68 0.320	0.855 0.825	ND	Average SD	7.02 1.55	0.186 0.086	ND
200	18A0909	43.2	ND	ND	18A0899	53.5	0.632	ND	18A0889	42.6	0.302	0.813
	18A0910	49.4	ND	ND	18A0900	40.8	0.322	ND	18A0890	34.0	0.113	ND
	18A0911	55.7	2.38	ND	18A0901	47.5	0.189	ND	18A0891	31.2	0.390	0.404
	18A0912	46.2	<LLQ (0.0383)	ND	18A0902	45.4	0.529	0.607	18A0892	38.3	0.377	0.402
	18A0913	44.7	ND	ND	18A0903	47.5	0.125	ND	18A0893	27.7	0.0799	ND
	Average SD	47.8 4.97	1.21 1.65	NA ^a	Average SD	46.9 4.58	0.359 0.217	NA ^a	Average SD	34.8 5.83	0.252 0.147	0.540 0.237
600	18A0939	130	2.93	ND	18A0929	130	2.03	ND	18A0919	99.1	1.24	1.42
	18A0940	167	5.14	ND	18A0930	137	4.16	ND	18A0920	125	0.556	ND
	18A0941	144	1.53	ND	18A0931	142	0.269	ND	18A0921	104	0.988	0.724
	18A0942	163	3.07	ND	18A0932	134	0.924	ND	18A0922	140	0.741	0.355
	18A0943	131	0.198	ND	18A0933	171	0.294	ND	18A0923	121	0.216	ND
	Average SD	147 17.6	2.58 1.85	ND	Average SD	143 16.1	1.54 1.63	ND	Average SD	118 16.5	0.749 0.395	0.832 0.539
2000	18A0969	465	4.84	ND	18A0959	510	1.024	ND	18A0949	342	0.711	0.274
	18A0970	523	7.85	ND	18A0960	513	0.882	8.06	18A0950	394	1.32	0.483
	18A0971	469	4.31	ND	18A0961	504	0.380	0.462	18A0951	374	0.935	0.285
	18A0972	520	54.1	ND	18A0962	418	0.727	ND	18A0952	333	0.544	0.290
	18A0973	519	1.77	ND	18A0963	518	0.409	ND	18A0953	385	0.972	0.356
	Average SD	499 29.7	14.6 22.2	ND	Average SD	493 41.9	0.684 0.285	4.26 5.37	Average SD	366 26.7	0.896 0.294	0.338 0.087
6000	18A0999	1522	80.7	ND	18A0989	1463	6.37	ND	18A0979	1102	8.21	210
	18A1000	1273	12.2	ND	18A0990	1285	1.01	ND	18A0980	1046	1.13	5.50
	18A1001	1451	41.0	ND	18A0991	1434	1.44	ND	18A0981	987	9.40	125
	18A1002	1318	49.2	ND	18A0992	1350	5.49	ND	18A0982	1004	0.984	3.40
	18A1003	1304	34.3	ND	18A0993	1300	3.16	44.8	18A0983	1393	9.81	60.1
	Average SD	1373 107	43.5 24.9	ND	Average SD	1366 79.7	3.49 2.39	NA ^a	Average SD	1106 166	5.91 4.46	80.8 87.7

ND: Not detected; LLQ (Low Limit of Quantitation) for HEAA: 0.05 µg/mL blood; LLQ for 1,4-DX: 0.2 µg/mL blood; SD: Standard Deviation; NA^a: Not applicable, not enough data for average
TMI: Test Material Intake

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

TABLE 29. Summary of Dose, Blood Concentrations, and TK Analysis Results for 1,4-dioxane and HEAA

7-Day	Applied Dose (ppm)		0	40	200	600	2000	6000	Dose-Proportionality	
	1,4-DX TMI (mg/kg/day)		Mean	0	9.19	47.8	147	499	1373	
			SD		0.910	4.97	17.6	29.7	107	
	Blood Concentration (µg/g)	1,4-DX	Mean	ND	ND	ND	ND	ND	ND	NA ^b
			SD							
	HEAA	Mean	ND	ND	1.21	2.58	14.6	43.5	Linear	
		SD			1.65	1.85	22.2	24.9		
28-Day	Applied Dose (ppm)		0	40	200	600	2000	6000	Dose-Proportionality	
	1,4-DX TMI (mg/kg/day)		Mean	0	9.68	46.9	143	493	1366	
			SD		0.320	4.58	16.1	41.9	79.7	
	Blood Concentration (µg/g)	1,4-DX	Mean	ND	ND	NA ^a	ND	4.26	NA ^a	NA ^b
			SD					5.37		
	HEAA	Mean	ND	0.855	0.359	1.54	0.684	3.49	Linear	
		SD		0.825	0.217	1.63	0.285	2.39		
90-Day	Applied Dose (ppm)		0	40	200	600	2000	6000	Dose-Proportionality	
	1,4-DX TMI (mg/kg/day)		Mean	0	7.02	34.8	118	366	1106	
			SD		1.55	5.83	16.5	26.7	166	
	Blood Concentration (µg/g)	1,4-DX	Mean	ND	ND	0.540	0.832	0.338	80.8	Supralinear at 6000 ppm*; Sublinear at 2000 ppm
			SD			0.237	0.539	0.0873	87.7	
	HEAA	Mean	ND	0.186	0.252	0.749	0.896	5.91	Linear	
		SD		0.0864	0.147	0.395	0.294	4.46		

*: Due to the huge variability of the blood levels of 1,4-DX at this dose group, the linearity was estimated graphically.
ND: not detectable; NA^a: Not applicable, not enough data points for average; NA^b: Not Applicable, not enough data for TK analysis.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 1. Individual Clinical Observations – 7-Day

Dose	Animal Number	Day Observed		Observation/Comment
		First	Last	

0 PPM				
	849	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	850	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	851	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	852	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	853	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	854	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	855	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	856	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	857	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	858	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day

40 PPM				
	879	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	880	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 1. Individual Clinical Observations – 7-Day (continued)

Dose	Animal Number	Day Observed		Observation/Comment
		First	Last	

40 PPM				
	881	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	882	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	883	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	884	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	885	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	886	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	887	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	888	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day

200 PPM				
	909	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	910	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	911	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	912	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 1. Individual Clinical Observations – 7-Day (continued)

Dose	Animal Number	Day Observed		Observation/Comment
		First	Last	

200 PPM				
	913	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	914	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	915	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	916	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	917	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	918	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day

600 PPM				
	939	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	940	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	941	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	942	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	943	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	944	1	1	No Remarkable Observations
		8	8	Skin, Scab, Focal, Upper Back (Thoracic)

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/CrI Mice

APPENDIX TABLE 1. Individual Clinical Observations – 7-Day (continued)

Dose	Animal Number	Day Observed		Observation/Comment
		First	Last	

600 PPM				
	944	8	8	Disposition, Scheduled Necropsy - 7 Day
	945	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	946	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	947	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	948	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day

2000 PPM				
	969	1	1	No Remarkable Observations
		8	8	Skin, Scab, Focal, Upper Back (Thoracic)
		8	8	Disposition, Scheduled Necropsy - 7 Day
	970	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	971	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	972	1	1	No Remarkable Observations
		8	8	Skin, Scab, Focal, Upper Back (Thoracic)
		8	8	Disposition, Scheduled Necropsy - 7 Day
	973	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	974	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	975	1	8	No Remarkable Observations

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/CrI Mice

APPENDIX TABLE 1. Individual Clinical Observations – 7-Day (continued)

Dose	Animal Number	Day Observed		Observation/Comment
		First	Last	

2000 PPM				
	975	8	8	Disposition, Scheduled Necropsy - 7 Day
	976	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	977	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	978	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day

6000 PPM				
	999	1	1	No Remarkable Observations
		8	8	Skin, Scab, Focal, Upper Back (Thoracic)
		8	8	Disposition, Scheduled Necropsy - 7 Day
	1000	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	1001	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	1002	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	1003	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	1004	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	1005	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	1006	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 1. Individual Clinical Observations – 7-Day (continued)

Dose	Animal Number	Day Observed		Observation/Comment
		First	Last	

6000 PPM	1007	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day
	1008	1	8	No Remarkable Observations
		8	8	Disposition, Scheduled Necropsy - 7 Day

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 2. Individual Clinical Observations – 28-Day

Dose	Animal Number	Day Observed		Observation/Comment
		First	Last	

0 PPM				
	839	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	840	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	841	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	842	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	843	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	844	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day
	845	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day
	846	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day
	847	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day
	848	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day

40 PPM				
	869	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	870	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 2. Individual Clinical Observations – 28-Day (continued)

Dose	Animal Number	Day Observed		Observation/Comment
		First	Last	

40 PPM				
	871	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	872	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	873	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	874	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day
	875	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day
	876	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day
	877	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day
	878	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day

200 PPM				
	899	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	900	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	901	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	902	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 2. Individual Clinical Observations – 28-Day (continued)

Dose	Animal Number	Day Observed		Observation/Comment
		First	Last	

200 PPM				
	903	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	904	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day
	905	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day
	906	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day
	907	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day
	908	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day

600 PPM				
	929	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	930	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	931	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	932	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	933	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	934	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 2. Individual Clinical Observations – 28-Day (continued)

Dose	Animal Number	Day Observed		Observation/Comment
		First	Last	

600 PPM				
	935	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day
	936	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day
	937	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day
	938	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day

2000 PPM				
	959	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	960	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	961	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	962	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	963	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	964	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day
	965	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day
	966	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 2. Individual Clinical Observations – 28-Day (continued)

Dose	Animal Number	Day Observed		Observation/Comment
		First	Last	

2000 PPM				
	967	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day
	968	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day

6000 PPM				
	989	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	990	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	991	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	992	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	993	1	29	No Remarkable Observations
		29	29	Disposition, Scheduled Necropsy - 28-Day
	994	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day
	995	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day
	996	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day
	997	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day
	998	1	29	No Remarkable Observations
		30	30	Disposition, Scheduled Necropsy - 28-Day

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 3. Individual Clinical Observations – 90-Day

Dose	Animal Number	Day Observed		Observation/Comment
		First	Last	

0 PPM				
	829	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	830	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	831	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	832	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	833	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	834	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day
	835	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day
	836	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day
	837	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day
	838	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day

40 PPM				
	859	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	860	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 3. Individual Clinical Observations – 90-Day (continued)

Dose	Animal Number	Day Observed		Observation/Comment
		First	Last	

40 PPM				
	861	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	862	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	863	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	864	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day
	865	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day
	866	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day
	867	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day
	868	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day

200 PPM				
	889	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	890	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	891	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	892	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 3. Individual Clinical Observations – 90-Day (continued)

Dose	Animal Number	Day Observed		Observation/Comment
		First	Last	

200 PPM				
	893	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	894	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day
	895	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day
	896	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day
	897	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day
	898	1	22	No Remarkable Observations
		29	29	Injury, Apparent Mechanical, Kinked, Tail, Tip
		36	91	Missing Part of Tail, Sloughed
		92	92	Disposition, Scheduled Necropsy - 90 Day

600 PPM				
	919	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	920	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	921	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	922	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	923	1	83	No Remarkable Observations
		91	91	Skin, Scab, Focal, Lower Back (Lumbar)
		91	91	Disposition, Scheduled Necropsy - 90 Day

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 3. Individual Clinical Observations – 90-Day (continued)

Dose	Animal Number	Day Observed		Observation/Comment
		First	Last	

600 PPM				
	924	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day
	925	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day
	926	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day
	927	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day
	928	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day

2000 PPM				
	949	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	950	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	951	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	952	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	953	1	83	No Remarkable Observations
		91	91	Skin, Scab, Focal, Shoulder, Right
		91	91	Disposition, Scheduled Necropsy - 90 Day
	954	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day
	955	1	91	No Remarkable Observations

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/CrI Mice

APPENDIX TABLE 3. Individual Clinical Observations – 90-Day (continued)

Dose	Animal Number	Day Observed		Observation/Comment
		First	Last	

2000 PPM				
	955	92	92	Disposition, Scheduled Necropsy - 90 Day
	956	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day
	957	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day
	958	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day

6000 PPM				
	979	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	980	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	981	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	982	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	983	1	91	No Remarkable Observations
		91	91	Disposition, Scheduled Necropsy - 90 Day
	984	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day
	985	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day
	986	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 3. Individual Clinical Observations – 90-Day (continued)

Dose	Animal Number	Day Observed		Observation/Comment
		First	Last	

6000 PPM	987	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day
	988	1	91	No Remarkable Observations
		92	92	Disposition, Scheduled Necropsy - 90 Day

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 4. Individual Body Weights/Body Weight Gains (g) – 7-Day

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST		
		1	8	GAIN
0	849	21.2	22.3	1.1
	850	20.7	22.3	1.6
	851	20.6	22.8	2.2
	852	19.0	21.3	2.3
	853	20.1	21.3	1.2
	854	19.0	20.8	1.8
	855	19.7	20.6	0.9
	856	21.6	23.3	1.7
	857	19.0	20.9	1.9
	858	22.4	24.1	1.7
	MEAN	20.3	22.0	1.6
	S.D.	1.2	1.2	0.5
	N=	10	10	10
40	879	22.3	24.5	2.2
	880	19.6	21.5	1.9
	881	19.4	21.1	1.7
	882	21.8	23.3	1.5
	883	20.9	22.5	1.6
	884	22.1	23.0	0.9
	885	19.9	21.1	1.2
	886	20.3	21.9	1.6
	887	18.6	20.5	1.9
	888	20.4	20.9	0.5
	MEAN	20.5	22.0	1.5
	S.D.	1.2	1.3	0.5
	N=	10	10	10

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 4. Individual Body Weights/Body Weight Gains (g) – 7-Day (continued)

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST		
		1	8	GAIN
200	909	21.0	22.5	1.5
	910	19.1	21.4	2.3
	911	21.2	23.3	2.1
	912	21.1	23.1	2.0
	913	19.0	21.3	2.3
	914	20.4	22.1	1.7
	915	19.5	20.8	1.3
	916	19.0	20.5	1.5
	917	21.2	23.0	1.8
	918	22.9	25.5	2.6
	MEAN	20.4	22.4	1.9
	S.D.	1.3	1.5	0.4
	N=	10	10	10
600	939	21.6	22.8	1.2
	940	18.6	20.2	1.6
	941	21.8	23.3	1.5
	942	19.9	21.3	1.4
	943	19.2	21.2	2.0
	944	20.9	22.5	1.6
	945	21.9	23.9	2.0
	946	20.4	21.6	1.2
	947	20.4	21.2	0.8
	948	19.9	20.8	0.9
	MEAN	20.5	21.9	1.4
	S.D.	1.1	1.2	0.4
	N=	10	10	10

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/CrI Mice

APPENDIX TABLE 4. Individual Body Weights/Body Weight Gains (g) – 7-Day (continued)

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST		
		1	8	GAIN
2000	969	21.3	22.6	1.3
	970	21.5	22.1	0.6
	971	22.3	23.8	1.5
	972	19.7	20.3	0.6
	973	20.0	21.6	1.6
	974	21.4	23.5	2.1
	975	18.8	20.0	1.2
	976	19.3	21.3	2.0
	977	22.0	24.7	2.7
	978	21.5	23.5	2.0
	MEAN	20.8	22.3	1.6
	S.D.	1.2	1.6	0.7
	N=	10	10	10
6000	1000	21.4	22.9	1.5
	1001	20.6	22.4	1.8
	1002	20.6	22.2	1.6
	1003	19.5	21.0	1.5
	1004	18.9	21.1	2.2
	1005	21.1	22.6	1.5
	1006	18.3	19.7	1.4
	1007	20.2	22.2	2.0
	1008	21.2	23.6	2.4
	999	19.7	22.1	2.4
	MEAN	20.2	22.0	1.8
	S.D.	1.0	1.1	0.4
	N=	10	10	10

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 5. Individual Body Weights/Body Weight Gains (g) – 28-Day

[illegible]

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 5. Individual Body Weights/Body Weight Gains (g) – 28-Day (continued)

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST										
		1	8	GAIN	15	GAIN	21	GAIN	25	GAIN	29	GAIN
200	899	20.1	19.7	-0.4	20.2	0.1	21.0	0.9	21.5	1.4	22.6	2.5
	900	20.5	22.1	1.6	24.2	3.7	24.5	4.0	25.1	4.6	23.9	3.4
	901	20.7	20.2	-0.5	21.6	0.9	22.6	1.9	21.7	1.0	22.1	1.4
	902	19.9	21.5	1.6	21.9	2.0	22.5	2.6	23.3	3.4	23.4	3.5
	903	19.3	20.7	1.4	20.8	1.5	21.5	2.2	21.5	2.2	23.1	3.8
	904	18.3	19.5	1.2	20.1	1.8	21.0	2.7	20.8	2.5	21.6	3.3
	905	19.2	19.3	0.1	20.9	1.7	20.4	1.2	19.8	0.6	20.8	1.6
	906	19.9	21.8	1.9	21.4	1.5	24.0	4.1	22.4	2.5	22.7	2.8
	907	18.4	19.4	1.0	19.4	1.0	19.5	1.1	20.4	2.0	20.4	2.0
	908	17.8	19.2	1.4	20.0	2.2	20.4	2.6	20.4	2.6	20.8	3.0
	MEAN	19.4	20.3	0.9	21.1	1.6	21.7	2.3	21.7	2.3	22.1	2.7
	S.D.	1.0	1.1	0.9	1.4	0.9	1.6	1.1	1.6	1.2	1.2	0.8
	N=	10	10	10	10	10	10	10	10	10	10	10
600	929	19.4	20.2	0.8	20.3	0.9	21.2	1.8	22.1	2.7	22.1	2.7
	930	17.3	18.7	1.4	19.4	2.1	20.3	3.0	20.3	3.0	20.9	3.6
	931	20.0	19.4	-0.6	20.4	0.4	20.3	0.3	21.1	1.1	21.9	1.9
	932	19.6	19.3	-0.3	20.8	1.2	22.1	2.5	21.0	1.4	21.9	2.3
	933	19.1	19.2	0.1	19.6	0.5	19.9	0.8	21.2	2.1	21.7	2.6
	934	21.3	20.5	-0.8	23.7#	2.4	21.8	0.5	22.0	0.7	22.6	1.3
	935	19.0	20.1	1.1	20.6	1.6	21.0	2.0	21.5	2.5	22.2	3.2
	936	20.2	19.5	-0.7	21.5	1.3	22.5	2.3	20.9	0.7	21.3	1.1
	937	20.4	20.2	-0.2	20.9	0.5	21.6	1.2	21.2	0.8	22.1	1.7
	938	18.0	18.7	0.7	19.7	1.7	20.1	2.1	20.2	2.2	20.6	2.6
	MEAN	19.4	19.6	0.1	20.7	1.3	21.1	1.7	21.2	1.7	21.7	2.3
	S.D.	1.2	0.6	0.8	1.2	0.7	0.9	0.9	0.6	0.9	0.6	0.8
	N=	10	10	10	10	10	10	10	10	10	10	10

STATISTICAL OUTLIERS INCLUDED.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 5. Individual Body Weights/Body Weight Gains (g) – 28-Day (continued)

[illegible]

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 6. Individual Body Weights/Body Weight Gains (g) – 90-Day

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST												
		1	8	GAIN	15	GAIN	22	GAIN	29	GAIN	36	GAIN	43	GAIN
0	829	19.6	20.0	0.4	19.7	0.1	21.1	1.5	22.4	2.8	22.1	2.5	23.4	3.8
	830	19.7	19.9	0.2	19.8	0.1	21.1	1.4	20.8	1.1	22.0	2.3	23.7	4.0
	831	19.6	22.1	2.5	20.9	1.3	23.1	3.5	24.0	4.4	24.9	5.3	26.8	7.2#
	832	19.0	19.9	0.9	21.0	2.0	22.6	3.6	21.4	2.4	23.5	4.5	23.7	4.7
	833	17.8	18.5	0.7	20.6	2.8	19.9	2.1	21.8	4.0	22.0	4.2	21.9	4.1
	834	19.1	18.9	-0.2	20.5	1.4	20.1	1.0	22.0	2.9	20.5	1.4	22.3	3.2
	835	19.0	18.7	-0.3	20.0	1.0	21.8	2.8	21.1	2.1	22.9	3.9	22.2	3.2
	836	17.5	17.4	-0.1	18.6	1.1	20.2	2.7	19.5	2.0	21.4	3.9	20.7	3.2
	837	16.9	17.8	0.9	18.3	1.4	18.8	1.9	20.4	3.5	20.2	3.3	20.2	3.3
	838	17.2	18.2	1.0	19.2	2.0	19.3	2.1	19.4	2.2	21.2	4.0	21.1	3.9
	MEAN	18.5	19.1	0.6	19.9	1.3	20.8	2.3	21.3	2.7	22.1	3.5	22.6	4.1
	S.D.	1.1	1.4	0.8	0.9	0.8	1.4	0.9	1.4	1.0	1.4	1.2	1.9	1.2
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
40	859	16.1	16.7	0.6	18.3	2.2	18.6	2.5	19.5	3.4	18.8	2.7	20.9	4.8
	860	18.6	19.4	0.8	19.9	1.3	21.9	3.3	21.1	2.5	22.4	3.8	22.1	3.5
	861	19.6	21.3	1.7	20.4	0.8	22.4	2.8	21.7	2.1	22.3	2.7	22.6	3.0
	862	19.0	18.7	-0.3	20.0	1.0	21.5	2.5	21.5	2.5	22.3	3.3	25.4	6.4
	863	19.9	21.0	1.1	21.5	1.6	20.4	0.5	23.3	3.4	23.3	3.4	21.3	1.4
	864	18.6	19.8	1.2	20.5	1.9	19.7	1.1	21.8	3.2	20.3	1.7	21.5	2.9
	865	17.4	17.6	0.2	18.0	0.6	18.9	1.5	21.1	3.7	19.8	2.4	21.4	4.0
	866	19.6	19.8	0.2	20.7	1.1	20.7	1.1	22.4	2.8	21.1	1.5	22.6	3.0
	867	17.8	17.4	-0.4	18.3	0.5	19.1	1.3	20.2	2.4	19.9	2.1	21.3	3.5
	868	18.5	20.9	2.4	20.9	2.4	23.0	4.5	23.0	4.5	25.1	6.6#	24.9	6.4
	MEAN	18.5	19.3	0.7	19.9	1.3	20.6	2.1	21.6	3.1	21.5	3.0	22.4	3.9
	S.D.	1.2	1.6	0.9	1.2	0.7	1.5	1.2	1.2	0.7	1.9	1.5	1.6	1.6
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10

STATISTICAL OUTLIERS INCLUDED.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 6. Individual Body Weights/Body Weight Gains (g) – 90-Day (continued)

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST												
		1	8	GAIN	15	GAIN	22	GAIN	29	GAIN	36	GAIN	43	GAIN
200	889	17.2	18.6	1.4	20.2	3.0	20.9	3.7	20.2	3.0	20.9	3.7	21.5	4.3
	890	18.7	19.5	0.8	21.2	2.5	21.0	2.3	21.6	2.9	22.4	3.7	23.8	5.1
	891	20.5	20.9	0.4	22.9	2.4	22.6	2.1	23.0	2.5	25.5	5.0	25.8	5.3
	892	17.8	18.0	0.2	19.2	1.4	19.9	2.1	20.7	2.9	21.2	3.4	20.8	3.0
	893	18.2	19.0	0.8	19.5	1.3	20.6	2.4	20.4	2.2	22.3	4.1	21.3	3.1
	894	18.8	18.4	-0.4	18.9	0.1	19.4	0.6	20.3	1.5	21.4	2.6	21.4	2.6
	895	19.4	21.1	1.7	21.7	2.3	21.6	2.2	23.5	4.1	23.8	4.4	22.9	3.5
	896	17.7	19.1	1.4	19.2	1.5	20.1	2.4	21.2	3.5	20.3	2.6	20.2	2.5
	897	17.0	18.0	1.0	18.3	1.3	19.0	2.0	20.1	3.1	19.8	2.8	21.2	4.2
	898	20.0	18.3	-1.7	19.4	-0.6	21.0	1.0	21.3	1.3	22.1	2.1	21.7	1.7
	MEAN	18.5	19.1	0.6	20.1	1.5	20.6	2.1	21.2	2.7	22.0	3.4	22.1	3.5
	S.D.	1.2	1.1	1.0	1.4	1.1	1.1	0.8	1.2	0.9	1.7	0.9	1.7	1.2
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
600	919	19.2	20.6	1.4	21.2	2.0	21.5	2.3	24.3	5.1	22.8	3.6	24.2	5.0
	920	17.1	17.7	0.6	20.3	3.2	20.0	2.9	21.6	4.5	22.0	4.9	22.9	5.8
	921	20.0	22.1	2.1	21.5	1.5	22.5	2.5	24.8	4.8	26.0#	6.0	23.4	3.4
	922	16.3	17.2	0.9	18.2	1.9	20.6	4.3	20.5	4.2	22.0	5.7	22.0	5.7
	923	18.5	18.4	-0.1	18.9	0.4	20.6	2.1	21.5	3.0	21.3	2.8	23.7	5.2
	924	18.6	19.1	0.5	19.0	0.4	20.2	1.6	22.7	4.1	21.3	2.7	21.3	2.7
	925	18.3	20.0	1.7	19.8	1.5	20.3	2.0	21.9	3.6	21.6	3.3	22.3	4.0
	926	19.8	19.9	0.1	21.1	1.3	21.0	1.2	22.0	2.2	22.2	2.4	23.1	3.3
	927	17.7	20.0	2.3	20.0	2.3	21.8	4.1	20.5	2.8	22.3	4.6	24.6	6.9
	928	18.3	19.6	1.3	20.5	2.2	20.7	2.4	22.4	4.1	21.9	3.6	24.3	6.0
	MEAN	18.4	19.5	1.1	20.1	1.7	20.9	2.5	22.2	3.8	22.3	4.0	23.2	4.8
	S.D.	1.1	1.4	0.8	1.1	0.9	0.8	1.0	1.4	0.9	1.4	1.3	1.1	1.4
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10

STATISTICAL OUTLIERS INCLUDED.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 6. Individual Body Weights/Body Weight Gains (g) – 90-Day (continued)

[illegible]

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 6. Individual Body Weights/Body Weight Gains (g) – 90-Day (continued)

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST												
		1	50	GAIN	57	GAIN	64	GAIN	71	GAIN	78	GAIN	83	GAIN
0	829	19.6	24.4	4.8	22.3	2.7	23.5	3.9	25.2	5.6	25.3	5.7	26.8	7.2
	830	19.7	21.7	2.0	22.8	3.1	25.0	5.3	24.4	4.7	22.3	2.6	22.3	2.6
	831	19.6	27.9	8.3	26.8	7.2	28.4	8.8	30.1	10.5	33.4#	13.8#	32.0	12.4
	832	19.0	23.3	4.3	25.0	6.0	25.9	6.9	28.3	9.3	25.7	6.7	25.9	6.9
	833	17.8	22.0	4.2	24.7	6.9	22.7	4.9	24.4	6.6	22.9	5.1	25.9	8.1
	834	19.1	24.3	5.2	22.4	3.3	22.9	3.8	22.6	3.5	25.1	6.0	23.0	3.9
	835	19.0	24.6	5.6	22.7	3.7	23.5	4.5	24.8	5.8	27.1	8.1	23.8	4.8
	836	17.5	22.8	5.3	21.4	3.9	23.3	5.8	21.9	4.4	24.0	6.5	24.5	7.0
	837	16.9	22.0	5.1	20.5	3.6	21.4	4.5	22.8	5.9	24.1	7.2	21.6	4.7
	838	17.2	20.1	2.9	22.0	4.8	21.9	4.7	23.0	5.8	22.1	4.9	22.5	5.3
	MEAN	18.5	23.3	4.8	23.1	4.5	23.9	5.3	24.8	6.2	25.2	6.7	24.8	6.3
	S.D.	1.1	2.1	1.7	1.9	1.6	2.1	1.5	2.6	2.2	3.3	2.9	3.1	2.7
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
40	859	16.1	19.5	3.4	20.5	4.4	21.5	5.4	20.8	4.7	21.5	5.4	22.3	6.2
	860	18.6	22.7	4.1	24.9	6.3	24.0	5.4	24.3	5.7	24.6	6.0	24.7	6.1
	861	19.6	23.0	3.4	26.9	7.3	23.6	4.0	24.7	5.1	29.2	9.6	25.8	6.2
	862	19.0	22.5	3.5	24.8	5.8	27.5	8.5	25.3	6.3	27.3	8.3	27.7	8.7
	863	19.9	25.0	5.1	24.0	4.1	25.9	6.0	24.9	5.0	26.7	6.8	25.5	5.6
	864	18.6	23.8	5.2	22.2	3.6	24.2	5.6	23.2	4.6	25.3	6.7	24.7	6.1
	865	17.4	20.6	3.2	23.2	5.8	21.9	4.5	22.9	5.5	24.7	7.3	22.4	5.0
	866	19.6	22.1	2.5	22.7	3.1	23.4	3.8	24.7	5.1	24.1	4.5	24.9	5.3
	867	17.8	20.4	2.6	21.2	3.4	20.8	3.0	20.4	2.6	21.3	3.5	21.3	3.5
	868	18.5	25.0	6.5	23.6	5.1	27.2	8.7	24.8	6.3	29.9	11.4	26.7	8.2
	MEAN	18.5	22.5	4.0	23.4	4.9	24.0	5.5	23.6	5.1	25.5	7.0	24.6	6.1
	S.D.	1.2	1.9	1.3	1.9	1.4	2.3	1.9	1.8	1.1	2.9	2.4	2.0	1.5
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10

STATISTICAL OUTLIERS INCLUDED.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 6. Individual Body Weights/Body Weight Gains (g) – 90-Day (continued)

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST												
		1	50	GAIN	57	GAIN	64	GAIN	71	GAIN	78	GAIN	83	GAIN
200	889	17.2	23.4	6.2	21.9	4.7	23.6	6.4	22.7	5.5	23.3	6.1	23.5	6.3
	890	18.7	23.4	4.7	26.3	7.6	23.9	5.2	25.6	6.9	26.2	7.5	28.3	9.6
	891	20.5	23.9	3.4	25.3	4.8	27.2	6.7	29.8	9.3	27.1	6.6	30.6	10.1
	892	17.8	21.8	4.0	23.7	5.9	21.9	4.1	23.5	5.7	22.3	4.5	24.3	6.5
	893	18.2	23.7	5.5	23.5	5.3	26.0	7.8	25.0	6.8	27.0	8.8	27.9	9.7
	894	18.8	23.3	4.5	21.5	2.7	22.9	4.1	22.5	3.7	22.8	4.0	24.0	5.2
	895	19.4	25.3	5.9	24.9	5.5	25.1	5.7	25.7	6.3	25.6	6.2	26.7	7.3
	896	17.7	22.2	4.5	21.8	4.1	23.0	5.3	24.3	6.6	23.0	5.3	23.4	5.7
	897	17.0	20.4	3.4	22.2	5.2	21.7	4.7	22.0	5.0	25.0	8.0	22.4	5.4
	898	20.0	22.3	2.3	23.3	3.3	23.6	3.6	24.9	4.9	23.1	3.1	23.5	3.5
	MEAN	18.5	23.0	4.4	23.4	4.9	23.9	5.4	24.6	6.1	24.5	6.0	25.5	6.9
	S.D.	1.2	1.3	1.2	1.6	1.4	1.8	1.3	2.3	1.5	1.8	1.8	2.7	2.2
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
600	919	19.2	27.2	8.0	25.4	6.2	28.7	9.5	28.6	9.4	30.0	10.8	28.1	8.9
	920	17.1	22.8	5.7	24.2	7.1	25.3	8.2	23.6	6.5	24.3	7.2	24.2	7.1
	921	20.0	27.6	7.6	28.3#	8.3	28.2	8.2	26.8	6.8	28.3	8.3	32.0	12.0
	922	16.3	21.1	4.8	24.2	7.9	21.8	5.5	23.8	7.5	24.9	8.6	23.0	6.7
	923	18.5	21.5	3.0	25.1	6.6	23.8	5.3	26.5	8.0	23.5	5.0	23.2	4.7
	924	18.6	22.8	4.2	24.2	5.6	22.4	3.8	24.3	5.7	23.1	4.5	24.4	5.8
	925	18.3	22.0	3.7	23.9	5.6	23.4	5.1	24.5	6.2	26.0	7.7	23.6	5.3
	926	19.8	23.7	3.9	24.5	4.7	26.4	6.6	24.5	4.7	26.2	6.4	27.4	7.6
	927	17.7	22.3	4.6	24.5	6.8	22.8	5.1	24.0	6.3	25.5	7.8	27.1	9.4
	928	18.3	22.5	4.2	23.4	5.1	24.5	6.2	23.4	5.1	26.8	8.5	23.0	4.7
	MEAN	18.4	23.4	5.0	24.8	6.4	24.7	6.4	25.0	6.6	25.9	7.5	25.6	7.2
	S.D.	1.1	2.3	1.7	1.4	1.2	2.4	1.8	1.7	1.4	2.1	1.8	3.0	2.3
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10

STATISTICAL OUTLIERS INCLUDED.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 6. Individual Body Weights/Body Weight Gains (g) – 90-Day (continued)

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST												
		1	50	GAIN	57	GAIN	64	GAIN	71	GAIN	78	GAIN	83	GAIN
2000	949	17.7	22.4	4.7	20.7	3.0	21.7	4.0	23.2	5.5	22.9	5.2	24.4	6.7
	950	16.2	20.6	4.4	21.6	5.4	21.4	5.2	21.7	5.5	23.6	7.4	22.1	5.9
	951	20.0	25.6	5.6	24.3	4.3	26.1	6.1	24.8	4.8	24.9	4.9	25.1	5.1
	952	19.0	22.3	3.3	23.6	4.6	22.8	3.8	24.4	5.4	23.3	4.3	23.1	4.1
	953	18.6	22.1	3.5	21.7	3.1	24.1	5.5	22.1	3.5	24.5	5.9	22.5	3.9
	954	17.9	21.5	3.6	22.8	4.9	24.0	6.1	23.7	5.8	25.8	7.9	24.1	6.2
	955	19.8	24.9	5.1	23.8	4.0	27.2	7.4	25.0	5.2	28.6	8.8	28.9	9.1
	956	17.4	21.2	3.8	22.2	4.8	24.4	7.0	22.6	5.2	25.3	7.9	24.6	7.2
	957	19.4	23.1	3.7	23.6	4.2	25.9	6.5	23.9	4.5	27.2	7.8	25.6	6.2
	958	19.1	23.2	4.1	23.9	4.8	23.5	4.4	25.6	6.5	23.9	4.8	23.7	4.6
	MEAN	18.5	22.7	4.2	22.8	4.3	24.1	5.6	23.7	5.2	25.0	6.5	24.4	5.9
	S.D.	1.2	1.6	0.8	1.2	0.8	1.9	1.2	1.3	0.8	1.8	1.6	1.9	1.6
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
6000	979	20.2	22.4	2.2	23.7	3.5	24.0	3.8	25.6	5.4	23.4	3.2	23.7	3.5
	980	18.8	21.8	3.0	23.7	4.9	22.5	3.7	22.2	3.4#	22.5	3.7	22.5	3.7
	981	17.8	22.6	4.8	22.0	4.2	22.3	4.5	22.9	5.1	24.8	7.0	23.4	5.6
	982	20.0	22.8	2.8	24.2	4.2	24.3	4.3	25.4	5.4	23.2	3.2	22.5	2.5
	983	16.4	21.5	5.1	22.2	5.8	22.5	6.1	21.5	5.1	23.3	6.9	21.9	5.5
	984	16.9	22.0	5.1	23.4	6.5	23.2	6.3	23.0	6.1	25.2	8.3	21.9	5.0
	985	19.9	24.0	4.1	28.1	8.2	25.3	5.4	25.4	5.5	26.8	6.9	27.7	7.8
	986	18.5	24.0	5.5	22.7	4.2	24.3	5.8	24.0	5.5	24.2	5.7	24.1	5.6
	987	19.5	26.9	7.4	26.8	7.3	24.9	5.4	25.1	5.6	26.0	6.5	28.1	8.6
	988	16.6	20.1	3.5	21.1	4.5	20.6	4.0	22.0	5.4	20.9	4.3	22.0	5.4
	MEAN	18.5	22.8	4.4	23.8	5.3	23.4	4.9	23.7	5.3	24.0	5.6	23.8	5.3
	S.D.	1.5	1.8	1.5	2.2	1.6	1.4	1.0	1.6	0.7	1.7	1.8	2.3	1.9
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10

STATISTICAL OUTLIERS INCLUDED.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 6. Individual Body Weights/Body Weight Gains (g) – 90-Day (continued)

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST		
		1	91/92	GAIN
0	829	19.6	24.6	5.0
	830	19.7	23.7	4.0
	831	19.6	29.4#	9.8
	832	19.0	26.2	7.2
	833	17.8	24.3	6.5
	834	19.1	23.1	4.0
	835	19.0	24.3	5.3
	836	17.5	23.0	5.5
	837	16.9	22.5	5.6
	838	17.2	23.3	6.1
		MEAN	18.5	24.4
	S.D.	1.1	2.0	1.7
	N=	10	10	10
40	859	16.1	21.7	5.6
	860	18.6	24.5	5.9
	861	19.6	24.9	5.3
	862	19.0	25.3	6.3
	863	19.9	23.6	3.7
	864	18.6	23.7	5.1
	865	17.4	22.9	5.5
	866	19.6	23.8	4.2
	867	17.8	21.9	4.1
	868	18.5	25.0	6.5
		MEAN	18.5	23.7
	S.D.	1.2	1.3	0.9
	N=	10	10	10
# STATISTICAL OUTLIERS INCLUDED.				

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 6. Individual Body Weights/Body Weight Gains (g) – 90-Day (continued)

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST		
		1	91/92	GAIN
200	889	17.2	23.5	6.3
	890	18.7	24.7	6.0
	891	20.5	27.1	6.6
	892	17.8	22.7	4.9
	893	18.2	24.0	5.8
	894	18.8	23.3	4.5
	895	19.4	24.6	5.2
	896	17.7	23.5	5.8
	897	17.0	22.5	5.5
	898	20.0	24.6	4.6
	MEAN	18.5	24.1	5.5
	S.D.	1.2	1.3	0.7
	N=	10	10	10
600	919	19.2	26.4	7.2
	920	17.1	24.8	7.7
	921	20.0	27.1	7.1
	922	16.3	23.4	7.1
	923	18.5	24.5	6.0
	924	18.6	24.7	6.1
	925	18.3	25.4	7.1
	926	19.8	24.7	4.9
	927	17.7	25.3	7.6
	928	18.3	24.3	6.0
	MEAN	18.4	25.1	6.7
	S.D.	1.1	1.1	0.9
	N=	10	10	10

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 6. Individual Body Weights/Body Weight Gains (g) – 90-Day (continued)

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST		
		1	91/92	GAIN
2000	949	17.7	22.4	4.7
	950	16.2	22.6	6.4
	951	20.0	25.2	5.2
	952	19.0	24.9	5.9
	953	18.6	23.2	4.6
	954	17.9	24.2	6.3
	955	19.8	26.2	6.4
	956	17.4	24.3	6.9
	957	19.4	25.0	5.6
	958	19.1	24.4	5.3
	MEAN	18.5	24.2	5.7
	S.D.	1.2	1.2	0.8
	N=	10	10	10
6000	979	20.2	25.3	5.1
	980	18.8	23.4	4.6
	981	17.8	24.0	6.2
	982	20.0	24.1	4.1
	983	16.4	22.9	6.5
	984	16.9	23.6	6.7
	985	19.9	25.3	5.4
	986	18.5	24.0	5.5
	987	19.5	26.3	6.8
	988	16.6	21.3	4.7
	MEAN	18.5	24.0	5.6
	S.D.	1.5	1.4	1.0
	N=	10	10	10

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 7. Individual Feed Consumption (g/day) – 7-Day

DOSE	ANIMAL	DAYS ON
PPM	NUMBER	1-8
=====		
0	849	4.2
	850	4.3
	851	4.4
	852	4.6
	853	4.4
	854	4.2
	855	4.2
	856	4.8
	857	4.3
	858	4.7
	MEAN	4.4
	S.D.	0.2
	N=	10
=====		
40	879	4.4
	880	4.6
	881	4.0
	882	4.6
	883	4.5
	884	4.5
	885	4.4
	886	4.6
	887	4.3
	888	4.3
	MEAN	4.4
	S.D.	0.2
	N=	10
=====		

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/CrI Mice

APPENDIX TABLE 7. Individual Feed Consumption (g/day) – 7-Day (continued)

DOSE PPM	ANIMAL NUMBER	DAYS ON
		----- 1-8
=====		
200	909	4.2
	910	4.4
	911	4.8
	912	4.5
	913	4.1
	914	4.9
	915	4.6
	916	4.2
	917	4.7
	918	5.1
	MEAN	4.6
	S.D.	0.3
	N=	10
=====		
600	939	4.1
	940	4.5
	941	4.6
	942	4.7
	943	4.6
	944	4.7
	945	5.2
	946	4.5
	947	4.1
	948	4.6
	MEAN	4.6
	S.D.	0.3
	N=	10
=====		

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/CrI Mice

APPENDIX TABLE 7. Individual Feed Consumption (g/day) – 7-Day (continued)

DOSE PPM	ANIMAL NUMBER	DAYS ON
		----- 1-8
=====		
2000	969	4.7
	970	4.8
	971	4.6
	972	4.3
	973	4.6
	974	4.6
	975	4.6
	976	4.5
	977	4.5
	978	4.6
	MEAN	4.6
	S.D.	0.1
	N=	10
=====		
6000	1000	4.2
	1001	4.7
	1002	4.7
	1003	4.4
	1004	4.9
	1005	4.3
	1006	4.2
	1007	4.3
	1008	5.1
	999	4.5
	MEAN	4.5
	S.D.	0.3
	N=	10
=====		

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 8. Individual Feed Consumption (g/day) – 28-Day

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST			
		1-8	8-15	15-21	21-29
0	839	3.1	3.2	3.0	4.1
	840	3.1	3.2	3.0	3.9
	841	3.2	3.4	3.0	4.3
	842	3.2	3.4	3.0	3.8
	843	3.5	3.5	3.7	4.4
	844	3.5	3.5	3.7	4.3
	845	3.1	3.1	3.2	3.7
	846	3.1	3.1	3.2	3.9
	847	3.2	3.2	3.2	3.9
	848	3.2	3.2	3.2	3.9
	MEAN	3.2	3.3	3.2	4.0
	S.D.	0.2	0.2	0.3	0.2
40	N=	10	10	10	10
	869	3.7	3.7	3.8	4.8
	870	3.7	3.7	3.8	4.6
	871	3.6	3.7	3.6	4.3
	872	3.6	3.7	3.6	4.5
	873	3.3	3.5	3.5	4.0
	874	3.3	3.5	3.5	4.0
	875	3.3	3.4	3.5	4.1
	876	3.3	3.4	3.5	3.7
	877	3.4	3.4	3.3	4.1
	878	3.4	3.4	3.3	4.2
	MEAN	3.5	3.5	3.5	4.2
	S.D.	0.2	0.1	0.2	0.3
	N=	10	10	10	10

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 8. Individual Feed Consumption (g/day) – 28-Day (continued)

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST			
		1-8	8-15	15-21	21-29
200	899	3.7	4.3	3.8	4.6
	900	3.7	4.3	3.8	4.8
	901	3.5	3.5	3.6	4.2
	902	3.5	3.5	3.6	4.6
	903	3.3	3.3	3.7	4.3
	904	3.3	3.3	3.7	4.0
	905	3.5	3.6	3.8	4.0
	906	3.5	3.6	3.8	4.1
	907	3.2	3.3	3.3	4.0
	908	3.2	3.3	3.3	3.9
	MEAN	3.4	3.6	3.6	4.2
	S.D.	0.2	0.4	0.2	0.3
600	N=	10	10	10	10
	929	2.9	3.1	3.2	4.0
	930	2.9	3.1	3.2	4.0
	931	3.2	3.3	3.4	4.3
	932	3.2	3.3	3.4	4.0
	933	3.4	3.6	3.1	4.4
	934	3.4	3.6	3.1	4.4
	935	3.4	3.5	3.7	4.5
	936	3.4	3.5	3.7	4.1
	937	2.9	3.1	3.0	3.9
	938	2.9	3.1	3.0	3.9
	MEAN	3.2	3.3	3.3	4.2
	S.D.	0.2	0.2	0.3	0.2
	N=	10	10	10	10

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 8. Individual Feed Consumption (g/day) – 28-Day (continued)

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST			
		1-8	8-15	15-21	21-29
2000	959	3.4	3.4	3.4	4.2
	960	3.4	3.4	3.4	4.3
	961	3.2	3.3	3.3	4.1
	962	3.2	3.3	3.3	4.0
	963	3.2	3.4	3.6	4.3
	964	3.2	3.4	3.6	4.1
	965	3.5	3.5	3.5	4.3
	966	3.5	3.5	3.5	3.6#
	967	3.5	3.4	3.2	4.2
	968	3.5	3.4	3.2	4.2
	MEAN	3.4	3.4	3.4	4.1
	S.D.	0.1	0.1	0.1	0.2
	N=	10	10	10	10
6000	989	3.3	3.3	3.3	4.1
	990	3.3	3.3	3.3	4.2
	991	3.0	3.2	3.1	4.2
	992	3.0	3.2	3.1	4.0
	993	3.3	3.2	3.4	4.2
	994	3.3	3.2	3.4	4.3
	995	3.1	3.0	3.3	3.8
	996	3.1	3.0	3.3	3.7
	997	3.2	3.3	3.2	4.1
	998	3.2	3.3	3.2	4.3
	MEAN	3.2	3.2	3.3	4.1
	S.D.	0.1	0.1	0.1	0.2
	N=	10	10	10	10
# STATISTICAL OUTLIERS INCLUDED.					

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 9. Individual Feed Consumption (g/day) – 90-Day

[illegible]

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 9. Individual Feed Consumption (g/day) – 90-Day (continued)

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST												
		1-8	8-15	15-22	22-29	29-36	36-43	43-50	50-57	57-64	64-71	71-78	78-83	83-91
200	889	3.4	3.3	3.4	4.2#	3.7	3.6	3.6	3.8	3.5	3.7	3.7	4.1	4.1
	890	3.4	3.3	3.4	4.2#	3.7	3.6	3.6	3.8	3.5	3.7	3.7	4.1	3.6
	891	3.3	3.5	3.3	3.4	3.5	3.3	3.6	3.8	3.5	4.1	3.0	4.5	3.6
	892	3.3	3.5	3.3	3.4	3.5	3.3	3.6	3.8	3.5	4.1	3.0	4.5	3.4
	893	3.0	3.1	3.4	3.5	3.6	3.5	3.7	3.5	3.7	3.3	3.7	3.4	3.3
	894	3.0	3.1	3.4	3.5	3.6	3.5	3.7	3.5	3.7	3.3	3.7	3.4	3.7
	895	3.3	3.2	3.3	3.4	3.2	3.3	3.5	3.1	3.6	3.4	3.2	3.8	3.4
	896	3.3	3.2	3.3	3.4	3.2	3.3	3.5	3.1	3.6	3.4	3.2	3.8	4.0
	897	3.0	3.2	3.2	3.3	3.3	3.3	3.2	3.5	3.4	3.3	3.5	3.3	3.7
	898	3.0	3.2	3.2	3.3	3.3	3.3	3.2	3.5	3.4	3.3	3.5	3.3	4.0
	MEAN	3.2	3.3	3.3	3.6	3.5	3.4	3.5	3.5	3.5	3.6	3.4	3.8	3.7
	S.D.	0.2	0.1	0.1	0.3	0.2	0.1	0.2	0.3	0.1	0.3	0.3	0.5	0.3
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10
600	919	3.1	3.5	3.6	3.9	3.5	3.9	4.0	3.7	4.1	3.6	4.1	3.2	3.7
	920	3.1	3.5	3.6	3.9	3.5	3.9	4.0	3.7	4.1	3.6	4.1	3.2	3.9
	921	3.4	3.4	3.7	3.8	3.7	3.7	3.8	3.9	3.6	3.2	3.9	4.4	3.5
	922	3.4	3.4	3.7	3.8	3.7	3.7	3.8	3.9	3.6	3.2	3.9	4.4	4.3
	923	3.2	3.3	3.6	3.6	3.6	3.7	3.5	4.0	3.0	3.8	2.8#	3.7	4.3
	924	3.2	3.3	3.6	3.6	3.6	3.7	3.5	4.0	3.0	3.8	2.8#	3.7	3.9
	925	3.4	3.3	3.9	4.1	4.0	3.8	3.7	3.9	3.7	3.7	4.0	3.7	4.4
	926	3.4	3.3	3.9	4.1	4.0	3.8	3.7	3.9	3.7	3.7	4.0	3.7	3.4
	927	3.4	3.5	3.8	3.6	3.8	3.8	3.3	4.0	3.6	3.8	4.0	3.5	3.9
	928	3.4	3.5	3.8	3.6	3.8	3.8	3.3	4.0	3.6	3.8	4.0	3.5	4.3
	MEAN	3.3	3.4	3.7	3.8	3.7	3.8	3.7	3.9	3.6	3.6	3.8	3.7	4.0
	S.D.	0.1	0.1	0.1	0.2	0.2	0.1	0.3	0.1	0.4	0.2	0.5	0.4	0.4
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10

STATISTICAL OUTLIERS INCLUDED.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 9. Individual Feed Consumption (g/day) – 90-Day (continued)

[illegible]

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 10. Individual Water Consumption (g/day) – 7-Day

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST	
		1-4	4-8
=====			
0	849	4.4	4.6
	850	4.4	4.9
	851	4.5	4.5
	852	5.4	5.3
	853	4.9	4.9
	854	5.0	4.7
	855	4.9	4.9
	856	6.1	6.4#
	857	4.6	4.4
	858	5.6	5.4
	MEAN	5.0	5.0
	S.D.	0.6	0.6
	N=	10	10
=====			
40	879	4.6	4.6
	880	4.7	4.9
	881	4.4	4.4
	882	5.1	5.7
	883	4.6	5.3
	884	5.2	4.6
	885	5.7	5.0
	886	5.5	4.8
	887	4.2	4.2
	888	5.0	4.7
	MEAN	4.9	4.8
	S.D.	0.5	0.4
	N=	10	10
=====			
# STATISTICAL OUTLIERS INCLUDED.			

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 10. Individual Water Consumption (g/day) – 7-Day (continued)

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST	
		1-4	4-8
200	909	4.6	4.7
	910	4.5	5.0
	911	5.5	6.2
	912	4.8	5.1
	913	4.7	4.5
	914	6.5	5.5
	915	5.0	5.2
	916	4.9	4.4
	917	5.5	5.0
	918	5.2	4.8
	MEAN	5.1	5.0
	S.D.	0.6	0.5
	N=	10	10
600	939	4.5	4.8
	940	5.6	5.4
	941	4.6	5.4
	942	5.1	5.6
	943	4.3	4.4
	944	6.1	5.2
	945	5.6	5.3
	946	5.4	4.6
	947	4.4	4.4
	948	4.7	4.7
	MEAN	5.0	5.0
	S.D.	0.6	0.4
	N=	10	10

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 10. Individual Water Consumption (g/day) – 7-Day (continued)

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST	
		1-4	4-8
2000	969	4.7	5.1
	970	5.0	5.7
	971	5.1	5.4
	972	5.4	5.2
	973	5.0	5.4
	974	4.6	4.9
	975	4.9	5.3
	976	5.4	4.8
	977	5.5	5.6
	978	5.2	5.5
	MEAN	5.1	5.3
	S.D.	0.3	0.3
N=	10	10	
6000	1000	4.4	4.7
	1001	4.7	5.2
	1002	3.7	4.7
	1003	3.8	4.4
	1004	5.1	5.0
	1005	3.7	4.4
	1006	4.4	4.3
	1007	3.3	3.6
	1008	5.1	5.6
	999	4.7	5.3
	MEAN	4.3	4.7
	S.D.	0.6	0.6
N=	10	10	

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 11. Individual Water Consumption (g/day) – 28-Day

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST							
		1-4	4-8	8-11	11-15	15-18	18-21	21-25	25-29
0	839	3.7	3.5	3.8	3.8	3.6	3.9	5.0	5.4
	840	3.7	3.5	3.8	3.8	3.6	3.9	2.9	4.5
	841	3.7	3.4	4.0	3.9	3.5	4.0	6.5	4.5
	842	3.7	3.4	4.0	3.9	3.5	4.0	4.1	4.5
	843	4.3	4.0	4.2	4.2	4.6	4.4	5.6	5.7
	844	4.3	4.0	4.2	4.2	4.6	4.4	4.8	5.0
	845	4.1	3.1	3.9	3.6	3.9	3.6	3.8	4.6
	846	4.1	3.1	3.9	3.6	3.9	3.6	4.5	4.7
	847	4.0	4.0	4.3	3.9	4.0	4.1	4.7	5.4
	848	4.0	4.0	4.3	3.9	4.0	4.1	4.2	5.0
	MEAN	4.0	3.6	4.0	3.9	3.9	4.0	4.6	4.9
	S.D.	0.2	0.4	0.2	0.2	0.4	0.3	1.0	0.4
	N=	10	10	10	10	10	10	10	10
40	869	4.2	4.3	4.3	4.5	4.4	4.8	4.8	5.7
	870	4.2	4.3	4.3	4.5	4.4	4.8	5.2	5.2
	871	4.3	3.9	4.3	4.1	4.1	4.6	5.0	5.3
	872	4.3	3.9	4.3	4.1	4.1	4.6	4.9	5.0
	873	3.7	3.5	4.2	3.9	3.6	4.3	4.5	5.1
	874	3.7	3.5	4.2	3.9	3.6	4.3	4.9	5.3
	875	3.8	3.8	4.4	4.5	4.7	4.8	5.1	5.2
	876	3.8	3.8	4.4	4.5	4.7	4.8	4.1	5.1
	877	3.8	3.9	4.4	4.3	4.0	4.2	4.4	4.5
	878	3.8	3.9	4.4	4.3	4.0	4.2	5.4	8.9@
	MEAN	4.0	3.9	4.3	4.3	4.2	4.5	4.8	5.2
	S.D.	0.3	0.3	0.1	0.2	0.4	0.3	0.4	0.3
	N=	10	10	10	10	10	10	10	9

@ VALUES EXCLUDED FROM ANALYSIS.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 11. Individual Water Consumption (g/day) – 28-Day (continued)

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST							
		1-4	4-8	8-11	11-15	15-18	18-21	21-25	25-29
200	899	3.9	4.1	4.8	4.9	5.0	4.9	6.2	5.9
	900	3.9	4.1	4.8	4.9	5.0	4.9	5.7	5.0
	901	4.1	3.7	4.3	4.4	4.1	4.4	4.6	5.2
	902	4.1	3.7	4.3	4.4	4.1	4.4	4.9	5.3
	903	4.0	3.9	4.1	4.1	4.6	4.2	5.1	5.3
	904	4.0	3.9	4.1	4.1	4.6	4.2	4.3	5.6
	905	4.4	4.5	5.2	4.7	4.5	4.7	4.8	5.3
	906	4.4	4.5	5.2	4.7	4.5	4.7	5.4	6.1
	907	3.6	3.7	4.0	4.2	4.0	4.1	4.7	4.7
	908	3.6	3.7	4.0	4.2	4.0	4.1	4.0	4.6
	MEAN	4.0	4.0	4.5	4.5	4.4	4.5	5.0	5.3
	S.D.	0.3	0.3	0.5	0.3	0.4	0.3	0.7	0.5
	N=	10	10	10	10	10	10	10	10
600	929	3.4	3.5	3.6	3.8	3.8	3.9	4.7	4.8
	930	3.4	3.5	3.6	3.8	3.8	3.9	4.8	4.7
	931	4.0	3.6	4.1	4.2	4.1	4.5	5.0	5.1
	932	4.0	3.6	4.1	4.2	4.1	4.5	4.4	4.8
	933	3.9	3.6	4.2	4.0	3.5	4.4	5.6	6.1
	934	3.9	3.6	4.2	4.0	3.5	4.4	4.5	5.6
	935	3.8	4.0	4.3	4.4	4.5	4.4	5.3	5.7
	936	3.8	4.0	4.3	4.4	4.5	4.4	4.5	4.9
	937	3.7	3.5	3.8	3.8	3.8	4.1	4.4	5.0
	938	3.7	3.5	3.8	3.8	3.8	4.1	5.0	5.2
	MEAN	3.8	3.6	4.0	4.0	3.9	4.3	4.8	5.2
	S.D.	0.2	0.2	0.3	0.2	0.4	0.2	0.4	0.5
	N=	10	10	10	10	10	10	10	10

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/CrI Mice

APPENDIX TABLE 11. Individual Water Consumption (g/day) – 28-Day (continued)

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST							
		1-4	4-8	8-11	11-15	15-18	18-21	21-25	25-29
2000	959	3.8	3.8	4.1	4.3	4.2	4.6	5.2	5.8
	960	3.8	3.8	4.1	4.3	4.2	4.6	5.1	5.4
	961	3.5	3.4	4.3	4.0	4.3	4.0	4.9	5.3
	962	3.5	3.4	4.3	4.0	4.3	4.0	4.7	4.6
	963	3.6	3.8	4.4	4.1	4.4	4.6	4.8	5.7
	964	3.6	3.8	4.4	4.1	4.4	4.6	4.7	5.1
	965	4.1	3.9	4.1	4.2	4.0	4.2	4.8	5.6
	966	4.1	3.9	4.1	4.2	4.0	4.2	3.6#	4.5
	967	4.3	3.9	4.3	4.3	4.2	4.0	4.5	5.1
	968	4.3	3.9	4.3	4.3	4.2	4.0	4.9	5.1
	MEAN	3.9	3.8	4.2	4.2	4.2	4.3	4.7	5.2
	S.D.	0.3	0.2	0.1	0.1	0.1	0.3	0.4	0.4
N=	10	10	10	10	10	10	10	10	
6000	989	4.6	4.0	4.7	3.8	4.8	4.0	5.0	5.5
	990	4.6	4.0	4.7	3.8	4.8	4.0	4.7	4.7
	991	3.5	3.3	4.1	3.5	3.6	4.0	4.7	4.9
	992	3.5	3.3	4.1	3.5	3.6	4.0	4.3	4.6
	993	3.6	3.8	3.7	3.7	3.8	3.1	4.4	4.7
	994	3.6	3.8	3.7	3.7	3.8	3.1	4.6	5.8
	995	3.2	3.5	3.7	3.4	3.6	3.4	3.9	4.5
	996	3.2	3.5	3.7	3.4	3.6	3.4	4.1	4.5
	997	3.5	3.1	3.7	3.3	3.4	3.8	5.1	5.0
	998	3.5	3.1	3.7	3.3	3.4	3.8	4.6	5.2
	MEAN	3.7	3.5	4.0	3.5	3.8	3.7	4.5	4.9
	S.D.	0.5	0.3	0.4	0.2	0.5	0.4	0.4	0.4
N=	10	10	10	10	10	10	10	10	

STATISTICAL OUTLIERS INCLUDED.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 12. Individual Water Consumption (g/day) – 90-Day

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST												
		1-5	5-8	8-12	12-15	15-19	19-22	22-26	26-29	29-33	33-36	36-40	40-43	43-47
0	829	4.1	3.7	4.0	3.8	4.2	4.2	4.2	4.7	0.0@	4.8	4.1	4.5	3.8
	830	4.1	3.7	4.0	3.8	4.2	4.2	4.2	4.7	0.0@	4.8	4.1	4.5	3.8
	831	4.4	3.9	3.8	4.0	4.5	4.0	4.4	5.0	4.4	3.7	4.4	4.5	4.4
	832	4.4	3.9	3.8	4.0	4.5	4.0	4.4	5.0	4.4	3.7	4.4	4.5	4.4
	833	3.7	4.2	3.7	4.5	4.3	4.3	4.5	4.4	3.5	4.0	4.1	4.0	4.1
	834	3.7	4.2	3.7	4.5	4.3	4.3	4.5	4.4	3.5	4.0	4.1	4.0	4.1
	835	3.6	3.8	3.8	4.0	3.6	4.0	3.6	4.6	4.2	3.8	3.5	4.2	4.2
	836	3.6	3.8	3.8	4.0	3.6	4.0	3.6	4.6	4.2	3.8	3.5	4.2	4.2
	837	3.8	4.0	3.7	3.9	4.7	4.7	5.5	5.3	4.9	5.3	4.7	4.2	4.8
	838	3.8	4.0	3.7	3.9	4.7	4.7	5.5	5.3	4.9	5.3	4.7	4.2	4.8
	MEAN	3.9	3.9	3.8	4.0	4.3	4.2	4.4	4.8	4.3	4.3	4.2	4.3	4.3
	S.D.	0.3	0.2	0.1	0.3	0.4	0.3	0.6	0.3	0.5	0.7	0.4	0.2	0.4
	N=	10	10	10	10	10	10	10	10	8	10	10	10	10
40	859	3.9	3.8	2.9@	4.1	4.4	4.2	4.0	4.1	4.1	4.0	4.0	4.1	3.9
	860	3.9	3.8	2.9@	4.1	4.4	4.2	4.0	4.1	4.1	4.0	4.0	4.1	3.9
	861	4.4	4.2	3.9	4.2	4.3	4.2	4.2	3.9	4.1	4.5	4.4	4.5	4.0
	862	4.4	4.2	3.9	4.2	4.3	4.2	4.2	3.9	4.1	4.5	4.4	4.5	4.0
	863	3.5	3.9	2.9	4.1	4.0	3.4	3.6	4.1	3.1	3.9	3.8	3.4	4.0
	864	3.5	3.9	2.9	4.1	4.0	3.4	3.6	4.1	3.1	3.9	3.8	3.4	4.0
	865	3.3	3.4	3.3	3.8	3.9	4.2	4.0	4.1	3.3	3.9	3.7	4.2	4.2
	866	3.3	3.4	3.3	3.8	3.9	4.2	4.0	4.1	3.3	3.9	3.7	4.2	4.2
	867	3.8	3.9	4.0	3.8	4.4	4.6	3.9	4.3	4.0	4.2	3.6	4.2	4.4
	868	3.8	3.9	4.0	3.8	4.4	4.6	3.9	4.3	4.0	4.2	3.6	4.2	4.4
	MEAN	3.8	3.8	3.5	4.0	4.2	4.1	3.9	4.1	3.7	4.1	3.9	4.1	4.1
	S.D.	0.4	0.3	0.5	0.2	0.2	0.4	0.2	0.1	0.5	0.2	0.3	0.4	0.2
	N=	10	10	8	10	10	10	10	10	10	10	10	10	10

@ VALUES EXCLUDED FROM ANALYSIS.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 12. Individual Water Consumption (g/day) – 90-Day (continued)

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST												
		1-5	5-8	8-12	12-15	15-19	19-22	22-26	26-29	29-33	33-36	36-40	40-43	43-47
200	889	3.8	3.9	3.7	4.1	3.8	4.2	7.9#	4.0	4.2	4.1	3.9	4.2	4.0
	890	3.8	3.9	3.7	4.1	3.8	4.2	7.9#	4.0	4.2	4.1	3.9	4.2	4.0
	891	3.8	4.0	3.7	4.0	3.8	4.3	3.9	4.3	4.3	4.5	3.9	4.4	1.3@
	892	3.8	4.0	3.7	4.0	3.8	4.3	3.9	4.3	4.3	4.5	3.9	4.4	1.3@
	893	3.3	3.2	3.5	3.7	4.1	4.2	4.3	4.3	4.4	4.4	4.2	4.2	4.5
	894	3.3	3.2	3.5	3.7	4.1	4.2	4.3	4.3	4.4	4.4	4.2	4.2	4.5
	895	3.6	3.6	3.5	3.7	3.9	3.7	3.8	3.7	3.4	3.8	3.7	3.5	3.9
	896	3.6	3.6	3.5	3.7	3.9	3.7	3.8	3.7	3.4	3.8	3.7	3.5	3.9
	897	3.5	3.3	3.7	4.1	3.7	3.9	4.0	4.1	0.9@	4.2	3.9	4.4	3.9
	898	3.5	3.3	3.7	4.1	3.7	3.9	4.0	4.1	0.9@	4.2	3.9	4.4	3.9
	MEAN	3.6	3.6	3.6	3.9	3.9	4.1	4.8	4.1	4.1	4.2	3.9	4.1	4.1
	S.D.	0.2	0.3	0.1	0.2	0.1	0.2	1.7	0.2	0.4	0.3	0.2	0.4	0.3
	N=	10	10	10	10	10	10	10	10	8	10	10	10	8
600	919	3.8	3.9	3.8	4.1	4.4	4.0	4.4	4.4	4.2	4.8	4.5	4.3	4.7
	920	3.8	3.9	3.8	4.1	4.4	4.0	4.4	4.4	4.2	4.8	4.5	4.3	4.7
	921	3.9	4.2	4.3	4.8	4.4	4.7	4.6	4.5	4.1	4.6	4.2	3.9	4.6
	922	3.9	4.2	4.3	4.8	4.4	4.7	4.6	4.5	4.1	4.6	4.2	3.9	4.6
	923	3.8	4.3	3.9	4.4	4.2	4.4	4.4	4.5	4.6	4.8	4.4	4.5	4.6
	924	3.8	4.3	3.9	4.4	4.2	4.4	4.4	4.5	4.6	4.8	4.4	4.5	4.6
	925	3.9	4.4	3.9	4.1	4.3	4.4	4.6	4.5	4.7	4.4	4.3	4.3	4.6
	926	3.9	4.4	3.9	4.1	4.3	4.4	4.6	4.5	4.7	4.4	4.3	4.3	4.6
	927	3.7	4.0	4.1	4.9	4.4	4.8	4.4	4.3	4.4	4.6	4.7	4.2	3.8#
	928	3.7	4.0	4.1	4.9	4.4	4.8	4.4	4.3	4.4	4.6	4.7	4.2	3.8#
	MEAN	3.8	4.2	4.0	4.5	4.3	4.5	4.5	4.4	4.4	4.6	4.4	4.2	4.5
	S.D.	0.1	0.2	0.2	0.4	0.1	0.3	0.1	0.1	0.2	0.2	0.2	0.2	0.4
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10

@ VALUES EXCLUDED FROM ANALYSIS.

STATISTICAL OUTLIERS INCLUDED.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 12. Individual Water Consumption (g/day) – 90-Day (continued)

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST												
		1-5	5-8	8-12	12-15	15-19	19-22	22-26	26-29	29-33	33-36	36-40	40-43	43-47
2000	949	3.4	3.4	3.2	2.0@	3.8	3.9	3.8	3.7	3.9	3.9	3.5	3.5	4.0
	950	3.4	3.4	3.2	2.0@	3.8	3.9	3.8	3.7	3.9	3.9	3.5	3.5	4.0
	951	3.6	3.9	3.6	4.0	3.8	4.1	3.9	4.3	4.1	4.2	3.6	4.5	4.1
	952	3.6	3.9	3.6	4.0	3.8	4.1	3.9	4.3	4.1	4.2	3.6	4.5	4.1
	953	3.6	3.7	3.7	4.0	3.7	3.9	3.8	4.0	4.1	3.9	3.8	4.1	4.0
	954	3.6	3.7	3.7	4.0	3.7	3.9	3.8	4.0	4.1	3.9	3.8	4.1	4.0
	955	3.6	3.6	3.5	3.6	4.1	3.9	3.8	4.0	4.1	3.8	3.7	4.2	4.3
	956	3.6	3.6	3.5	3.6	4.1	3.9	3.8	4.0	4.1	3.8	3.7	4.2	4.3
	957	3.9	4.1	3.8	4.3	4.3	4.8#	4.4#	4.6	4.2	4.3	4.2	4.5	3.9
	958	3.9	4.1	3.8	4.3	4.3	4.8#	4.4#	4.6	4.2	4.3	4.2	4.5	3.9
	MEAN	3.6	3.7	3.6	4.0	3.9	4.1	3.9	4.1	4.1	4.0	3.8	4.2	4.1
	S.D.	0.2	0.3	0.2	0.3	0.2	0.4	0.2	0.3	0.1	0.2	0.3	0.4	0.1
	N=	10	10	10	8	10	10	10	10	10	10	10	10	10
6000	979	3.5	3.2	3.1	3.5	3.6	3.6	3.3	3.5	3.5	4.0	3.4	3.8	3.2
	980	3.5	3.2	3.1	3.5	3.6	3.6	3.3	3.5	3.5	4.0	3.4	3.8	3.2
	981	3.3	2.9	3.0	3.1	3.8	3.4	3.3	3.3	3.6	3.4	3.2	3.7	3.4
	982	3.3	2.9	3.0	3.1	3.8	3.4	3.3	3.3	3.6	3.4	3.2	3.7	3.4
	983	2.8	2.8	2.6	3.2	2.9	3.2	2.9	3.6	3.5	3.6	3.0	3.3	3.3
	984	2.8	2.8	2.6	3.2	2.9	3.2	2.9	3.6	3.5	3.6	3.0	3.3	3.3
	985	3.4	2.9	3.1	3.5	3.9	4.0	3.5	3.7	4.0	3.4	3.3	3.5	3.7
	986	3.4	2.9	3.1	3.5	3.9	4.0	3.5	3.7	4.0	3.4	3.3	3.5	3.7
	987	3.3	3.0	3.2	3.5	3.8	3.4	3.6	4.2	3.8	3.9	3.7	3.7	3.9
	988	3.3	3.0	3.2	3.5	3.8	3.4	3.6	4.2	3.8	3.9	3.7	3.7	3.9
	MEAN	3.3	3.0	3.0	3.4	3.6	3.5	3.3	3.7	3.7	3.7	3.3	3.6	3.5
	S.D.	0.3	0.1	0.2	0.2	0.4	0.3	0.3	0.3	0.2	0.3	0.2	0.2	0.3
	N=	10	10	10	10	10	10	10	10	10	10	10	10	10

@ VALUES EXCLUDED FROM ANALYSIS.

STATISTICAL OUTLIERS INCLUDED.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 12. Individual Water Consumption (g/day) – 90-Day (continued)

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST											
		47-50	50-54	54-57	57-61	61-64	64-68	68-71	71-75	75-78	78-83	83-88	88-93
0	829	5.1	4.5	4.3	4.4	4.4	4.0	4.5	4.4	4.2	4.5	5.0	4.5
	830	5.1	4.5	4.3	4.4	4.4	4.0	4.5	4.4	4.2	4.5	4.6	5.3
	831	4.3	4.8	4.3	4.5	4.4	4.6	4.3	4.0	4.2	4.1	4.1	4.5
	832	4.3	4.8	4.3	4.5	4.4	4.6	4.3	4.0	4.2	4.1	5.0	6.3
	833	4.3	3.9	4.9	4.2	3.7	4.2	4.1	3.6	4.4	4.2	4.6	5.2
	834	4.3	3.9	4.9	4.2	3.7	4.2	4.1	3.6	4.4	4.2	4.3	4.6
	835	4.1	3.3	4.5	4.3	4.2	3.7	4.3	4.2	4.2	3.6	4.4	5.1
	836	4.1	3.3	4.5	4.3	4.2	3.7	4.3	4.2	4.2	3.6	4.0	4.7
	837	5.2	5.9	5.2	5.9#	5.4	5.2	4.7	4.8	4.6	4.8	4.4	4.7
	838	5.2	5.9	5.2	5.9#	5.4	5.2	4.7	4.8	4.6	4.8	4.7	5.4
	MEAN	4.6	4.5	4.6	4.7	4.4	4.3	4.4	4.2	4.3	4.2	4.5	5.0
S.D.	0.5	0.9	0.4	0.7	0.6	0.5	0.2	0.4	0.2	0.4	0.3	0.6	
N=	10	10	10	10	10	10	10	10	10	10	10	10	
40	859	4.0	4.2	4.8	3.9	5.6	3.9	4.5	4.1	4.1	4.2	4.4	5.0
	860	4.0	4.2	4.8	3.9	5.6	3.9	4.5	4.1	4.1	4.2	4.7	4.7
	861	4.4	4.4	4.6	4.2	4.2	4.0	4.3	4.5	4.3	3.8	4.7	4.6
	862	4.4	4.4	4.6	4.2	4.2	4.0	4.3	4.5	4.3	3.8	4.8	4.0
	863	3.7	2.9	3.6	3.4	3.6	3.7	3.0	3.7	3.5	2.7	3.8	3.1
	864	3.7	2.9	3.6	3.4	3.6	3.7	3.0	3.7	3.5	2.7	3.7	4.4
	865	3.3	3.9	4.3	3.9	3.5	4.3	4.0	3.8	3.9	3.7	4.5	4.7
	866	3.3	3.9	4.3	3.9	3.5	4.3	4.0	3.8	3.9	3.7	4.3	3.8
	867	3.6	3.7	4.1	4.1	4.6	4.3	3.7	4.4	4.6	3.7	4.9	4.9
	868	3.6	3.7	4.1	4.1	4.6	4.3	3.7	4.4	4.6	3.7	4.5	4.4
	MEAN	3.8	3.8	4.3	3.9	4.3	4.0	3.9	4.1	4.1	3.6	4.4	4.4
S.D.	0.4	0.5	0.4	0.3	0.8	0.2	0.6	0.3	0.4	0.5	0.4	0.6	
N=	10	10	10	10	10	10	10	10	10	10	10	10	
# STATISTICAL OUTLIERS INCLUDED.													

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 12. Individual Water Consumption (g/day) – 90-Day (continued)

[illegible]

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 12. Individual Water Consumption (g/day) – 90-Day (continued)

DOSE PPM	ANIMAL NUMBER	DAYS ON TEST											
		47-50	50-54	54-57	57-61	61-64	64-68	68-71	71-75	75-78	78-83	83-88	88-91
2000	949	3.8	3.6	4.0	3.9	3.8	3.9	3.8	3.4	3.3	3.9	3.5	4.0
	950	3.8	3.6	4.0	3.9	3.8	3.9	3.8	3.4	3.3	3.9	4.6	4.4
	951	4.3	4.7	4.6	4.8	4.2	4.0	3.9	3.8	3.6	4.1	5.1	4.7
	952	4.3	4.7	4.6	4.8	4.2	4.0	3.9	3.8	3.6	4.1	4.2	4.0
	953	3.8	4.0	4.8	4.1	3.9	3.8	3.6	3.9	4.3	3.6	4.9	4.4
	954	3.8	4.0	4.8	4.1	3.9	3.8	3.6	3.9	4.3	3.6	4.2	4.6
	955	4.4	4.0	4.8	4.4	4.3	4.0	4.0	4.3	4.7	4.0	4.1	4.6
	956	4.4	4.0	4.8	4.4	4.3	4.0	4.0	4.3	4.7	4.0	4.3	4.8
	957	4.0	4.4	5.0	4.5	4.1	4.0	4.5	3.7	4.3	3.9	4.9	5.4
	958	4.0	4.4	5.0	4.5	4.1	4.0	4.5	3.7	4.3	3.9	4.3	4.6
	MEAN	4.1	4.1	4.6	4.3	4.1	3.9	4.0	3.8	4.0	3.9	4.4	4.6
	S.D.	0.3	0.4	0.4	0.3	0.2	0.1	0.3	0.3	0.5	0.2	0.5	0.4
	N=	10	10	10	10	10	10	10	10	10	10	10	10
6000	979	3.7	3.5	4.2	3.6	3.7	3.6	3.7	3.6	3.0#	3.6	4.4	4.5
	980	3.7	3.5	4.2	3.6	3.7	3.6	3.7	3.6	3.0#	3.6	3.8	4.0
	981	3.7	3.3	4.2	3.6	3.4	3.4	3.5	3.1	3.6	3.5	4.7	3.9
	982	3.7	3.3	4.2	3.6	3.4	3.4	3.5	3.1	3.6	3.5	4.1	3.9
	983	3.3	3.0	4.1	3.0	3.7	5.3#	3.2	3.4	3.7	3.0	5.1	5.2
	984	3.3	3.0	4.1	3.0	3.7	5.3#	3.2	3.4	3.7	3.0	3.9	4.8
	985	3.9	3.1	5.0	3.4	3.9	3.4	3.8	3.9	3.8	4.0	4.3	4.7
	986	3.9	3.1	5.0	3.4	3.9	3.4	3.8	3.9	3.8	4.0	3.8	4.4
	987	4.1	3.1	4.8	3.8	3.5	3.7	4.0	3.6	3.7	4.0	4.8	4.1
	988	4.1	3.1	4.8	3.8	3.5	3.7	4.0	3.6	3.7	4.0	4.2	4.1
	MEAN	3.7	3.2	4.5	3.5	3.6	3.9	3.6	3.5	3.6	3.6	4.3	4.4
	S.D.	0.3	0.2	0.4	0.3	0.2	0.8	0.3	0.3	0.3	0.4	0.4	0.4
	N=	10	10	10	10	10	10	10	10	10	10	10	10

STATISTICAL OUTLIERS INCLUDED.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/CrI Mice

APPENDIX TABLE 13. Individual Clinical Chemistry – 7-Day

DOSE PPM	ANIMAL NUMBER	ALP U/L	ALT U/L	AST U/L	GGT U/L
=====					
0	849	122	25	61	1.5
	850	119	32	120#	1.5
	851	93	24	50	1.5
	852	95	21	52	1.5
	853	126	22	60	1.5
	854	127	23	51	1.5
	855	113	26	49	1.5
	856	98	25	41	1.5
	857	109	20	53	1.5
	858	132	35	46	1.5
	MEAN	113	25	58	1.5
	S.D.	14	5	22	0.0
	N=	10	10	10	10
=====					
40	879	123	26	55	1.5
	880	112	20	51	1.5
	881	125	25	45	1.5
	882	96	27	50	1.5
	883	128	67	83	1.5
	884	105	59	78	1.5
	885	132	27	81	1.5
	886	133	20	48	1.5
	887	93	45	60	1.5
	888	64	29	54	1.5
	MEAN	111	35	61	1.5
	S.D.	22	17	15	0.0
	N=	10	10	10	10
=====					

GGT LOWEST DETECTION LIMIT IS 3.0. VALUES <3.0 ARE REPORTED
AS 1.5 (ONE-HALF THE DETECTION LIMIT) FOR STATISTICAL ANALYSIS.
STATISTICAL OUTLIERS INCLUDED.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/CrI Mice

APPENDIX TABLE 13. Individual Clinical Chemistry – 7-Day (continued)

DOSE PPM	ANIMAL NUMBER	ALP U/L	ALT U/L	AST U/L	GGT U/L
=====					
200	909	98	130#	69#	1.5
	910	108	23	44	1.5
	911	69#	26	44	1.5
	912	101	25	54	1.5
	913	112	23	54	1.5
	914	115	23	50	1.5
	915	115	27	48	1.5
	916	115	24	46	1.5
	917	108	17#	46	1.5
	918	112	26	48	1.5
	MEAN	105	34	50	1.5
	S.D.	14	34	7	0.0
	N=	10	10	10	10
=====					
600	939	129	28	67	1.5
	940	115	19	44	1.5
	941	111	21	47	1.5
	942	144	21	48	1.5
	943	112	20	51	1.5
	944	120	32	82	1.5
	945	122	23	42	1.5
	946	116	21	53	1.5
	947	101	26	54	1.5
	948	96	49#	74	1.5
	MEAN	117	26	56	1.5
	S.D.	14	9	14	0.0
	N=	10	10	10	10
=====					

GGT LOWEST DETECTION LIMIT IS 3.0. VALUES <3.0 ARE REPORTED
AS 1.5 (ONE-HALF THE DETECTION LIMIT) FOR STATISTICAL ANALYSIS.
STATISTICAL OUTLIERS INCLUDED.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/CrI Mice

APPENDIX TABLE 13. Individual Clinical Chemistry – 7-Day (continued)

DOSE PPM	ANIMAL NUMBER	ALP U/L	ALT U/L	AST U/L	GGT U/L
=====					
2000	969	84	30	58	1.5
	970	114	28	69	1.5
	971	102	24	53	1.5
	972	103	33	67	1.5
	973	94	31	41	1.5
	974	107	27	52	1.5
	975	130	28	86	1.5
	976	94	29	64	1.5
	977	88	24	63	1.5
	978	110	24	45	1.5
	MEAN	103	28	60	1.5
	S.D.	14	3	13	0.0
	N=	10	10	10	10
=====					
6000	1000	87	19	48	1.5
	1001	119	33	59	1.5
	1002	126	25	59	1.5
	1003	109	23	53	1.5
	1004	106	22	51	1.5
	1005	120	27	44	1.5
	1006	116	23	50	1.5
	1007	100	29	63	1.5
	1008	83	56#	72	1.5
	999	84	22	49	1.5
	MEAN	105	28	55	1.5
	S.D.	16	11	8	0.0
	N=	10	10	10	10
=====					

GGT LOWEST DETECTION LIMIT IS 3.0. VALUES <3.0 ARE REPORTED
AS 1.5 (ONE-HALF THE DETECTION LIMIT) FOR STATISTICAL ANALYSIS.
STATISTICAL OUTLIERS INCLUDED.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 14. Individual Clinical Chemistry – 28-Day

DOSE PPM	ANIMAL NUMBER	ALP U/L	ALT U/L	AST U/L	GGT U/L
=====					
0	839	127	20	61	1.5
	840	112	20	47	1.5
	841	98	23	57	1.5
	842	103	50#	63	1.5
	843	95	77#	279#	1.5
	844	119	32	55	1.5
	845	113	27	57	1.5
	846	103	21	49	1.5
	847	107	22	54	1.5
	848	111	22	55	1.5
	MEAN	109	31	78	1.5
	S.D.	10	18	71	0.0
	N=	10	10	10	10
=====					
40	869	107	20	44	1.5
	870	94	21	59	1.5
	871	83	34#	144#	1.5
	872	98	20	39	1.5
	873	93	24	74	1.5
	874	106	24	70	1.5
	875	118	24	69	1.5
	876	141	24	61	1.5
	877	113	20	51	1.5
	878	110	24	47	1.5
	MEAN	106	24	66	1.5
	S.D.	16	4	30	0.0
	N=	10	10	10	10
=====					

GGT LOWEST DETECTION LIMIT IS 3.0. VALUES <3.0 ARE REPORTED
AS 1.5 (ONE-HALF THE DETECTION LIMIT) FOR STATISTICAL ANALYSIS.
STATISTICAL OUTLIERS INCLUDED.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 14. Individual Clinical Chemistry – 28-Day (continued)

DOSE PPM	ANIMAL NUMBER	ALP U/L	ALT U/L	AST U/L	GGT U/L
=====					
200	899	109	33	90#	1.5
	900	118	24	57	1.5
	901	105	20	47	1.5
	902	125	277#	160#	1.5
	903	114	36	66	1.5
	904	111	29	53	1.5
	905	90	21	41	1.5
	906	78	19	53	1.5
	907	75	21	49	1.5
	908	123	23	54	1.5
	MEAN	105	50	67	1.5
	S.D.	18	80	35	0.0
	N=	10	10	10	10
=====					
600	929	102	22	63	1.5
	930	118	52	128#	1.5
	931	116	42	84	1.5
	932	108	21	40	1.5
	933	97	36	77	1.5
	934	108	21	46	1.5
	935	103	23	44	1.5
	936	106	24	48	1.5
	937	114	23	43	1.5
	938	128	23	49	1.5
	MEAN	110	29	62	1.5
	S.D.	9	11	28	0.0
	N=	10	10	10	10
=====					

GGT LOWEST DETECTION LIMIT IS 3.0. VALUES <3.0 ARE REPORTED
AS 1.5 (ONE-HALF THE DETECTION LIMIT) FOR STATISTICAL ANALYSIS.
STATISTICAL OUTLIERS INCLUDED.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 14. Individual Clinical Chemistry – 28-Day (continued)

DOSE PPM	ANIMAL NUMBER	ALP U/L	ALT U/L	AST U/L	GGT U/L
=====					
2000	959	100	27	50	1.5
	960	103	40	74	1.5
	961	96	57	77	1.5
	962	88	44	61	1.5
	963	93	46	82	1.5
	964	111	26	59	1.5
	965	103	24	55	1.5
	966	96	27	50	1.5
	967	115	27	65	1.5
	968	105	26	47	1.5
	MEAN	101	34	62	1.5
	S.D.	8	11	12	0.0
	N=	10	10	10	10
=====					
6000	989	114	131#	167#	1.5
	990	90	56#	79	1.5
	991	102	100#	79	1.5
	992	99	30	42	1.5
	993	109	23	52	1.5
	994	124	36	62	1.5
	995	102	26	49	1.5
	996	102	23	56	1.5
	997	111	27	56	1.5
	998	102	22	50	1.5
	MEAN	106	47	69	1.5
	S.D.	9	38	36	0.0
	N=	10	10	10	10
=====					

GGT LOWEST DETECTION LIMIT IS 3.0. VALUES <3.0 ARE REPORTED
AS 1.5 (ONE-HALF THE DETECTION LIMIT) FOR STATISTICAL ANALYSIS.
STATISTICAL OUTLIERS INCLUDED.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/CrI Mice

APPENDIX TABLE 15. Individual Clinical Chemistry – 90-Day

DOSE PPM	ANIMAL NUMBER	ALP U/L	ALT U/L	AST U/L	GGT U/L
=====					
0	829	87	31	66	1.5
	830	71	28	51	1.5
	831	82	41	83	1.5
	832	78	59	97	1.5
	833	89	116#	195#	1.5
	834	69	33	63	1.5
	835	79	33	72	1.5
	836	82	25	59	1.5
	837	86	21	43	1.5
	838	79	20	51	1.5
	MEAN	80	41	78	1.5
	S.D.	7	29	44	0.0
	N=	10	10	10	10
=====					
40	859	69	31	65	1.5
	860	70	31	83	1.5
	861	78	51	113	1.5
	862	69	41	69	1.5
	863	84	45	93	1.5
	864	63	38	65	1.5
	865	97	35	68	1.5
	866	73	22	51	1.5
	867	73	24	48	1.5
	868	77	18	41	1.5
	MEAN	75	34	70	1.5
	S.D.	10	11	22	0.0
	N=	10	10	10	10
=====					

GGT LOWEST DETECTION LIMIT IS 3.0. VALUES <3.0 ARE REPORTED
AS 1.5 (ONE-HALF THE DETECTION LIMIT) FOR STATISTICAL ANALYSIS.
STATISTICAL OUTLIERS INCLUDED.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/CrI Mice

APPENDIX TABLE 15. Individual Clinical Chemistry – 90-Day (continued)

DOSE PPM	ANIMAL NUMBER	ALP U/L	ALT U/L	AST U/L	GGT U/L
200	889	101	29	55	1.5
	890	74	25	66	1.5
	891	77	36	84	1.5
	892	75	20	78	1.5
	893	89	46	70	1.5
	894	88	31	51	1.5
	895	86	35	76	1.5
	896	87	26	56	1.5
	897	85	22	45	1.5
	898	84	29	60	1.5
	MEAN	85	30	64	1.5
	S.D.	8	8	13	0.0
	N=	10	10	10	10
600	919	80	32	84	1.5
	920	78	22	54	1.5
	921	68	21	55	1.5
	922	80	22	57	1.5
	923	86	30	68	1.5
	924	84	26	49	1.5
	925	74	27	43	1.5
	926	86	35	98	1.5
	927	80	24	50	1.5
	928	77	19	51	1.5
	MEAN	79	26	61	1.5
	S.D.	6	5	17	0.0
	N=	10	10	10	10

GGT LOWEST DETECTION LIMIT IS 3.0. VALUES <3.0 ARE REPORTED
AS 1.5 (ONE-HALF THE DETECTION LIMIT) FOR STATISTICAL ANALYSIS.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/CrI Mice

APPENDIX TABLE 15. Individual Clinical Chemistry – 90-Day (continued)

DOSE PPM	ANIMAL NUMBER	ALP U/L	ALT U/L	AST U/L	GGT U/L
=====					
2000	949	78	77	95	1.5
	950	78	25	57	1.5
	951	78	22	55	1.5
	952	77	96	143#	1.5
	953	79	29	67	1.5
	954	80	51	69	1.5
	955	78	22	41	1.5
	956	82	27	52	1.5
	957	84	26	44	1.5
	958	83	20	50	1.5
	MEAN	80	40	67	1.5
	S.D.	2	27	31	0.0
	N=	10	10	10	10
=====					
6000	979	74	35	56	1.5
	980	84	32	65	1.5
	981	96	30	73	1.5
	982	79	34	57	1.5
	983	93	31	85	1.5
	984	92	27	64	1.5
	985	97	49	72	1.5
	986	110	45	73	1.5
	987	85	37	59	1.5
	988	93	30	54	1.5
	MEAN	90	35	66	1.5
	S.D.	10	7	10	0.0
	N=	10	10	10	10
=====					

GGT LOWEST DETECTION LIMIT IS 3.0. VALUES <3.0 ARE REPORTED
AS 1.5 (ONE-HALF THE DETECTION LIMIT) FOR STATISTICAL ANALYSIS.
STATISTICAL OUTLIERS INCLUDED.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 16. Individual Organ Weights – 7-Day

DOSE PPM	ANIMAL NUMBER	FINAL	LIVER	
		BODY WT. (G)	(G)	(G/100)
=====				
0	849	22.3	1.068	4.789
	850	22.3	1.084	4.860
	851	22.8	1.210	5.308
	852	21.3	1.168	5.485
	853	21.3	1.062	4.987
	854	20.8	1.073	5.158
	855	20.6	1.090	5.291
	856	23.3	1.274	5.468
	857	20.9	1.086	5.198
	858	24.1	1.296	5.376
	MEAN	22.0	1.141	5.192
	S.D.	1.2	0.090	0.244
	N=	10	10	10
=====				
40	879	24.5	1.296	5.288
	880	21.5	1.136	5.283
	881	21.1	1.060	5.024
	882	23.3	1.205	5.173
	883	22.5	1.119	4.971
	884	23.0	1.125	4.892
	885	21.1	1.126	5.338
	886	21.9	1.148	5.242
	887	20.5	1.069	5.212
	888	20.9	1.060	5.074
	MEAN	22.0	1.134	5.150
	S.D.	1.3	0.072	0.151
	N=	10	10	10
=====				

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 16. Individual Organ Weights – 7-Day (continued)

DOSE PPM	ANIMAL NUMBER	FINAL	LIVER	
		BODY WT. (G)	(G)	(G/100)
=====				
200	909	22.5	1.160	5.157
	910	21.4	1.188	5.551
	911	23.3	1.257	5.394
	912	23.1	1.151	4.981
	913	21.3	1.064	4.993
	914	22.1	1.203	5.443
	915	20.8	1.115	5.363
	916	20.5	1.086	5.299
	917	23.0	1.222	5.312
	918	25.5	1.301	5.102
	MEAN	22.4	1.175	5.259
	S.D.	1.5	0.075	0.193
	N=	10	10	10
=====				
600	939	22.8	1.192	5.227
	940	20.2	1.084	5.365
	941	23.3	1.266	5.433
	942	21.3	1.135	5.329
	943	21.2	1.055	4.977
	944	22.5	1.240	5.512
	945	23.9	1.320	5.523
	946	21.6	1.147	5.309
	947	21.2	1.043	4.921
	948	20.8	1.068	5.136
	MEAN	21.9	1.155	5.273
	S.D.	1.2	0.096	0.208
	N=	10	10	10
=====				

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 16. Individual Organ Weights – 7-Day (continued)

DOSE PPM	ANIMAL NUMBER	FINAL BODY WT. (G)	LIVER	
			(G)	(G/100)
2000	969	22.6	1.176	5.202
	970	22.1	1.156	5.229
	971	23.8	1.380	5.796
	972	20.3	1.131	5.573
	973	21.6	1.111	5.143
	974	23.5	1.275	5.427
	975	20.0	1.118	5.592
	976	21.3	1.198	5.626
	977	24.7	1.269	5.139
	978	23.5	1.245	5.296
	MEAN	22.3	1.206	5.402
	S.D.	1.6	0.086	0.233
	N=	10	10	10
6000	1000	22.9	1.293	5.647
	1001	22.4	1.309	5.843
	1002	22.2	1.243	5.598
	1003	21.0	1.131	5.386
	1004	21.1	1.204	5.705
	1005	22.6	1.271	5.624
	1006	19.7	1.065	5.404
	1007	22.2	1.239	5.580
	1008	23.6	1.410	5.973
	999	22.1	1.255	5.678
	MEAN	22.0	1.242	5.644
	S.D.	1.1	0.095	0.178
	N=	10	10	10

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 17. Individual Organ Weights – 28-Day

DOSE PPM	ANIMAL NUMBER	FINAL	LIVER	
		BODY WT. (G)	(G)	(G/100)
=====				
0	839	22.3	1.166	5.230
	840	22.4	1.216	5.427
	841	24.2	1.287	5.317
	842	21.8	1.131	5.188
	843	22.1	1.176	5.323
	844	23.0	1.215	5.284
	845	22.3	1.187	5.325
	846	22.5	1.158	5.146
	847	21.5	1.172	5.450
	848	20.6	1.045	5.074
	MEAN	22.3	1.175	5.276
	S.D.	0.9	0.062	0.119
	N=	10	10	10
=====				
40	869	23.4	1.279	5.467
	870	23.0	1.246	5.416
	871	21.9	1.140	5.207
	872	21.1	1.092	5.175
	873	20.9	1.131	5.411
	874	23.0	1.226	5.330
	875	21.7	1.120	5.162
	876	22.0	1.108	5.038
	877	21.4	1.020	4.767
	878	23.7	1.168	4.928
	MEAN	22.2	1.153	5.190
	S.D.	1.0	0.078	0.228
	N=	10	10	10
=====				

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 17. Individual Organ Weights – 28-Day (continued)

DOSE PPM	ANIMAL NUMBER	FINAL BODY	LIVER	
		WT. (G)	(G)	(G/100)
200	899	22.6	1.198	5.300
	900	23.9	1.290	5.397
	901	22.1	1.121	5.070
	902	23.4	1.257	5.373
	903	23.1	1.229	5.322
	904	21.7	1.166	5.374
	905	21.2	1.156	5.453
	906	22.9	1.226	5.355
	907	20.6	1.054	5.117
	908	20.9	1.031	4.934
	MEAN	22.2	1.173	5.270
	S.D.	1.1	0.085	0.169
	N=	10	10	10
600	929	22.1	1.153	5.216
	930	20.9	1.165	5.573
	931	21.9	1.174	5.360
	932	21.9	1.141	5.209
	933	21.7	1.135	5.229
	934	22.9	1.314	5.736
	935	22.3	1.200	5.380
	936	21.9	1.228	5.609
	937	22.9	1.272	5.556
	938	20.4	1.084	5.315
	MEAN	21.9	1.186	5.418
	S.D.	0.8	0.069	0.188
	N=	10	10	10

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 17. Individual Organ Weights – 28-Day (continued)

DOSE PPM	ANIMAL NUMBER	FINAL	LIVER	
		BODY WT. (G)	(G)	(G/100)
=====				
2000	959	23.0	1.319	5.734
	960	21.4	1.251	5.844
	961	21.4	1.206	5.637
	962	22.4	1.172	5.230
	963	22.3	1.179	5.287
	964	21.5	1.184	5.506
	965	23.1	1.310	5.672
	966	20.8	1.127	5.417
	967	22.8	1.320	5.788
	968	21.9	1.144	5.225
	MEAN	22.1	1.221	5.534
	S.D.	0.8	0.074	0.234
	N=	10	10	10
=====				
6000	989	23.0	1.355	5.890
	990	22.4	1.337	5.969
	991	21.1	1.269	6.016
	992	20.3	1.204	5.931
	993	22.0	1.264	5.747
	994	22.6	1.319	5.835
	995	20.8	1.216	5.846
	996	22.6	1.270	5.619
	997	21.5	1.244	5.786
	998	23.2	1.339	5.771
	MEAN	22.0	1.282	5.841
	S.D.	1.0	0.053	0.117
	N=	10	10	10
=====				

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 18. Individual Organ Weights – 90-Day

DOSE PPM	ANIMAL NUMBER	FINAL	LIVER	
		BODY WT. (G)	(G)	(G/100)
=====				
0	829	24.6	1.265	5.140
	830	23.7	1.200	5.061
	831	29.4#	1.339	4.553
	832	26.2	1.327	5.065
	833	24.3	1.150	4.733
	834	23.1	1.173	5.076
	835	24.3	1.230	5.060
	836	23.0	1.188	5.167
	837	22.5	1.101	4.894
	838	23.3	1.171	5.025
	MEAN	24.4	1.214	4.977
	S.D.	2.0	0.076	0.195
	N=	10	10	10
=====				
40	859	21.7	1.109	5.111
	860	24.5	1.261	5.147
	861	24.9	1.272	5.106
	862	25.3	1.184	4.681
	863	23.6	1.076	4.558
	864	23.7	1.170	4.935
	865	22.9	1.115	4.869
	866	23.8	1.084	4.554
	867	21.9	1.085	4.956
	868	25.0	1.180	4.721
	MEAN	23.7	1.154	4.864
	S.D.	1.3	0.072	0.225
	N=	10	10	10
=====				
# STATISTICAL OUTLIERS INCLUDED.				

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 18. Individual Organ Weights – 90-Day (continued)

DOSE PPM	ANIMAL NUMBER	FINAL	LIVER	
		BODY WT. (G)	(G)	(G/100)
=====				
200	889	23.5	1.199	5.104
	890	24.7	1.215	4.920
	891	27.1	1.321	4.875
	892	22.7	1.105	4.866
	893	24.0	1.150	4.790
	894	23.3	1.171	5.027
	895	24.6	1.217	4.948
	896	23.5	1.213	5.163
	897	22.5	1.104	4.908
	898	24.6	1.185	4.819
	MEAN	24.1	1.188	4.942
	S.D.	1.3	0.063	0.121
	N=	10	10	10
=====				
600	919	26.4	1.307	4.951
	920	24.8	1.343	5.414
	921	27.1	1.311	4.837
	922	23.4	1.284	5.487
	923	24.5	1.304	5.322
	924	24.7	1.172	4.746
	925	25.4	1.389	5.468
	926	24.7	1.228	4.971
	927	25.3	1.262	4.988
	928	24.3	1.294	5.326
	MEAN	25.1	1.289	5.151
	S.D.	1.1	0.060	0.280
	N=	10	10	10
=====				

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 18. Individual Organ Weights – 90-Day (continued)

DOSE PPM	ANIMAL NUMBER	FINAL BODY WT. (G)	LIVER	
			(G)	(G/100)
2000	949	22.4	1.088	4.858
	950	22.6	1.246	5.515
	951	25.2	1.311	5.202
	952	24.9	1.355	5.443
	953	23.2	1.220	5.259
	954	24.2	1.352	5.586
	955	26.2	1.370	5.228
	956	24.3	1.260	5.185
	957	25.0	1.341	5.364
	958	24.4	1.291	5.290
	MEAN	24.2	1.283	5.293
	S.D.	1.2	0.085	0.205
	N=	10	10	10
6000	979	25.3	1.521	6.011
	980	23.4	1.264	5.402
	981	24.0	1.351	5.631
	982	24.1	1.299	5.389
	983	22.9	1.281	5.593
	984	23.6	1.306	5.534
	985	25.3	1.279	5.055
	986	24.0	1.250	5.209
	987	26.3	1.336	5.078
	988	21.3	1.177	5.523
	MEAN	24.0	1.306	5.442
	S.D.	1.4	0.090	0.286
	N=	10	10	10

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 19. Individual Hepatocellular Proliferation – 7-Day

DOSE PPM	ANIMAL NUMBER	CENTRI- LOBULAR LI %	MIDZONAL LI %	PERI- PORTAL LI %	PAN- LOBULAR LI %
=====					
0	849	10.5	12.0	6.8	9.8
	850	15.5	15.6	14.7	15.3
	851	20.2	22.3	12.2	18.2
	852	34.3	41.1	25.3	33.4
	853	16.4	17.0	8.0	13.8
	854	7.3	8.4	4.8	6.8
	855	8.7	12.6	6.1	9.1
	856	9.9	11.1	7.3	9.4
	857	25.8	27.6	17.9	23.8
	858	6.4	5.4	3.3	5.0
MEAN		15.5	17.3	10.6	14.5
S.D.		9.0	10.6	6.9	8.7
N=		10	10	10	10
=====					
40	879	5.9	7.7	5.9	6.5
	880	21.1	24.2	15.2	20.2
	881	36.1	41.2	25.8	34.4
	882	19.6	21.5	12.3	17.8
	883	3.0	4.5	2.7	3.4
	884	17.6	19.2	16.5	17.7
	885	11.7	12.4	4.8	9.6
	886	3.0	5.2	2.9	3.7
	887	16.6	21.1	11.3	16.3
	888	6.1	6.3	4.7	5.7
MEAN		14.1	16.3	10.2	13.5
S.D.		10.4	11.5	7.5	9.7
N=		10	10	10	10
=====					
LI - LABELING INDEX					

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 19. Individual Hepatocellular Proliferation – 7-Day (continued)

DOSE	ANIMAL	CENTRI- LOBULAR	MIDZONAL	PERI- PORTAL	PAN- LOBULAR
PPM	NUMBER	LI %	LI %	LI %	LI %
=====					
200	909	10.3	10.5	8.0	9.6
	910	12.6	16.9	10.0	13.2
	911	12.0	11.1	5.9	9.6
	912	2.7	6.8	3.5	4.3
	913	60.0#	75.4#	33.9#	56.4#
	914	6.9	8.5	6.4	7.3
	915	21.8	24.7	9.8	18.7
	916	27.2	25.1	17.5	23.3
	917	6.6	8.2	5.1	6.6
	918	1.2	1.7	1.9	1.6
	MEAN	16.1	18.9	10.2	15.1
	S.D.	17.4	21.3	9.4	15.9
	N=	10	10	10	10
=====					
600	939	10.6	14.0	6.3	10.3
	940	19.4	19.1	13.9	17.5
	941	16.1	17.1	15.0	16.1
	942	36.1	41.1	21.9	33.0
	943	46.5	52.1	32.0	43.5
	944	9.6	11.1	6.8	9.2
	945	33.7	36.1	22.5	30.7
	946	8.1	9.4	6.7	8.0
	947	24.4	24.8	17.6	22.2
	948	13.4	14.2	10.4	12.6
	MEAN	21.8	23.9	15.3	20.3
	S.D.	13.1	14.4	8.4	11.9
	N=	10	10	10	10
=====					

STATISTICAL OUTLIERS INCLUDED.
LI - LABELING INDEX

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 19. Individual Hepatocellular Proliferation – 7-Day (continued)

DOSE PPM	ANIMAL NUMBER	CENTRI- LOBULAR LI %	MIDZONAL LI %	PERI- PORTAL LI %	PAN- LOBULAR LI %
=====					
2000	969	14.1	15.3	8.8	12.7
	970	8.5	10.2	5.8	8.2
	971	4.4	5.7	3.4	4.5
	972	5.9	9.4	3.7	6.3
	973	20.7	25.1	18.1	21.3
	974	9.6	12.4	7.9	10.0
	975	32.6	42.0	19.3	31.3
	976	25.3	27.9	17.4	23.5
	977	19.6	22.6	11.7	18.0
	978	7.0	11.6	6.3	8.3
	MEAN	14.8	18.2	10.2	14.4
	S.D.	9.4	11.1	6.1	8.8
	N=	10	10	10	10
=====					
6000	1000	1.8	3.2	2.1	2.4
	1001	25.6	33.3	20.1	26.3
	1002	16.9	15.8	9.3	14.0
	1003	8.1	10.2	6.0	8.1
	1004	33.4	42.6	21.3	32.4
	1005	6.1	7.2	3.4	5.6
	1006	10.7	13.3	10.2	11.4
	1007	33.1	30.4	15.5	26.3
	1008	7.8	4.6	4.1	5.5
	999	16.7	18.9	10.1	15.2
	MEAN	16.0	18.0	10.2	14.7
	S.D.	11.3	13.3	6.8	10.3
	N=	10	10	10	10
=====					

LI - LABELING INDEX

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 20. Individual Hepatocellular Proliferation – 28-Day

DOSE PPM	ANIMAL NUMBER	CENTRI- LOBULAR	MIDZONAL	PERI- PORTAL	PAN- LOBULAR
		LI %	LI %	LI %	LI %
0	839	27.6	33.1#	20.0	26.9#
	840	5.0	6.1	4.7	5.3
	841	6.5	6.6	6.0	6.4
	842	21.5	18.0	16.5	18.7#
	843	8.0	8.8	6.3	7.7
	844	3.5	4.7	2.4	3.5
	845	11.1	8.9	5.5	8.5
	846	10.7	10.5	6.7	9.3
	847	3.6	3.2	3.1	3.3
	848	9.5	9.5	7.8	8.9
	MEAN	10.7	10.9	7.9	9.9
	S.D.	7.9	8.8	5.7	7.4
	N=	10	10	10	10
40	869	4.6	6.2	3.7	4.8
	870	10.9	13.9	8.7	11.2
	871	30.6#	31.2	16.2	26.0
	872	19.5	24.2	13.7	19.1
	873	12.0	7.7	7.5	9.1
	874	2.3	2.0	1.7	2.0
	875	4.5	5.4	5.0	5.0
	876	4.7	5.2	4.7	4.9
	877	4.9	3.7	3.2	3.9
	878	3.9	5.0	4.5	4.5
	MEAN	9.8	10.5	6.9	9.1
	S.D.	9.0	9.8	4.7	7.8
	N=	10	10	10	10

STATISTICAL OUTLIERS INCLUDED.

LI - LABELING INDEX

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 20. Individual Hepatocellular Proliferation – 28-Day (continued)

DOSE PPM	ANIMAL NUMBER	CENTRI- LOBULAR LI %	MIDZONAL LI %	PERI- PORTAL LI %	PAN- LOBULAR LI %
=====					
200	899	26.6	30.7	20.3	25.9
	900	8.1	10.3	8.0	8.8
	901	5.3	4.8	3.9	4.7
	902	30.1	30.8	19.1	26.7
	903	35.2	40.7	24.7	33.5
	904	17.7	15.8	14.9	16.1
	905	6.2	4.8	3.8	4.9
	906	3.9	5.0	4.8	4.6
	907	27.9	19.5	15.3	20.9
	908	9.6	11.4	8.9	10.0
	MEAN	17.1	17.4	12.4	15.6
	S.D.	11.9	12.8	7.5	10.6
	N=	10	10	10	10
=====					
600	929	16.8	18.2	11.1	15.4
	930	25.6	22.2	15.0	20.9
	931	14.7	18.1	14.5	15.8
	932	8.2	6.2	4.2	6.2
	933	35.7	37.0	26.9	33.2
	934	10.0	14.3	8.7	11.0
	935	20.7	22.2	15.2	19.4
	936	1.5	1.0	0.7	1.1
	937	11.8	12.7	7.4	10.6
	938	3.1	1.9	2.5	2.5
	MEAN	14.8	15.4	10.6	13.6
	S.D.	10.4	10.8	7.7	9.6
	N=	10	10	10	10
=====					

LI - LABELING INDEX

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 20. Individual Hepatocellular Proliferation – 28-Day (continued)

DOSE PPM	ANIMAL NUMBER	CENTRI- LOBULAR LI %	MIDZONAL LI %	PERI- PORTAL LI %	PAN- LOBULAR LI %
=====					
2000	959	21.4	24.0	18.3	21.2
	960	6.9	9.4	9.1	8.5
	961	3.5	4.7	3.8	4.0
	962	31.7	30.4	24.8	29.0
	963	27.2	32.8	19.4	26.5
	964	1.8	3.3	2.7	2.6
	965	6.1	8.2	4.5	6.3
	966	42.4	36.1	28.7	35.7
	967	6.1	8.2	4.5	6.3
	968	27.2	21.8	13.7	20.9
	MEAN	17.4	17.9	13.0	16.1
	S.D.	14.3	12.5	9.5	12.0
	N=	10	10	10	10
=====					
6000	989	11.7	17.4	14.8	14.6
	990	20.3	29.8	26.4	25.5
	991	9.6	19.1	14.4	14.4
	992	7.9	11.2	13.3	10.8
	993	2.4	6.0	5.8	4.7
	994	3.2	4.6	5.2	4.3
	995	6.7	13.9	10.2	10.3
	996	1.4	3.3	5.6	3.4
	997	8.5	12.8	11.5	10.9
	998	3.3	4.7	4.8	4.3
	MEAN	7.5	12.3	11.2	10.3
	S.D.	5.6	8.3	6.6	6.8
	N=	10	10	10	10
=====					

LI - LABELING INDEX

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 21. Individual Hepatocellular Proliferation – 90-Day

DOSE PPM	ANIMAL NUMBER	CENTRI- LOBULAR LI %	MIDZONAL LI %	PERI- PORTAL LI %	PAN- LOBULAR LI %
=====					
0	829	2.6	4.0	3.2	3.3
	830	4.2	4.8	2.4	3.8
	831	1.3	1.6	2.3	1.7
	832	4.4	7.5	4.2	5.4
	833	6.4	7.7	4.1	6.1
	834	3.4	4.9	3.3	3.9
	835	2.5	2.7	2.4	2.5
	836	5.0	5.8	3.7	4.8
	837	5.6	6.9	4.6	5.7
	838	6.7	7.1	3.9	5.9
	MEAN	4.2	5.3	3.4	4.3
	S.D.	1.8	2.1	0.8	1.5
	N=	10	10	10	10
=====					
40	859	10.6	9.8	7.0	9.1
	860	7.0	8.6	4.3	6.6
	861	1.1	2.4	1.0	1.5
	862	11.8	13.7	10.8	12.1
	863	3.2	3.0	2.5	2.9
	864	4.5	5.0	3.2	4.2
	865	3.2	4.7	3.4	3.8
	866	7.5	8.3	5.0	6.9
	867	14.0	21.0	11.6	15.5
	868	10.9	7.6	7.0	8.5
	MEAN	7.4	8.4	5.6	7.1
	S.D.	4.3	5.6	3.5	4.3
	N=	10	10	10	10
=====					
LI - LABELING INDEX					

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 21. Individual Hepatocellular Proliferation – 90-Day (continued)

DOSE PPM	ANIMAL NUMBER	CENTRI- LOBULAR LI %	MIDZONAL LI %	PERI- PORTAL LI %	PAN- LOBULAR LI %
=====					
200	889	3.9	6.0	2.7	4.2
	890	5.3	5.3	5.2	5.3
	891	1.2	3.1	1.4	1.9
	892	2.0	4.3	2.8	3.0
	893	1.4	2.7	2.4	2.2
	894	10.1	10.0	8.7	9.6
	895	1.6	3.7	1.2	2.2
	896	7.7	5.6	5.0	6.1
	897	8.4	6.6	6.4	7.1
	898	13.2	8.6	8.5	10.1
	MEAN	5.5	5.6	4.4	5.2
	S.D.	4.2	2.3	2.8	3.0
	N=	10	10	10	10
=====					
600	919	0.9	1.3	1.7	1.3
	920	3.7	4.8	5.4	4.6
	921	1.4	3.6	2.9	2.6
	922	8.4	11.6	7.7	9.2
	923	3.7	6.0	4.6	4.8
	924	5.1	6.7	3.3	5.0
	925	7.1	4.9	3.8	5.3
	926	3.2	2.9	2.5	2.9
	927	8.5	11.7	8.5	9.6
	928	3.0	3.6	1.6	2.7
	MEAN	4.5	5.7	4.2	4.8
	S.D.	2.7	3.5	2.4	2.7
	N=	10	10	10	10
=====					

LI - LABELING INDEX

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 21. Individual Hepatocellular Proliferation – 90-Day (continued)

DOSE PPM	ANIMAL NUMBER	CENTRI- LOBULAR LI %	MIDZONAL LI %	PERI- PORTAL LI %	PAN- LOBULAR LI %
=====					
2000	949	2.3	5.5	4.8	4.2
	950	3.4	7.0	7.3	5.9
	951	9.7	12.4	14.0#	12.0#
	952	18.4#	22.5#	18.8#	19.9#
	953	1.5	3.5	1.6	2.2
	954	3.3	5.7	4.7	4.6
	955	1.1	1.4	2.1	1.5
	956	2.7	4.3	3.4	3.5
	957	4.3	6.7	4.8	5.3
	958	5.7	6.0	3.2	5.0
	MEAN	5.2	7.5	6.5	6.4
	S.D.	5.2	6.0	5.6	5.5
	N=	10	10	10	10
=====					
6000	979	21.5	38.2	34.4	31.3
	980	22.8	30.5	25.9	26.4
	981	7.0	12.0	10.5	9.8
	982	10.4	13.0	15.8	13.1
	983	16.3	29.6	23.2	23.0
	984	2.5	4.4	5.9	4.3
	985	12.0	20.4	14.4	15.6
	986	12.1	22.8	18.5	17.8
	987	30.2	42.1	39.6	37.3
	988	20.1	34.2	32.7	29.0
	MEAN	15.5	24.7	22.1	20.8
	S.D.	8.3	12.3	11.0	10.4
	N=	10	10	10	10
=====					

STATISTICAL OUTLIERS INCLUDED.
LI - LABELING INDEX

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 22. Individual Apoptosis Quantification as Measured by Caspase-3 – 28-Day

DOSE PPM	ANIMAL NUMBER	CASPASE-3 POSITIVE PER 10000
=====		
0	839	0.00
	840	0.00
	841	0.21#
	842	0.00
	843	0.00
	844	0.00
	845	0.00
	846	0.00
	847	0.00
	848	0.55#
	MEAN	0.08
	S.D.	0.18
	N=	10
=====		
40	869	0.00
	870	0.00
	871	0.00
	872	0.17#
	873	0.00
	874	0.15#
	875	0.00
	876	0.00
	877	0.00
	878	0.00
	MEAN	0.03
	S.D.	0.07
	N=	10
=====		
# STATISTICAL OUTLIERS INCLUDED.		

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/CrI Mice

APPENDIX TABLE 22. Individual Apoptosis Quantification as Measured by Caspase-3 – 28-Day (continued)

DOSE PPM	ANIMAL NUMBER	CASPASE-3 POSITIVE PER 10000
=====		
200	899	0.00
	900	0.00
	901	0.00
	902	0.00
	903	0.00
	904	0.00
	905	0.00
	906	0.00
	907	0.00
	908	0.00
	MEAN	0.00
	S.D.	0.00
	N=	10
=====		
600	929	0.00
	930	0.00
	931	0.20#
	932	0.00
	933	0.00
	934	0.00
	935	0.00
	936	0.00
	937	0.00
	938	0.00
	MEAN	0.02
	S.D.	0.06
	N=	10
=====		
# STATISTICAL OUTLIERS INCLUDED.		

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 22. Individual Apoptosis Quantification as Measured by Caspase-3 – 28-Day (continued)

DOSE PPM	ANIMAL NUMBER	CASPASE-3 POSITIVE PER 10000
=====		
2000	959	0.00
	960	0.00
	961	0.00
	962	0.34
	963	0.00
	964	0.00
	965	0.00
	966	0.00
	967	0.20
	968	0.20
	MEAN	0.07
	S.D.	0.13
	N=	10
=====		
6000	989	0.70
	990	0.58
	991	0.46
	992	0.49
	993	0.00
	994	0.44
	995	0.00
	996	1.19
	997	0.17
	998	0.53
	MEAN	0.46
	S.D.	0.35
	N=	10
=====		

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 23. Individual Apoptosis Quantification as Measured by Caspase-3 – 90-Day

DOSE PPM	ANIMAL NUMBER	CASPASE-3 POSITIVE PER 10000
=====		
0	829	0.00
	830	0.23#
	831	0.00
	832	0.00
	833	0.00
	834	0.00
	835	0.15#
	836	0.00
	837	0.00
	838	0.00
	MEAN	0.04
	S.D.	0.08
	N=	10
=====		
40	859	0.54
	860	0.00
	861	0.61
	862	0.00
	863	0.00
	864	0.30
	865	0.13
	866	0.00
	867	0.00
	868	0.22
	MEAN	0.18
	S.D.	0.23
	N=	10
=====		
# STATISTICAL OUTLIERS INCLUDED.		

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 23. Individual Apoptosis Quantification as Measured by Caspase-3 – 90-Day (continued)

DOSE PPM	ANIMAL NUMBER	CASPASE-3 POSITIVE PER 10000
=====		
200	889	0.00
	890	0.00
	891	0.00
	892	0.00
	893	0.19#
	894	0.16#
	895	0.00
	896	0.00
	897	0.00
	898	0.00
	MEAN	0.04
	S.D.	0.07
	N=	10
=====		
600	919	0.00
	920	0.56#
	921	0.00
	922	0.00
	923	0.00
	924	0.14#
	925	0.00
	926	0.00
	927	0.00
	928	0.00
	MEAN	0.07
	S.D.	0.18
	N=	10
=====		
# STATISTICAL OUTLIERS INCLUDED.		

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX TABLE 23. Individual Apoptosis Quantification as Measured by Caspase-3 – 90-Day (continued)

DOSE PPM	ANIMAL NUMBER	CASPASE-3 POSITIVE PER 10000
=====		
2000	949	0.00
	950	0.35
	951	0.00
	952	0.00
	953	0.51
	954	0.20
	955	0.00
	956	0.00
	957	0.00
	958	0.16
	MEAN	0.12
	S.D.	0.18
	N=	10
=====		
6000	979	0.40
	980	1.50
	981	0.00
	982	0.90
	983	0.68
	984	0.77
	985	1.23
	986	2.19
	987	2.94
	988	0.23
	MEAN	1.08
	S.D.	0.91
	N=	10
=====		

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

APPENDIX A. Osmotic Pump Implant Procedure

Pre-Operative:

- Surgical site will be clipped up to 24 hours prior to surgery within the animal room.
- Assistant will induce animals and monitor anesthesia throughout the procedure.
 - Animals will be induced with (approximately 4%) isoflurane admixed with (approximately 2L) medical grade oxygen within an induction box.
 - Animals will be transferred to nose cone upon lateral recumbency. Animals will be maintained at the lowest percentage of isoflurane which maintains a surgical level of anesthesia.
 - Animals will be placed in ventral recumbency on a heating pad and supportive care will be administered:
 - eye lube (petroleum based ointment) is administered bilaterally.
 - Analgesia (Buprenex) will be administered SQ at a dose of 0.05 mg/kg.
 - The surgical site will be prepped with povidone-iodine:sterile water solution (15:85 solution of 10% povidone-iodine:sterile water) and 70% isopropyl alcohol.
 - The surgical site will be draped with sterile gauze.
- Concurrently, the surgeon will don a sterile gown and sterile gloves. Once attired, the surgeon will open a sterile pack aseptically and prep instruments.

Intraoperative: Aseptic technique will be adhered to throughout the surgical procedure.

- Surgeon: Transverse incision will be made through skin in the center of the clipped region of the back using sterile scissors and forceps. Sterile hemostats will be used to tunnel a subcutaneous pocket for the osmotic pump. The pump will be implanted into the subcutaneous pocket using sterile instruments with the opening of the pumping mechanism pointing away from the incision. Incision will be closed with sterile skin staples.
- Assistant:
 - Incision will be cleansed with the povidone-iodine:sterile water solution.
 - Animal will be removed from nose-cone and recovered.

Post-Operative:

- Animals will be held by personnel until recovered from anesthesia, then will be returned to solid bottom cage with paper towel bedding to prevent contamination of incision.
- Surgical instruments will be re-sterilized between animals with bead sterilizer followed by submersion in povidone-iodine:sterile water solution.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female
B6D2F1/Crl Mice

APPENDIX A. Osmotic Pump Implant Procedure (continued)

After-care and Monitoring

- Animals will be returned to home caging upon full recovery.
- Animals will be monitored at the end of the business day on the day of surgery by the study personnel.
- Incision sites will be monitored once daily by study staff for signs of infection, loss of skin staples or other problems, as part of the routine daily observations.

A member of the veterinary team will be contacted if any problem arises.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female
B6D2F1/Crl Mice

APPENDIX B. Immunohistochemical Staining Procedures

Caspase-3 (Cleaved) Immunohistochemistry

Formalin fixed, paraffin embedded tissue blocks were sectioned at 5 microns and placed on charged slides. Slides were air dried at room temperature overnight then refrigerated until needed. Before staining, the slides were placed on a slide dryer at approximately 60°C for 20 minutes. Slides were deparaffinized and hydrated through graded alcohols to deionized water. Antigen retrieval was performed using Dako Target Retrieval Solution, pH6, (Dako, Carpinteria, CA; #2369) diluted 1:10 with deionized water and Biocare Decloaker (Biocare Medical, Concord, CA) set to 125°C for 30 seconds then 90°C for 10 seconds. The slides were removed from the Decloaking chamber and allowed to cool for 20 minutes, rinsed thoroughly with deionized water, then placed in Dako Tris Buffered Saline Wash Buffer (#S3006) diluted 1:10 with deionized water for 5 minutes. Slides were treated with 3% hydrogen peroxide for 15 minutes to quench endogenous peroxidase activity. Biocare Rodent Block R (#RBR962) was used for 20 minutes to reduce non-specific background staining. Biocare Rabbit polyclonal anti-Caspase-3 (cleaved) antibody (#CP229) was diluted 1:100 with Biocare Da Vinci antibody diluent (#PD900) and incubated for overnight at 4°C in a humidified chamber. Biocare Rabbit-on Rodent HRP-Polymer (#RMR622) was placed on the slides for 30 minutes. The slides were rinsed twice between all steps with Dako Tris Buffered Saline Wash Buffer (#S3006) diluted 1:10 with deionized water. Dako Liquid DAB+ Substrate Chromogen (#K3467) was applied to the slides for 7 minutes to allow visualization of the positive cells followed by a tap water rinse. The slides were counterstained using Biocare CAT Hematoxylin (#CATHE-G) diluted 1:5 with deionized water for 1 minute, then rinsed with deionized water. Slides were dipped 10 times in 1% ammonia water to blue the hematoxylin, rinsed in tap water, dehydrated through graded alcohols, cleared in xylene, coverslipped with a synthetic mounting media and allowed to dry overnight before evaluation.

GST-P Immunohistochemistry

Formalin fixed, paraffin embedded tissue blocks were sectioned at 5 microns and placed on charged slides. Slides were air dried at room temperature overnight then refrigerated until needed. Before staining, the slides were placed on a slide dryer at approximately 60°C for 20 minutes. Slides were deparaffinized and hydrated through graded alcohols to deionized water. The slides were placed in Dako Tris Buffered Saline Wash Buffer (#S3006) diluted 1:10 with deionized water for 5 minutes. The slides were rinsed twice between all steps using the working Dako Tris Buffered Saline Wash Buffer. Slides were treated with 3% hydrogen peroxide for 15 minutes to quench endogenous peroxidase activity. Biocare Rodent Block M (#RBM961) and Vector Labs 2.5% RTU Normal Goat serum (#S1012) were used for 30 minutes and 20 minutes respectively to reduce non-specific background staining. Biogenex polyclonal anti-GST Pi antibody (#PU249-UP)

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female
B6D2F1/Crl Mice

APPENDIX B. Immunohistochemical Staining Procedures (continued)

was diluted 1:150 with Biogenex Common Antibody Diluent (#HK156-5K) and slides were incubated for 2 hours at room temperature in a humidified chamber. For the next two steps, Biogenex One-Step use Super Sensitive Polymer-HRP Detection Kit/DAB (#QD630) was used. Polymer-HRP was placed on the slides for 15 minutes, followed by Liquid DAB for 10 minutes to allow visualization of the positive cells. DAB was followed by a DI water rinse. The slides were counterstained using Biocare CAT Hematoxylin (#CATHE-G) diluted 1:5 with deionized water for 1 minute, then rinsed with deionized water. Slides were dipped 10 times in 1% ammonia water to blue the hematoxylin, rinsed in tap water, dehydrated through graded alcohols, cleared in xylene, coverslipped with a synthetic mounting media and allowed to dry overnight before evaluation.

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female
B6D2F1/Crl Mice

APPENDIX C. Dose Confirmation, Homogeneity, and Stability Report

Toxicology Information Collection (TIC) Report
The Dow Chemical Company

Report Title:
Dose Confirm, Homogeneity, and Stability (Study 181012; 1,4 Dioxane)

SIGNATURES REDACTED

Patent Status	Date Issued	Page Count	Lab Report Code
No action required	05/13/2019	18	TERC-ACL- 2018-17
Geographic Location	Department	Databook Numbers	CRI Number
Midland, Michigan	TERC	n/a	NA

Study Number:	181012
Study Title:	1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/CrI Mice
Project / Sample Description (optional):	Drinking water dose confirmation and homogeneity. Stability in Ultrapure water
Test Material(s):	1,4 Dioxane
Test Material lot #:	SHBJ7415
Report Recipient(s):	Golden, Rachel
Date Samples collected/prepared:	8/30, 9/6, 10/18/2018
Number of Samples or estimate:	6
Date samples prepared for analysis:	08/30, 09/04, 09/06, 09/10, 10/18/2018
Analysis date:	08/30, 08/31, 09/04, 09/05, 09/06, 09/10, 09/11, 10/18/2018
Number of samples analyzed:	6
Analysis method:	GC/MS-SIM
Method reference:	See below

Summary:

Dose formulations were prepared at concentrations ranging from 40.0 to 6,000 µg 1,4-Dioxane / mL drinking water, plus a carrier control, by the Toxicology & Environmental Research and Consulting (TERC) pharmacy on 09/06/2018 and 10/18/2018 for dose confirmation and homogeneity and on 8/30/2018 for stability determination. Dose formulations were analyzed by gas chromatography with positive ion electrospray ionization and mass spectrometry detection operating in the selected ion monitoring mode (GC/MS-SIM).

Dose formulation concentrations for 1,4-Dioxane in drinking water prepared on 09/06/2018 and 10/18/2018 ranged from 93.8% to 102% of nominal. The homogeneity from the low concentration (40 µg/mL) on 9/06/2018 and 10/18/2018 was 5.55% and 0.637% RSD, respectively. The homogeneity from the high concentration (6000 µg/mL) on 9/06/2018 and 10/18/2018 was 3.11% and 1.61% RSD, respectively. Carrier controls are reported at less than the lower limit of quantitation (LLQ) for each analysis day.

Stability of 1,4-Dioxane in drinking water was evaluated on stability days 0, 5, and 11. 1,4-Dioxane was demonstrated to be stable in drinking water for up to 11 days at concentrations ranging from 40 µg/mL to 6000 µg/mL based on the acceptance criteria of $\pm 15\%$ of corresponding Day 0 concentrations.

The dose formulations were diluted with methanol to a target concentration of approximately 1.00 µg/mL and analyzed. The LLQ was established at 1.00 µg 1,4-Dioxane / mL drinking water.

A stock standard prepared in drinking water and diluted with methanol to a calibration range of approximately 0.100 – 10.0 µg 1,4-Dioxane/mL and exhibited a coefficient of determination (R^2) value of > 0.995 (1/x weighting) for each day of analysis. Final concentrations of 1,4-Dioxane were determined using a stable isotope internal standard (1,4-Dioxane-D8 at 732 µg/mL) to facilitate quantitation and was added post preparation to standards and samples.

Test Material/Reference Substance Information:

Test Material Name: 1,4-Dioxane

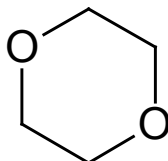
Chemical Name: 1,4-Dioxane

Synonyms: p-Dioxane

Molecular Formula: C₄H₈O₂

Molecular Weight: 88.1

Chemical Structure:



CAS Number: 123-91-1

Lot#: SHBJ7415

Purity: The non-GLP purity of the test material was determined to be 99.98% by gas chromatography with identification by Infrared spectroscopy (Grady, 2018).

Internal Standard:

Name: 1,4-Dioxane-D8

Chemical Name: 1,4-Dioxane-D8

Synonyms: p-Dioxane-D8

Molecular Formula: C₄D₈O₂

Molecular Weight: 96.15

Lot #: SDDL-024A

Purity: The purity of the test material was determined to be $\geq 98\%$ by gas chromatography with identification by mass spectrometry (Eckersley, 2014).

The internal standard was used to facilitate quantitation of 1,4-Dioxane in water.

Standard Preparation – Prepared With Each Sample Set:

A stock solution was prepared for each analysis day at 1,000 μg 1,4-Dioxane /mL Ultrapure water and was further diluted, with methanol to prepare standards at approximate concentrations between 0.100 and 10.0 $\mu\text{g}/\text{mL}$, which encompassed the expected prepared sample

concentrations. One milliliter of each standard was transferred into an autosampler vial for analysis. In addition, 25 μL of internal standard solution (1,4-Dioxane-D8, $\sim 30.0 \mu\text{g/mL}$) was added to each standard, via Eppendorf pipette, resulting in a nominal internal standard concentration of $0.732 \mu\text{g/mL}$. The standards were briefly vortex-mixed and then analyzed by GC/MS-SIM.

Sample Preparation:

The bulk dose mix solutions (prepared on 09/06/2018 and 10/18/2018) were sampled for dose formulation verification. Sample aliquots ($\sim 10 \text{ mL}$) were transferred to 20 mL vials. Homogeneity samples ($n=3$) of the 40 and 6000 $\mu\text{g/mL}$ drinking water dose formulations were collected from random locations. All other samples (control, 200, 600, and 2000 $\mu\text{g/mL}$) were collected in duplicate from random locations.

The sample aliquots were diluted with methanol to a target concentration of $\sim 1.00 \mu\text{g/mL}$. One milliliter of each final dilution was transferred to glass autosampler vials. In addition, 25 μL of internal standard solution (1,4-Dioxane-D8, $\sim 30.0 \mu\text{g/mL}$) was added to each sample, resulting in a nominal internal standard concentration of $0.732 \mu\text{g/mL}$. The samples were briefly vortex-mixed and then analyzed by GC/MS-SIM. The concentrations of 1,4-Dioxane were quantified using external standard calibration and reported concentrations were not corrected for purity of the starting material.

Stability Preparation:

Stability of 1,4-Dioxane in drinking water was evaluated in drinking water stored at ambient conditions from the test solutions prepared on 08/30/2018. The stability samples were prepared for analysis in the same manner as described in the sample preparation section of this report. All stability test solutions were tested for stability on stability days 0, 5, and 11.

Representative Analysis Conditions:

Gas Chromatograph:	Agilent 7890B; G3440B
Autosampler:	Agilent 7693; G4514A
Injector:	Agilent 7693; G4513A
Mass Spectrometer:	Agilent 7000C; G7011A

Wash Solvent: Methanol

Analytical Column: Restek RTX-20; 60 m x 320 μ m x 1 μ m
Pressure: 12.0 psi
Flow: 2.0 mL/min

GC Inlet Liner: 4mm ID Inlet liner, split, single taper, glass wool, deactivated

Inlet: Injection Volume: 3.0 μ L
Mode: Split
Split Ratio: 100:1
Split Flow: ~200 mL/min
Initial temperature: 250 $^{\circ}$ C
Pressure: 12 psi
Septum Purge Flow: 1.0 mL/min
Total flow: ~200 mL/min
Gas type: Helium

Oven: Initial temp: 35 $^{\circ}$ C – hold 4 min;
Ramp @ 30 $^{\circ}$ C/min to 250 $^{\circ}$ C – hold 0 min

MS-SIM: Transfer Line: 300 $^{\circ}$ C
Ion Source: Electron ionization (EI)
Source Temperature: 200 $^{\circ}$ C
Solvent Delay: 6.7 min
Scan Type: MS1 SIM
Dwell: 100 ms
Mass: 96 amu – 1,4-Dioxane – D8
Mass: 88 amu – 1,4-Dioxane

MS-Scan: Transfer Line: 300 $^{\circ}$ C
Ion Source: Electron ionization (EI)
Source Temperature: 200 $^{\circ}$ C

Solvent Delay: 6.7 min

Scan Type: MS1 Scan

Step Size: 0.1 amu

Scan time: 200 ms

Start Mass: 40 amu

End Mass: 150 amu

Results and Discussion:

The dose concentration and homogeneity verification results for 1,4-Dioxane in drinking water are presented in Tables 1 and 2. Stability of 1,4-Dioxane in drinking water are presented in Table 3. Typical chromatograms of a standard, test solution, control, and solvent blank for 1,4-Dioxane and 1,4-Dioxane-d8 are shown in Figures 2 through 5, respectively.

Dose Concentration and Homogeneity Analyses

The overall mean measured concentrations from the dose formulations for 1,4-Dioxane in drinking water prepared on 09/06/2018 and 10/18/2018 ranged from 93.8% to 102% of nominal. The homogeneity for the low concentration (40 µg/mL) prepared on 9/06/2018 and 10/18/2018 was 5.55% and 0.637% RSD, respectively. The homogeneity for the high concentration (6000 µg/mL) prepared on 9/06/2018 and 10/18/2018 was 3.11% and 1.61% RSD, respectively. Drinking water control samples did not exceed the lower limit of quantitation (LLQ = 1.00 µg/mL) for each respective analysis day.

Stability

1,4-Dioxane proved to be stable in drinking water for up to 11 days at concentrations ranging from 40 µg/mL to 6000 µg/mL based on the acceptance criteria of $\pm 15\%$ of corresponding Day 0 concentrations.

Lower Limit of Quantitation (LLQ)

The LLQ for the 1,4-Dioxane analysis by GC/MS-SIM was 1.00 µg/mL. The LLQ value was based on the concentration of the lowest standard analyzed multiplied by the lowest dilution factor for the samples. This value is 40-fold lower than the lowest nominal concentration employed in this study.

Linearity

The GC/MS-SIM instrumentation exhibited a linear response (1/x weighting) for 1,4-Dioxane over a concentration range of 0.100 – 10.0 µg 1,4-Dioxane / mL water, which encompassed the anticipated range of prepared sample concentrations. A coefficient of determination (R^2) value was > 0.997 for each day of analysis. Representative calibration data is presented in Table 4. The corresponding calibration curve, analyte concentration (µg/mL) vs. analyte peak area, is shown in Figure 1.

Spectra

Representative GC/Full Scan-Electron Ionization mass spectra of 100 mg/L 1,4-Dioxane in methanol is shown in Figure 6. Representative GC/Full Scan-Electron Ionization mass spectra of 30.0 mg/L 1,4-Dioxane-D8 in methanol is shown in Figure 7.

Reference

Eckersley, T. (2014). Certificate of Analysis of 1,4-Dioxane-D8, Lot # SDDL-024A.
Cambridge Isotope Laboratories Inc., Andover, Massachusetts.

Grady, M. (2018). Certificate of Analysis of 1,4-Dioxane, Lot # SHBJ7415. Sigma-Aldrich,
Sheboygan Falls, Wisconsin.

Table 1. Results of Concentration and Homogeneity Analyses for 1,4-Dioxane in Drinking Water on 09/06/2018

Date Mixed: 09/06/18		
Control	Target Conc. (ppm):	0.00
	A	<LLQ
	B	<LLQ
	Mean Measured Conc:	<LLQ
40 ppm	Target Conc. (ppm):	40
	A	39.9
	B	41.9
	C	37.5
	Mean Measured Conc:	39.7
	% of Target Conc:	99.3%
Homogeneity % R.S.D.		5.55%
200 ppm	Target Conc. (ppm):	200
	A	193
	B	204
	Mean Measured Conc:	198
% of Target Conc:		99.1%
600 ppm	Target Conc. (ppm):	600
	A	582
	B	560
	Mean Measured Conc:	571
% of Target Conc:		95.2%
2000 ppm	Target Conc. (ppm):	2000
	A	1959
	B	1894
	Mean Measured Conc:	1926
% of Target Conc:		96.3%
6000 ppm	Target Conc. (ppm):	6000
	A	6079
	B	6086
	C	5761
	Mean Measured Conc:	5975
	% of Target Conc:	99.6%
Homogeneity % R.S.D.		3.11%
LLQ		1.00
<LLQ = less than lower limit of quantitation		

Table 2. Results of Concentration and Homogeneity Analyses for 1,4-Dioxane in Drinking Water on 10/18/2018

Date Mixed: 10/18/18	
Control	Target Conc. (ppm): 0.00
	A <LLQ
	B <LLQ
	Mean Measured Conc: <LLQ
40 ppm	Target Conc. (ppm): 40
	A 39.0
	B 39.2
	C 39.5
	Mean Measured Conc: 39.2
	% of Target Conc: 98.1%
Homogeneity % R.S.D. 0.637%	
200 ppm	Target Conc. (ppm): 200
	A 212
	B 197
	Mean Measured Conc: 204
% of Target Conc: 102%	
600 ppm	Target Conc. (ppm): 600
	A 590
	B 535
	Mean Measured Conc: 563
% of Target Conc: 93.8%	
2000 ppm	Target Conc. (ppm): 2000
	A 2081
	B 1938
	Mean Measured Conc: 2009
% of Target Conc: 100%	
6000 ppm	Target Conc. (ppm): 6000
	A 5944
	B 5758
	C 5878
	Mean Measured Conc: 5860
	% of Target Conc: 97.7%
Homogeneity % R.S.D. 1.61%	
LLQ 1.00	
<LLQ = less than lower limit of quantitation	

Table 3. Results of Stability Analyses for 1,4-Dioxane in Drinking Water

Date Mixed: 08/30/18		Stability Day: 0 5 11		
Control	Target Conc. (ppm):	0.00	0.00	0.00
	A	<LLQ	<LLQ	<LLQ
	B	<LLQ	<LLQ	<LLQ
	Mean Measured Conc:	<LLQ	<LLQ	<LLQ
40 ppm	Target Conc. (ppm):	40	40	40
	1	36.6	39.7	39.9
	2	38.6	38.6	37.8
	3	37.6	37.5	38.8
	Mean Measured Conc:	37.6	38.6	38.9
	% of Target Conc:	94.0%	96.5%	97.1%
	Homogeneity % R.S.D.	2.55%	2.92%	2.77%
	% of Day 0:	100%	103%	103%
200 ppm	Target Conc. (ppm):	200	200	200
	1	182	189	190
	2	188	196	198
	3	183	185	199
	Mean Measured Conc:	184	190	196
	% of Target Conc:	92.0%	95.0%	97.8%
	Homogeneity % R.S.D.	1.74%	3.15%	2.57%
	% of Day 0:	100%	103%	106%
600 ppm	Target Conc. (ppm):	600	600	600
	1	564	548	578
	2	565	591	542
	3	573	584	547
	Mean Measured Conc:	567	574	556
	% of Target Conc:	94.6%	95.7%	92.6%
	Homogeneity % R.S.D.	0.922%	4.03%	3.58%
	% of Day 0:	100%	101%	97.9%
2000 ppm	Target Conc. (ppm):	2000	2000	2000
	1	2097	1933	1907
	2	2040	1910	1890
	3	2147	1997	1888
	Mean Measured Conc:	2095	1946	1895
	% of Target Conc:	105%	97.3%	94.7%
	Homogeneity % R.S.D.	2.55%	2.31%	0.537%
	% of Day 0:	100%	92.9%	90.5%
6000 ppm	Target Conc. (ppm):	6000	6000	6000
	1	5965	5647	5742
	2	6474	6034	5865
	3	6475	5751	5745
	Mean Measured Conc:	6305	5811	5784
	% of Target Conc:	105%	96.8%	96.4%
	Homogeneity % R.S.D.	4.66%	3.44%	1.21%
	% of Day 0:	100%	92.2%	91.7%
LLQ		1.00	1.00	1.00
<LLQ = less than lower limit of quantitation				

Table 4. Representative Standards/Refit Table of 1,4-Dioxane Standards in Methanol

Sample Name	Sample ID	Analyte Concentration (µg/mL)	Analyte Peak Area (counts)	IS Peak Area (counts)	ISTD Resp. Ratio	Calculated Concentration (µg/mL)	Accuracy (%)
Standard A	181012_091018_005.D	0.100	109045	332022	0.328	0.106	106
Standard B	181012_091018_006.D	0.500	794352	384223	2.07	0.485	97.1
Standard C	181012_091018_007.D	1.00	2085731	483049	4.32	0.977	97.7
Standard D	181012_091018_008.D	5.00	9738959	426337	22.8	5.02	100
Standard E	181012_091018_009.D	10.0	14171611	305018	46.5	10.2	102
Standard A	181012_091018_132.D	0.100	151565	445670	0.340	0.108	108
Standard B	181012_091018_133.D	0.500	1044476	499549	2.09	0.491	98.1
Standard C	181012_091018_134.D	1.00	2024926	486894	4.16	0.942	94.2
Standard D	181012_091018_135.D	5.00	10472203	478988	21.9	4.81	96.2
Standard E	181012_091018_136.D	10.0	28062342	610845	45.9	10.1	101

ISTD Resp. Ratio = Analyte Peak Area / IS Peak Area

Calculated Concentration = (ISTD Resp. Ratio – b) / m

Regression equation is $y = mx + b$ (See Figure 1 for values for m and b)

Accuracy % = Calculated Concentration / Analyte Concentration * 100

Figure 1. Typical Standard Curve from GC/MS-SIM Analysis of 1,4-Dioxane Standards

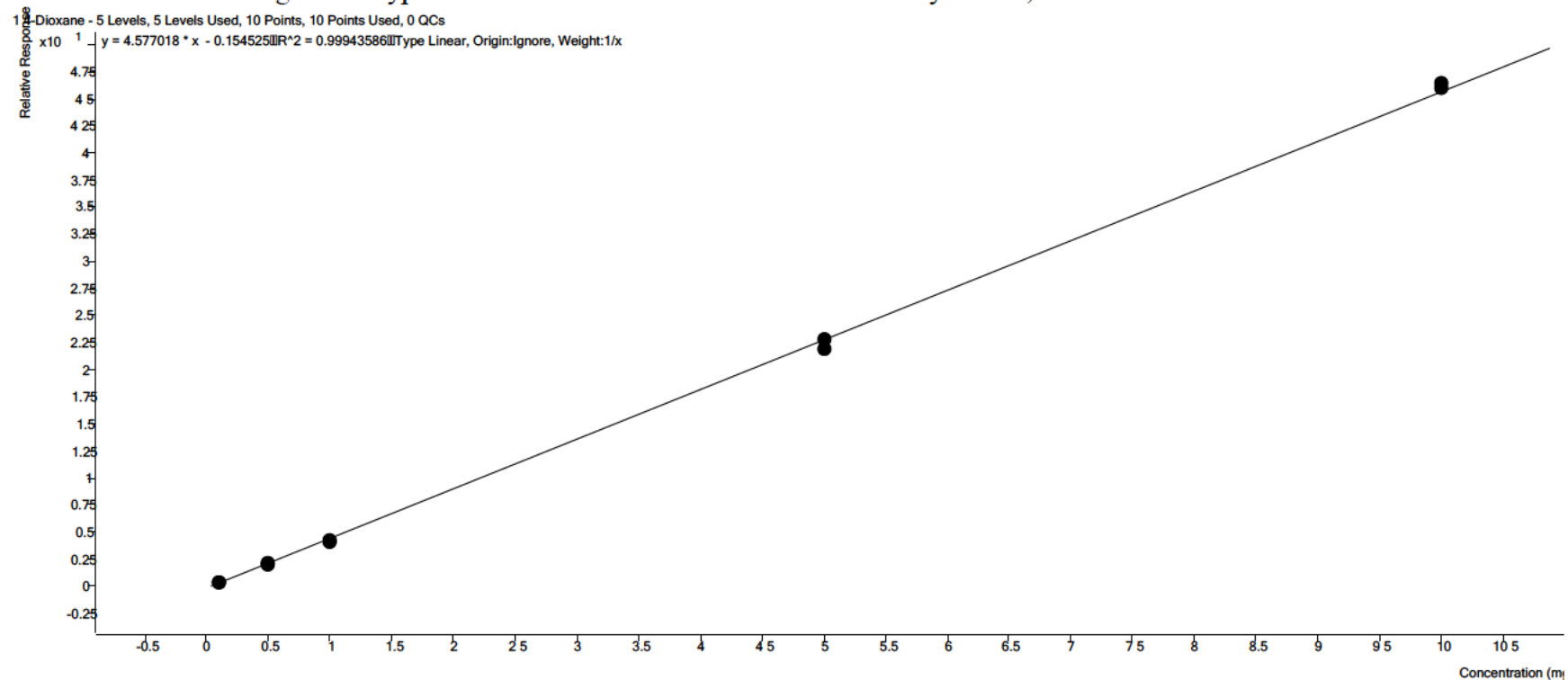


Figure 2. Typical Chromatogram (GC/MS-SIM) of a Standard Solution Prepared at a Concentration of 1.00 μg 1,4-Dioxane / mL Methanol; Internal Standard 1,4-Dioxane-D8 at 30.0 $\mu\text{g/mL}$

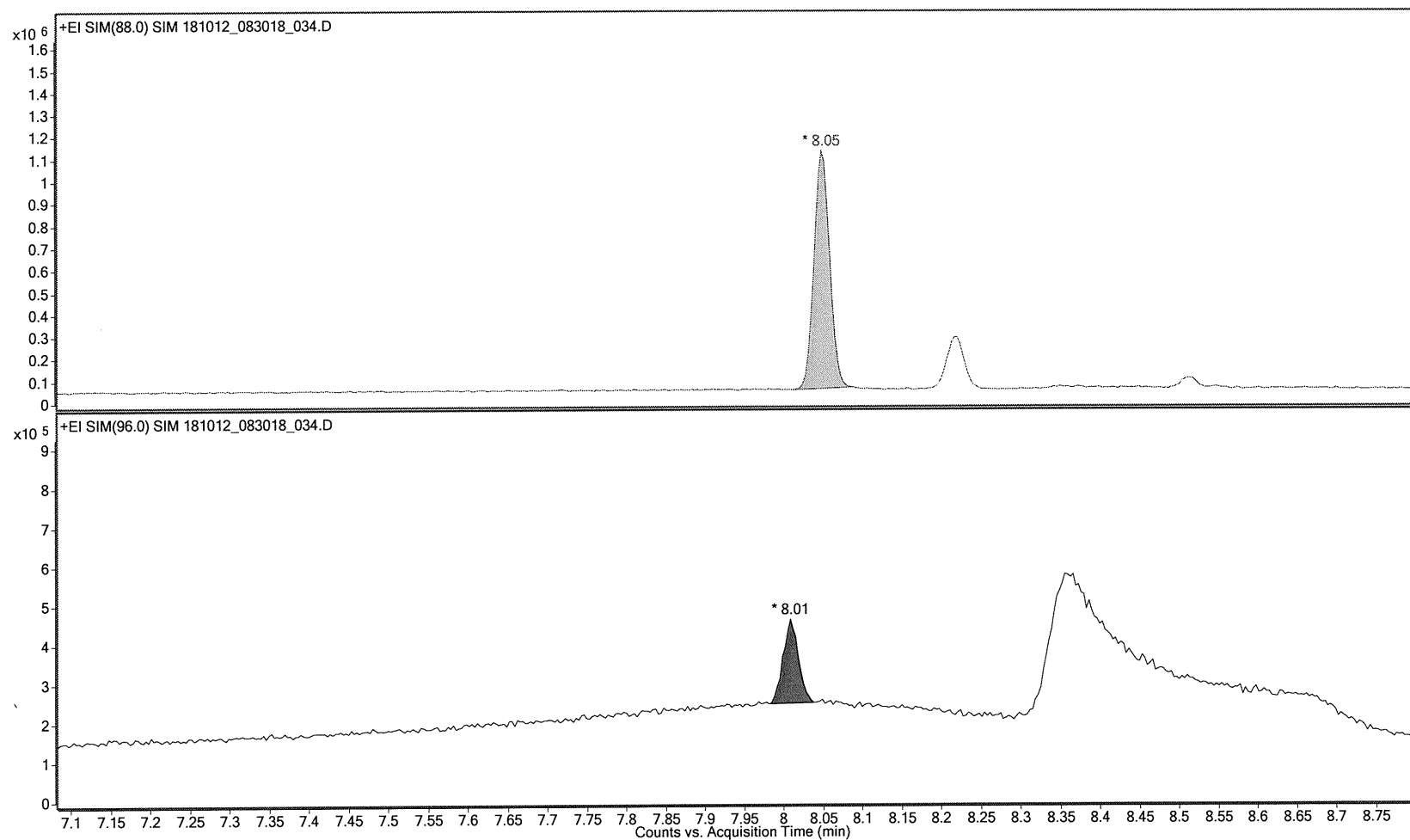


Figure 3. Typical Chromatogram (GC/MS-SIM) of Ultrapure Water Fortified with 2000 μg 1,4-Dioxane / mL Ultrapure Water and Prepared for Analysis. Target Concentration of 1.00 μg 1,4-Dioxane / mL Ultrapure water; Internal Standard 1,4-Dioxane-D8 at 30.0 $\mu\text{g/mL}$

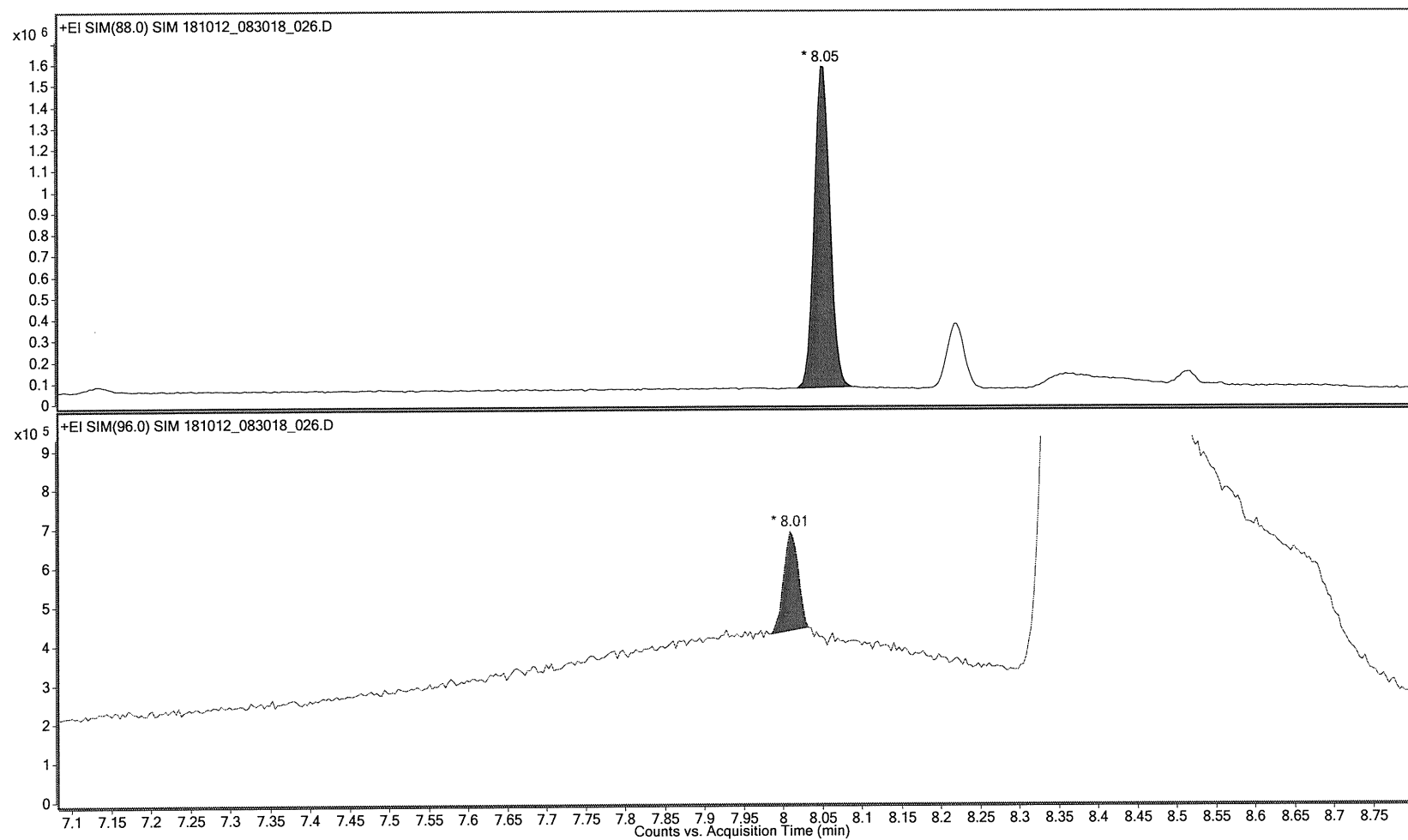


Figure 4. Typical Chromatogram (GC/MS-SIM) of Matrix Control Ultrapure Water; Internal Standard 1,4-Dioxane-D8 at 30.0 µg/mL

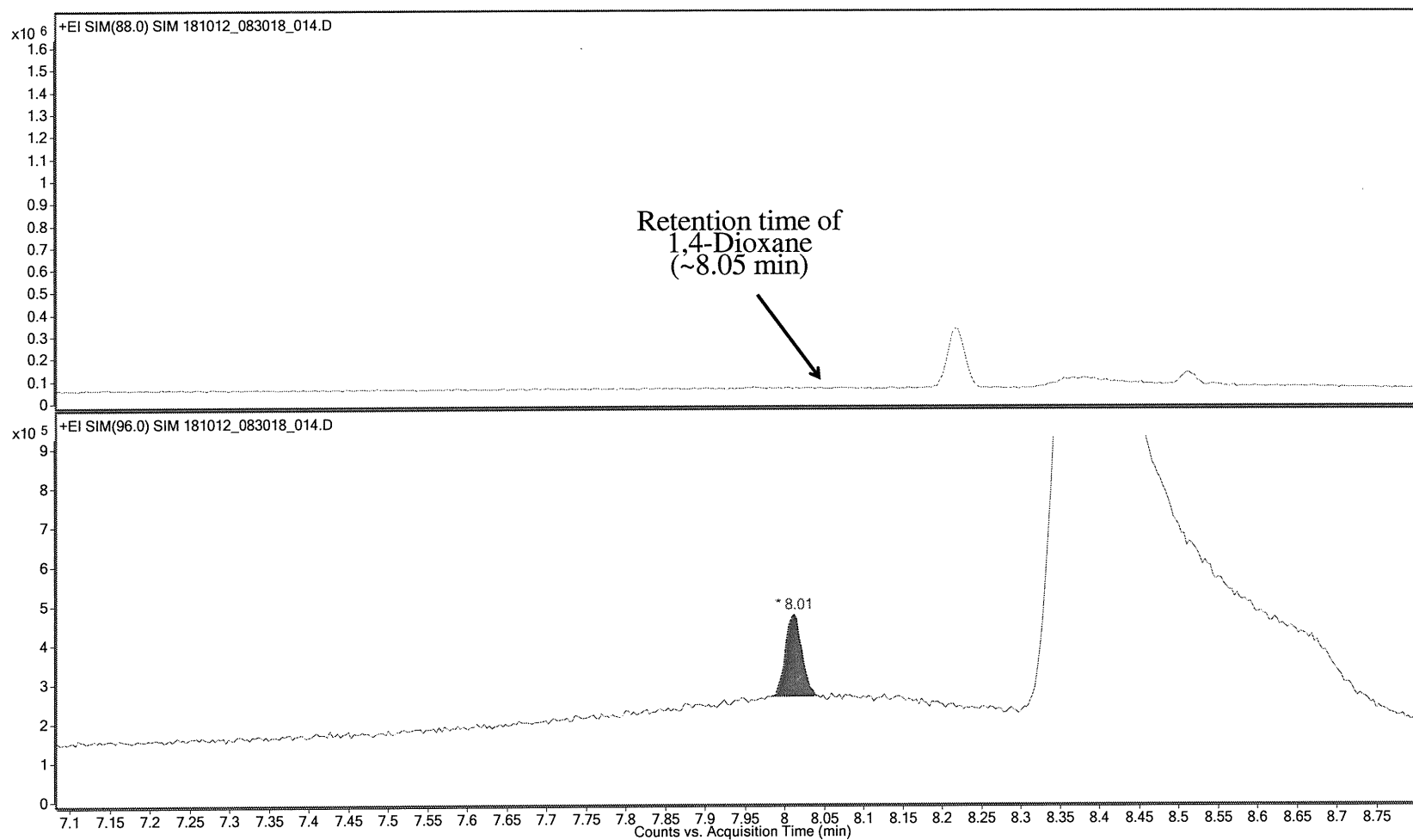


Figure 5. Typical Chromatogram (GC/MS-SIM) of Methanol Solvent Blank

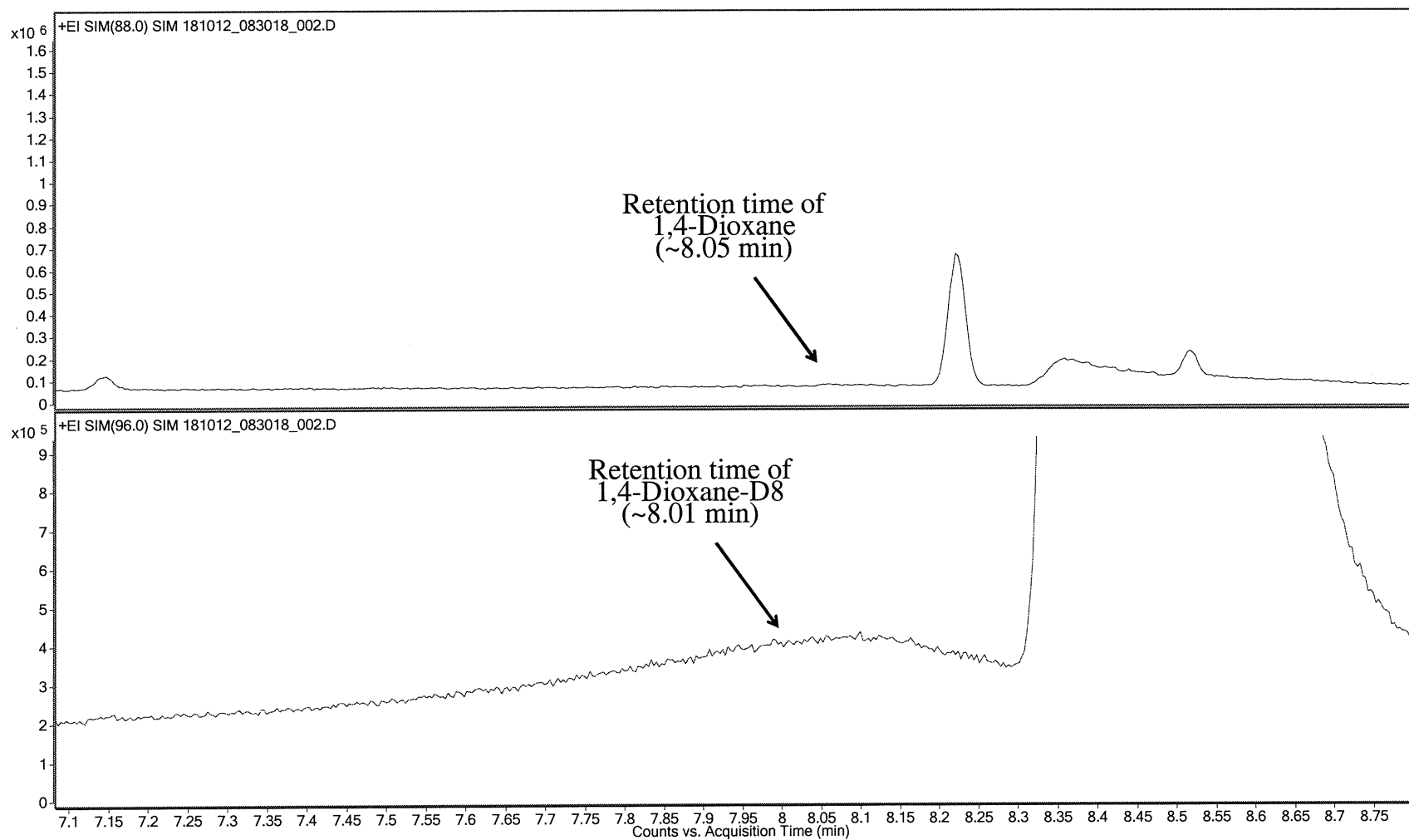


Figure 6. Example Full Scan Electron Ionization Mass Spectra of 100 mg 1,4-Dioxane / L Methanol

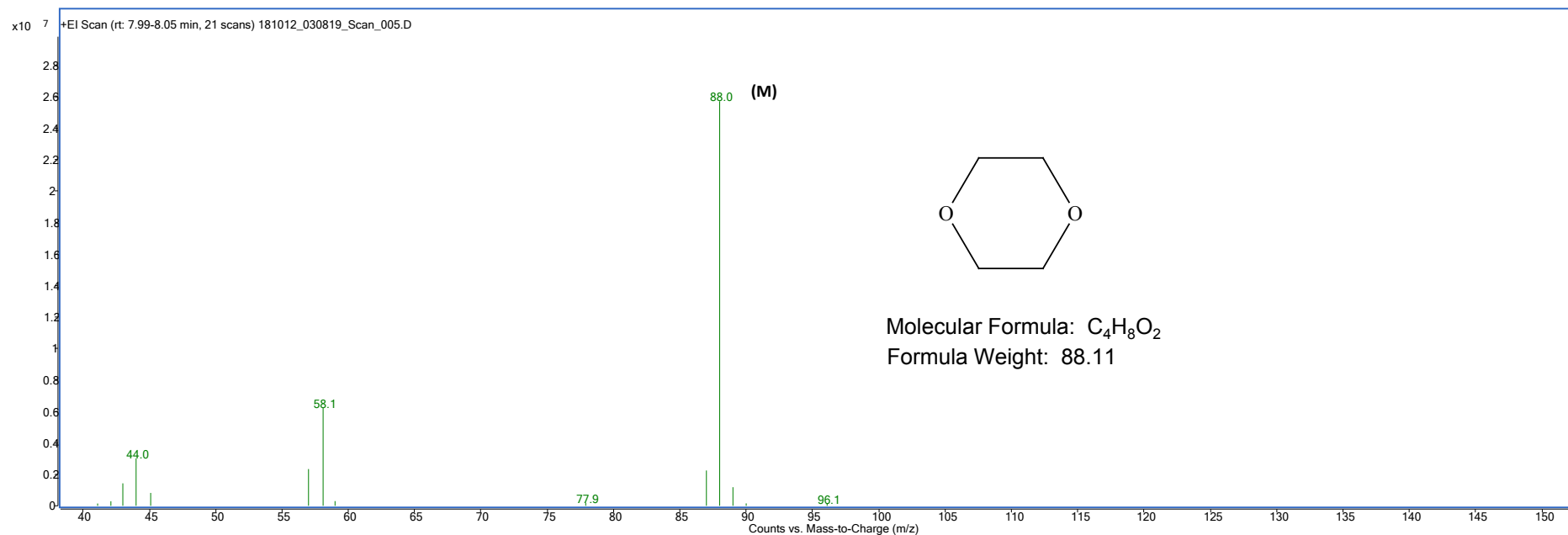
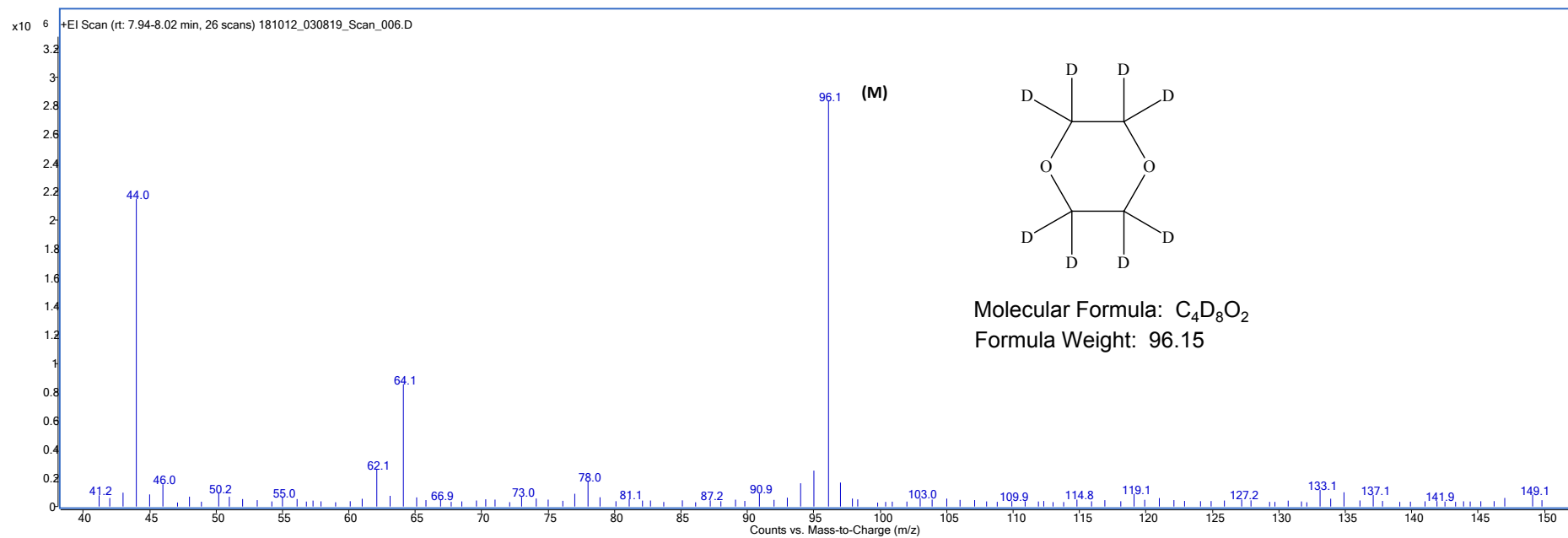


Figure 7. Example Full Scan Electron Ionization Mass Spectra of 30 mg 1,4-Dioxane-D8 / L Methanol



1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female
B6D2F1/Crl Mice

APPENDIX D. Histopathology Report



Vet Path Services

ANATOMIC PATHOLOGY REPORT

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice

The Dow Chemical Company Study ID: 181012

Prepared for:

**The Dow Chemical Company
Toxicology and Environmental Research and Consulting
1803 Building
Midland, Michigan 48674**

Prepared by:

**Vet Path Services, Inc. (VPS)
6450 Castle Drive
Mason, Ohio 45040**

**Telephone (513) 469-0777
Fax (513) 469-2474**

**SIGNATURE
REDACTED**

TABLE OF CONTENTS

QUALITY ASSURANCE	Page
Quality Assurance Statement.....	3
NARRATIVE	
Introduction.....	4
Methods.....	4
Results and Discussion	5
Conclusions.....	8
References.....	8
TABULATED PATHOLOGY DATA	
Table 1 – Intergroup Comparison of Histopathology Observations – 7 Day	9
Table 2 – Intergroup Comparison of Histopathology Observations – 28 Day	11
Table 3 – Intergroup Comparison of Histopathology Observations – 90 Day	13
Table 4 – Individual Animal Data – 7 Day.....	15
Table 5 – Individual Animal Data – 28 Day.....	76
Table 6 – Individual Animal Data – 90 Day.....	137

Anatomic Pathology Report

The Dow Chemical Company
Study ID: 181012
Page 3

Quality Assurance Statement

Study Identity: The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced
Liver Tumors in Female B6D2F1/Crl Mice

Study Director: R.M. Golden, B.S.
The Dow Chemical Company
Toxicology and Environmental Research and Consulting
1803 Building
Midland, Michigan 48674

Principal Investigator, James W. Crissman, D.V.M., Ph.D., Diplomate, A.C.V.P.
Histopathology: Vet Path Services, Inc. (VPS)
6450 Castle Drive
Mason, Ohio 45040

Study Aspect	Reported to Principal Investigator and VPS Management	Reported to Study Director and Management
QA Date		
Draft Anatomic Pathology Report		
20-21 December 2018	21 December 2018	21 December 2018
Final Anatomic Pathology Report		
1, 4, 7 March 2019	7 March 2019	7 March 2019

SIGNATURE
REDACTED

INTRODUCTION

The objectives of this study were to investigate key events that will test a threshold Mode-of-Action (MOA) for mouse liver tumors following 1,4-Dioxane drinking water administration.

The portion of this study performed by Vet Path Services, Inc. (VPS) was conducted in compliance with the study protocol, protocol amendment numbers 01-06, applicable test site standard operating procedures and the U.S. Environmental Protection Agency Toxic Substances Control Act (TSCA) Good Laboratory Practice Title 40 CFR, Part 792; Good Laboratory Practice Standards, Final Rule, with no known circumstances which would affect the quality or integrity of the pathology data.

METHODS

The study was sponsored by Foundation for Chemistry Research & Initiatives, American Chemistry Council (ACC), 700 Second St. NE, Washington, DC 20002, where S. Risotto, M.S. served as the Sponsor Designee. In-life procedures were conducted at The Dow Chemical Company, Toxicology and Environmental Research and Consulting, 1803 Building, Midland, Michigan 48674, where R.M. Golden, B.S. served as the Study Director. Liver histopathology evaluation was conducted at Vet Path Services, Inc. (VPS), 6450 Castle Drive, Mason, Ohio 45040, where James W. Crissman, D.V.M., Ph.D., Diplomate, A.C.V.P. served as the Principal Investigator, Histopathology.

Full details of the study are described in the study protocol and protocol amendment numbers 01-06. Stained (Hematoxylin and Eosin, H&E) slides of livers from 180 female mice were hand delivered, in good condition, to Principal Investigator James W. Crissman, D.V.M., Ph.D., Diplomate, A.C.V.P., and were evaluated microscopically. Provantis™ pathology software v10.1.0.1 was utilized for data capture and table generation. Stained histologic sections were examined by light microscopy and observations were entered into Provantis™ by the Principal Investigator. Histologic sections were of adequate size and quality for detailed evaluation, and the liver tissue examined from each treatment group was sufficient to allow detection of test article-related histologic alterations.

Histopathologic changes typically are graded responses that vary in severity from animal to animal, with few animals exhibiting exactly the same degree of response. Historically, these graded responses have been subjectively grouped into ordinal classes that are called severity grades.^[i] Severity grades in the present study were assigned to non-neoplastic histopathologic diagnoses in compliance with general guidelines from the INHAND Program and SEND Initiative, as presented in the following text table.^{[ii], [iii]} Severity grades were assigned to a diagnosis to reflect a combination of considerations including the organ or tissue affected, the extent of the process (i.e., how many of its subordinate components are present), the distribution (i.e., focal to diffuse), and the degree of alteration in the examined histologic sections. Lesion grades apply only to the tissue sections examined, and may not reflect the overall severity of the pathologic process in the entire tissue, organ, or animal. The severity grades do not necessarily correlate with interpretations of adversity. Unless noted otherwise, the histopathology tables

contain all of the recorded data and serve as the basis for this narrative report. Microscopic findings were given a severity score based upon a scale of minimal, mild, moderate, marked and severe.

Severity Grades

Unremarkable (NVL)	Tissue considered to be within normal limits (NVL), under the conditions of the study and considering the age, sex, and strain of the animal concerned.
Present	A non-gradable histologic change for which no additional information would be gained by assigning a severity grade (e.g., cyst).
Grade 1 (Minimal)	The first (lowest) level of severity in an ordered list based on a five-level scale of minimal, mild, moderate, marked, and severe.
Grade 2 (Mild)	The second level of severity in an ordered list based on a five-level scale of minimal, mild, moderate, marked, and severe.
Grade 3 (Moderate)	The third level of severity in an ordered list based on a five-level scale of minimal, mild, moderate, marked, and severe.
Grade 4 (Marked)	The fourth level of severity in an ordered list based on a five-level scale of minimal, mild, moderate, marked, and severe.
Grade 5 (Severe)	The fifth (highest) level of severity in an ordered list based on a five-level scale of minimal, mild, moderate, marked, and severe.

Due to Provantis[™] limitations, animal numbers “18A0829”, etc. are abbreviated as ‘0829’, etc. in Tables 4-6. There were no missing tissues. Gross exams were not conducted at necropsy so no gross observations were available or recorded in Provantis[™].

In brief, the portion of this investigative protocol germane to this report is as follows: 180 female B6D2F1/Crl mice were divided into groups of ten and administered 1,4-Dioxane in drinking water at concentrations of 0, 40, 200, 600, 2000 or 6000 ppm prior to necropsy after 7, 28, or 90 days of exposure. The targeted dose levels were 0, 10, 50, 150, 500, and 1500 mg/kg/day. At necropsy, the livers were weighed and fixed in 10% formalin prior to routine processing and histopathologic examination of three standard sections from each liver. This anatomic pathology report includes only the microscopic findings.

All study-related materials and specimens were returned to The Dow Chemical Company, upon issuance of the final pathology report, for archiving.

RESULTS AND DISCUSSION

Mortality

There were no early deaths reported; all animals survived to scheduled necropsy dates.

Microscopic Observations

The intergroup comparison of histopathology observations is in [Tables 1-3](#) and individual animal data are in [Tables 4-6](#).

7-Day exposure findings.

There were no exposure-related findings at dosages ≤ 200 ppm. Dose-related vacuolation, centrilobular, minimal or mild, was observed at ≥ 600 ppm. This finding was characterized by flocculent cytoplasm characteristic of glycogen storage, as seen by light microscopy, occupying approximately the inner half of each lobule.

Other findings were considered incidental, spontaneous occurrences, typical of mice of this age, strain, and husbandry.

Text Table 1. Seven-day drinking water 1,4-Dioxane exposure-related microscopic findings in the liver of female B6D2F1/Crl mice

Dose Level 1,4-Dioxane (ppm)		0	40	200	600	2000	6000
Finding	Number examined	10	10	10	10	10	10
Vacuolation, centrilobular	minimal	0	0	0	2	6	0
	mild	0	0	0	0	4	10

28-Day exposure findings.

There were no exposure-related findings at dosages ≤ 200 ppm. Similar to the 7-day exposure group, dose-related vacuolation, centrilobular, minimal or mild, was observed at ≥ 600 ppm.

In mice exposed to 6000 ppm, in hepatocytes closest to central veins, cytoplasmic vacuolation was replaced by generous, slightly granular eosinophilic cytoplasm; this finding was not observed in the Day-7 cohort, and was recorded as hepatocellular hypertrophy, centrilobular, minimal or mild. The glycogen-type hepatocellular vacuolation generally persisted at the periphery of the hypertrophic centrilobular hepatocytes.

In most mice exposed to 6000 ppm, in centrilobular areas directly adjacent to central veins, there was scattered cell death, recorded as apoptosis, increased, centrilobular, minimal or mild. The finding was characterized by condensed cytoplasm, pyknotic or fragmented nuclei, and apoptotic bodies.

Other findings were considered incidental, spontaneous occurrences, typical of mice of this age, strain, and husbandry.

Text Table 2. Twenty-eight-day drinking water 1,4-Dioxane exposure-related microscopic findings in the liver of female B6D2F1/Crl mice

Dose Level 1,4-Dioxane (ppm)		0	40	200	600	2000	6000
Finding	Number examined	10	10	10	10	10	10
Vacuolation, centrilobular	minimal	0	0	0	3	6	1
	mild	0	0	0	0	3	9
Hepatocellular hypertrophy, centrilobular	minimal	0	0	0	0	0	6
	mild	0	0	0	0	0	4
Apoptosis, increased, centrilobular	minimal	0	0	0	0	0	7
	mild	0	0	0	0	0	1

90-Day exposure findings.

There were no exposure-related findings at dosages ≤ 200 ppm. Similar to the 7 and 28-day exposure cohorts, dose-related vacuolation, centrilobular, minimal or mild, was observed at ≥ 2000 ppm.

At 6000 ppm, and in one mouse at 2000 ppm, similar to the 28-Day cohort findings in hepatocytes closest to central veins, cytoplasmic vacuolation was replaced by generous eosinophilic slightly granular cytoplasm; this finding was recorded as hepatocellular hypertrophy, centrilobular, minimal to moderate. At moderate hypertrophy severity, nearly all of the centrilobular hepatocytes, observed to have vacuolated cytoplasm at earlier time points, had uniformly finely-granular eosinophilic cytoplasm, which accounts for the decreased incidence of the vacuolation, centrilobular finding at the highest exposure level.

Also similar to the 28-Day cohort, in one mouse at 2000 ppm and all mice at 6000 ppm, there was scattered cell death in centrilobular areas directly adjacent to central veins, which was recorded as apoptosis, increased, centrilobular, minimal or mild.

Other findings were considered incidental, spontaneous occurrences, typical of mice of this age, strain, and husbandry.

Text Table 3. Ninety-day drinking water 1,4-Dioxane exposure-related microscopic findings in the liver of female B6D2F1/Crl mice

Dose Level 1,4-Dioxane (ppm)		0	40	200	600	2000	6000
Finding	Number examined	10	10	10	10	10	10
Vacuolation, centrilobular	minimal	0	0	0	0	8	1
	mild	0	0	0	0	1	1
Hepatocellular hypertrophy, centrilobular	minimal	0	0	0	0	1	0
	mild	0	0	0	0	0	1
	moderate	0	0	0	0	0	9
Apoptosis, increased, centrilobular	minimal	0	0	0	0	1	6
	mild	0	0	0	0	0	4

CONCLUSIONS

One hundred-eighty female B6D2F1/Crl mice were divided into groups of ten and administered 1,4-Dioxane in drinking water at concentrations of 0, 40, 200, 600, 2000 or 6000 ppm prior to necropsy after 7, 28, or 90 days of exposure. The targeted dose levels were 0, 10, 50, 150, 500, and 1500 mg/kg/day. At necropsy, the livers were weighed and fixed in 10% formalin prior to routine processing and histopathologic examination of three standard sections from each liver. This anatomic pathology report includes only the microscopic liver findings.

There were no exposure-related findings at dosages ≤ 200 ppm at any exposure duration. After 7 days of exposure, dose-related vacuolation, centrilobular, minimal or mild, was observed at ≥ 600 ppm; this finding was also observed in 28-day cohort; in the 90-day cohort, the finding was observed at ≥ 2000 ppm. After 28 days of exposure, additional liver findings at the 6000 ppm exposure level included minimal or mild centrilobular hepatocyte hypertrophy in all mice and minimal or mild increased centrilobular apoptosis in most. After 90 days of exposure, hepatocyte hypertrophy was slightly more severe in 6000 ppm mice (moderate grade), and there was one mouse at 2000 ppm with the finding. Also after 90 days of exposure, minimal or mild centrilobular apoptosis of hepatocytes affected all mice at 6000 ppm and one mouse at 2000 ppm. Increased centrilobular apoptosis is considered adverse.

For female B6D2F1/Crl mice exposed to 1,4-Dioxane in drinking water for 7, 28, or 90 days, the No Observed Effect Level (NOEL) for microscopic findings was 200 ppm. The No Observed Adverse Effect Level for microscopic findings was 600 ppm.

REFERENCES

- [i] Holland T. The comparative power of the discriminant methods used in toxicological pathology. *Toxicol Pathol.* 2005. 33(4):490-494.
- [ii] Mann PC, Vahle J, Keenan CM, et al. International harmonization of toxicologic pathology nomenclature: an overview and review of basic principles. *Toxicol Pathol.* 2012. 40(4):7S-13S.
- [iii] Clinical Data Interchange Standards Consortium (CDISC). CDISC Standardization for Exchange of Nonclinical Data (SEND) Controlled Terminology, 2013-04-12. Retrieved online from <http://evs.nci.nih.gov/ftp1/CDISC/SEND/SEND%20Terminology.pdf>, 2013.

Table 1 – Intergroup Comparison of Histopathology Observations – 7 Day

Anatomic Pathology Report

Page: 10

Table 1 - Intergroup Comparison of Histopathology Observations - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Removal Reason(s): 7 DAY EXPOSURE	Female					
	0	40	200	600	2000	6000
	ppm	ppm	ppm	ppm	ppm	ppm
Number of Animals	10	10	10	10	10	10
Number of Completed Animals	10	10	10	10	10	10
LIVER						
Examined	10	10	10	10	10	10
Infiltrate, mononuclear cell	10	10	10	10	9	10
.... minimal	8	9	10	10	9	10
.... mild	2	1	0	0	0	0
Vacuolation; Centrilobular	0	0	0	2	10	10
.... minimal	0	0	0	2	6	0
.... mild	0	0	0	0	4	10
Necrosis, single cell	6	4	1	1	2	3
.... minimal	6	4	1	1	2	3
Mitosis; increased	1	1	1	2	0	0
.... minimal	1	0	1	2	0	0
.... mild	0	1	0	0	0	0

Table 2 – Intergroup Comparison of Histopathology Observations – 28 Day

Anatomic Pathology Report

Page: 12

Table 2 - Intergroup Comparison of Histopathology Observations - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Removal Reason(s): 28 DAY EXPOSURE	Female					
	0	40	200	600	2000	6000
	ppm	ppm	ppm	ppm	ppm	ppm
Number of Animals	10	10	10	10	10	10
Number of Completed Animals	10	10	10	10	10	10
LIVER						
Examined	10	10	10	10	10	10
Infiltrate, mononuclear cell	10	10	10	10	10	10
.... minimal	9	10	10	10	10	10
.... mild	1	0	0	0	0	0
Vacuolation; Centrilobular	0	0	0	3	9	10
.... minimal	0	0	0	3	6	1
.... mild	0	0	0	0	3	9
Hepatocellular hypertrophy; Centrilobular	0	0	0	0	0	10
.... minimal	0	0	0	0	0	6
.... mild	0	0	0	0	0	4
Necrosis, single cell	1	5	8	5	2	6
.... minimal	1	5	8	5	2	6
Mitosis; increased	1	0	0	0	0	0
.... minimal	1	0	0	0	0	0
Necrosis, focal; Subcapsular	0	0	1	0	0	0
.... minimal	0	0	1	0	0	0
Apoptosis, increased; Centrilobular	0	0	0	0	0	8
.... minimal	0	0	0	0	0	7
.... mild	0	0	0	0	0	1

Table 3 – Intergroup Comparison of Histopathology Observations – 90 Day

Anatomic Pathology Report

Page: 14

Table 3 - Intergroup Comparison of Histopathology Observations - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Removal Reason(s): 90 DAY EXPOSURE	Female					
	0	40	200	600	2000	6000
	ppm	ppm	ppm	ppm	ppm	ppm
Number of Animals	10	10	10	10	10	10
Number of Completed Animals	10	10	10	10	10	10
LIVER						
Examined	10	10	10	10	10	10
Infiltrate, mononuclear cell	10	10	10	10	10	10
.... minimal	10	10	10	10	10	10
Vacuolation; Centrilobular	0	0	0	0	9	2
.... minimal	0	0	0	0	8	1
.... mild	0	0	0	0	1	1
Hepatocellular hypertrophy; Centrilobular	0	0	0	0	1	10
.... minimal	0	0	0	0	1	0
.... mild	0	0	0	0	0	1
.... moderate	0	0	0	0	0	9
Necrosis, single cell	3	6	7	5	3	0
.... minimal	3	6	7	5	3	0
Apoptosis, increased; Centrilobular	0	0	0	0	1	10
.... minimal	0	0	0	0	1	6
.... mild	0	0	0	0	0	4
Lipidosis; Subcapsular; focal	0	0	1	0	0	0
.... minimal	0	0	1	0	0	0

Table 4 – Individual Animal Data – 7 Day

Anatomic Pathology Report

Page: 16

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0849	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 17

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0850	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; mild

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 18

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0851	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 19

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0852	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

LIVER : Mitosis; increased, minimal

Anatomic Pathology Report

Page: 20

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0853	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; mild

Anatomic Pathology Report

Page: 21

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0854	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 22

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0855	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 23

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0856	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 24

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0857	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 25

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0858	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 26

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0879	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 27

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0880	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; mild

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 28

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0881	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 29

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0882	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 30

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0883	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 31

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0884	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 32

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0885	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 33

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0886	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 34

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0887	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Mitosis; increased, mild

Anatomic Pathology Report

Page: 35

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0888	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 36

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0909	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 37

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0910	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 38

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0911	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Mitosis; increased, minimal

Anatomic Pathology Report

Page: 39

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0912	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 40

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0913	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 41

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0914	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 42

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0915	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 43

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0916	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 44

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0917	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 45

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0918	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 46

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0939	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

Anatomic Pathology Report

Page: 47

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0940	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 48

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0941	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

Anatomic Pathology Report

Page: 49

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0942	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Mitosis; increased, minimal

Anatomic Pathology Report

Page: 50

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0943	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 51

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0944	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Mitosis; increased, minimal

Anatomic Pathology Report

Page: 52

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0945	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 53

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0946	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 54

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0947	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 55

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0948	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 56

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0969	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild : (comment) This finding signifies hepatocytes with clear, flocculated, cytoplasm, typical of cells with increased glycogen.

Anatomic Pathology Report

Page: 57

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0970	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 58

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0971	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

Anatomic Pathology Report

Page: 59

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0972	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

Anatomic Pathology Report

Page: 60

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0973	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

Anatomic Pathology Report

Page: 61

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0974	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

Anatomic Pathology Report

Page: 62

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0975	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

Anatomic Pathology Report

Page: 63

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0976	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 64

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0977	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Vacuolation; Centrilobular; mild

Anatomic Pathology Report

Page: 65

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0978	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

Anatomic Pathology Report

Page: 66

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0999	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

Anatomic Pathology Report

Page: 67

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 1000	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

Anatomic Pathology Report

Page: 68

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 1001	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

Anatomic Pathology Report

Page: 69

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 1002	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 70

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 1003	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 10/9/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/9/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

Anatomic Pathology Report

Page: 71

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 1004	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

Anatomic Pathology Report

Page: 72

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 1005	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

Anatomic Pathology Report

Page: 73

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 1006	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

Anatomic Pathology Report

Page: 74

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 1007	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 75

Table 4 - Individual Animal Data - 7 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 1008	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 10/10/2018	Removal Reason: 7 Day Exposure	
Necropsy Date: 10/10/2018	Study Day (Week) of Death: 8 (2)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

LIVER : Necrosis, single cell; minimal

Table 5 – Individual Animal Data – 28 Day

Anatomic Pathology Report

Page: 77

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0839	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Mitosis; increased, minimal

Anatomic Pathology Report

Page: 78

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0840	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; mild

Anatomic Pathology Report

Page: 79

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0841	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 80

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0842	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 81

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0843	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 82

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0844	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 83

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0845	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 84

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0846	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 85

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0847	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 86

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0848	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 87

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0869	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 88

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0870	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 89

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0871	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 90

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0872	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 91

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0873	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 92

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0874	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 93

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0875	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 94

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0876	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 95

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0877	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 96

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0878	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 97

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0899	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 98

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0900	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 99

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0901	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 100

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0902	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 101

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0903	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 102

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0904	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 103

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0905	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 104

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0906	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal
LIVER : Necrosis, single cell; minimal
LIVER : Necrosis, focal; Subcapsular; minimal

Anatomic Pathology Report

Page: 105

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0907	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 106

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0908	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 107

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0929	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 108

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0930	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 109

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0931	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

Anatomic Pathology Report

Page: 110

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0932	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 111

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0933	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 112

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0934	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 113

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0935	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 114

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0936	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

Anatomic Pathology Report

Page: 115

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0937	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 116

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0938	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 117

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0959	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

Anatomic Pathology Report

Page: 118

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0960	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

Anatomic Pathology Report

Page: 119

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0961	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 120

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0962	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

Anatomic Pathology Report

Page: 121

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0963	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 122

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0964	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

Anatomic Pathology Report

Page: 123

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0965	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

Anatomic Pathology Report

Page: 124

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0966	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 125

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0967	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

Anatomic Pathology Report

Page: 126

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0968	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

Anatomic Pathology Report

Page: 127

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0989	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

LIVER : Hepatocellular hypertrophy; Centrilobular; minimal : (comment) This finding signifies centrilobular hepatocytes, especially those closest to central veins, with generous, finely granular, eosinophilic cytoplasm.

LIVER : Apoptosis, increased; Centrilobular; minimal : (comment) This finding signifies scattered cell death in hepatocytes directly adjacent to centrilobular veins, characterized condensed cytoplasm, fragmented or pyknotic nuclei, and apoptotic bodies.

Anatomic Pathology Report

Page: 128

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0990	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

LIVER : Hepatocellular hypertrophy; Centrilobular; minimal

LIVER : Apoptosis, increased; Centrilobular; minimal

Anatomic Pathology Report

Page: 129

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0991	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

LIVER : Hepatocellular hypertrophy; Centrilobular; minimal

Anatomic Pathology Report

Page: 130

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0992	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

LIVER : Hepatocellular hypertrophy; Centrilobular; minimal

LIVER : Necrosis, single cell; minimal

LIVER : Apoptosis, increased; Centrilobular; minimal

Anatomic Pathology Report

Page: 131

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0993	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 11/6/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/6/2018	Study Day (Week) of Death: 29 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

LIVER : Hepatocellular hypertrophy; Centrilobular; minimal

LIVER : Necrosis, single cell; minimal

LIVER : Apoptosis, increased; Centrilobular; minimal

Anatomic Pathology Report

Page: 132

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0994	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

LIVER : Hepatocellular hypertrophy; Centrilobular; mild

LIVER : Necrosis, single cell; minimal

LIVER : Apoptosis, increased; Centrilobular; mild

Anatomic Pathology Report

Page: 133

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0995	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

LIVER : Hepatocellular hypertrophy; Centrilobular; minimal

LIVER : Apoptosis, increased; Centrilobular; minimal

Anatomic Pathology Report

Page: 134

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0996	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

LIVER : Hepatocellular hypertrophy; Centrilobular; mild

LIVER : Necrosis, single cell; minimal

LIVER : Apoptosis, increased; Centrilobular; minimal

Anatomic Pathology Report

Page: 135

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0997	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

LIVER : Hepatocellular hypertrophy; Centrilobular; mild

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 136

Table 5 - Individual Animal Data - 28 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0998	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 11/7/2018	Removal Reason: 28 Day Exposure	
Necropsy Date: 11/7/2018	Study Day (Week) of Death: 30 (5)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

LIVER : Hepatocellular hypertrophy; Centrilobular; mild

LIVER : Necrosis, single cell; minimal

LIVER : Apoptosis, increased; Centrilobular; minimal

Table 6 – Individual Animal Data – 90 Day

Anatomic Pathology Report

Page: 138

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0829	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 139

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0830	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 140

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0831	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 141

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0832	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 142

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0833	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 143

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0834	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 144

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0835	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 145

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0836	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 146

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0837	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 147

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0838	Group: 1	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 0 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 148

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0859	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 149

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0860	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 150

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0861	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 151

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0862	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 152

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0863	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 153

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0864	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 154

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0865	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 155

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0866	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 156

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0867	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 157

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0868	Group: 2	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 40 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 158

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0889	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 159

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0890	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 160

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0891	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 161

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0892	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 162

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0893	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Lipidosis; Subcapsular; focal, minimal

Anatomic Pathology Report

Page: 163

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0894	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 164

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0895	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 165

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0896	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 166

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0897	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 167

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0898	Group: 3	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 200 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 168

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0919	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 169

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0920	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 170

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0921	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 171

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0922	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 172

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0923	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 173

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0924	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 174

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0925	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 175

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0926	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 176

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0927	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

Anatomic Pathology Report

Page: 177

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0928	Group: 4	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 600 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 178

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0949	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

Anatomic Pathology Report

Page: 179

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0950	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 180

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0951	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 181

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0952	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Hepatocellular hypertrophy; Centrilobular; minimal

Anatomic Pathology Report

Page: 182

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0953	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

Anatomic Pathology Report

Page: 183

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0954	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

LIVER : Necrosis, single cell; minimal

Anatomic Pathology Report

Page: 184

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0955	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

LIVER : Apoptosis, increased; Centrilobular; minimal

Anatomic Pathology Report

Page: 185

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0956	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

Anatomic Pathology Report

Page: 186

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0957	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

Anatomic Pathology Report

Page: 187

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0958	Group: 5	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 2000 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

Anatomic Pathology Report

Page: 188

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0979	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Hepatocellular hypertrophy; Centrilobular; moderate

LIVER : Apoptosis, increased; Centrilobular; minimal

Anatomic Pathology Report

Page: 189

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0980	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Hepatocellular hypertrophy; Centrilobular; moderate

LIVER : Apoptosis, increased; Centrilobular; mild

Anatomic Pathology Report

Page: 190

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0981	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Hepatocellular hypertrophy; Centrilobular; moderate

LIVER : Apoptosis, increased; Centrilobular; minimal

Anatomic Pathology Report

Page: 191

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0982	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; minimal

LIVER : Hepatocellular hypertrophy; Centrilobular; mild

LIVER : Apoptosis, increased; Centrilobular; minimal

Anatomic Pathology Report

Page: 192

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0983	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 12/6/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/6/2018	Study Day (Week) of Death: 91 (13)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Vacuolation; Centrilobular; mild

LIVER : Hepatocellular hypertrophy; Centrilobular; moderate

LIVER : Apoptosis, increased; Centrilobular; minimal

Anatomic Pathology Report

Page: 193

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0984	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Hepatocellular hypertrophy; Centrilobular; moderate

LIVER : Apoptosis, increased; Centrilobular; minimal

Anatomic Pathology Report

Page: 194

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0985	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Hepatocellular hypertrophy; Centrilobular; moderate

LIVER : Apoptosis, increased; Centrilobular; mild

Anatomic Pathology Report

Page: 195

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0986	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Hepatocellular hypertrophy; Centrilobular; moderate

LIVER : Apoptosis, increased; Centrilobular; mild

Anatomic Pathology Report

Page: 196

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0987	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Hepatocellular hypertrophy; Centrilobular; moderate

LIVER : Apoptosis, increased; Centrilobular; mild

Anatomic Pathology Report

Page: 197

Table 6 - Individual Animal Data - 90 Day
The Dow Chemical Company Study ID: 181012
1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver
Tumors in Female B6D2F1/Crl Mice

Animal: 0988	Group: 6	Sex: Female
Species: Mouse	Strain: B6D2F1/Crl	Study Type: Investigational
Material: 1,4-Dioxane	Dose: 6000 ppm	Route: Drinking Water
Death Date: 12/7/2018	Removal Reason: 90 Day Exposure	
Necropsy Date: 12/7/2018	Study Day (Week) of Death: 92 (14)	

Histopathology Observations [Correlation]:

LIVER : Infiltrate, mononuclear cell; minimal

LIVER : Hepatocellular hypertrophy; Centrilobular; moderate

LIVER : Apoptosis, increased; Centrilobular; minimal

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female
B6D2F1/Crl Mice

APPENDIX E. Toxicokinetic Analytical Report

Toxicology Information Collection (TIC) Report
The Dow Chemical Company

Report Title:			
Metabolite Quantitation - Blood Analysis (Study 181012; 1,4 Dioxane)			
Authors(s)	ID	Date	
Eric J. Nelson	(756831)	07/18/2019	
Reviewer	ID	Date	
Grant T. Marty	(367812)	7/16/2019	
Management Approval	ID	Date	
Dan A. Markham	(085140)	7/17/2019	
Patent Status	Date Issued	Page Count	Lab Report Code
No action required	07/18/2019	33	TERC-ACL- 2018-20
Geographic Location	Department	Databook Numbers	CRI Number
Midland, Michigan	TERC	n/a	NA

Study Number:	181012
Study Title:	1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female B6D2F1/Crl Mice
Project / Sample Description (optional):	Blood Sample Analysis for 1,4-Dioxane and its major metabolite, β -hydroxyethoxyacetic acid (HEAA)
Test Material(s):	1,4 Dioxane
Test Material lot #:	SHBJ7415
Report Recipient(s):	Golden, Rachel
Date Samples collected/prepared:	10/09, 11/06, and 12/06/2018
Number of Samples or estimate:	6 Dose groups

Date samples prepared for analysis:	01/27/19, 01/29/19 – 01/31/19, 02/04/19 - 02/06/19, 02/08/19, 02/09/19, 02/11/19 - 02/15/19
Analysis date:	01/27/19 – 01/28/19, 01/30/19 – 02/01/19, 02/05/19 - 02/07/19, 02/09/19, 02/12/19 - 02/15/19, 03/01/19, 03/05/19, 03/07/19, 03/13/19, 03/15/19
Number of samples analyzed:	5 per dose group
Analysis method:	GC/MS-SIM for 1,4-Dioxane and GC/MS-MS for Derivatized β -hydroxyethoxyacetic acid (HEAA)
Method reference:	See below

Summary:

This report summarizes the analysis of 1,4-Dioxane and its major metabolite, β -hydroxyethoxyacetic acid (HEAA) in mouse blood. The blood samples were collected on days 7, 28, and 90, directly into vials containing 1.00 mL of methanol + 1% formic acid and extracted with ethyl acetate. Analysis of 1,4-Dioxane was performed by gas chromatography with electron ionization mass spectrometry detection operating in the selected ion monitoring mode (GC/EI-MS-SIM) using stable isotope internal standard calibration to facilitate quantitation. Analysis of HEAA was performed by derivatizing HEAA to a trimethylsilyl form and analyzing by gas chromatography with electron ionization and tandem mass spectrometry detection operating in the multiple reaction ion monitoring mode (GC/EI-MS-MS) using stable isotope internal standard calibration to facilitate quantitation.

Stability of 1,4-Dioxane and HEAA in mouse blood was evaluated concurrent with the test samples prepared on 11/02/2018 and stored at -80 °C. All stability test samples were extracted on stability day 118. 1,4-Dioxane and HEAA proved to be stable in mouse blood for up to 118 days at -80 °C at concentrations ranging from 0.500 $\mu\text{g/mL}$ to 500 $\mu\text{g/mL}$ based on the acceptance criteria of $\pm 15\%$ of nominal concentration.

Additionally, stability of 1,4-Dioxane and HEAA in extracted mouse blood was evaluated with the test samples prepared on 01/27/2019 and stored at ambient conditions. 1,4-Dioxane and HEAA proved to be stable in extracts of mouse blood at ambient conditions for 45 days at concentrations of 0.0500 $\mu\text{g/mL}$ and 200 $\mu\text{g/mL}$ and 39 days at concentrations of 0.200 $\mu\text{g/mL}$ and 200 $\mu\text{g/mL}$, respectively, based on the acceptance criteria of $\pm 15\%$ of nominal concentration..

The GC/MS-SIM instrumentation exhibited a quadratic response ($1/x$ weighting) for 1,4-Dioxane over a concentration range of approximately 0.200 – 200 μg 1,4-Dioxane / mL blood, which encompassed the anticipated range of sample concentrations. A coefficient of determination (R^2) value was > 0.998 for each day of analysis.

The GC/MS-MS instrumentation exhibited a quadratic response ($1/x$ weighting) for the derivative of HEAA over a concentration range of approximately 0.0500 – 200 μg HEAA / mL blood, which encompassed the anticipated range of sample concentrations. A coefficient of determination (R^2) value was > 0.996 for each day of analysis.

Test Material/Reference Substance Information:

Test Material Name: 1,4-Dioxane

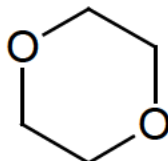
Chemical Name: 1,4-Dioxane

Synonyms: p-Dioxane

Molecular Formula: $C_4H_8O_2$

Molecular Weight: 88.1

Chemical Structure:



CAS Number: 123-91-1

Lot#: SHBJ7415

Purity: The non-GLP purity of the reference material was determined to be 99.98% by gas chromatography with identification by Infrared spectroscopy (Grady, 2018).

Metabolite

Test Material Name: β -hydroxyethoxyacetic acid

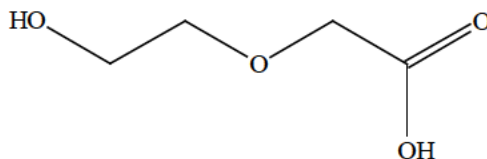
Chemical Name: β -hydroxyethoxyacetic acid

Synonyms: HEAA

Molecular Formula: $C_4H_8O_4$

Molecular Weight: 120.1

Chemical Structure:



CAS Number: 123-91-1

Lot#: LN01871500

Purity: The non-GLP purity of the reference material was listed to be 95% by the supplier (Wuxi AppTec).

Internal Standards:

Name: 1,4-Dioxane-D8

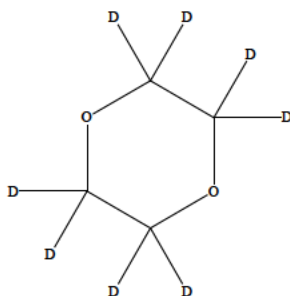
Chemical Name: 1,4-Dioxane-D8

Synonyms: p-Dioxane-D8

Molecular Formula: C₄D₈O₂

Molecular Weight: 96.15

Chemical Structure:



Lot #: SDDL-024A

Purity: The purity of the test material was determined to be $\geq 98\%$ by gas chromatography with identification by mass spectrometry (Eckersley, 2014).

The internal standard was used to facilitate quantitation of 1,4-Dioxane in mouse blood.

Name: β -hydroxyethoxyacetic acid-D4

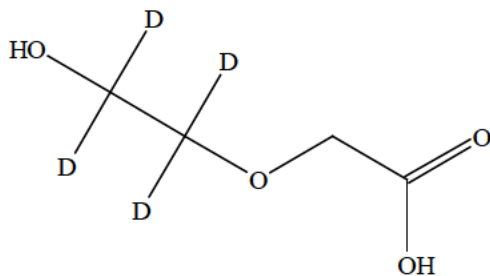
Chemical Name: β -hydroxyethoxyacetic acid-D4

Synonyms: HEAA-D4

Molecular Formula: C₄H₄D₄O₄

Molecular Weight: 124.1

Chemical Structure:



Lot #: 018-19-01
Purity: The purity of the test material was determined to be $\geq 95\%$ by HNMR (Cao, 2018).

The internal standard was used to facilitate quantitation of HEAA in mouse blood.

Internal Standard Preparation:

A stock standard of 1,4-Dioxane-D8 was prepared at 1000 $\mu\text{g/mL}$ methanol. A 30.0 $\mu\text{g/mL}$ internal standard stock was prepared by diluting 300.0 μL of the 1,4-Dioxane-D8 stock with 9.70 mL of methanol.

A stock standard of HEAA-D4 was prepared at 1000 $\mu\text{g/mL}$ Ultrapure water. A 100 $\mu\text{g/mL}$ internal standard stock was prepared by diluting 1.00 mL of HEAA-D4 stock with 9.00 mL of Ultrapure water.

Standard Preparation – Prepared With Each Sample Set:

Stock standards of 1,4-Dioxane and HEAA were prepared for each analysis day at 1,000 $\mu\text{g/mL}$ in Ultrapure water and were further diluted with Ultrapure water to prepare working stock standards at 10.0 $\mu\text{g/mL}$. The 10.0 $\mu\text{g/mL}$ HEAA stock standard was further diluted with Ultrapure water to prepare a diluted stock standard at 1.00 $\mu\text{g/mL}$. Appropriate amounts of these 1,4-Dioxane and HEAA stock standards (0.0250 – 0.100 mL) were diluted with methanol + 1% formic acid to a total volume of 1.00 mL in 4 mL screw top autosampler vials. Control mouse blood (0.500 mL) was added to each vial to prepare matrix standards at approximate concentrations between 0.200 to 200 μg 1,4-Dioxane / mL mouse blood and 0.0500 to 200 μg HEAA / mL mouse blood, which encompassed the expected sample concentrations.

Each matrix standard was extracted by adding 3 mL of ethyl acetate to each vial. The standards were briefly vortex-mixed, placed on a flatbed shaker for approximately 1 hour, and then centrifuged at 1939 G for 10 minutes. See standard and sample analysis section for further preparation and analysis for 1,4-Dioxane and HEAA.

Sample Preparation:

The blood samples were collected into 4 mL screw top autosampler vials containing 1.00 mL of methanol + 1% formic acid and stored at $-80\text{ }^{\circ}\text{C}$ until analysis to inhibit any further biological

activity. Samples were equilibrated to ambient temperature and 3.00 mL of ethyl acetate was added to each sample. The samples were briefly vortex-mixed, placed on a flatbed shaker for approximately 1 hour, and then centrifuged at 1939 G for 10 minutes. See standard and sample analysis section for further preparation and analysis for 1,4-Dioxane and HEAA.

Standard and Sample Analysis:

For the 1,4-Dioxane analysis, 1 mL of the ethyl acetate layer was transferred to a glass autosampler vial. In addition, 25 μ L of internal standard solution (1,4-Dioxane-D8, 30.0 μ g/mL) was added to each sample and standard, resulting in a nominal internal standard concentration of 0.732 μ g/mL. The samples and standards were briefly vortex-mixed and then analyzed by GC/MS-SIM.

For the HEAA analysis, 0.300 mL of each ethyl acetate extract layer was transferred to a glass autosampler vial. In addition, 25 μ L of internal standard solution (HEAA-D4, 100 μ g/mL) was added to each sample and standard, resulting in a nominal internal standard concentration of 7.69 μ g/mL. To aid in the analysis of HEAA, a derivatization agent was used to increase the volatility of HEAA by the addition of two trimethylsilyl groups. This was completed by evaporating the samples and standards to dryness under nitrogen followed by the addition of 0.300 mL of acetonitrile and 0.050 mL of N,O-Bis(trimethylsilyl)trifluoroacetamide (BSTFA) derivatization agent. The samples and standards were briefly vortex-mixed, allowed to derivatize overnight at ambient conditions, and then analyzed by GC/MS-MS for the HEAA trimethylsilyl derivative as the HEAA equivalent.

Stability Preparation:

Stability of 1,4-Dioxane and HEAA in mouse blood was evaluated with the test samples prepared on 11/02/2018, day 0, and prepared stability aliquots were stored at -80 °C. All stability test samples were extracted on stability day 118. Analysis followed the same procedures as the samples and standards.

Additionally, stability of 1,4-Dioxane and HEAA in mouse blood extracts was evaluated with the test samples extracted on 01/27/2019, time 0, and stored at ambient conditions. Analysis followed the same procedures as the samples and standards.

Representative Analysis Conditions – 1,4-Dioxane:

Gas Chromatograph: Agilent 7890B; G3440B

Autosampler: Agilent 7693; G4514A

Injector: Agilent 7693; G4513A

Mass Spectrometer: Agilent 7000C; G7011A

Wash Solvent: Ethyl Acetate

Analytical Column: Restek RTX-20; 60 m x 320 μ m x 1 μ m

Pressure: 12.0 psi

Flow: 2.0 mL/min

GC Inlet Liner: 4mm ID Inlet liner, split, single taper, glass wool, deactivated

Inlet: Injection Volume: 3.0 μ L

Mode: Split

Split Ratio: 100:1

Split Flow: 204 mL/min

Initial temperature: 250 °C

Pressure: 12.0 psi

Septum Purge Flow: 1.0 mL/min

Total flow: 207 mL/min

Gas type: Helium

Oven: Initial temp: 35 °C – hold 4 min;

Ramp @ 30 °C/min to 250 °C – hold 0 min

MSD: Transfer Line: 300 °C

Ion Source: Electron ionization (EI)

Source Temperature: 200 °C

Solvent Delay: 6.7 min

SIM Settings:

Scan Type: MS1 SIM

Dwell: 100 ms

Mass: 96 amu – 1,4-Dioxane – D8

Mass: 88 amu – 1,4-Dioxane

Scan Settings:

Scan Type: MS1 Scan

Start Mass: 40 amu

End Mass: 150 amu

Scan Time: 200 ms

Scan Step Size: 0.1 amu

Representative Analysis Conditions – Derivatized HEAA:

Gas Chromatograph: Agilent 7890B; G3440B

Autosampler: Agilent 7693; G4514A

Injector: Agilent 7693; G4513A

Mass Spectrometer: Agilent 7000C; G7014D

Wash Solvent: Acetonitrile

Analytical Column: Agilent HP-5MS; 30 m x 250 μ m x 0.25 μ m

Pressure: 10.0 psi

Flow: 1.05 mL/min

GC Inlet Liner: 4mm ID Inlet liner, split, single taper, glass wool, deactivated

Inlet: Injection Volume: 1.3 μ L

Mode: Splitless

Pure Flow: 75 mL/min at 1 min

Initial temperature: 230 $^{\circ}$ C

Pressure: 10.0 psi
Septum Purge Flow: 1.2 mL/min
Total flow: 77.3 mL/min
Gas type: Helium

Oven: Initial temp: 80 °C – hold 3 min;
Ramp @ 5 °C/min to 180 °C – hold 0 min
Ramp @ 50 °C/min to 270 °C – hold 2 min

MSD: Transfer Line: 280 °C
Ion Source: Electron ionization (EI)
Source Temperature: 300 °C
Solvent Delay: 3.5 min
Scan Settings:
Scan Type: MS1 Scan
Start Mass: 70 amu
End Mass: 300 amu
Scan Time: 200 ms
Scan Step Size: 0.1 amu
Product Ion Scan Settings:
Scan Type: Product Ion
Precursor Ion Derivatized HEAA: 249 amu
Precursor Ion Derivatized HEAA-D4: 253 amu
Start Mass: 70 amu
End Mass: 300 amu
Scan Time: 200 ms
Scan Step Size: 0.1 amu
Collision Energy: 20 V

MRM Settings:

Scan Type: MRM

Dwell: 150 ms

Collision Energy: 20 V

Analyte	Q1 Mass (amu)	Q3 Mass (amu)
Derivatized HEAA	249	147
Derivatized HEAA - IS	253	147

Results and Discussion:

The analyses for 1,4-Dioxane and HEAA in mouse blood are located in Tables 1 through 3. The 1,4-Dioxane in mouse blood stability results are located in Table 4. The HEAA in mouse blood stability results are located in Table 5. Typical chromatograms for analyses of a standard, dose group blood sample extract, control, and solvent blank for 1,4-Dioxane are shown in Figures 3 through 6, respectively. Typical chromatograms for analyses of a standard, dose group blood sample extract, control, and solvent blank for the HEAA derivative are shown in Figures 7 through 10, respectively.

Dose Concentrations

None of the blood analyses of the dose control group exhibited a 1,4-Dioxane or HEAA concentration exceeding the lower limit of quantitation (LLQ) for each analysis day.

Stability

Stability of 1,4-Dioxane and HEAA in mouse blood was evaluated with the test sample prepared on 11/02/2018 and stored at -80 °C. All stability test samples were extracted on stability day 118. 1,4-Dioxane and HEAA proved to be stable in mouse blood for up to 118 days at -80 °C at concentrations ranging from 0.500 µg/mL to 500 µg/mL based on the acceptance criteria of ± 15% of nominal concentration.

Additionally, stability of 1,4-Dioxane and HEAA in extracted mouse blood was evaluated with the test sample prepared on 01/27/2019 and stored at ambient conditions. 1,4-Dioxane and HEAA proved to be stable in extracts of mouse blood at ambient conditions for 45 days and 39 days, respectively, based on the acceptance criteria of ± 15% of nominal concentration.. Extract

concentrations were 0.0500 µg/mL and 200 µg/mL for 1,4-Dioxane and 0.200 µg/mL and 200 µg/mL for HEAA.

Lower Limit of Quantitation (LLQ)

The LLQ for the 1,4-Dioxane analysis by GC/MS-SIM was 0.200 µg 1,4-Dioxane / mL mouse blood. The LLQ for the HEAA analysis by GC/MS-MS was 0.0500 µg HEAA / mL mouse blood. The LLQ value was based on the concentration of the lowest matrix standard analyzed.

Linearity

The GC/MS-SIM instrumentation exhibited a quadratic response (1/x weighting) for 1,4-Dioxane over a concentration range of approximately 0.200 – 200 µg 1,4-Dioxane / mL blood, which encompassed the anticipated range of sample concentrations. A coefficient of determination (R^2) value was > 0.998 for each day of analysis. A spreadsheet of representative calibration data is shown in Table 4. The corresponding calibration curve, analyte concentration (µg/mL) vs. analyte peak area, is shown in Figure 1.

The GC/MS-MS instrumentation exhibited a quadratic response (1/x weighting) for derivatized HEAA over a concentration range of approximately 0.0500 – 200 µg HEAA / mL blood, which encompassed the anticipated range of sample concentrations. A coefficient of determination (R^2) value was > 0.996 for each day of analysis. A spreadsheet of representative calibration data is shown in Table 5. The corresponding calibration curve, analyte concentration (µg/mL) vs. analyte peak area, is shown in Figure 2.

Scan Data

Representative GC/MS Full Scan-Electron Ionization of 100 µg/mL 1,4-Dioxane in ethyl acetate is shown in Figure 11. Representative GC/MS Full Scan-Electron Ionization of 30.0 µg/mL 1,4-Dioxane-D8 in ethyl acetate is shown in Figure 12. Representative GC/MS-MS Full Scan-Electron Ionization and GC/MS-MS Product Ion Scan-Electron Ionization mass spectra of 200 µg/mL derivatized HEAA in acetonitrile is shown in Figures 13 and 14, respectively. Representative GC/MS-MS/Full Scan-Electron Ionization and GC/Product Ion Scan-Electron Ionization mass spectra of 200 µg/mL derivatized HEAA-D4 in acetonitrile is shown in Figures 15 and 16, respectively.

Reference

- Cao, G. (2018). Certificate of Analysis of Lithium Salt of HEAA, Lot # 018-19-01.
ChemDepo, Camarillo, California.
- Eckersley, T. (2014). Certificate of Analysis of 1,4-Dioxane-D8, Lot # SDDL-024A.
Cambridge Isotope Laboratories Inc., Andover, Massachusetts.
- Grady, M. (2018). Certificate of Analysis of 1,4-Dioxane, Lot # SHBJ7415. Sigma-Aldrich,
Sheboygan Falls, Wisconsin.

Table 1. Results of Concentration Analyses for 1,4-Dioxane and HEAA in Mouse Blood
Extracts – Day 7

10/09/2018 (Day 7)			
Animal Number	Target Exposure Concentration	µg 1,4-Dioxane / mL Blood	µg HEAA / mL Blood
18A0849	Control	ND	ND
18A0850		ND	ND
18A0851		ND	ND
18A0852		ND	ND
18A0853		ND	ND
18A0879	40 ppm	ND	ND
18A0880		ND	ND
18A0881		ND	ND
18A0882		ND	ND
18A0883		ND	ND
18A0909	200 ppm	ND	ND
18A0910		ND	ND
18A0911		ND	2.38
18A0912		ND	< LLQ (0.0500)
18A0913		ND	ND
18A0939	600 ppm	ND	2.93
18A0940		ND	5.14
18A0941		ND	1.53
18A0942		ND	3.07
18A0943		ND	< LLQ (0.0500)
18A0969	2000 ppm	ND	4.84
18A0970		ND	7.85
18A0971		ND	4.31
18A0972		ND	54.1
18A0973		ND	1.77
18A0999	6000 ppm	ND	80.7
18A1000		ND	12.2
18A1001		ND	41.0
18A1002		ND	49.2
18A1003		ND	34.3

ND = No Detect

Table 2. Results of Concentration Analyses for 1,4-Dioxane and HEAA in Mouse Blood
Extracts – Day 28

11/06/2018 (Day 28)			
Animal Number	Target Exposure Concentration	µg 1,4-Dioxane / mL Blood	µg HEAA / mL Blood
18A0839	Control	ND	ND
18A0840		ND	ND
18A0841		ND	ND
18A0842		ND	ND
18A0843		ND	ND
18A0869	40 ppm	ND	2.22
18A0870		ND	0.932
18A0871		ND	< LLQ (0.0500)
18A0872		ND	0.701
18A0873		ND	< LLQ (0.0500)
18A0899	200 ppm	ND	< LLQ (0.0500)
18A0900		ND	0.322
18A0901		ND	< LLQ (0.0500)
18A0902		< LLQ (0.200)	0.529
18A0903		ND	< LLQ (0.0500)
18A0929	600 ppm	ND	2.03
18A0930		ND	4.16
18A0931		ND	0.269
18A0932		ND	0.924
18A0933		ND	0.294
18A0959	2000 ppm	ND	1.02
18A0960		8.06	0.882
18A0961		< LLQ (0.200)	0.380
18A0962		ND	0.727
18A0963		ND	0.409
18A0989	6000 ppm	ND	6.37
18A0990		ND	1.01
18A0991		ND	1.44
18A0992		ND	5.49
18A0993		44.8	3.16

ND = No Detect

Table 3. Results of Concentration Analyses for 1,4-Dioxane and HEAA in Mouse Blood
Extracts – Day 90

12/06/2018 (Day 90)			
Animal Number	Target Exposure Concentration	µg 1,4-Dioxane / mL Blood	µg HEAA / mL Blood
18A0829	Control	ND	ND
18A0830		ND	ND
18A0831		ND	ND
18A0832		ND	ND
18A0833		ND	ND
18A0859	40 ppm	ND	0.227
18A0860		ND	< LLQ (0.0500)
18A0861		ND	0.298
18A0862		ND	< LLQ (0.0500)
18A0863		ND	< LLQ (0.0500)
18A0889	200 ppm	< LLQ (0.200)	0.302
18A0890		ND	< LLQ (0.0500)
18A0891		< LLQ (0.200)	0.390
18A0892		< LLQ (0.200)	0.377
18A0893		ND	< LLQ (0.0500)
18A0919	600 ppm	1.42	1.24
18A0920		ND	0.556
18A0921		< LLQ (0.200)	0.988
18A0922		< LLQ (0.200)	0.741
18A0923		ND	< LLQ (0.0500)
18A0949	2000 ppm	< LLQ (0.200)	0.711
18A0950		< LLQ (0.200)	1.32
18A0951		< LLQ (0.200)	0.935
18A0952		< LLQ (0.200)	0.544
18A0953		< LLQ (0.200)	0.972
18A0979	6000 ppm	210	8.21
18A0980		5.50	1.13
18A0981		125	9.40
18A0982		3.40	0.984
18A0983		60.1	9.81

ND = No Detect

Table 4. Representative Standards/Refit Table of 1,4-Dioxane Matrix Standards in Ethyl Acetate

Sample Name	Sample ID	Analyte Concentration (µg/mL)	Analyte Peak Area (counts)	IS Peak Area (counts)	ISTD Resp. Ratio	Calculated Concentration (µg/mL)	Accuracy (%)
Standard A	181012_020519_007.D	0.200	67152	3595788	0.0187	0.205	103
Standard B	181012_020519_008.D	2.00	814763	3687423	0.221	2.06	103
Standard C	181012_020519_009.D	20.0	8010424	3731414	2.15	19.6	97.8
Standard D	181012_020519_010.D	100	43078151	3717453	11.6	102	102
Standard E	181012_020519_011.D	200	89242085	3752653	23.8	200	100
Standard A	181012_020519_029.D	0.200	65983	3818422	0.0173	0.192	96.2
Standard B	181012_020519_030.D	2.00	835343	3908801	0.214	1.99	99.7
Standard C	181012_020519_031.D	20.0	8371135	3876197	2.16	19.7	98.4
Standard D	181012_020519_032.D	100	43717600	3768076	11.6	102	102
Standard E	181012_020519_033.D	200	92631667	3901700	23.7	200	100
Standard A	181012_020519_051.D	0.200	74368	3986429	0.0187	0.205	103
Standard B	181012_020519_052.D	2.00	837124	3863075	0.217	2.02	101
Standard C	181012_020519_053.D	20.0	8490058	3991848	2.13	19.4	97.0
Standard D	181012_020519_054.D	100	45030738	4020742	11.2	98.5	98.5
Standard E	181012_020519_055.D	200	91357749	3872989	23.6	199	99.4

ISTD Resp. Ratio = Analyte Peak Area / IS Peak Area

Calculated Concentration = (ISTD Resp. Ratio – b) / m

Regression equation is $y = mx + b$ (See Figure 1 for values for m and b)

Accuracy % = Calculated Concentration / Analyte Concentration * 100

Figure 1. Typical Standard Curve from GC/MS-SIM Analysis of 1,4-Dioxane Matrix Standards

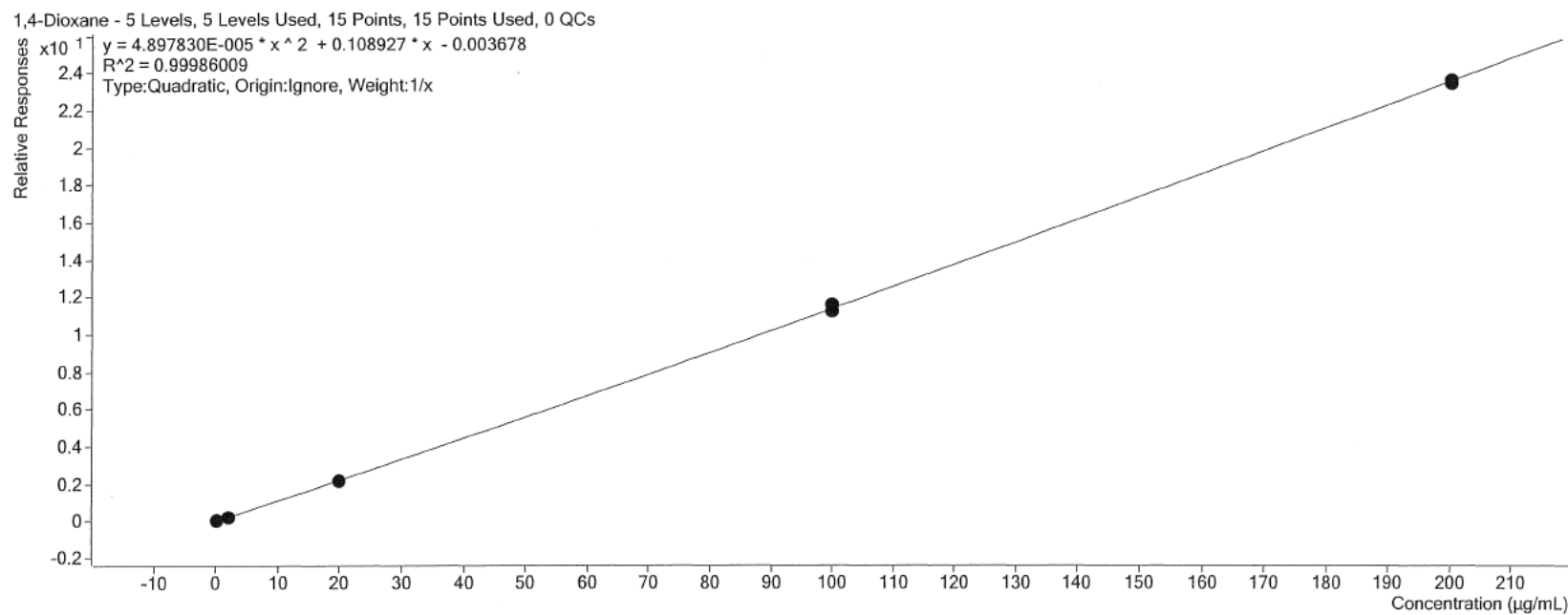


Table 5. Representative Standards/Refit Table of Derivatized HEAA Matrix Standards in Acetonitrile

Sample Name	Sample ID	Analyte Concentration (µg/mL)	Analyte Peak Area (counts)	IS Peak Area (counts)	ISTD Resp. Ratio	Calculated Concentration (µg/mL)	Accuracy (%)
Standard A	181012_020619_007.D	0.0500	15201	3335399	0.00456	0.0587	117
Standard B	181012_020619_008.D	0.200	44934	2924781	0.0154	0.175	87.6
Standard C	181012_020619_009.D	2.00	474022	2669734	0.178	1.92	96.2
Standard D	181012_020619_010.D	20.0	6583152	3596396	1.83	19.8	98.8
Standard E	181012_020619_011.D	200	56907663	3186868	17.9	195	97.6
Standard A	181012_020619_029.D	0.0500	12600	3048347	0.00413	0.0541	108
Standard B	181012_020619_030.D	0.200	43221	2839519	0.0152	0.174	86.8
Standard C	181012_020619_031.D	2.00	482919	2678504	0.180	1.95	97.6
Standard D	181012_020619_032.D	20.0	6674755	3586529	1.86	20.1	100
Standard E	181012_020619_033.D	200	55615492	3041048	18.3	200	100
Standard A	181012_020619_051.D	0.0500	14487	3126938	0.00463	0.0595	119
Standard B	181012_020619_052.D	0.200	42106	2735987	0.0154	0.175	87.7
Standard C	181012_020619_053.D	2.00	450802	2477220	0.182	1.97	98.5
Standard D	181012_020619_054.D	20.0	6418736	3401549	1.89	20.4	102
Standard E	181012_020619_055.D	200	54583531	2914441	18.7	205	102

$$\text{ISTD Resp. Ratio} = \text{Analyte Peak Area} / \text{IS Peak Area}$$

$$\text{Calculated Concentration} = (\text{ISTD Resp. Ratio} - b) / m$$

Regression equation is $y = mx + b$ (See Figure 2 for values for m and b)

$$\text{Accuracy \%} = \text{Calculated Concentration} / \text{Analyte Concentration} * 100$$

Figure 2. Typical Standard Curve from GC/MS-MS Analysis of Derivatized HEAA Matrix Standards

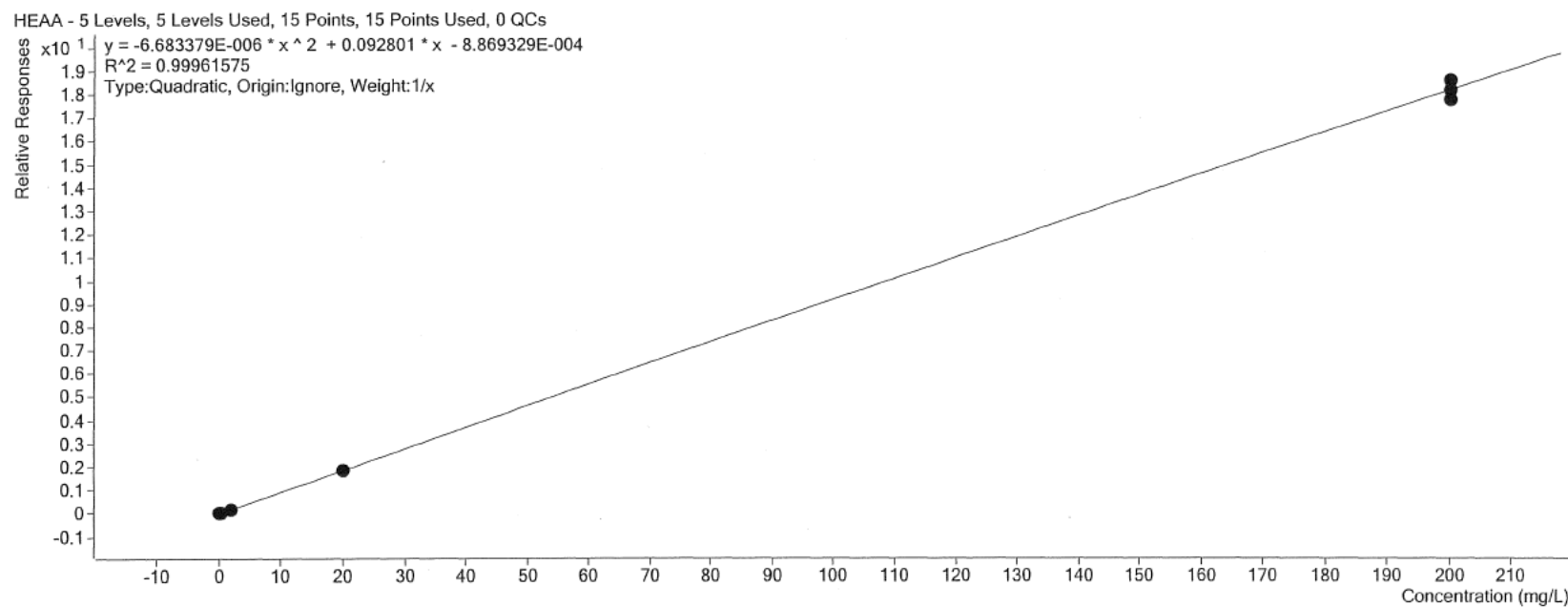


Figure 3. Typical Chromatogram (GC/MS-SIM) of a Matrix Calibration Standard Prepared at a Concentration of 20.0 μg 1,4-Dioxane / mL Mouse Blood; Internal Standard 1,4-Dioxane-D8 at 0.732 $\mu\text{g/mL}$

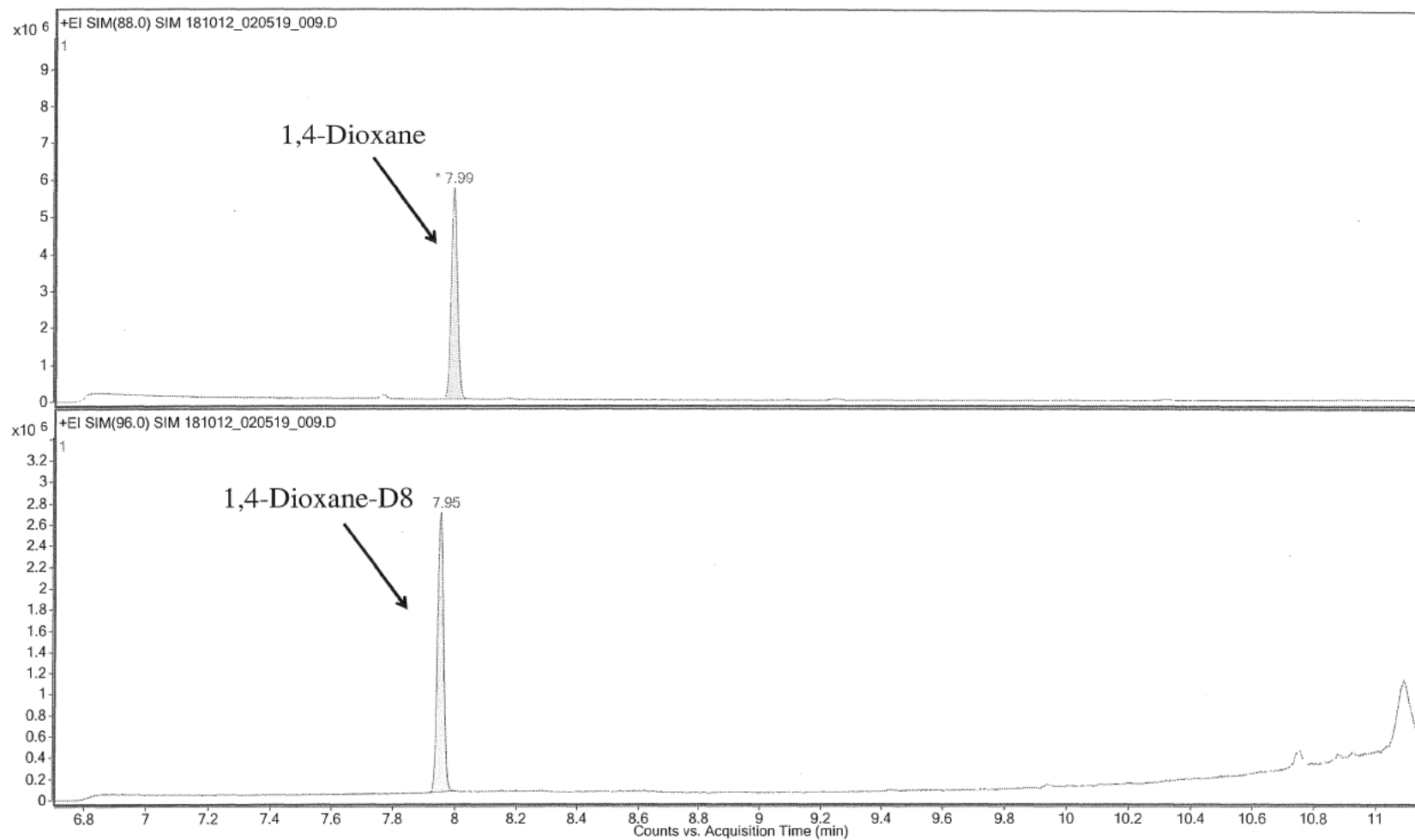


Figure 4. Typical Chromatogram (GC/MS-SIM) of a 6000 ppm Dose Group Blood Sample Extract; Internal Standard 1,4-Dioxane-D8 at 0.732 $\mu\text{g/mL}$

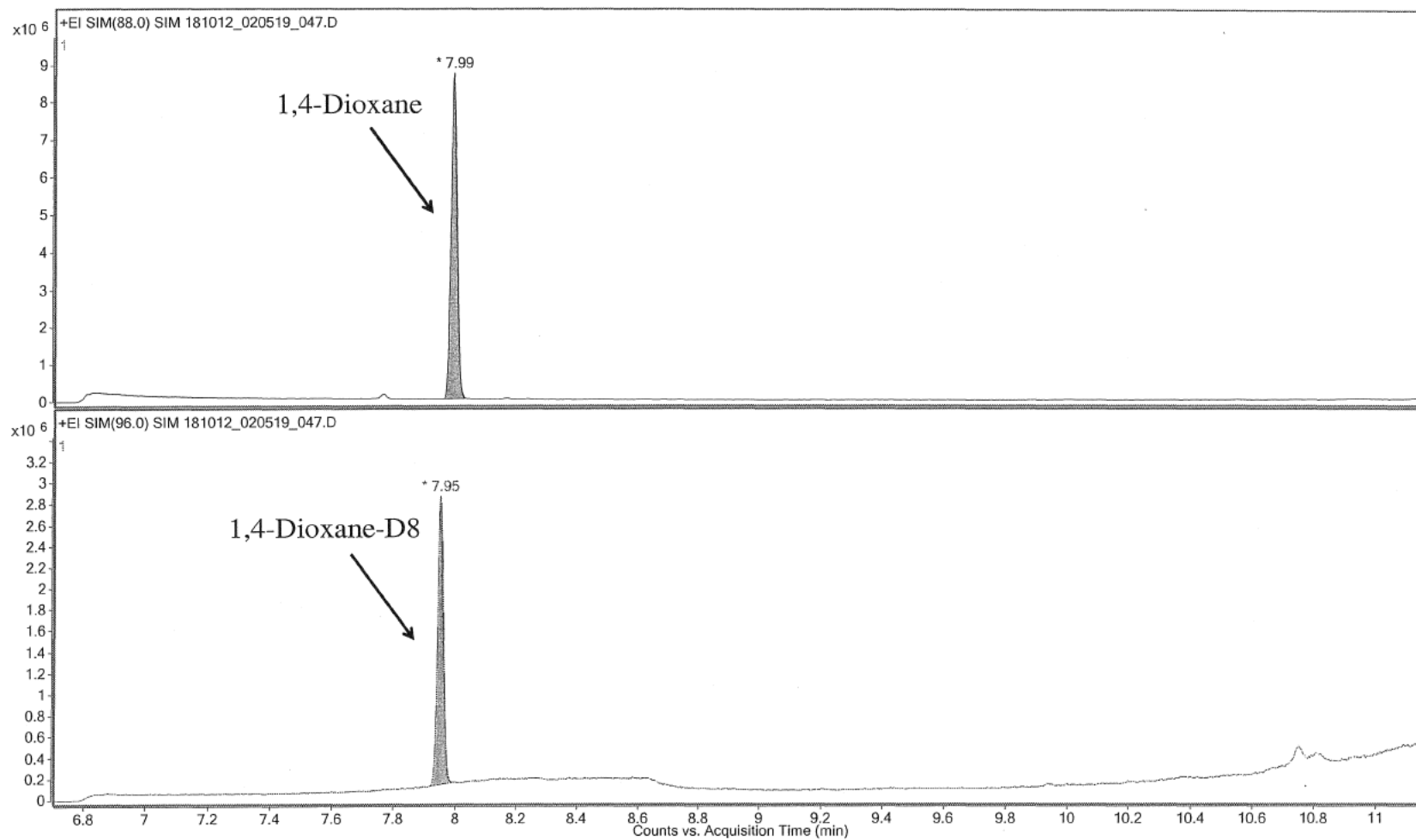


Figure 5. Typical Chromatogram (GC/MS-SIM) of a Control Dose Group Blood Sample Extract; Internal Standard 1,4-Dioxane-D8 at 0.732 $\mu\text{g/mL}$

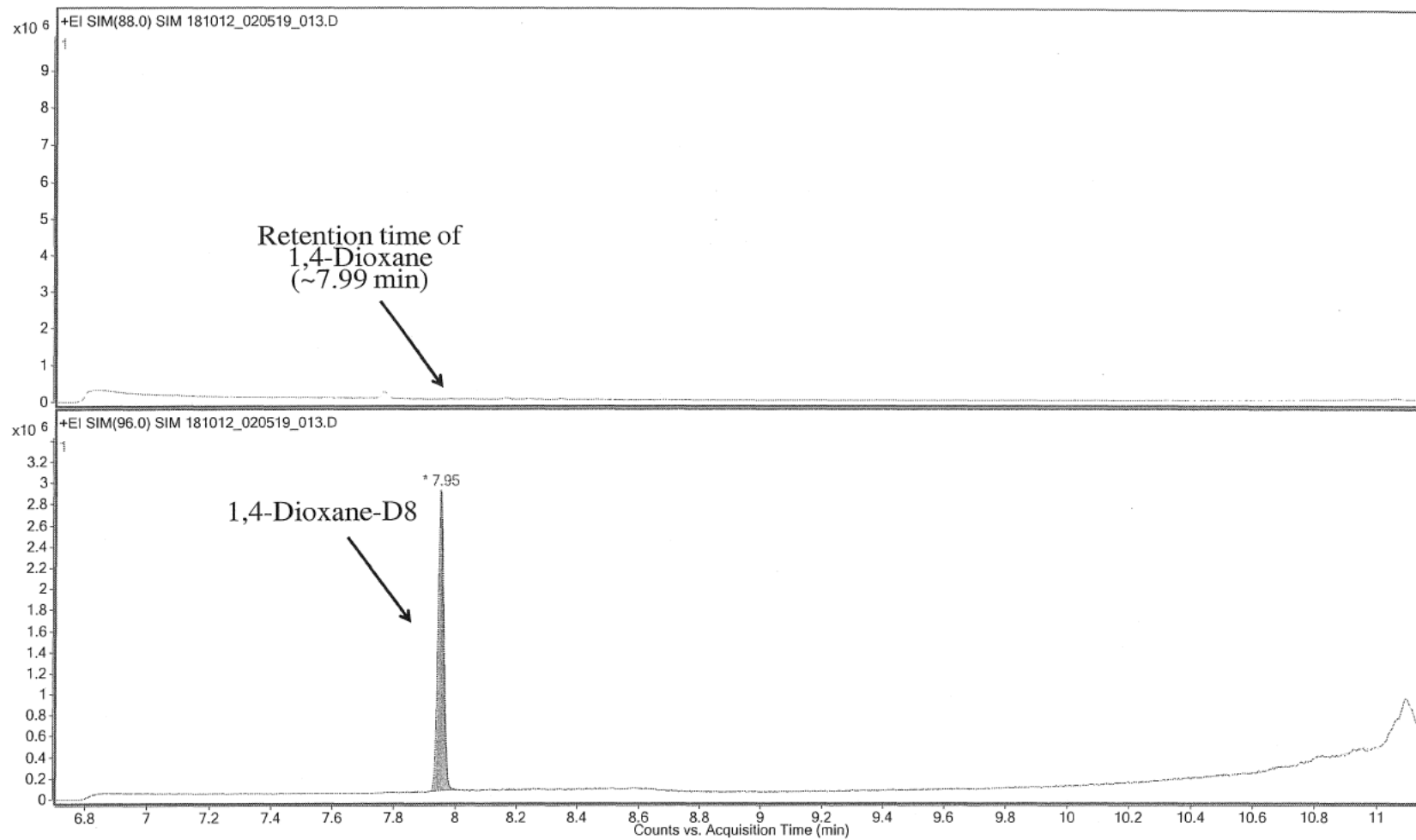


Figure 6. Typical Chromatogram (GC/MS-SIM) of Ethyl Acetate Solvent Blank

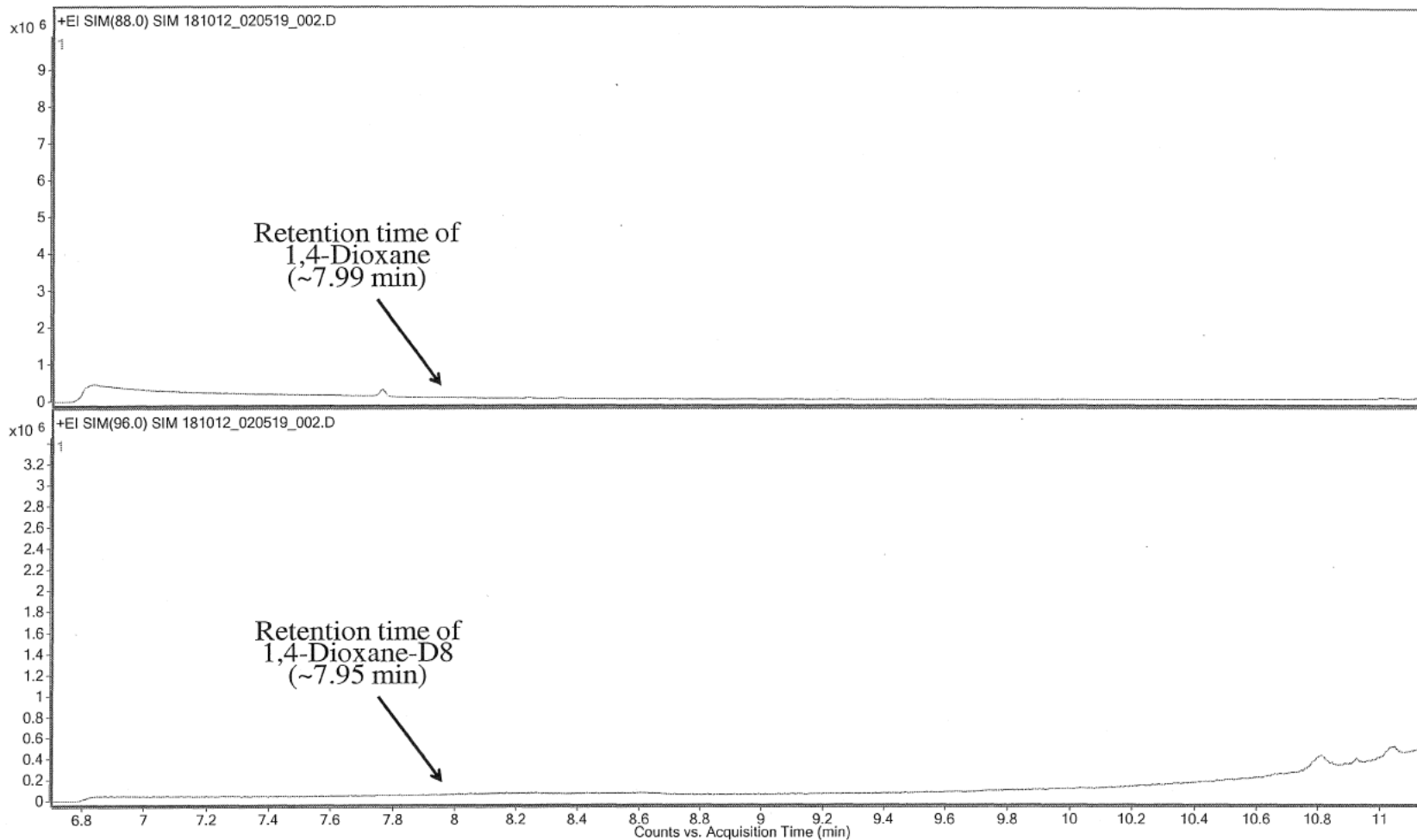


Figure 7. Typical Chromatogram (GC/MS-MRM) of a Matrix Calibration Standard Prepared at a Concentration of 2.00 μg Derivatized HEAA / mL Mouse Blood; Internal Standard Derivatized HEAA-D4 at 7.69 $\mu\text{g/mL}$

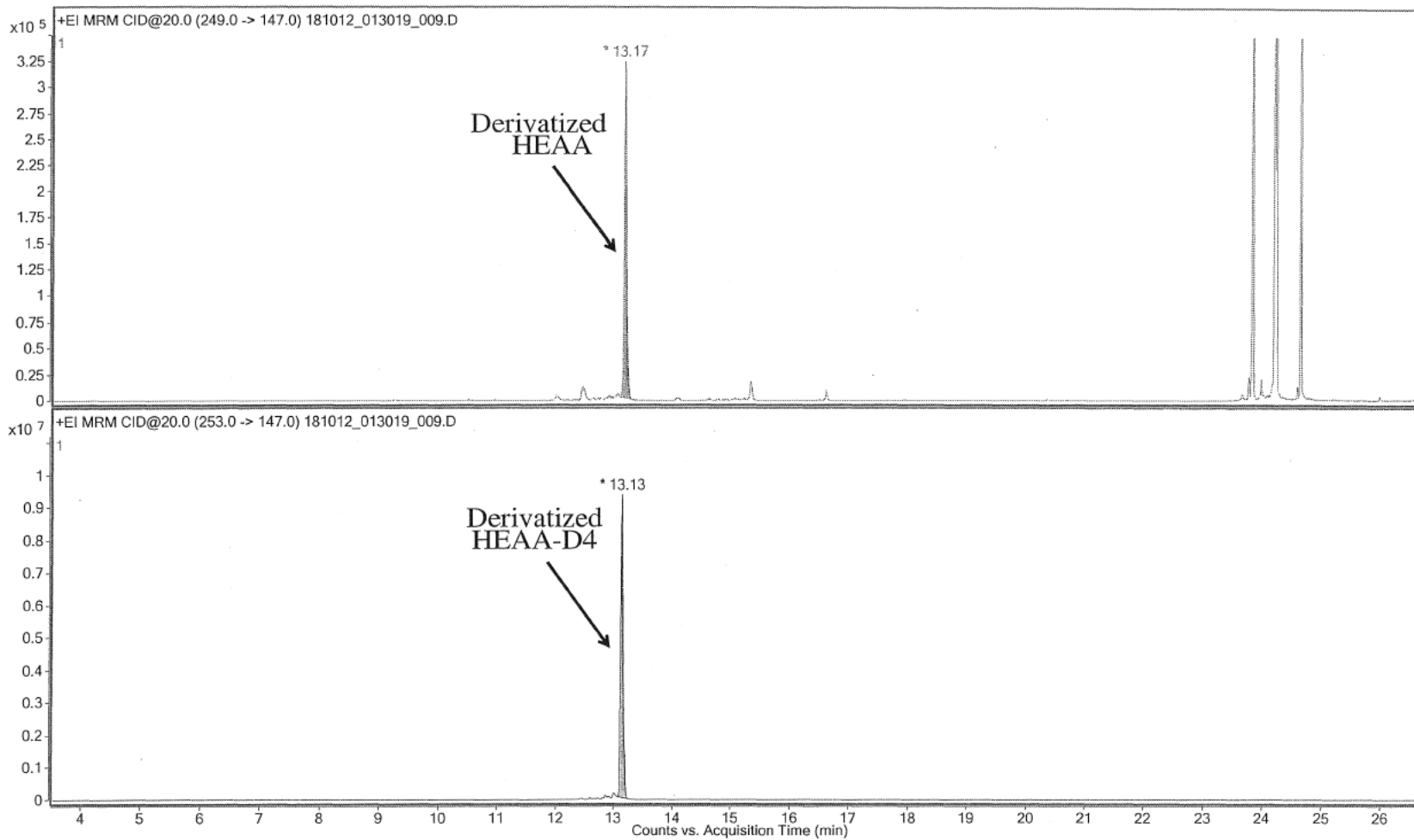


Figure 8. Typical Chromatogram (GC/MS-MRM) of a 6000 ppm Dose Group Blood Sample Extract; Internal Standard Derivatized HEAA-D4 at 7.69 $\mu\text{g/mL}$

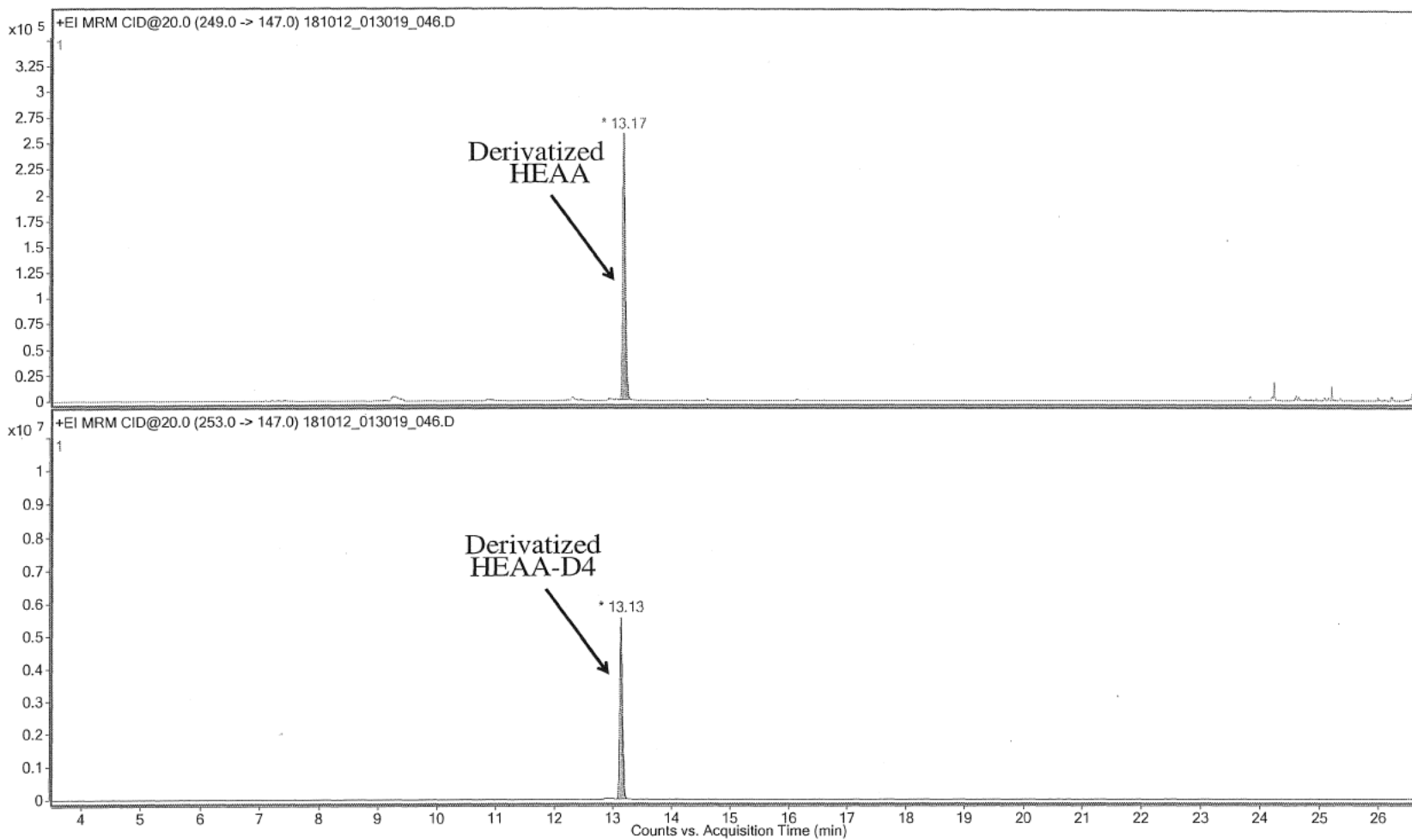


Figure 9. Typical Chromatogram (GC/MS-MRM) of a Control Dose Group Blood Sample Extract; Internal Standard Derivatized HEAA-D4 at 7.69 $\mu\text{g/mL}$

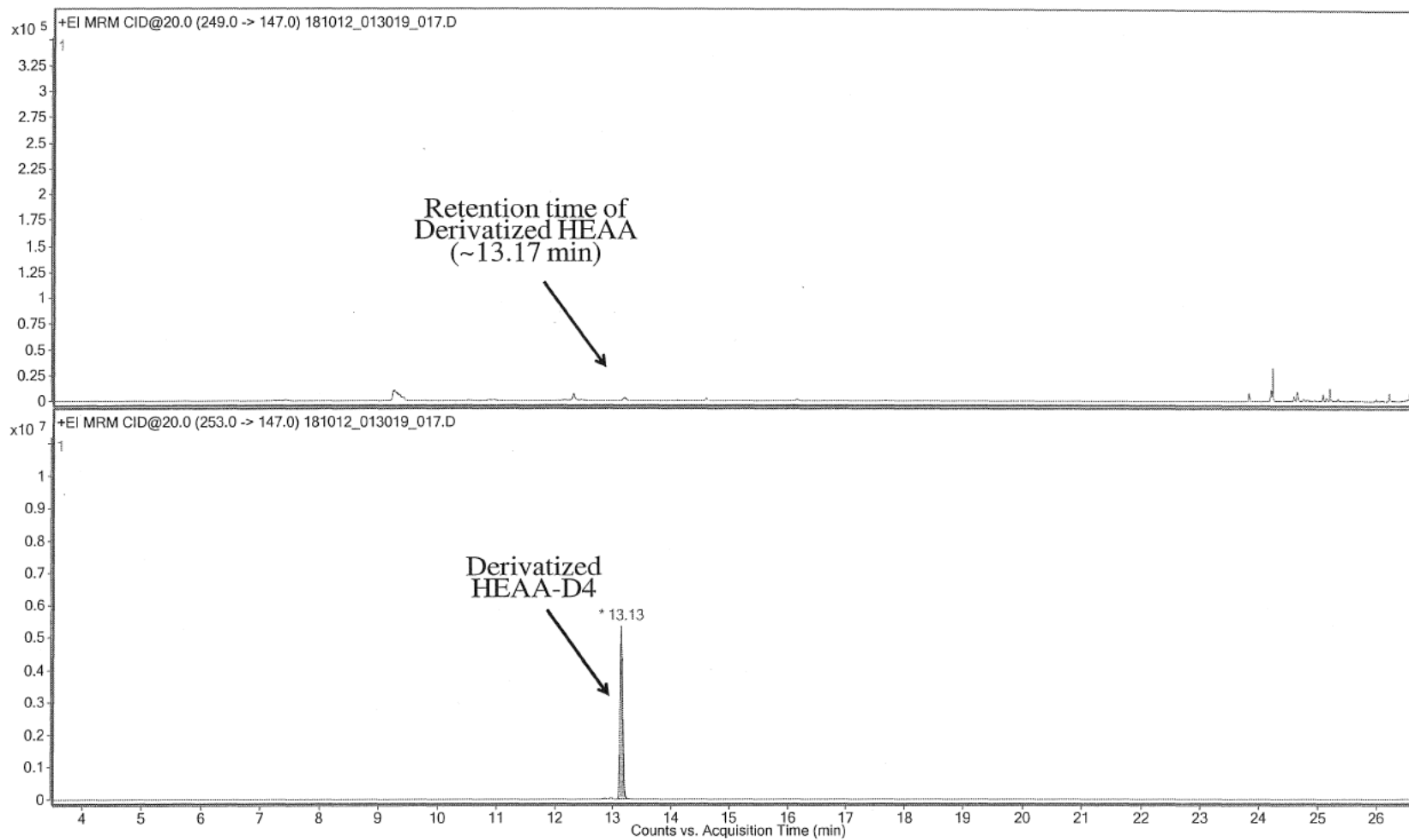


Figure 10. Typical Chromatogram (GC/MS-MRM) of Acetonitrile Solvent Blank

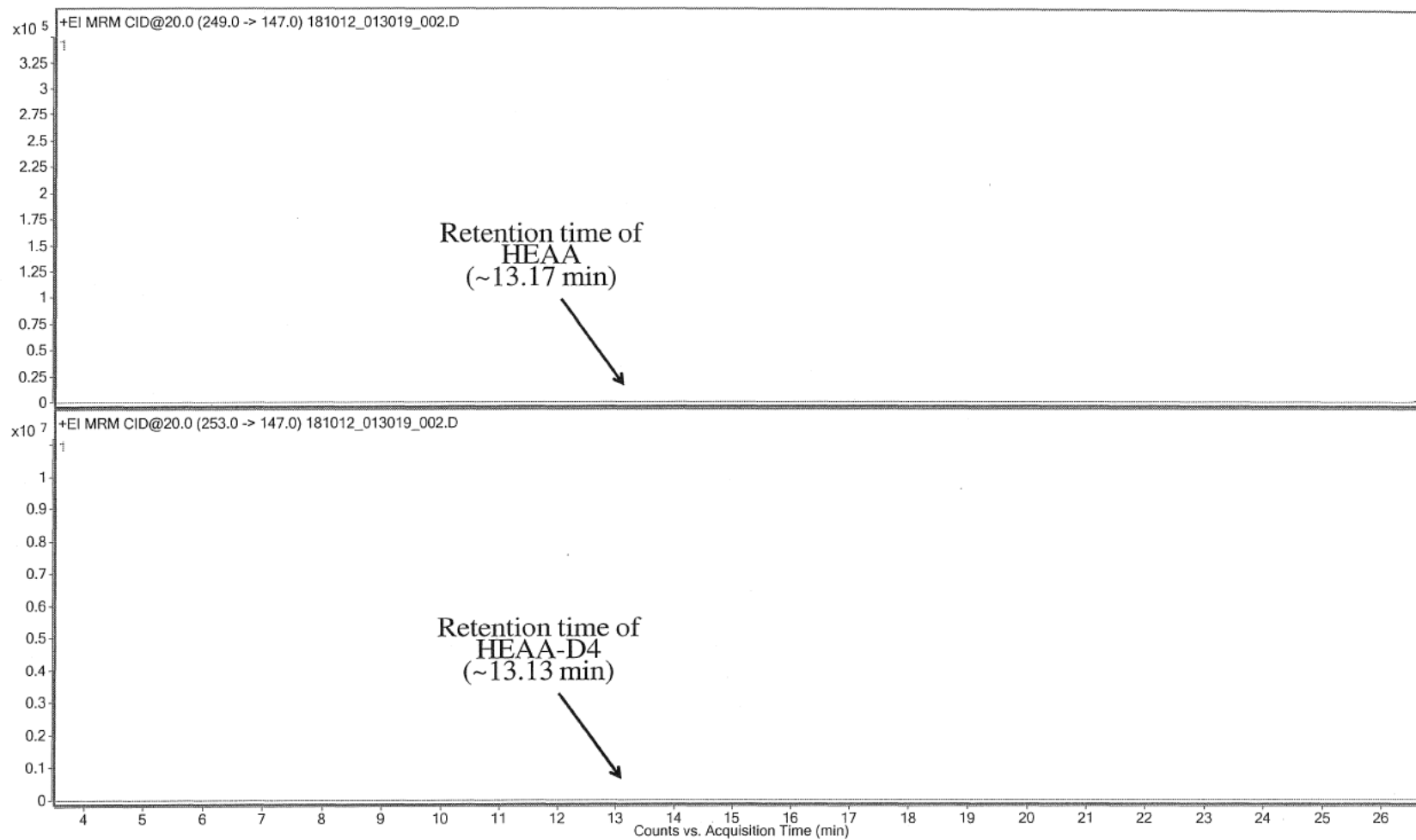


Figure 11. Example GC/MS Full Scan Electron Ionization Mass Spectra of 100 mg 1,4-Dioxane / L Ethyl Acetate

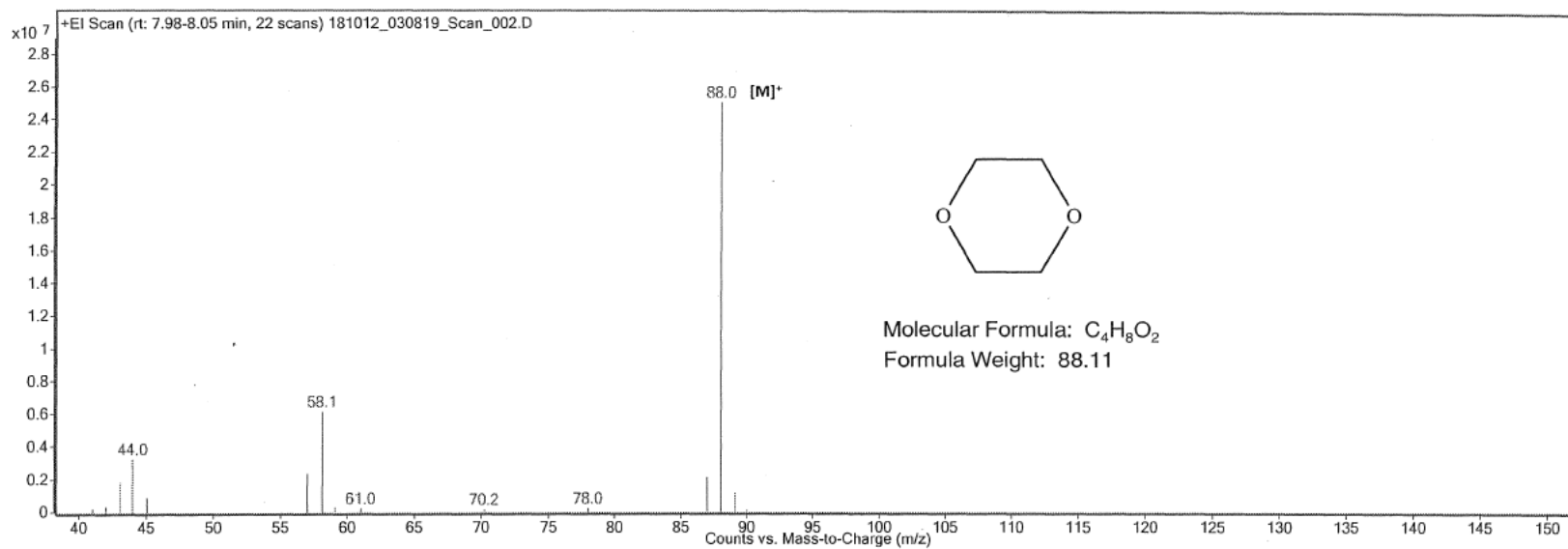


Figure 12. Example GC/MS Full Scan Electron Ionization Mass Spectra of 30 mg 1,4-Dioxane-D8 / L Ehtyl Acetate

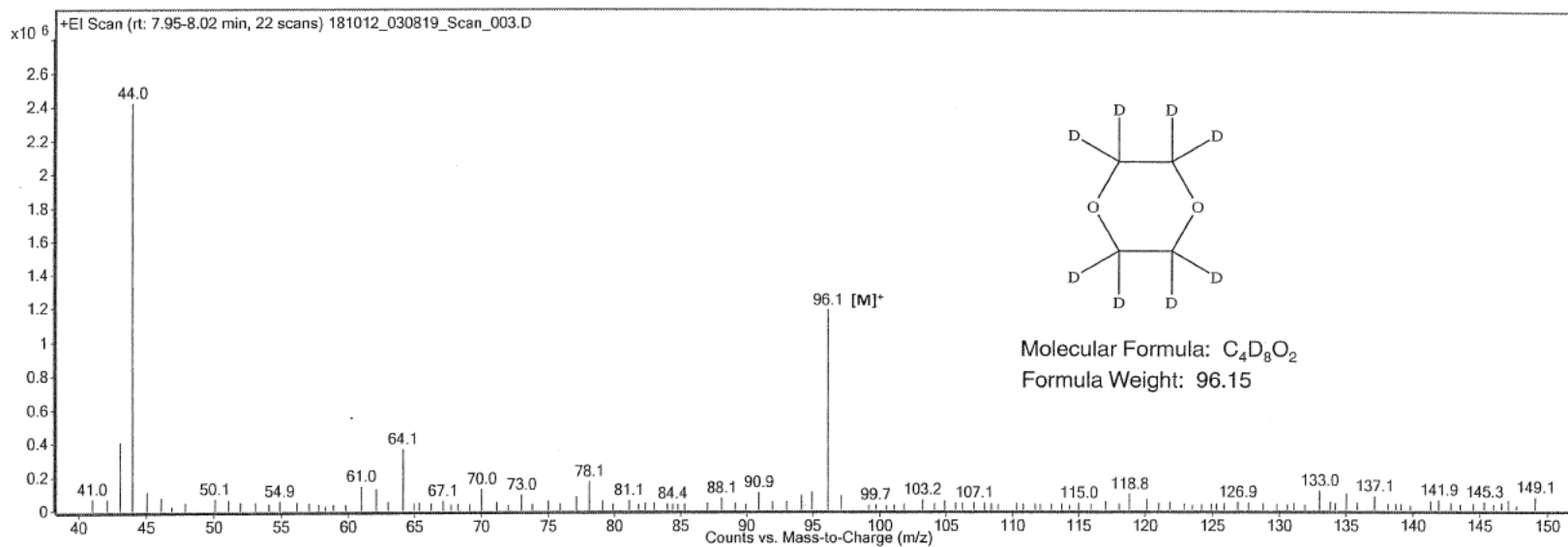


Figure 13. Example GC/MS-MS Full Scan Electron Ionization Mass Spectra of 200 mg Derivatized HEAA / L Acetonitrile

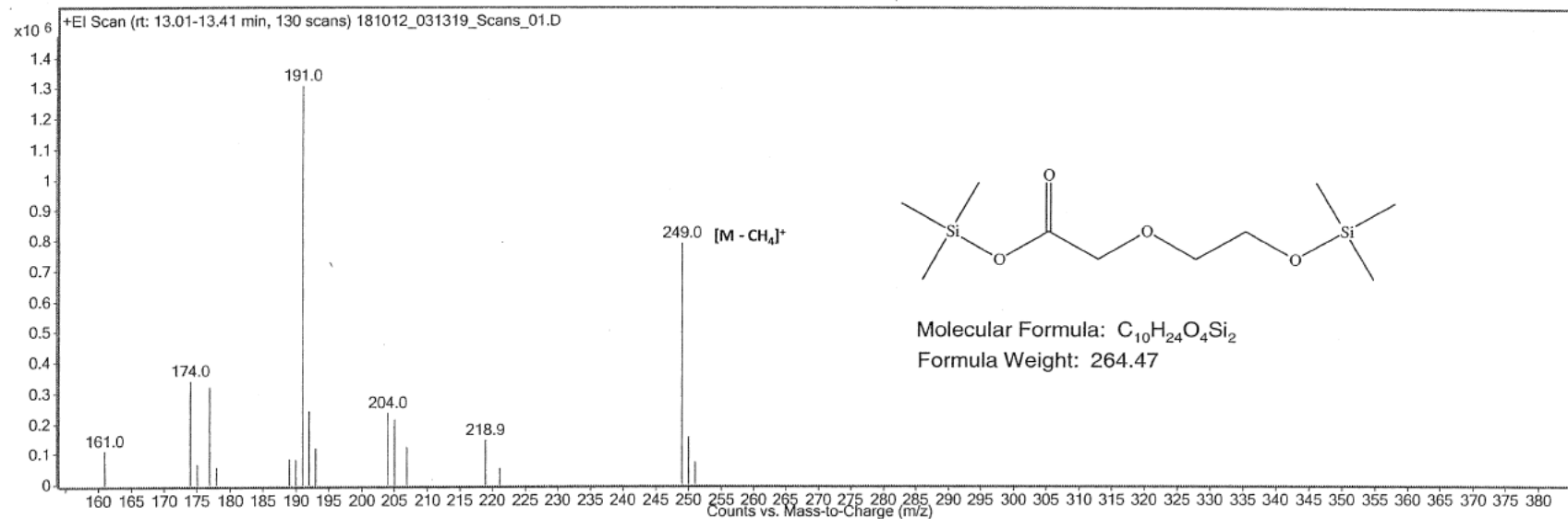


Figure 14. Example GC/MS-MS Product Ion Scan Electron Ionization Mass Spectra of 200 mg Derivatized HEAA / L Acetonitrile (m/z 249)

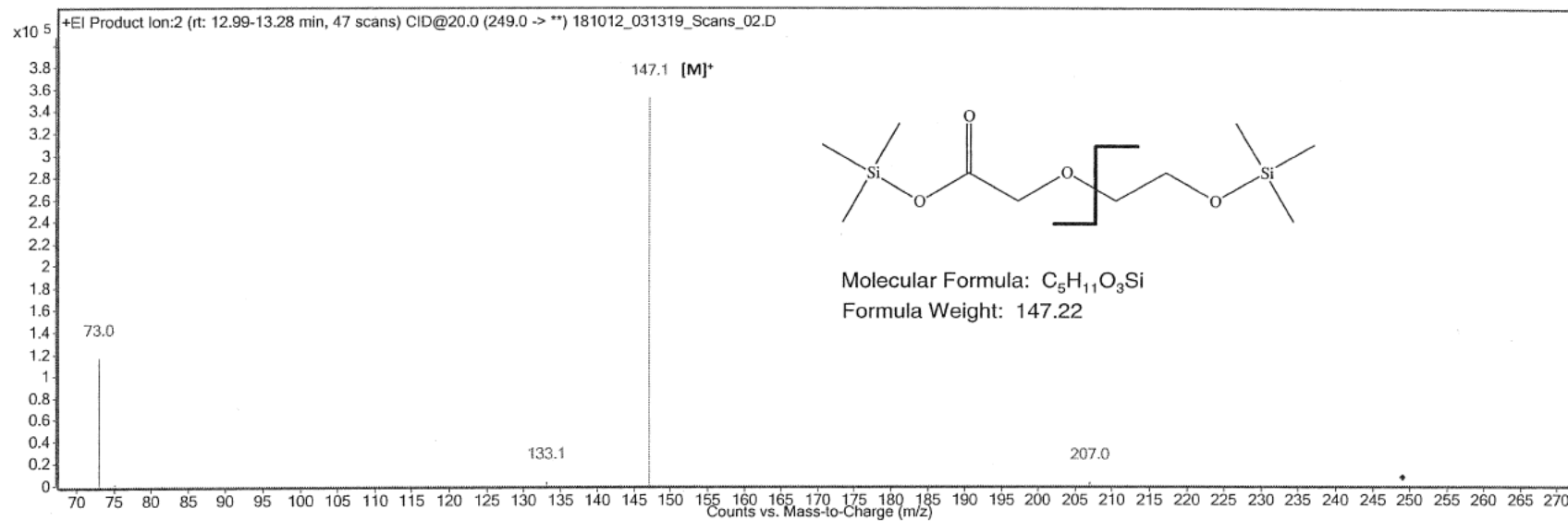
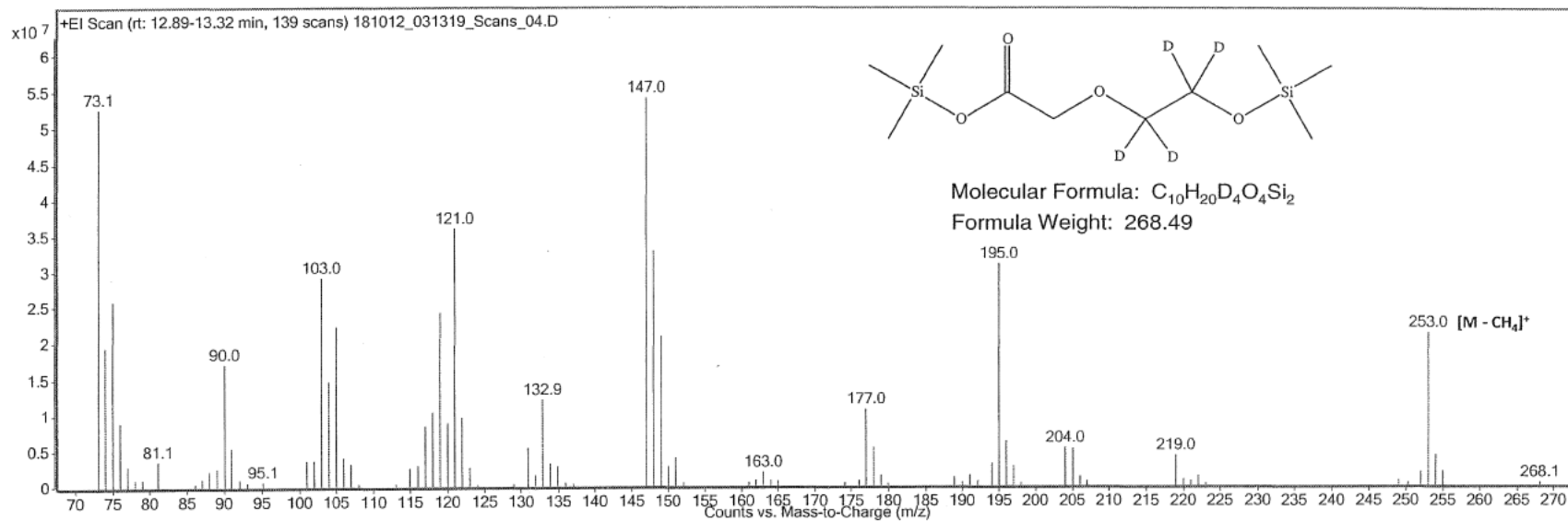
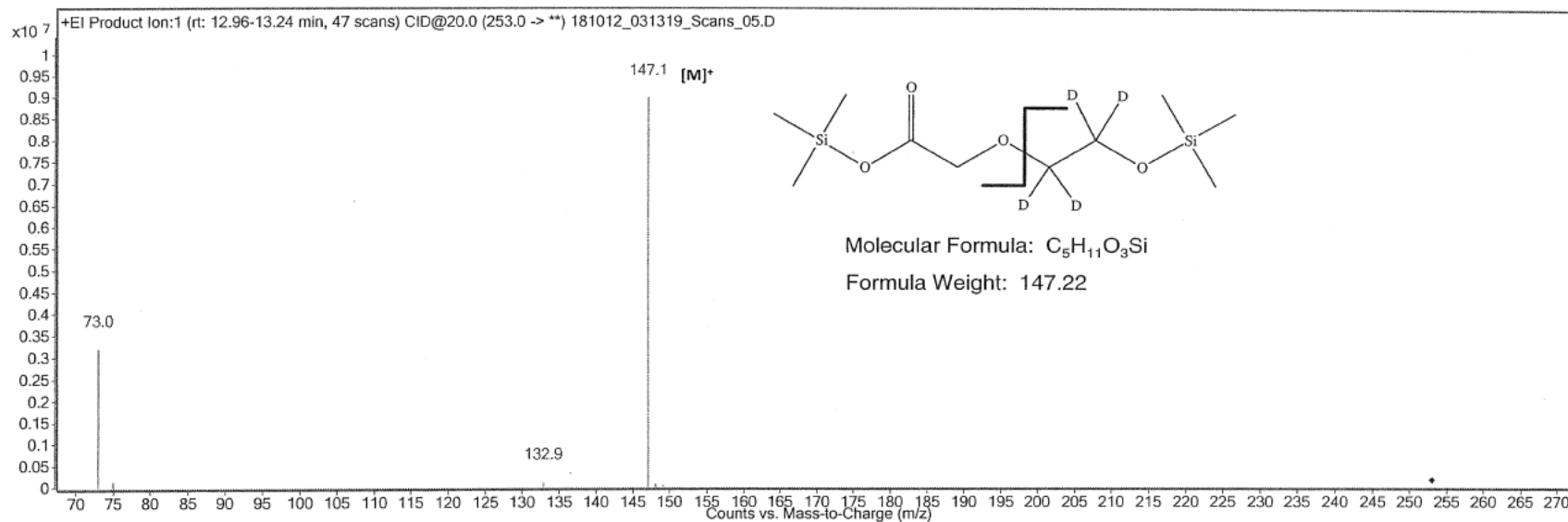


Figure 15. Example GC/MS-MS Full Scan Electron Ionization Mass Spectra of 200 mg Derivatized HEAA-D4 / L Acetonitrile



/ L Acetonitrile (m/z 253)

1,4-Dioxane: Investigating the Mode of Action for 1,4-Dioxane-Induced Liver Tumors in Female
B6D2F1/Crl Mice

APPENDIX F. Transcriptomics Report

Transcriptomic analyses of the liver in female mice exposed to 1,4-dioxane in drinking water: summary of findings

AUGUST 27, 2019

ToxStrategies

Innovative solutions
Sound science

Transcriptomic analyses of the liver in female mice exposed to 1,4-dioxane in drinking water: summary of findings

AUGUST 27, 2019

PREPARED FOR:

Stephen Risotto
American Chemistry Council

PREPARED BY:

ToxStrategies, Inc.
31 College Place
Suite B118
Asheville, NC 28801

Table of Contents

1	Background	4
2	Analysis Methods	4
2.1	RNA Sequencing	4
2.2	Data processing and analysis	5
2.3	Identification of genes with significant differential expression across concentrations	5
2.4	Identification of pathway-level alterations across concentrations	6
2.5	Benchmark Dose Analysis.....	8
3	Results	8
3.1	Identification of differentially expressed genes and enrichment of gene sets (signaling pathways)	8
3.2	Benchmark dose modeling analysis.....	9
4	Summary.....	10
5	References.....	11
	Appendix I	12

1 Background

ToxStrategies, Inc. reviewed gene expression data from livers collected from female B6D2F1(BDF1)/Crl mice exposed to 0, 40, 200, 600, 2000, or 6000 ppm 1,4-dioxane in the drinking water for 7, 28, or 90 days in support of an investigation of the mode of action for 1,4-dioxane-induced murine liver tumors. Transcriptomic responses in 1,4-dioxane-exposed mice were compared to time-matched control mice. Pathway analysis based on altered genes, as well as benchmark dose modeling and functional classification were conducted, and a summary of the results of these analyses is presented herein.

2 Analysis Methods

Liver tissues collected from female mice were formalin-fixed, paraffin-embedded and sectioned on to slides. Tissue was scraped from these sections and processed for RNA sequencing using the TempO-Seq platform (BioSpyder Technologies, Carlsbad, CA). RNA sequencing data were processed, and comparative analyses were conducted to identify genes that were significantly differentially expressed for each treatment group compared to appropriate controls for the same timepoint. Samples that did not pass quality control metrics intended to ensure a successful sequencing experiment were removed from the analysis. The differential expression analysis results were then applied to identify enriched gene sets and signaling pathways among the treatment-related alterations in transcriptomic signaling. Gene set enrichment analysis was conducted two ways: 1.) genes that were significantly differentially expressed according using the criterion of a p-value adjusted for multiple hypothesis testing of <0.1 (i.e., a false discovery rate (FDR) $< 10\%$) were queried for significant enrichment of known gene sets and signaling pathways using a hypergeometric test and known gene sets from the Molecular Signature Database (MSigDB)¹; 2.) all genes were included in enrichment analysis using a ranked list based on statistical significance according to the method published by Subramanian et al., 2005². A fold change filter was not applied; in other words, genes with consistent altered expression compared to controls for a certain treatment group were carried forward to pathway analysis even if they demonstrated a small magnitude of change. Additionally, gene expression data were applied in benchmark dose (BMD) modeling and results were used to identify enriched gene sets and signaling pathways among the significantly dose-responsive genes. This analysis was conducted using the BMDExpress software, v2.2³.

2.1 RNA Sequencing

A single 4-6 μm section was microtomed from one formalin-fixed paraffin embedded (FFPE) block per liver sample (one per animal) for 5 animals per treatment group (study

¹ <http://software.broadinstitute.org/gsea/msigdb>

² Subramanian, A et al., 2005. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *PNAS*

³ <https://github.com/auerbachs/BMDExpress-2/wiki>

day and concentration). Sections were mounted on a glass slide (uncovered), yielding a total of 40 samples for RNA sequencing. Slides were shipped to BioSpyder Technologies (Carlsbad, CA) where liver tissue was scraped from each unstained slide into lysis buffer. The resulting cell lysates were processed according to the TempO-Seq protocol, as previously described (Yeakley et al., 2017). Briefly, mRNA targets were hybridized with a detector oligomer probe mix. Nuclease digestion of excess oligomers was conducted, followed by ligation to result in a pool of amplification templates sharing PCR primer “landing sites.” Following PCR, clean-up, and pooling (all libraries have a unique adapter barcode such that all data may be appropriately separated by individual sample following sequencing), the DNA libraries from each liver sample from each animal were sequenced using a HiSeq 2500 Ultra-High-Throughput Sequencing System (Illumina, San Diego, CA). There was no sample pooling for analytical purposes, nor were technical replicates run.

2.2 Data processing and analysis

Sequencing data were analyzed using multiple packages in the R software, v3.5.2 (cran.r-project.org/). The number of sequenced reads per probe were extracted from FASTQ files generated from the sequencing experiment, with each probe representing a gene-specific sequence. Some genes are targeted with multiple probes to detect important alternative splicing variants. An alignment step was not required because the gene-specific probe sequences are known. A “counts file” was generated that includes the number of counts for each probe, for each sample. The number of counts represents the number of times the probe was read by the sequencer, and each sample represents a FFPE liver section from an individual animal. Samples with an overall sequencing depth (total reads across all probes) lower than two standard deviations below the mean sequencing depth across all samples were excluded from the comparative analysis. A total of 7 samples were removed from the analysis based on this data quality criterion. The DESeq2 R package (v.1.22.2) (Love, Huber, & Anders, 2014) was used to normalize data such that sample-to-sample variation in sequencing depth was considered.

2.3 Identification of genes with significant differential expression across concentrations

Statistical methods within DESeq2 were used to identify differentially expressed genes associated with exposure by conducting comparisons between groups that share a characteristic (i.e., test agent concentration), with betaPrior set to “false.” (Love et al., 2014). In the present study, the various treatment groups were compared to controls of the same sex. The DESeq2 method is based on the calculation of shrunken logarithmic fold changes in expression (representing ratio of exposure over unexposed samples), which are then divided by their standard errors to conduct Wald tests for differential expression. These tests produce z-statistics that are compared against standard normal distribution curves, resulting in Wald test p-values, that are then adjusted for multiple testing using the Benjamini and Hochberg (BH) procedure (Love et al., 2014). Differentially expressed probes (DEPs) were defined as those with false discovery rate (FDR) <10% for any chosen comparison between treatment groups, based on a BH-adjusted p-values, paralleling

methods previously used to analyze RNA sequencing data (Chappell et al., 2017; Rooney et al., 2017). All samples that share an assigned characteristic, in this case the concentration of 1,4-dioxane, are grouped together to evaluate the differences between each group. The expression level of each probe is averaged across the samples that are commonly classified before statistical tests are conducted between the various groups. Unique differentially expressed genes (DEGs) were identified from respective DEPs.

2.4 Identification of pathway-level alterations across concentrations

Biological pathways that were associated with the transcriptomic response profiles were identified using gene set enrichment analysis. For the genes for which multiple probes were used to measure expression, the probe with the highest sequencing count (total number of reads) across all samples was selected as the representative gene to be used in the enrichment analysis. Mouse gene identifiers were converted into human identifiers, when available, using the R package biomaRt (v2.38.0) based on the Ensembl genome database⁴. Human gene identifiers were then queried for enrichment of gene sets within the Canonical Pathways sub-collection several curated genesets available through the Molecular Signatures Database (MSigDB)⁵. Specifically, the following collections were used: Hallmark gene sets, Curated gene sets (Chemical and genetic perturbations and Canonical pathways), and Gene Ontology (GO) gene sets. The sub-collection Canonical Pathways was used as the primary source for evaluation, because this collection provides a well-characterized and well-maintained (i.e., updated) list of genesets and pathways. The Canonical Pathways sub-collection includes gene sets from several pathway databases, including the BioCarta online maps of metabolic and signaling pathways (BIOCARTA) (Nishimura, 2001), the Kyoto Encyclopedia of Genes and Genomes (KEGG) (Ogata et al., 1999), the Pathway Interaction Database (PID) (Schaefer et al., 2009), and the Reactome database of reactions, pathways, and biological processes (REACTOME) (Croft et al., 2011)). The other collections were included for confirmation of geneset enrichment profiles and to identify any novel genesets that may only be represented in one collection. More information regarding the various collections can be found within the Broad Institute's GSEA Molecular Signatures Database website: <http://software.broadinstitute.org/gsea/msigdb/index.jsp>.

Enrichment of gene sets and pathways was evaluated by two different methods: 1) GSEA computational method - employed the GSEA platform made available by the Broad Institute (Subramanian et al., 2005), 2) general hypergeometric method - employed a more simple hypergeometric test. The GSEA computational method⁶ determines whether sets of genes (e.g., a molecular signaling pathway) are significantly concordant between various defined groups (in the case presented herein, different doses) based on a ranking all genes evaluated according to a designated metric (in this, the statistical measure of significance of expression differences between treated and control mice). An enrichment score is

⁴ <http://uswest.ensembl.org/index.html>

⁵ <http://software.broadinstitute.org/gsea/msigdb/index.jsp>

⁶ <http://software.broadinstitute.org/gsea/index.jsp>

calculated for each gene set in the defined list, which reflects the degree to which a gene set is overrepresented at either end of the ranked list (i.e. down- vs. up-regulated genes). The GSEA statistical method was applied within the Platform for Integrative Analysis of Omics data (PIANO) R package (v1.22.0) (Varemo, Nielsen, & Nookaew, 2013) (the GSEA R package was not used because it has not been maintained since 2005). Genes were first ranked according to Wald statistical values generated during the DESeq2 analysis, where genes with the greatest magnitude of significant increases in expression having the highest positive Wald statistical value, and genes showing the greatest magnitude of a significant decrease in expression having the lowest negative Wald statistical value. Genes with minimal expression changes (i.e., low or no change associated with treatment) had Wald statistical values near zero. The GSEA method was then used to determine whether the defined set of genes in each pathway were randomly distributed throughout the ranked gene list, representing a non-significant pathway enrichment; conversely, if the defined set of genes were primarily present at the top/bottom of the ranked list, this represented a significant pathway enrichment with distinct directionality (i.e., primarily up- or down-regulated). Gene set enrichment significance was calculated using permutation-based nominal p-values based on weighted Kolmogorov Smirnov test enrichment scores, and adjusted for multiple hypothesis testing by calculating FDRs using the BH method, as previously described (Subramanian et al., 2005). Gene sets with an FDR <10% were considered to be significantly enriched. A requirement was set that at least 5 and no more than 500 genes from each gene set queried must also been included in the experimental data being evaluated for enrichment (slightly more inclusive than the minimums of 15 and 25 in the original GSEA article (Subramanian et al., 2005) and the current GSEA online User's Guide, respectively).

For the hypergeometric method, all DEGs for each treatment group (i.e., an FDR of <10% as described above) were tested for over-representation among the gene sets in the Canonical Pathways sub-collection using Fisher's combined probability test function with the PIANO package. The magnitude of induction/reduction of the genes was not used as a limiter in this approach; i.e., no fold-change filter was applied. Gene sets with an FDR <10% were considered to be significantly enriched. As stated above, a requirement was set that at least 5 and no more than 500 genes from each gene set queried must also been included in the experimental data being evaluated for enrichment.

The results of both gene set enrichment analysis methods were evaluated to inform and understand treatment-related effects. The results of the hypergeometric test for overrepresentation were the focus of the results described in the main body of this report as the pre-ranked GSEA method was determined to not be as robust of a method based on the fact that minimal change was seen at the lower doses. Although the top-most significantly enriched gene sets were similar across the two methods, the nature of the algorithm resulted in significant enrichment of some gene sets for which no members (individual genes) were differentially expressed in the lower dose groups.

To investigate enrichment of gene sets related to DNA damage response and repair further than looking at relevant gene sets within the Canonical Pathways collection, a collection of gene sets was curated by searching all gene sets in MSigDB for key words related to

DNA damage response. A hypergeometric test was used to test enrichment of this specific curated list of 77 gene sets related to DNA damage response.

2.5 Benchmark Dose Analysis

Dose–response modeling of the DEGs was conducted using the BMDEExpress software (v2.2) (Phillips et al., 2019). Briefly, probe IDs from the TempO-Seq experiment were translated into Ensembl IDs using the biomaRt R package (v2.38.0). Normalized expression data as generated using DESeq2 were then loaded into BMDEExpress without transformation. A Williams trend test (with p-value cutoff = 0.05) was used to identify genes altered by exposure to 1,4-dioxane. No fold-change filters or correction for multiple tests were applied. BMD analysis was conducted using the following models: linear, power, Hill, 2° and 3° polynomial models, and exponential models 2-5. The models were run assuming constant variance and a benchmark response (BMR) of 1 standard deviation.

3 Results

3.1 Identification of differentially expressed genes and enrichment of gene sets (signaling pathways)

Results of these analyses demonstrate that there is an overall lack of transcriptomic response at the 40 and 200 ppm concentrations. Using the criterion detailed above for the gene set enrichment analysis, very few genes were changed in the mice exposed to these concentrations relative to the time-matched controls. At 90 days, only 20 genes were altered by 200 ppm 1,4-dioxane, with fewer genes altered by this concentration at the earlier timepoints, and practically no response at any timepoints for 40 ppm (only one gene was differentially expressed in the 40 ppm group at 28 and 90 days, none at 7 days). Pathway enrichment analysis of significantly differentially expressed genes, thus, did not yield any significantly enriched gene sets/pathways using the hypergeometric test.

At the 600 ppm concentration, a general stress response to the treatment was observed at 7 days, indicated by the down-regulation of a broad range of normal metabolic and cellular processes (e.g., citric acid cycle, metabolism of amino acids, and glucose metabolism, among others), with up-regulation of only 5 gene sets (e.g., ribosome biogenesis and translational regulation). The same response was not observed at 28 days. At 90 days, the signal shifted to a response that is similar to what is seen at the higher concentrations (described below) in regard to up-regulation of xenobiotic metabolism, particularly phase I metabolism (e.g., KEGG “Metabolism of xenobiotics by cytochrome P450” enriched by the up-regulation of *Cyp3a4* and several *Ugt2b* isoforms). Down-regulation of complement and coagulation cascade-related gene sets was observed at both 7 and 90 days, which is discussed further in the following paragraphs for the higher concentrations.

At both the 2000 and 6000 ppm concentrations, genes that were significantly differentially expressed reflected up-regulation of xenobiotic metabolism pathways at all timepoints. This signal was seen at a higher degree at 6000 than at 2000 ppm, and increased over the

timepoints evaluated, both in the number of significantly differentially expressed genes within the gene sets (which confers a greater level of statistical significance), as well as the number of gene sets/pathways that were significantly enriched between the treatment groups and time points. In other words, the enrichment of these xenobiotic metabolism gene sets appears to increase with both dose and time. Gene sets related to xenobiotic metabolism were significantly enriched (up-regulated), for example KEGG “Metabolism of xenobiotics by cytochrome P450”, Reactome “Biological oxidations” and Reactome “Phase II conjugation”, among others. The enrichment of these gene sets was driven by genes that encode relevant glutathione transferases, UDP-glucuronosyltransferases, and CYPs.

Another major signal at these two higher concentrations is the enrichment of the complement and coagulation cascade gene set, and related gene sets, in the negative direction (loss of signal), owing to the down-regulation of genes encoding proteolytic subunits in the complement system and gene members of the serpin family (serine protease inhibitors), relative to controls. Deficiency in certain serpins (e.g., *Serpina1*) has been observed in relation to liver damage⁷, and the complement system is related to innate immune responses. Down-regulation of genes involved in lipid metabolism was also observed, which is a signal aligned with a liver injury at these higher concentrations. These down-regulated signals were observed at a greater degree in the 6000 vs. the 2000 ppm treatment group.

At the 90-day timepoint, gene sets related to mitotic cell cycle and DNA synthesis were also significantly enriched, indicating a proliferative response and mitosis. This was seen primarily in the 6000 ppm treatment group, but also minimally in the 2000 ppm group. This proliferative response was not evident at earlier time points.

Gene sets related to DNA damage response and repair were not significantly enriched when utilizing the Canonical Pathways collection of gene sets available in the MSigDB. Additionally, using the more extensive collection of gene sets that was curated to identify all gene sets related to DNA damage response as described in the Methods (2.4), no treatments had any significant enrichment at 7 or 28 days. At 90 days, some of these gene sets were significantly enriched; however, the enrichment of these gene sets was due to up-regulation of genes involved in apoptotic signaling, while DNA damage repair genes were not up-regulated.

3.2 Benchmark dose modeling analysis

Benchmark dose modeling analysis and functional classification of the gene-level BMD results confirmed the gene set enrichment results detailed above that were obtained from analysis of each individual concentration separately. For example, at 90 days, the Reactome⁸ gene set “Glutathione conjugation” was significantly enriched (median BMD for the gene set >1500 ppm). Also at 90 days, “Innate immune system” was down-regulated (median BMD >3200 ppm), which is related to the down-regulation of

⁷ Law, RHP et al., 2006. An overview of the serpin superfamily. *Genome Biol*

⁸ <https://reactome.org/>

complement and coagulation cascade signal as discussed above. Gene sets related to cell cycle and mitosis were also up-regulated and enriched according to the BMD analysis (median BMDs for these gene sets were 3400 ppm or higher). A single “DNA repair” gene set was significantly enriched among dose-responsive genes (median BMD >4000 ppm). The genes within this gene set that were identified as dose-responsive are primarily histone- and polymerase-encoding genes involved in DNA synthesis. The *Rad51* repair gene was identified as dose-responsive, although it should be noted that this gene was not significantly differentially expressed at any of the doses when compared to the controls and had a low level of expression across all of the samples.

At 28 days, the phase II metabolism gene sets were significantly enriched similar to 90 days, with similar BMD values. Gene sets related to cell cycle or mitosis were up-regulated according to the BMD analysis at 28 days, and down-regulation of fatty acid metabolism and immune responses was observed, all of which had a lower level of statistical significance compared to results from 90 day data. At 7 days, the phase II metabolism-related gene sets were also enriched among dose-responsive genes, although the BMD median values were higher compared to those at 28 and 90 days. At 7 days, the same “DNA repair” gene set was enriched as discussed above for 90 days, with histone and ubiquitination genes underlying the enrichment, which are involved in DNA synthesis and may be related to cellular proliferation. Results of the BMDExpress Functional Classification analysis can be found in Appendix I.

4 Summary

In summary, the findings from the transcriptomics analyses of livers from female mice exposed to 1,4-dioxane in drinking water demonstrate an increase in xenobiotic metabolism, a subtle yet significant dose- and time-responsive increase in mitotic cell cycle and cellular proliferation, and a decrease in complement cascade processes and lipid metabolism. The proliferative response appears to only occur at concentrations above 2000 ppm, while xenobiotic metabolism alterations occur as low as 600 ppm. The lack of significant changes in signaling pathways/gene sets at the transcriptomic level at concentrations below 600 ppm indicates that 600 ppm represents a threshold between a lack of response and a response. However, the response at 600 ppm appears to be temporally sensitive with a transient non-specific cellular stress response after one week of exposure and with up-regulation of xenobiotic metabolism at the 90 day timepoint. Thus, a threshold for transcriptomic responses related to adverse effects may in fact be higher than 600 ppm, as enrichment of gene sets related to a proliferative response appears at higher concentrations, and BMDs for all enriched genesets are > 600 ppm according to BMD analysis. Importantly, activation of DNA damage response and/or repair mechanisms was not evident at the concentrations and time points evaluated.

5 References

- Chappell, G. A., Israel, J. W., Simon, J. M., Pott, S., Safi, A., Eklund, K., . . . Furey, T. S. (2017). Variation in DNA-Damage Responses to an Inhalational Carcinogen (1,3-Butadiene) in Relation to Strain-Specific Differences in Chromatin Accessibility and Gene Transcription Profiles in C57BL/6J and CAST/EiJ Mice. *Environmental Health Perspectives*, 125(10), 107006. doi:10.1289/EHP1937
- Croft, D., O'Kelly, G., Wu, G., Haw, R., Gillespie, M., Matthews, L., . . . Stein, L. (2011). Reactome: a database of reactions, pathways and biological processes. *Nucleic Acids Research*, 39(Database issue), D691-697. doi:10.1093/nar/gkq1018
- Love, M. I., Huber, W., & Anders, S. (2014). Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. *Genome Biology*, 15(12), 550. doi:10.1186/s13059-014-0550-8
- Nishimura, D. (2001). BioCarta. *Biotech Softw Internet Rep*, 2, 117-120.
- Ogata, H., Goto, S., Sato, K., Fujibuchi, W., Bono, H., & Kanehisa, M. (1999). KEGG: Kyoto Encyclopedia of Genes and Genomes. *Nucleic Acids Research*, 27(1), 29-34. doi:10.1093/nar/27.1.29
- Phillips, J. R., Svoboda, D. L., Tandon, A., Patel, S., Sedykh, A., Mav, D., . . . Auerbach, S. S. (2019). BMDEExpress 2: enhanced transcriptomic dose-response analysis workflow. *Bioinformatics*, 35(10), 1780-1782. doi:10.1093/bioinformatics/bty878
- Rooney, J. P., Ryan, N., Chorley, B. N., Hester, S. D., Kenyon, E. M., Schmid, J. E., . . . Corton, J. C. (2017). From the Cover: Genomic Effects of Androstenedione and Sex-Specific Liver Cancer Susceptibility in Mice. *Toxicological Sciences*, 160(1), 15-29. doi:10.1093/toxsci/kfx153
- Schaefer, C. F., Anthony, K., Krupa, S., Buchoff, J., Day, M., Hannay, T., & Buetow, K. H. (2009). PID: the Pathway Interaction Database. *Nucleic Acids Research*, 37(Database issue), D674-679. doi:10.1093/nar/gkn653
- Subramanian, A., Tamayo, P., Mootha, V. K., Mukherjee, S., Ebert, B. L., Gillette, M. A., . . . Mesirov, J. P. (2005). Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proceedings of the National Academy of Sciences of the United States of America*, 102(43), 15545-15550. doi:10.1073/pnas.0506580102
- Varemo, L., Nielsen, J., & Nookaew, I. (2013). Enriching the gene set analysis of genome-wide data by incorporating directionality of gene expression and combining statistical hypotheses and methods. *Nucleic Acids Research*, 41(8), 4378-4391. doi:10.1093/nar/gkt111
- Yeakley, J. M., Shepard, P. J., Goyena, D. E., VanSteenhouse, H. C., McComb, J. D., & Seligmann, B. E. (2017). A trichostatin A expression signature identified by TempO-Seq targeted whole transcriptome profiling. *PloS One*, 12(5), e0178302. doi:10.1371/journal.pone.0178302

Appendix I

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets within BMDExpress2.2 software.

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
90Day	Signal Transduction	2.17E-50	1	4.31E-50	hnrnpf;gpnmb;klb;notum;arhgef6;tme d5;cenpu;fmln12;rhov;hist1h4h;tubb6;ppid;gng11;lpar3;ranbp9;iqgap2;hgfac;rdh7;ccnc;cbx6;irs2;c5ar2;hist1h4i;hist1h3c;pdk4;adh4;nr5a2;mapk14;aldh1a7;olfr1033;ift52;wasf2;pin1;apob;aldh8a1;gata2b;pdk1;tubb4b;yy1;ywhaz;fgd4;vav1;ube2m;tubb2a;tuba1b;ttr;tnfrsf10b;tln1;tiam1;rasa1;tgifa;tek;wwc1;nrg1;sdca4;kntc1;camkk2;sos1;sh3gl3;rarg;rtkn;rock2;rock1;rbp1;rarg;psen2;psap;pml;plg;pcsk5;gpr143;nudc;ntrk2;nfkbia;myo9b;mtnr1a;rdh11;mdm2;il1rap;ikbkg;hsp90aa1;h2afx;hebp1;hdac2;gna13;gfra1;gab1;fn1;fgf1;opn3;dli1;ddx5;cdkn1a;cdc42;cbfb;ctnnb1;casr;c3;btrc;areg;ar;apoe;apoc3;ap2m1;adra1b;adora1;abca4;sec13;cenpf;lgr4	3180.5077	3387.63	74.8133	1774.83128	3292.92402	1816.33815	CONFLICT	0.545454545	0.454545455	
90Day	Signaling by GPCR	2.00E-36	1	4.31E-36	arhgef6;gng11;lpar3;rdh7;c5ar2;olfr1033;apob;ttr;sdca4;camkk2;sos1;rock2;rock1;rbp1;psap;gpr143;mtnr1a;rdh11;hebp1;gna13;opn3;cdc42;casr;c3;apoe;apoc3;adra1b;adora1;abca4	3497.3139	3874.11	98.0082	2108.92646	3964.51885	2022.13737	CONFLICT	0.551724138	0.448275862	
90Day	GPCR downstream signalling	6.06E-36	1	1.27E-35	arhgef6;gng11;lpar3;rdh7;olfr1033;apob;ttr;sdca4;camkk2;sos1;rock2;rock1;rbp1;psap;gpr143;mtnr1a;rdh11;hebp1;gna13;opn3;cdc42;casr;c3;apoe;apoc3;adra1b;adora1;abca4	3443.04833	3718.565	98.0082	2126.90737	3953.14582	2031.24843	CONFLICT	0.535714286	0.464285714	
7Day	Signal Transduction	2.94E-35	1	5.38E-35	akr1c6;clasp2;ranbp10;tmed5;rps6kb1;myh14;rgs12;reep6;hist1h4h;rraga;hist1h2bc;ppid;cenpk;ranbp9;gsk3b;vps29;ptges3;metap2;kalrn;iqgap2;hgfac;avpr1a;suz12;tax1bp1;nckap1;dli1;hist2h2ac;pdhx;mapk3;polr2h;klhl12;pebp1;apob;lingo1;sept7;tubb4b;ywhaz;yes1;pak2;uba52;tubb2a;tuba4a;ttr;rasa1;tgifbr1;tfdp1;rdh16f2;sdca3;stat1;sox6;smpd2;sel1l;rgs9;ptpn11;flna;pten;prkar2a;ppp2cb;prkc;prkci;pfn2;pfn1;pcsk5;ncoa2;ncoa1;myh9;mdk;lrp5;lrp1;kras;kif2a;jak1;itpr2;il1rap;hsp90aa1;hist2h2aa1;hebp1;gna13;gfra1;fgf1;f2;adgre1;eif4ebp1;dld;csnk2b;cdkn1a;cdc42;ccnk;ctnnb1;casp9;calm3;calm2;cab39;btrc;bmi1;cxcr5;atp6v1e1;apoe;xiap;abl1;wpp1;jak1;c14;xpo1;brk1	3316.45352	3443.57	54.5232	1516.89313	3318.4404	1535.54406	CONFLICT	0.596153846	0.403846154	
90Day	G alpha (s) signalling events	6.28E-35	1	9.68E-35	gng11;olfr1033	4747.235	4747.235	4640.23	151.327922	4677.79404	115.134904	UP	1	0	
7Day	G alpha (s) signalling events	3.63E-30	1	7.07E-30	reep6	2593.62	2593.62	2593.62		2593.62		DOWN	0	1	
90Day	Olfactory Signalling Pathway	3.68E-29	1	6.68E-29	olfr1033	4640.23	4640.23	4640.23		4640.23		UP	1	0	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
28Day	Signal Transduction	1.44E-28	1	2.25E-28	phlpp1;akr1c6;atp6v0e2;arhgap45;pyg o2;zwilch;ppid;nts;akr1c12;cysl1r1;ranb p9;dynl1;iqgap2;tax1bp1;reep1;dlc1;akr1c19;cenpt;hist1h4;adh4;map3k11;olfr378;apob;aldh8a1;sept7;a2m;cdc14a;tubb4b;stradb;ube2m;tubb2a;tnfrsf10b;tfdp1;rdh16f2;cx3cl1;polr2a;arhgdia;ppp3cb;pfn1;pdpk1;p4hb;sqstm1;notch1;cxcl9;mdm2;mapkapk2;lrp1;il1rap;ikbk;hgs;hbegf;gpc4;gnb5;fn1;fgf1;f2;cdc42;ccnk;c3;bmi1;atp6v1e1;app;apoe;birc2;agt;adora1;adcy9;mylk;akr1c14;brk1	3861.86604	4068.31	160.43	1724.51206	3869.25966	1672.47843	CONFLICT	0.542857143	0.457142857	
7Day	Signaling by GPCR	3.11E-28	1	4.70E-28	akr1c6;rgs12;reep6;metap2;kalrn;avpr1a;mapk3;apob;ttr;rdh16f2;sd3;rgs9;prkar2a;ppp2cb;lrp1;kras;itpr2;hebp1;gnai3;f2;adgre1;cdc42;calm3;calm2;cxcr5;apoe;akr1c14	3241.27322	3627.04	113.316	1726.92825	3070.17697	1684.78312	DOWN	0.37037037	0.62962963	
7Day	GPCR downstream signalling	6.03E-28	1	9.20E-28	akr1c6;rgs12;reep6;metap2;kalrn;avpr1a;mapk3;apob;ttr;rdh16f2;sd3;rgs9;prkar2a;ppp2cb;lrp1;kras;itpr2;hebp1;gnai3;f2;cdc42;calm3;calm2;cxcr5;apoe;akr1c14	3252.61296	3638.015	113.316	1760.10274	3079.1862	1745.97574	DOWN	0.384615385	0.615384615	
7Day	Olfactory Signaling Pathway	5.14E-24	1	1.15E-23	reep6	2593.62	2593.62	2593.62		2593.62		DOWN	0	1	
28Day	G alpha (s) signalling events	1.35E-17	1	2.01E-17	reep1;olfr378;gnb5;adcy9	3762.577	4079.355	953.648	2070.66227	3627.58322	2285.46734	UP	0.75	0.25	
28Day	Signaling by GPCR	4.40E-17	1	1.01E-16	akr1c6;nts;akr1c12;cysl1r1;reep1;akr1c19;olfr378;apob;rdh16f2;cx3cl1;pdpk1;cxcl9;lrp1;hbegf;gpc4;gnb5;f2;cdc42;c3;app;apoe;agt;adora1;adcy9;akr1c14	3394.649	3361.03	192.988	1888.93514	3334.38703	1842.60481	CONFLICT	0.44	0.56	
28Day	GPCR downstream signalling	2.05E-16	1	4.44E-16	akr1c6;nts;akr1c12;cysl1r1;reep1;akr1c19;olfr378;apob;rdh16f2;cx3cl1;pdpk1;cxcl9;lrp1;hbegf;gpc4;gnb5;f2;cdc42;c3;app;apoe;agt;adora1;adcy9;akr1c14	3394.649	3361.03	192.988	1888.93514	3334.38703	1842.60481	CONFLICT	0.44	0.56	
28Day	Olfactory Signaling Pathway	9.77E-16	1	2.30E-15	reep1;olfr378	4938.03	4938.03	3938.11	1414.10043	4908.99441	1413.50411	UP	1	0	
90Day	Immune System	1.49E-15	1	2.44E-15	erap1;irak3;defb30;tmem173;fbxo22;ist1;cpn2;fbxo9;anapc10;fbxw9;arel1;ndufc2;tubb6;fbxo32;pnp2;serpinb1a;asb2;tbk1;iqgap2;irf7;dcn3;prdx4;ube2k;keep1;znrf2;irs2;c5ar2;hist1h3c;sh2d1b1;slc27a2;mapk14;ceacam2;eda2r;kbtd8;wasf2;usp18;abce1;pin1;apob;mgam;tubb4b;ywhaz;vtg;vav1;ube2m;txn1;tubb2a;tuba1b;ttr;cdc34;pdck;tap2;stx3;serpina1e;sos1;snap23;sih2;rock1;psap;pnp;plaur;nfkbia;myo9b;myo10;mme;man2b1;ilfr;lamp1;il9r;il1rap;il15ra;ikbk;cd74;il18bp;ifngr2;ifnar1;icam1;hsp90aa1;h2-aa;gstp2;il1r4b;gm2a;ftl1;fcgr2b;ctsh;cts;csf1;crp;crf1;cdc42;cd1d1;ctnnb1;c3;btrc;ap2m1;prdx6;ahsg;sec13;mlec	2850.84586	3115.46	45.5307	1738.85671	2772.30212	1757.02643	CONFLICT	0.424242424	0.575757576	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
90Day	Metabolism of proteins	6.94E-14		1	1.44E-13	EIF3M;TRAPPC6B;NOTUM;CREBRF;SPP2;FBXO22;FBXO9;LMAN1;HIST1H4H;FBXW9;MRPL58;BABAM1;TOMM20;TUBB6;RPS27L;FBXO32;STX17;MRPS18B;EID3;GNG11;MRPL54;ASB2;MRPS30;NGLY1;PARK7;MRPS31;PSMD8;SAE1;PIGP;RNF5;DCTN3;UBE2K;MCRS1;ST6GALNAC6;KEAP1;ETFBKMT;HIST1H4I;TOMM70A;MBTPS2;NR5A2;CEACAM2;KBTBD8;DCAF10;USP18;PSMC4;APOB;WDC1;GALNT12;PSMF1;TUBB4B;YY1;INO80C;UBE2M;TXN1;TUBB2A;TUBA1B;TRF;TNC;NUP153;TGFA;MRPL22;CDC34;SERPINA1E;ST3GAL3;SIAH2;EXOC4;RPS12;RAD23A;PML;PLAUR;NFKBIA;MMP2;MME;MDM2;MAN1A;LY6D;LARGE1;ITIH2;INHBC;IKBK;IGFBP4;HDAC2;GPLD1;GNAI3;FN1;FEM1B;F7;DDX5;CTSH;CTSD;CSF1;C3;BTRC;AREG;AR;APOE;AHSG;SEC13;ADAMTS6;GOLM1;DCUN1D2;SPON2	2997.59553	3416.655	25.9884	1655.12855	2813.87591	1586.10242	CONFLICT	0.558823529	0.441176471
7Day	GPCR ligand binding	6.50E-13		1	1.12E-12	AVPR1A;HEBP1;F2;ADGRE1;CXCR5	2128.7362	836.92	156.627	2363.42894	2282.45635	2381.44419	DOWN	0.4	0.6
90Day	Transport of small molecules	1.14E-11		1	2.55E-11	ABCB8;AFG3L2;MICU2;GNG11;SLC29A1;RNF5;CES3A;ABCG2;APOB;TRF;SLC17A8;SLC22A1;SLC1A2;PCSK5;ILPC;SLC6A12;FTL1;CES3B;SLC26A2;BMP1;APOE;APOC3;AP2M1;ABCA4;ANO10;SLCO2B1	2834.34404	3070.33	175.96	1661.76142	2873.32404	1665.68923	CONFLICT	0.423076923	0.576923077
90Day	Post-translational protein modification	2.08E-11		1	3.47E-11	TRAPPC6B;NOTUM;SPP2;FBXO22;FBXO9;LMAN1;HIST1H4H;FBXW9;BABAM1;TOMM20;TUBB6;FBXO32;STX17;EID3;ASB2;NGLY1;PARK7;PSMD8;SAE1;PIGP;RNF5;DCTN3;UBE2K;MCRS1;ST6GALNAC6;KEAP1;ETFBKMT;HIST1H4I;TOMM70A;NR5A2;CEACAM2;KBTBD8;DCAF10;USP18;PSMC4;APOB;WDC1;GALNT12;PSMF1;TUBB4B;YY1;INO80C;UBE2M;TUBB2A;TUBA1B;TRF;TNC;NUP153;TGFA;CDC34;SERPINA1E;ST3GAL3;SIAH2;RAD23A;PML;PLAUR;NFKBIA;MDM2;MAN1A;LY6D;LARGE1;ITIH2;IKBK;IGFBP4;HDAC2;GPLD1;FN1;FEM1B;F7;DDX5;CSF1;C3;BTRC;AREG;AR;APOE;AHSG;SEC13;ADAMTS6;GOLM1;DCUN1D2;SPON2	2865.16206	3148.415	25.9884	1695.01582	2730.17627	1650.65443	CONFLICT	0.536585366	0.463414634
90Day	Gene expression (Transcription)	2.98E-11		1	5.70E-11	SMARCD2;CSF2T;INTS11;PCGF6;INTS14;HIST1H4H;SRSF6;THOC7;ZFP110;TRP53INP1;CCNC;TXNRD1;CBX6;HIST1H4I;HIST1H3C;ZFP354B;ELOA;ZFP747;NR5A2;MAPK14;ESRRG;PIN1;ZFP445;GATAD2B;YWHAZ;TXN1;PLK2;SMARCB1;RXRG;RARG;PML;MDM2;H2AFX;HDAC2;GSR;BRD2;CDKN1A;CDK7;CCNG1;CBFB;CTNNB1;BTG2;BAX;AR	3176.22566	3346.45	137.958	1715.77322	2934.0987	1739.14829	UP	0.659090909	0.340909091
90Day	GPCR ligand binding	1.04E-10		1	2.05E-10	GNG11;IPAR3;C5AR2;PSAP;GPR143;MTNR1A;HEBP1;OPN3;CASR;C3;ADRA1B;ADORA1	3750.93167	4062.31	639.57	1767.18456	4075.34824	1848.47526	CONFLICT	0.583333333	0.416666667
7Day	Class A/1 (Rhodopsin-like receptors)	1.01E-09		1	1.67E-09	AVPR1A;HEBP1;F2;CXCR5	1924.31025	813.537	156.627	2677.52286	2048.17584	2811.26815	CONFLICT	0.5	0.5
28Day	Biological oxidations	1	7.17E-09	7.17E-09	UGT1A6A;SULT2A8;ABHD14B;UGT2A3;BPH1;SULT2A7;CYP3A25;UGT1A1;UGT1A6B;AHCY;ADH4;UGT2B35;CES2E;CES2C;CES2B;UGT2B36;UGT3A2;UGT2B5;UGDH;GSTZ1;GSTP1;GSTP2;GSTM4;GSTA2;GSTA1;GCLM;GCLC;FDXR;CES3B;CYP4A12B;CYP3A11;CYP2E1;CYP2C37;CYP2C29;CYP2A5;CYP2A4;ALDH2;GM4737;GLYAT;CES2A;UGT2B34;GM3776;CYP3A59;CYP3A41B	2625.72486	2131.875	309.913	1866.42956	2525.80954	1748.51695	CONFLICT	0.5	0.5	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
28Day	Phase II - Conjugation of compounds	1	9.28E-09	9.28E-09	ugt1a6a;sult2a8;abhd14b;ugt2a3;sult2a7;ugt1a1;ugt1a6b;ahcy;ugt2b35;ugt2b36;ugt3a2;ugt2b5;ugdh;gstz1;gstp1;gstp2;gstm4;gsta2;gsta1;gclm;gclc;gm4737;glyat;ugt2b34;gm3776	2355.13768	1902.72	309.913	1709.63218	2343.74456	1632.88604	CONFLICT	0.56	0.44	
90Day	RNA Polymerase II Transcription	8.39E-09	1	1.71E-08	smarcd2;csf2t2;ints11;pcgf6;ints14;hist1h4h;srsf6;thoc7;zfp110;trp53inp1;ccnc;txnrd1;cbx6;hist1h4i;hist1h3c;zfp354b;eloa;zfp747;nr5a2;mapk14;esrrg;pin1;zfp445;gata2b;ywhaz;txn1;plk2;smarcb1;rxrg;rarg;pml;mdm2;h2afx;hdac2;gsr;brd2;cdkn1a;cdk7;ccng1;cbfb;ctnnb1;btg2;bax;ar	3176.22566	3346.45	137.958	1715.77322	2934.0987	1739.14829	UP	0.659090909	0.340909091	
90Day	Ion channel transport	1.40E-08	1	2.25E-08	ano10	3679.83	3679.83	3679.83		3679.83		UP	1	0	
90Day	Innate Immune System	1.49E-08	1	2.81E-08	defb30;tmem173;ist1;cpn2;ndufc2;pnpr2;serpinb1a;tbk1;iqgap2;irf7;prdx4;c5ar2;slc27a2;mapk14;ceacam2;wasf2;pin1;apob;mgam;tubb4b;vtm;vav1;ube2m;txn1;ttr;cdc34;pdck;serpina1e;sos1;snap23;rock1;psap;pnpr;plaur;nfkbia;myo9b;myo10;mme;man2b1;lamp1;ikbkg;hsp90aa1;gstp2;lilr4b;gm2a;ftl1;fcgr2b;ctsh;ctsd;crp;cdc42;ctnnb1;c3;btrc;prdx6;ahsg;mlec	2919.02877	3265.56	45.5307	1818.52597	3022.94114	1759.58219	DOWN	0.368421053	0.631578947	
90Day	Muscle contraction	6.83E-08	1	1.07E-07	scn3b;tln1	5174.92	5174.92	4478.93	984.278497	5430.61984	915.444886	CONFLICT	0.5	0.5	
90Day	Vesicle-mediated transport	7.40E-08	1	1.37E-07	trappc6b;st5;lman1;tubb6;stx17;ubap1;scoc;dctn3;dennd1b;pacsin2;apob;stx16;dennd1a;tubb4b;ywhaz;tubb2a;tuba1b;trf;tgfa;fnbp1;serpina1e;snap23;sh3gl3;man1a;acbd3;gjb2;ftl1;areg;apoe;ap2m1;sec13;kifc1	2897.27012	2871.225	137.958	1820.06836	2727.44092	1716.12068	UP	0.625	0.375	
90Day	Class A/1 (Rhodopsin-like receptors)	1.02E-07	1	1.65E-07	lpar3;c5ar2;psap;gpr143;mtnr1a;hebp1;opn3;c3;adra1b;adora1	3429.046	3191.495	639.57	1751.93278	3783.39488	1859.83665	CONFLICT	0.5	0.5	
7Day	Extracellular matrix organization	3.71E-07	1	5.96E-07	ttr;sd3;p3h3;dst;ctsb;bgn	3854.32833	3795.99	2968.59	996.379375	3842.1728	882.542529	DOWN	0.333333333	0.666666667	
90Day	Membrane Trafficking	3.99E-07	1	7.84E-07	trappc6b;st5;lman1;tubb6;stx17;ubap1;scoc;dctn3;dennd1b;pacsin2;apob;stx16;dennd1a;tubb4b;ywhaz;tubb2a;tuba1b;trf;tgfa;fnbp1;serpina1e;snap23;sh3gl3;man1a;acbd3;gjb2;ftl1;areg;ap2m1;sec13;kifc1	2934.28465	2983.55	137.958	1837.87014	2750.4141	1730.22063	UP	0.64516129	0.35483871	
90Day	Generic Transcription Pathway	4.15E-07	1	8.80E-07	smarcd2;pcgf6;hist1h4h;zfp110;trp53inp1;ccnc;txnrd1;cbx6;hist1h4i;hist1h3c;zfp354b;eloa;zfp747;nr5a2;mapk14;esrrg;pin1;zfp445;gata2b;ywhaz;txn1;plk2;smarcb1;rxrg;rarg;pml;mdm2;h2afx;hdac2;gsr;brd2;cdkn1a;cdk7;ccng1;cbfb;ctnnb1;btg2;bax;ar	3028.63664	3141.48	137.958	1706.73482	2793.28915	1770.54293	UP	0.666666667	0.333333333	
90Day	SLC-mediated transmembrane transport	1.09E-06	1	1.74E-06	slc29a1;slc17a8;slc22a1;slc1a2;slc6a12;slc26a2;slco2b1	2125.06986	1935.84	777.189	1245.83306	2249.01564	1085.52979	DOWN	0.142857143	0.857142857	
28Day	Glucuronidation	1	1.76E-06	1.76E-06	ugt1a6a;ugt2a3;ugt1a1;ugt1a6b;ugt2b35;ugt2b36;ugt3a2;ugt2b5;ugdh;ugt2b34	1940.1023	1092.105	309.913	1847.24982	1885.83694	1683.87445	CONFLICT	0.5	0.5	
28Day	Fatty acid metabolism	1	2.16E-06	2.69E-06	echs1;akr1c6;acox3;fads1;crot;ndufab1;gpx4;akr1c12;hacd3;hacl1;fads2;elovl2;acaa2;akr1c19;hacd1;acsf2;decr2;slc25a17;mapkapk2;ita4h;phyh;hsd17b4;hsd17b3;acsl1;cyp4a12b;cyp2c37;cyp2c29;elovl3;aldh3a2;acox1;acadi;akr1c14;acly	3239.48033	3384.83	250.729	1654.88681	3150.22605	1637.35895	DOWN	0.333333333	0.666666667	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
90Day	Adaptive Immune System	1.57E-06		1	2.83E-06	erap1;fbxo22;fbxo9;anapc10;fbxw9;ar el1;tubb6;fbxo32;asb2;dctn3;ube2k;ke ap1;znrf2;sh2d1b1;ktbtd8;tubb4b;ywh az;vav1;ube2m;tubb2a;tuba1b;cdc34;t ap2;sos1;snap23;siah2;nfbkia;ikbkg;cd 74;icam1;h2- aa;fcgr2b;ctsh;ctsd;cdc42;cd1d1;c3;btr cap2m1;sec13	2636.00384	2957.615	61.8554	1682.14578	2493.82028	1680.89375	CONFLICT	0.55	0.45
90Day	Keratinization	1.99E-06		1	4.01E-06	krt8;krt18;dsgr2	3414.55333	3788.19	2496.49	799.638993	3214.23654	807.558939	UP	0.666666667	0.333333333
90Day	Peptide ligand-binding receptors	2.55E-06		1	5.69E-06	c5ar2;psap;hebp1;c3	2739.995	2651.83	639.57	1828.98707	1834.41241	1622.50456	DOWN	0.25	0.75
90Day	Cardiac conduction	3.96E-06		1	6.69E-06	scn3b	5870.91	5870.91	5870.91		5870.91		UP	1	0
28Day	Developmental Biology	3.07E-06		1	6.86E-06	ranbp9;pkp4;tubb4b;tubb2a;pkp1;pf1; krt8;krt18;epha7;dag1;cdc42	3672.83427	3208.19	856.847	1664.0307	3542.36692	1536.76528	UP	0.909090909	0.090909091
28Day	Generic Transcription Pathway	4.20E-06		1	7.64E-06	meaf6;tmem219;med4;e2f7;txnrd1;nr 1d2;hist1h4i;cnot1;tfdp1;tal1;polr2a;ro rc;nrbp1;notch1;mdm2;ccnk;ccng1;bni p3l;bmi1;zfp729b	3648.58815	3712.885	908.573	1588.07557	3410.62998	1553.99857	UP	0.65	0.35
7Day	Generic Transcription Pathway	5.72E-06		1	1.01E-05	zfp266;pcgf5;zfp248;pcgf6;med6;hist1 h4h;zfp707;rraga;hist1h2bc;kmt5a;suz 12;txnrd1;hist2h2ac;polr2h;taf10;cnot1 ;ywhaz;uba52;tfdp1;prdx2;rorc;ptpn11; ppp2cb;kras;hist2h2aa1;csnk2b;cdkn1a ;ccnk;ccng1;ccne2;ctnnb1;bmi1;abl1	3385.01173	3489.14	54.5232	1214.8211	3339.00094	1237.87958	UP	0.787878788	0.212121212
90Day	G alpha (q) signalling events	6.88E-06		1	1.20E-05	gng11;lpar3;sos1;gpr143;casr;adra1b	4881.85833	5115.43	2444.64	1269.0783	5128.17895	1044.67841	UP	0.666666667	0.333333333
7Day	Neuronal System	8.01E-06		1	1.51E-05	gria3;slc22a1;slc1a2;ptprf;ptprd;prkar2 ;ajl1rap;gnai3;flot2;calm3;calm2	2866.22582	3050.32	131.024	1799.35932	2447.31331	1656.36542	DOWN	0.272727273	0.727272727
90Day	G alpha (i) signalling events	7.08E-06		1	1.51E-05	gng11;lpar3;rdh7;apob;ttr;sdca;camkk 2;rbp1;psap;mtnr1a;rdh11;hebp1;gnai 3;opn3;casr;c3;apoe;apoc3;adora1;abc a4	3406.20521	3416.7	98.0082	2098.44064	3924.51046	2055.30073	CONFLICT	0.5	0.5
28Day	GPCR ligand binding	7.31E-06		1	1.63E-05	nts;cysltr1;cx3cl1;cxcl9;gmb5;f2;c3;agt; adora1	3717.326	4610.42	907.506	2243.2963	3524.29581	2164.64592	CONFLICT	0.555555556	0.444444444
7Day	Glucuronidation	1	3.01E-05	3.01E-05	ugt1a6a;ugt2b1;ugt1a1;ugt1a9;ugt2b3 5;ugt2b36;ugt3a2;ugt2b5;ugdh;ugt2b3 4	1506.85551	1187.735	70.0701	1427.5697	1573.89544	1419.673	UP	0.6	0.4	
28Day	Metabolism	0.99998	2.35E-05	3.73E-05	ugp1;ugt1a6a;ectn1;akr1c6;acox3;sult 2a8;abhd14b;fads1;ippk;crot;phykpl;ug t2a3;ndufab1;ndufaf1;fitm1;pmvk;adip or2;ndufc2;bphl;nudt12;atp5g2;dgat2; pnpla8;pi4k2b;ormdl2;etfdh;ormdl3;as rgl1;tnfaip8l1;dpys;sult2a7;gpx4;akr1c 12;hacd3;atp5j2;hac11;tdo2;nme4;fads 2;serinc1;cyp3a25;prodh2;elovl2;nudt5 ;acaa2;txnrd1;akr1c19;ugt1a1;ugt1a6b ;agmo;hacd1;slc25a10;ahcy;adh4;acsf 2;decr2;hsd17b13;ugt2b35;hs2st1;apo b;phospho1;ces2e;ces2c;ces2b;pla2g4c ;sds;ugt2b36;coq3;pi4ka;ugt3a2;ugt2b 5;ugdh;etnk2;aldh4a1;sucig2;slc25a17; slc22a1;slc10a1;sardh;ptdss1;pnp;pfkl; enpp1;pcx;pcck1;otc;odc1;oat;me1;map kapk2;man2b2;man2b1;amacr;ita4h;lr p1;phyh;ldha;khk;hyal1;hsd17b4;hsd17 b3;hsd11b1;hprt;hpd;guk1;gstz1;gstp1; gstp2;gstm4;gsta2;gsta1;gpi1;gpc4;go t2;gmb5;glul;gclm;gclgc;gaa;fech;fdx r;acsl1;ces3b;ddc;cyp4a12b;cyp3a11;cy p2e1;cyp2c37;cyp2c29;cyp2a5;cyp2a4; elovl3;entpd5;bpgm;ass1;apoe;aldh3a 2;aldh2;gm4737;adss;adk;adcy9;acp5; acox1;acadi;aldh7a1;cyb5a;haao;glyat; acox1;acadi;aldh7a1;cyb5a;haao;glyat;	3000.7126	3049.42	67.9262	1681.12043	2868.78683	1654.39784	DOWN	0.333333333	0.666666667	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
28Day	Gene expression (Transcription)	2.26E-05	0.99999	3.93E-05	iws1;meaf6;ints14;tmem219;med4;wdr61;e2f7;cpsf2;txnr1;nr1d2;hist1h4i;el13;cnot1;rpap2;u2af2;tfdp1;tal1;polr2a;polr1a;rorc;nrbp1;papola;notch1;mdm2;ccnk;ccng1;bnip3l;bmi1;srsf1;thoc5;zf729b;bc005561	3686.92147	3663.77	860.451	1575.79133	3554.92322	1521.43705	CONFLICT	0.59375	0.40625	
7Day	Phase II - Conjugation of compounds	0.99999	4.11E-05	4.11E-05	ugt1a6a;gstk1;ugt2b1;ugt1a1;ugt1a9;ahcy;ugt2b35;ugt2b36;ugt3a2;ugt2b5;ugdh;gstp1;gstp2;gstm4;gsta1;gss;gclc;esd;acsm1;gm4737;glyat;ugt2b34;gm3776	2296.24338	2300.86	49.8526	1616.27738	2443.34515	1490.30542	UP	0.695652174	0.304347826	
7Day	Degradation of the extracellular matrix	3.16E-05	1	5.82E-05	ctsb	3881.76	3881.76	3881.76		3881.76		UP	1	0	
28Day	Peroxisomal lipid metabolism	0.99999	6.75E-05	6.75E-05	acox3;crot;hac11;decr2;slc25a17;phyh;hsd17b4;aldh3a2;acox1	2908.42444	3304.47	702.63	1027.3398	2984.9316	1073.13485	DOWN	0.333333333	0.666666667	
28Day	Glutathione conjugation	0.99999	6.75E-05	6.75E-05	gstz1;gstp1;gstp2;gstm4;gsta2;gsta1;gclm;gclc;gm3776	2302.22322	1681.57	691.166	1795.00689	2140.16119	1723.20689	UP	0.777777778	0.222222222	
90Day	Phospholipid metabolism	4.38E-05	0.99999	9.74E-05	osbpl10;dgat2;tnfaip8l1;tnfaip8l3;pi4k;a;plekha1	2875.24333	2893.34	1984.74	584.157484	2906.28296	452.413567	DOWN	0.333333333	0.666666667	
7Day	Peptide ligand-binding receptors	5.85E-05	0.99999	1.14E-04	avpr1a;hebp1;f2;cxcr5	1924.31025	813.537	156.627	2677.52286	2048.17584	2811.26815	CONFLICT	0.5	0.5	
7Day	Potassium Channels	6.43E-05	1	1.39E-04											
90Day	Developmental Biology	8.12E-05	0.99996	1.51E-04	tubb6;pdlim7;ranbp9;stx1b;irs2;mapk14;tubb4b;tubb2a;tuba1b;tlm1;tiam1;rasa1;sos1;slah2;rock2;rock1;myo9b;msn;mmp2;mef2a;krt8;krt18;hsp90aa1;gfra1;gab1;dsgr2;cdc42;ctnnb1;ap2m1;itga9	2629.31194	2740.02	74.8133	1896.9482	2353.19076	1962.87938	DOWN	0.4	0.6	
90Day	Glycerophospholipid biosynthesis	1.09E-04	0.99999	1.75E-04	osbpl10;dgat2	3115.43	3115.43	2903.14	300.223397	3131.64681	299.346151	CONFLICT	0.5	0.5	
90Day	Stimuli-sensing channels	7.44E-05	0.99999	1.77E-04	ano10	3679.83	3679.83	3679.83		3679.83		UP	1	0	
90Day	Neuronal System	1.08E-04	0.99996	2.03E-04	gng11;gria3;kcns3;lin7c;unc13b;camkk2;slc22a1;slc1a2;ptprd;mdm2;kcng8;il1rap;gna13;glul;slc6a12;gabrb3;epb41l1;ap2m1	3104.37596	3426.16	98.0082	1699.98764	3065.72998	1557.98412	CONFLICT	0.555555556	0.444444444	
90Day	Signaling by WNT	9.30E-05	0.99997	2.04E-04	tmed5;gng11;ywhaz;ctnnb1;btrc;ap2m1;lgr4	3715.97257	4087.04	137.958	1800.60819	4216.23304	1751.83661	UP	0.714285714	0.285714286	
7Day	Biological oxidations	0.99991	1.86E-04	2.68E-04	ugt1a6a;gstk1;ugt2b1;bphl;cyp3a25;ptges3;cyp39a1;ugt1a1;ugt1a9;ahcy;ugt2b35;ces2c;ugt2b36;ugt3a2;ugt2b5;ugdh;nqo2;ncoa2;ncoa1;gstp1;gstp2;gstm4;gsta1;gss;gclc;ces3b;esd;cyp3a11;cyp2e1;cyp2c37;cyp2c29;arnt;acsm1;aldh2;gm4737;maob;acy1;glyat;ces2a;ugt2b34;gm3776;cyp3a41b	2411.07542	2474.22	46.9364	1694.49369	2395.23376	1587.12073	CONFLICT	0.547619048	0.452380952	
28Day	Biosynthesis of specialized proresolving mediators (SPMs)	0.99995	2.79E-04	2.79E-04	gpx4;cyp3a25;ita4h;gstm4;cyp3a11;cyp2e1;cyp2c37;cyp2c29;cyp3a59;cyp3a41b	3195.6493	3231.855	792.488	2077.75928	2840.57897	1887.92444	DOWN	0.4	0.6	
90Day	Biosynthesis of specialized proresolving mediators (SPMs)	0.99993	2.85E-04	2.85E-04	gpx4;cyp3a25;cyp3a41a;cyp2c54;hpgd;gstm4;cyp2e1;cyp2d9;cyp2c38;cyp2c37;cyp1a2;cyp2c69;cyp3a41b	2473.49	1703.57	343.937	1801.37161	2020.27981	1623.45474	DOWN	0.384615385	0.615384615	
7Day	G alpha (q) signalling events	1.71E-04	0.99996	2.88E-04	kalm;avpr1a;mapk3;kras;itpr2;f2	2907.75617	3747.02	156.627	1931.77903	2394.3639	2163.35543	DOWN	0.333333333	0.666666667	
28Day	Alpha-oxidation of phytanate	0.99999	2.95E-04	2.95E-04	hac11;slc25a17;phyh;aldh3a2	3412.465	3374.64	3193.99	221.321757	3438.51723	213.47785	CONFLICT	0.5	0.5	
7Day	G alpha (i) signalling events	1.37E-04	0.99994	2.96E-04	akr1c6;rgs12;metap2;apob;ttr;rdh16f2;sdcs;rgs9;prkar2a;ppp2cb;lrp1;hebp1;gna13;calm3;calm2;cxcr5;apoe;akr1c14	3329.54889	3638.015	113.316	1810.61245	3201.8182	1665.41903	DOWN	0.388888889	0.611111111	
7Day	Keratinization	1.93E-04	0.99996	3.22E-04	dsg1c;krt8;krt18;dsp	1895.05825	2157.095	240.593	1294.67509	1764.83129	1510.73684	DOWN	0.25	0.75	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
7Day	RNA Polymerase II Transcription	1.70E-04	0.9999	3.39E-04	zfp266;pcgf5;rprd2;zfp248;ints13;pcgf6;rprd1b;med6;hist1h4h;zfp707;ssu72;rraga;hist1h2bc;gmt5a;fip1l1;wdr61;zcz3h8;phax;suz12;cpsf2;txnrd1;hist2h2ac;polr2h;taf10;cnot1;ywhaz;uba52;tfdp1;prdx2;rorc;ell2;ptpn11;ppp2cb;kras;hist2h2aa1;csnk2b;cdkn1a;ccnk;ccng1;ccne2;ctnnb1;bmi1;lsml0;abl1;srsf1;cstf2;thoc5	3442.55505	3489.14	54.5232	1139.09255	3375.29713	1101.08632	UP	0.85106383	0.14893617
90Day	Neutrophil degranulation	1.89E-04	0.9999	3.58E-04	tmem173;ist1;ndufc2;pnp2;serpinb1a;iqgap2;prdx4;slc27a2;mapk14;ceacam2;mgam;tubb4b;ttr;pdck;serpina1e;snap23;rock1;psap;pnp;plaur;mme;man2b1;lamp1;hsp90aa1;gstp2;il1r4b;gm2a;ftl1;fcgr2b;ctsh;ctsd;c3;prdx6;ahsg;mlec	2753.85175	3055.31	82.4742	1474.67171	2821.24407	1305.88853	DOWN	0.371428571	0.628571429
28Day	RNA Polymerase II Transcription	2.00E-04	0.9999	3.83E-04	iws1;meaf6;ints14;tmem219;med4;wdr61;e2f7;cpsf2;txnrd1;nr1d2;hist1h4i;ell3;cnot1;rpap2;u2af2;tfdp1;tal1;polr2a;rorc;nrbp1;papola;notch1;mdm2;ccnk;ccng1;bnip3l;bmi1;srsf1;thoc5;zfp729b;bc005561	3616.72345	3638.56	860.451	1550.14331	3507.41064	1499.7423	UP	0.612903226	0.387096774
90Day	Hemostasis	2.25E-04	0.99988	3.98E-04	spp2;tubb6;gng11;hist1h3c;mapk14;ceacam2;apob;tubb4b;ywhaz;vav1;tubb2a;tuba1b;trf;tnfrsf10b;tltn1;tek;sdca4;serpina1e;sos1;psap;plg;plaur;p2rx4;cd74;hdac2;gna13;fn1;f7;ecm1;cdc42;cbx5;anxa5;ahsg;rad51c;actn1;scppdh;dock9;kifc1	2387.51566	2155.07	82.4742	1820.18781	2556.03108	1826.9623	DOWN	0.394736842	0.605263158
7Day	Muscle contraction	3.02E-04	0.99993	5.12E-04	pak2;itpr2;dmpk;calm3;calm2	3620.406	3498.74	2538.2	924.565079	3509.03511	789.214299	DOWN	0.4	0.6
90Day	Glutathione conjugation	0.99988	6.16E-04	6.16E-04	gstk1;gstt1;gstp2;gstm4;gsta2;gsta1;gclm;gclcg10639;gm3776	1778.8786	1547.73	677.965	988.928952	1714.96755	984.223276	UP	0.8	0.2
90Day	Biosynthesis of DHA-derived SPMs	0.99985	6.52E-04	6.52E-04	cyp3a25;cyp3a41a;cyp2c54;gstm4;cyp2e1;cyp2d9;cyp2c38;cyp2c37;cyp1a2;cyp2c69;cyp3a41b	2180.32818	1652.41	343.937	1636.92385	1867.89167	1633.37688	DOWN	0.363636364	0.636363636
7Day	Integrin cell surface interactions	4.29E-04	1	6.93E-04										
28Day	Post-translational protein phosphorylation	0.9998	5.51E-04	7.24E-04	spp2;ano8;apob;trf;serpina1e;serpina1b;proc;p4hb;igals1;itih2;fn1;f5;c4b;c3;s	2829.69116	3089.4	248.527	1710.17032	2629.9656	1660.03367	DOWN	0.052631579	0.947368421
7Day	Glutathione conjugation	0.99986	7.46E-04	7.46E-04	gstk1;gstp1;gstp2;gstm4;gsta1;gss;gcl;c;esd;gm3776	2296.99696	2305	49.8526	1013.50727	2334.47548	657.20068	UP	0.888888889	0.111111111
28Day	Signaling by Receptor Tyrosine Kinases	3.94E-04	0.99985	8.05E-04	atp6v0e2;ranbp9;polr2a;pdpk1;mapkapk2;hgs;hbegf;fn1;fgf1;cdc42;atp6v1e1;brk1	3384.483	3188.36	192.988	1944.65333	3245.43064	1786.19736	CONFLICT	0.5	0.5
90Day	Biosynthesis of maresins	0.99982	8.47E-04	8.47E-04	cyp3a25;cyp3a41a;cyp2c54;cyp2e1;cyp2d9;cyp2c38;cyp2c37;cyp1a2;cyp2c69;cyp3a41b	2318.9941	1677.99	343.937	1655.96869	1958.81693	1674.89027	DOWN	0.3	0.7
90Day	Biosynthesis of maresin-like SPMs	0.99982	8.47E-04	8.47E-04	cyp3a25;cyp3a41a;cyp2c54;cyp2e1;cyp2d9;cyp2c38;cyp2c37;cyp1a2;cyp2c69;cyp3a41b	2318.9941	1677.99	343.937	1655.96869	1958.81693	1674.89027	DOWN	0.3	0.7
28Day	Class A/1 (Rhodopsin-like receptors)	4.53E-04	0.99985	9.00E-04	nts;cysltr1;cx3cl1;cxcl9;f2;c3;agt;adorna1	4062.78575	5060.73	907.506	2126.91495	4031.3968	1978.73091	CONFLICT	0.5	0.5
7Day	Gene expression (Transcription)	4.45E-04	0.99973	9.33E-04	sf3b1;zfp266;pcgf5;rprd2;zfp248;brf1;ints13;pcgf6;rprd1b;med6;hist1h4h;zfp707;ssu72;rraga;hist1h2bc;gmt5a;gtf3c6;fip1l1;wdr61;zcz3h8;phax;gsk3b;ddx21;suz12;cpsf2;txnrd1;hist2h2ac;mapk3;polr2h;taf10;cnot1;ywhaz;uba52;tfdp1;prdx2;ubtf;rorc;ell2;ptpn11;ppp2cb;mybbp1a;kras;hist2h2aa1;csnk2b;cdkn1a;ccnk;ccng1;ccne2;ctnnb1;bmi1;lsml0;abl1;srsf1;cstf2;thoc5	3402.4114	3439.85	54.5232	1123.11133	3377.49701	1067.07644	UP	0.836363636	0.163636364

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
7Day	DNA Repair	5.13E-04	0.9998	9.63E-04	ube2n;ube2v2;rnf168;hist1h4h;babam1;hist1h2bc;prpf19;polr2h;ino80c;uba52;rad51ap1;abl1	3633.865	3506.09	2423.08	669.512277	3532.19041	654.342441	UP	0.833333333	0.166666667	
7Day	Transport of small molecules	5.11E-04	0.99971	9.87E-04	nipa2;npc2;abcg8;apoa5;angptl8;slc2a8;slc5a3;rab11a;abca3;abca8b;elf2s3x;abcg2;abcc4;apob;erlin1;uba52;slc39a2;slc22a12;slc22a1;slc20a1;slc1a2;slc12a7;sel1l;prkar2a;abcb4;pcsk5;slc8b1;ldlr;ftl1;ces3b;calm3;calm2;azgp1;atp6v1e1;apoe;apoc1;slc12a6;wwp1	3538.88745	3773.925	73.2912	1364.89803	3640.53279	1213.94278	CONFLICT	0.5	0.5	
7Day	Ion channel transport	5.47E-04	0.99986	9.95E-04	uba52;calm3;calm2;atp6v1e1;wwp1	3867.372	3782.92	2825.5	956.630939	3563.6266	953.816092	UP	0.8	0.2	
28Day	Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)	0.99964	9.39E-04	9.98E-04	spp2;ano8;apob;trf;serpina1e;serpina1b;proc;p4hb;lgals1;itih2;igfals;fn1;f5;c4b;c3;serpinc1;app;apoe;qsox1;dnajc3	2871.6611	3122.7	248.527	1675.10638	2655.29964	1645.63506	DOWN	0.05	0.95	
7Day	Antimicrobial peptides	6.40E-04	1	0.0010497											
7Day	Transmission across Chemical Synapses	5.59E-04	0.99983	0.0010874	gria3;slc22a1;slc1a2;prkar2a;gna13;calm3;calm2	3232.68	3853.21	794.2	1484.36012	2849.44233	1488.84375	CONFLICT	0.428571429	0.571428571	
7Day	Rho GTPase cycle	6.59E-04	0.99987	0.0010984	kalrn;dlc1;cdc42	4559.47	4595.9	3395.83	1145.85941	4811.71558	1012.23125	UP	0.666666667	0.333333333	
90Day	Collagen formation	6.35E-04	0.99991	0.0011489	p4ha2;bmp1	2145.7695	2145.7695	190.369	2765.35391	1594.97401	2653.38103	CONFLICT	0.5	0.5	
90Day	DNA Repair	5.45E-04	0.99976	0.0011858	hist1h4h;babam1;pole4;ppp4c;mcrs1;hist1h4i;polk;fto;yy1;ino80c;rad51;rad23a;h2afx;cdk7;brca2;rad51c	3859.97325	4046.18	513.022	1448.58378	3617.74544	1504.7569	UP	0.625	0.375	
90Day	Signaling by Receptor Tyrosine Kinases	5.90E-04	0.9997	0.0012067	hnmrf;klb;ranbp9;hgfac;irs2;mapk14;wasf2;vav1;rasa1;tgifa;nrg1;sos1;sh3gl3;rock2;rock1;plg;pcsk5;ntrk2;hsp90aa1;gab1;fn1;fgf1;cdc42;ctnnb1;areg;ap2m1	2763.39574	3252.06	74.8133	1805.74442	2948.55441	1886.20894	CONFLICT	0.423076923	0.576923077	
28Day	alpha-linolenic acid (ALA) metabolism	0.99993	0.0012318	0.0012318	fads1;fads2;elovl2;acs1l	1638.0815	624.2485	250.729	2289.62951	1272.53137	1821.15387	DOWN	0	1	
28Day	Aflatoxin activation and detoxification	0.99983	0.0012792	0.0012792	cyp3a25;cyp3a11;cyp2a5;cyp2a4;cyp3a59;cyp3a41b	3035.18083	3021.61	850.005	1889.46966	2281.79161	1423.31367	UP	0.666666667	0.333333333	
28Day	Biosynthesis of DHA-derived SPMs	0.99972	0.0014083	0.0014083	cyp3a25;gstm4;cyp3a11;cyp2e1;cyp2c37;cyp2c29;cyp3a59;cyp3a41b	2780.31038	2051.215	792.488	2075.65676	2333.1099	1699.7196	CONFLICT	0.5	0.5	
90Day	Class I MHC mediated antigen processing & presentation	8.32E-04	0.99961	0.0014986	erap1;fbxo22;fbxo9;anapc10;fbxw9;arel1;fbxo32;asb2;ube2k;keap1;znrf2;kbtbd8;ube2m;cdc34;tap2;snap23;siah2;btrc;sec13	2775.44492	3141.94	61.8554	1900.69805	2661.07984	1851.57464	CONFLICT	0.578947368	0.421052632	
90Day	Biotin transport and metabolism	0.99987	0.0015353	0.0015353	mccc2;pcbc;pcx;hlcs;pcca	1945.4304	2782.05	410.825	1405.20854	2135.89599	1343.93766	DOWN	0	1	
90Day	RAB geranylgeranylation	6.64E-04	1	0.0015594											
7Day	RHO GTPases activate PAKs	0.99973	0.0016643	0.0016643	myh14;pak2;flna;myh9;cdc42;calm3;calm2	3764.03571	4226.97	2152.51	1159.16425	3589.38581	1087.60247	CONFLICT	0.428571429	0.571428571	
90Day	Potassium Channels	7.78E-04	0.99988	0.0017298	kcnj3;kcnj8	4052.335	4052.335	2260.22	2534.43334	3944.41493	2529.83376	UP	1	0	
28Day	Muscle contraction	9.86E-04	0.9998	0.0017546	scn7a;cald1;mylk	3957.77667	3855.8	2735.83	1275.99488	3761.01133	1144.21517	UP	1	0	
28Day	Cell-Cell communication	0.001123	1	0.0018011											
28Day	Potassium Channels	9.73E-04	1	0.00183											
7Day	ISG15 antiviral mechanism	0.9996	0.0020109	0.0020109	ube2n;flnb;elf4e2;mapk3;arih1;stat1;jak1;elf4a2	3537.26625	3499.555	2513.13	705.438918	3463.21926	677.179951	UP	0.75	0.25	
28Day	Translation	0.0010478	0.99984	0.0020817	elf3m;elf1ax	2737.81	2737.81	1517.45	1725.84966	2423.68091	1667.69388	CONFLICT	0.5	0.5	
28Day	alpha-linolenic (omega3) and linoleic (omega6) acid metabolism	0.99985	0.0020974	0.0020974	fads1;fads2;elovl2;acs1l	1638.0815	624.2485	250.729	2289.62951	1272.53137	1821.15387	DOWN	0	1	
90Day	Formation of the cornified envelope	9.32E-04	0.99982	0.0021022	krt8;krt18;dsg2	3414.55333	3788.19	2496.49	799.638993	3214.23654	807.558939	UP	0.666666667	0.333333333	
90Day	Antigen processing: Ubiquitination & Proteasome degradation	0.0012151	0.99946	0.00213	fbxo22;fbxo9;anapc10;fbxw9;arel1;fbxo32;asb2;ube2k;keap1;znrf2;kbtbd8;ubc2m;cdc34;siah2;btrc	2820.54156	3593.5	61.8554	2028.69844	2574.69183	2056.51767	UP	0.6	0.4	
28Day	Cardiac conduction	0.0011772	0.99989	0.002189	scn7a	3855.8	3855.8	3855.8		3855.8		UP	1	0	
90Day	Ion transport by P-type ATPases	0.0013661	1	0.0021949											
7Day	Bile acid and bile salt metabolism	0.99932	0.0022724	0.0022724	akr1c6;cyp39a1;slc27a5;osbpl2;slc10a2;slc10a1;ncoa2;ncoa1;hsd17b4;baat1;kr1c14;hsd3b7	2666.15472	3187.835	86.7986	1621.14041	2952.23825	1161.96383	CONFLICT	0.583333333	0.416666667	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.																
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down		
90Day	Extracellular matrix organization	0.0011863	0.99945	0.0023215	tmprss6;ceacam2;vtnttr;tnc;sdca4;plg;p4ha2;mp2;lum;icam1;fn1;ctsd;capn5;bmp1;bgn;tga9	3394.45092	4015.56	45.5307	1921.99598	3238.19909	2041.89909	CONFLICT	0.470588235	0.529411765		
28Day	Adaptive Immune System	0.0012343	0.99934	0.002344	ube2n;btbd1;fbxo22;ube2v2;ube2g1;asb3;dynl1;ube2k;arih2;tubb4b;ube2m;tubb2a;traip;cdc27;tap1;ppp3cb;pdpk1;ikbk;cd74;h2-q7;h2-d1;h2-ab1;h2-aa;ctss;cdc42;capza2;c3	3873.11733	4034.64	192.988	1566.20625	3957.75089	1415.04046	CONFLICT	0.555555556	0.444444444		
90Day	Intra-Golgi and retrograde Golgi-to-ER traffic	0.0011518	0.99959	0.0024086	tubb6;scoc;dctn3;stx16;tubb4b;tubb2a;tuba1b;man1a;kifc1	2824.6	1951.01	713.489	1853.06003	2202.43718	1832.87711	UP	0.777777778	0.222222222		
28Day	Histidine, lysine, phenylalanine, tyrosine, proline and tryptophan catabolism	0.99936	0.0025802	0.0025802	phylkl;asrgl1;tdo2;prodh2;aldh4a1;hpd;gstz1;aldh7a1;haao	3115.98467	3472.64	726.97	1756.35475	3039.82171	1764.54756	DOWN	0.222222222	0.777777778		
90Day	Antimicrobial peptides	0.0014525	0.99986	0.0026026	defb30	5550.64	5550.64	5550.64		5550.64		UP	1	0		
28Day	Biosynthesis of maresins	0.99944	0.0028635	0.0028635	cyp3a25;cyp3a11;cyp2e1;cyp2c37;cyp2c29;cyp3a59;cyp3a41b	3064.285	2751.06	850.005	2067.30614	2498.90637	1713.63668	CONFLICT	0.428571429	0.571428571		
28Day	Biosynthesis of maresin-like SPMs	0.99944	0.0028635	0.0028635	cyp3a25;cyp3a11;cyp2e1;cyp2c37;cyp2c29;cyp3a59;cyp3a41b	3064.285	2751.06	850.005	2067.30614	2498.90637	1713.63668	CONFLICT	0.428571429	0.571428571		
28Day	Activation of C3 and C5	0.9999	0.0028994	0.0028994	c4b;c3;c2	2076.44167	2572.88	520.995	1376.11119	1715.75301	1348.31746	DOWN	0	1		
28Day	Synthesis of very long-chain fatty acyl-CoAs	0.99952	0.0029475	0.0029475	hacd3;elovl2;hacd1;hsd17b3;acs1;elovl3	3076.84583	3507.97	411.194	2078.36776	2875.43094	2178.50476	UP	0.666666667	0.333333333		
28Day	Axon guidance	0.0015283	0.99949	0.0029929	ranbp9;tubb4b;tubb2a;pfn1;epha7;dag1;cdc42	4242.08286	4831.18	2359.45	1599.75749	4046.43703	1604.36544	UP	0.857142857	0.142857143		
28Day	Immune System	0.0017057	0.99883	0.0030996	ube2n;btbd1;atp6v0e2;fbxo22;arhgap45;ube2v2;c8g;ndufc2;npc2;cmtm6;ube2g1;ormdl3;psmd6;serpinb1a;asb3;golga7;dynl1;hepb2;methig1;iqgap2;ube2k;tax1bp1;map2k4;arih2;arih1;apob;clce12a;tubb4b;vtin;ube2m;tubb2a;traip;tnfrsf1b;cdc27;eea1;tap1;serpina1e;serpina1b;s100a11;rab18;ppp3cb;ppm1b;pnp;pa2g4;pkp1;pfkl;pdpk1;p4hb;sqstm1;mme;mapkapk2;man2b1;ly96;it4h1;ilfr;lbp;anpep;il1rap;ikbk;cd74;h2-q7;h2-d1;h2-ab1;h2-aa;gstp1;gstp2;gpi1;gaa;ftl1;f2;ctss;cluc;cdc42;capza2;c4b;c3;c2;bcl2l1;atp6v1e1;app;birc2;atad3a;acly;qsox1;brk1;dnajc3	3327.97043	3366.84	160.43	1870.47727	3301.38018	1889.66471	DOWN	0.360465116	0.639534884		
90Day	Chemokine receptors bind chemokines	0.0022101	1	0.0033521												
90Day	Ion homeostasis	0.0019597	1	0.0033635												
7Day	RHO GTPases activate IQGAPs	0.99925	0.0033771	0.0033771	iqgap2;tubb4b;tubb2a;tuba4a;cdc42;ctnnb1;calm3;calm2	2412.54115	1973.755	54.5232	1690.41653	2378.45461	1691.48367	UP	0.625	0.375		
90Day	Signaling by TGF-beta family members	0.0021282	0.99965	0.0034639	ccnc;ube2m	2361.655	2361.655	678.11	2380.89217	2437.24834	2378.49087	UP	1	0		
28Day	Signaling by WNT	0.0020461	0.99948	0.0038217	pygo2;ppp3cb;pfn1;gnb5	3454.282	4016.15	953.648	1712.02807	2868.89238	1933.14079	UP	0.75	0.25		
90Day	Assembly of collagen fibrils and other multimeric structures	0.0022364	0.99978	0.0038267	bmp1	190.369	190.369	190.369		190.369		DOWN	0	1		
7Day	Association of Tric/CCT with target proteins during biosynthesis	0.99968	0.0040199	0.0040199	tcp1;cct7;cct4;cct2	3408.39	3368.435	2526.48	892.357141	3029.35461	739.844083	UP	1	0		
28Day	Mitochondrial translation elongation	0.0023034	1	0.0041003												

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
90Day	Metabolism	0.0021658	0.99836	0.0041136	mtccc2;abnd140;gstkl1;pank1;osopr10;dmghd;nmnat3;aldh1b1;acad10;amdhd1;osbpl3;ndufab1;cyp4f16;slc52a3;ndufc2;dgat2;hoga1;sdha;pccb;ormdl2;etfdh;ndufaf3;pnp2;rpe;asrgl1;tnfaip8l1;ndufb9;gng11;dpys;gpx4;hacl1;serinc1;cyp3a25;sult1b1;ivd;pdss1;cyp39a1;fmo2;slc23a2;cyp3a41a;nudt5;acaa2;acsl4;txnr1;cyp2c54;ces3a;dnph1;agmo;cyp4a12a;pdk4;omd;pon3;ahcy;adh4;slc27a5;slc27a2;aldh1a7;tnfaip8l3;ugt2b35;ppm11;bpnt1;kncs3;apob;scap;ces2e;ces2c;blvrb;acer2;gmpps;fitm2;pdcl1;tkfc;pi4ka;ugdh;txn1;ttr;tst;tk1;slc25a21;pdxk;nudt15;nudt18;suox;sdca;sucgl2;sptlc2;slc25a17;slc22a1;slc10a1;st3gal3;scd1;rbp1;sardh;psap;pnp;pcx;oat;mut;mthfd2;minpp1;rdh11;man2b1;amacr;pfkfb3;lum;hyal1;hsp90aa1;hsd17b7;hsd11b1;hpgd;hpd;hdac3;gstz1;gstp2;gstm4;gsta2;gsta1;gsr;gm2a;glul;gclm;gclc;slc6a12;acsl1;ces3b;ephx2;ephx1;slc26a2;cyp4a12b;cyp2f2;cyp2e1;cyp2d9;cyp2c38;cyp2c37;cyp1a2;elovl3;cdo1;car5a;car3;bgn;atp5k;arg2;apoe;apoc3;aox1;ak2;gm4737;agxt;adk;hlcs;pcca;c	2932.49559	3114.2	54.2263	1542.94627	2914.92808	1498.55712	CONFLICT	0.422360248	0.577639752	
28Day	Mitochondrial translation termination	0.0019953	1	0.0042487											
7Day	Glyoxylate metabolism and glycine degradation	0.99901	0.0042857	0.0042857	lias;lipt2;prodh2;pdhx;hao1;gnmt;dld;bckdha	3387.13525	3613.145	174.982	1576.32093	3520.08702	1185.48464	DOWN	0.375	0.625	
28Day	Mitochondrial translation	0.001857	1	0.0043724											
90Day	TCF dependent signaling in response to WNT	0.0024797	0.99937	0.0044298	ywhaz;ctnnb1;btrc;lgr4	3673.517	4619.87	137.958	2419.23728	4348.60793	2076.6021	CONFLICT	0.5	0.5	
90Day	Cell Cycle	0.0022398	0.99865	0.0045451	haus7;esco2;cenpu;smc4;hist1h4h;gins1;anapc10;babam1;tubb6;mastl;pole4;cables1;nek6;arpp19;psmd8;orc6;dctn3;hist1h4i;gtse1;dbf4;cntrl;e2f2;psmc4;psmf1;tubb4b;ywhaz;cep76;tubb2a;tu ba1b;nup153;kntc1;nudc;mdm2;hsp90aa1;h2afx;cdkn1a;cdk7;btrc;sec13;cenp f	3118.54895	3428.245	137.958	1566.85982	3124.02404	1524.03414	UP	0.85	0.15	
90Day	Metabolism of carbohydrates	0.0025551	0.99891	0.0045761	rpe;omd;tkfc;sdca;st3gal3;pcx;man2b1;pfkfb3;lum;hyal1;slc26a2;bgn	2540.08853	2757.255	54.2263	2081.88494	2560.24861	1934.45153	DOWN	0.333333333	0.666666667	
28Day	TCF dependent signaling in response to WNT	0.0025538	0.99973	0.0046402	pygo2	3936.43	3936.43	3936.43		3936.43		DOWN	0	1	
90Day	Integration of energy metabolism	0.0028652	0.99951	0.0049959	gng11;kncs3	5349.345	5349.345	4854.24	700.184206	5679.2676	522.072862	UP	1	0	
7Day	Antiviral mechanism by IFN-stimulated genes	0.9987	0.0053711	0.0053711	ube2n;flnb;eif4e2;mapk3;arih1;stat1;jak1;eif4a2	3537.26625	3499.555	2513.13	705.438918	3463.21926	677.179951	UP	0.75	0.25	
7Day	Ribosomal scanning and start codon recognition	0.9981	0.0059113	0.0059113	eif3m;eif3j1;rps25;eif1ax;eif3b;rps3;eif2s3x;eif31;eif5;rps12;eif4a2	3192.10478	3441.48	84.8066	1709.32291	3140.99651	1569.93197	UP	0.909090909	0.090909091	
28Day	Signaling by Rho GTPases	0.0033816	0.99837	0.0060711	arhgap45;zwilch;dynll1;iqgap2;dlc1;cenpt;hist1h4i;a2m;tubb4b;tubb2a;arhgdia;pfn1;pdpl1;cdc42;mylk;brk1	3832.71738	4199.195	160.43	1861.07466	4147.03993	1520.25385	UP	0.6875	0.3125	
90Day	Biological oxidations	0.99788	0.0036741	0.0061525	abhd14b;gstkl1;aldh1b1;cyp4f16;cyp3a25;sult1b1;cyp39a1;fmo2;cyp3a41a;cyp2c54;ces3a;cyp4a12a;ahcy;adh4;aldh1a7;ugt2b35;bpnt1;ces2e;ces2c;ugdh;gstz1;gstp2;gstm4;gsta2;gsta1;gclm;gcl c;ces3b;ephx1;slc26a2;cyp4a12b;cyp2f2;cyp2e1;cyp2d9;cyp2c38;cyp2c37;cyp1a2;gm4737;cbx3;cyp2c69;gm10639;gm3776;cyp3a41b	2400.17416	2740.9	343.937	1365.07959	2332.53303	1350.22841	CONFLICT	0.581395349	0.418604651	
90Day	Rab regulation of trafficking	0.0035212	0.99907	0.0061619	trappc6b;st5;dennd1b;dennd1a	2873.6475	3095.14	1239.12	1313.98598	2663.10414	1396.8076	DOWN	0.25	0.75	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
28Day	RA biosynthesis pathway	0.99859	0.0061718	0.0061718	akr1c6;akr1c12;akr1c19;adh4;aldh8a1;rdh16f2;akr1c14	3658.91614	3384.83	912.843	1735.94718	3406.08354	1417.35316	DOWN	0.285714286	0.714285714
90Day	Asparagine N-linked glycosylation	0.0028362	0.99863	0.0063049	trappp6b;lman1;tubb6;stx17;ngly1;rnf5;dctn3;stg6alnac6;tubb4b;tubb2a;tuba1b;tgfa;serpina1e;st3gal3;man1a;areg;sec13	3308.12882	3728.57	779.791	1531.93311	2970.25226	1582.05092	UP	0.647058824	0.352941176
7Day	Recycling of bile acids and salts	0.99882	0.0063795	0.0063795	slc27a5;slc10a2;slc10a1;ncoa2;ncoa1;baat	2355.2856	3155.67	86.7986	1775.40354	2943.36028	1379.88539	UP	0.666666667	0.333333333
90Day	Metabolism of RNA	0.0032681	0.9981	0.0065211	hnmpf;csf2t2;rbm17;nop14;riok1;cd2b;p2;ppl3;srsf6;u2surp;rps27l;thoc7;wta;p;rc1;adar;exosc9;usp39;smg5;ywhaz;zrsr1;paip1;nup153;utp4;snrnp;rps12;p;rfp8;nxf7;emg1;fbl;ddx5;cdk7;sec13;tsr1	3550.62872	3439.425	137.958	1654.74194	3435.96135	1519.75857	UP	0.84375	0.15625
90Day	Chromatin modifying enzymes	0.0029179	0.99879	0.0066241	smarcd2;msl1;hist1h4h;atf7ip;mcrs1;hist1h4i;hist1h3c;gataad2b;smarcb1;hdac3;hdac2	3140.10673	3951.81	157.333	2193.96801	2787.1216	2259.85147	CONFLICT	0.545454545	0.454545455
90Day	Chromatin organization	0.0029179	0.99879	0.0066241	smarcd2;msl1;hist1h4h;atf7ip;mcrs1;hist1h4i;hist1h3c;gataad2b;smarcb1;hdac3;hdac2	3140.10673	3951.81	157.333	2193.96801	2787.1216	2259.85147	CONFLICT	0.545454545	0.454545455
90Day	Cellular responses to external stimuli	0.0032481	0.99817	0.006991	hist1h4h;anapc10;tubb6;gabarapl1;dnaja2;dctn3;atg13;gm45902;txnr1;nox4;cbx6;hist1h4i;hist1h3c;mapk14;tubb4b;txn1;tubb2a;tuba1b;nup153;mdm2;hsp90aa1;h2afx;gstp2;gsr;cdkn1a;aar;prdx6;sec13	2607.38339	2450.705	190.561	1617.05587	2227.99324	1672.21833	UP	0.642857143	0.357142857
28Day	Phase I - Functionalization of compounds	0.99774	0.0051178	0.0071459	bphl;cyp3a25;adh4;ces2e;ces2c;ces2b;fdxr;ces3b;cyp4a12b;cyp3a11;cyp2e1;cyp2c37;cyp2c29;cyp2a5;cyp2a4;aldh2;c;es2a;cyp3a59;cyp3a41b	2981.76063	2751.06	350.258	2046.75807	2781.49392	1915.8218	CONFLICT	0.421052632	0.578947368
7Day	Chylomicron clearance	0.99964	0.0072088	0.0072088	apob1;dlr;apoE	2349.262	1999.21	113.316	2429.95644	3125.65168	2337.73998	DOWN	0.333333333	0.666666667
28Day	Xenobiotics	0.99788	0.0072153	0.0072153	cyp3a25;cyp3a11;cyp2e1;cyp2c37;cyp2c29;cyp2a5;cyp2a4;cyp3a59;cyp3a41b	3093.69278	2751.06	850.005	1842.88683	2606.14147	1498.04441	CONFLICT	0.555555556	0.444444444
90Day	Transport of bile salts and organic acids, metal ions and amine compounds	0.0034891	0.99939	0.0073768	slc22a1;slc6a12	2247.86	2247.86	1050.57	1693.22376	3017.91745	1296.54531	DOWN	0	1
28Day	Chromatin modifying enzymes	0.0043301	0.99867	0.0074139	msl1;meaf6;hist1h4i;kat7;hcf1	4539.96	5043.8	2859.88	1234.05187	4409.47817	1273.01653	DOWN	0.4	0.6
28Day	Chromatin organization	0.0043301	0.99867	0.0074139	msl1;meaf6;hist1h4i;kat7;hcf1	4539.96	5043.8	2859.88	1234.05187	4409.47817	1273.01653	DOWN	0.4	0.6
28Day	MAPK1/MAPK3 signaling	0.0039223	0.9988	0.0074381	ranbp9;map3k11;hbegf;fn1;fgf1	3061.3016	3156	919.738	1930.82326	2739.58196	1684.15141	DOWN	0.4	0.6
7Day	Synthesis of bile acids and bile salts	0.99786	0.0074777	0.0074777	akr1c6;cyp39a1;osbpl2;ncoa2;ncoa1;hsd17b4;baat;akr1c14;hsd3b7	2767.57018	3262.32	86.7986	1601.414	3020.5072	1045.00713	UP	0.666666667	0.333333333
28Day	Plasma lipoprotein assembly	0.99872	0.007777	0.007777	apob2;m;phb;bmp1;apoE	3319.623	3212.68	939.205	2365.92573	3060.50873	2554.9319	DOWN	0.4	0.6
90Day	Cytokine Signaling in Immune system	0.0038609	0.99787	0.007985	irak3;tbk1;irs2;hist1h3c;mapk14;eda2r;usp18;abce1;ywhaz;vav1;ube2m;stx3;sos1;nfkbia;lifr;il9r;il1rap;il15ra;ikbk;il18bp;ifng2;ifna1;csf1;crf1;btcr	2954.53897	3265.56	74.8133	1829.65475	2691.21189	2022.46377	DOWN	0.36	0.64
28Day	Metabolism of proteins	0.0039509	0.99721	0.0080175	obs1;elf3m;c1gal1;ube2n;btbd1;spp2;asxl2;fbxo22;ube2v2;tomm20;narp;ube2g1;lman2;psmd6;wdr61;elf1ax;asb3;ngly1;psmd8;dynl1;rab9;pi3p;rab11a;ube2k;ppp6r3;uchl3;gme;ano8;hist1h4i;abca3;pi3n;apob;psmf1;tubb4b;sbspon;rab29;ino80c;usp12;ube2m;tubb2a;trf;mgat2;sec22c;serpina1e;serpina1b;exoc4;rad21;rab18;proc;polb;p4hb;mme;mdm2;man1a;ly6d;psmb8;lgals1;itih2;ikbk;igfals;hgs;hcf1;gnb5;gfpt1;fn1;f7;f5;f2;dag1;cct4;capza2;c4b;c3;brca1;bmi1;blm;bet1;serpinc1;asgr1;app;apoe;birc2;agt1;tpstg;gbf1;qsox1;dnajc3	3626.36022	3669.42	185.394	1741.86203	3614.166	1793.76577	CONFLICT	0.482758621	0.517241379

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
90Day	Hedgehog 'on' state	0.0040315	1	0.0080428											
7Day	Protein localization	0.99711	0.0074555	0.0081628	gstk1;pitrm1;pex14;ldhd;decr2;pex6;uba52;pex7;phyh;hsd17b4;hao1;ephx2;baat;pecr	2498.93566	3180.375	49.8526	1711.27218	2785.82251	1473.67705	DOWN	0.357142857	0.642857143	
90Day	Toll-like Receptor Cascades	0.0047	0.99832	0.0082625	tbk1;irf7;mapk14;a;apob;nfbkbia;ikbk;g;trc	3315.05286	3601.1	175.96	2038.92263	3429.19726	2034.27276	DOWN	0.285714286	0.714285714	
90Day	Synthesis of (16-20)-hydroxyeicosatetraenoic acids (HETE)	0.9981	0.0083924	0.0083924	cyp2c54;cyp4a12a;cyp4a12b;cyp2c38;cyp2c37;cyp1a2;cyp2c69	2799.36286	3033.17	928.37	1542.29973	3147.62503	1313.47036	CONFLICT	0.428571429	0.571428571	
7Day	The role of GTSE1 in G2/M progression after G2 checkpoint	0.99799	0.0085659	0.0085659	gtse1;tubb4b;uba52;tubb2a;tuba4a;hsp90aa1;cdkn1a	2535.598	2094.04	919.856	1523.88877	2300.31657	1444.24257	UP	1	0	
28Day	Beta-oxidation of pristanoyl-CoA	0.99935	0.0091429	0.0091429	acox3;crot;hsd17b4	2619.01667	3528.55	702.63	1660.35273	2925.08461	1487.54404	DOWN	0.333333333	0.666666667	
90Day	Cell Cycle, Mitotic	0.0052181	0.99679	0.0094389	haus7;esco2;cenpu;smc4;hist1h4h;gins1;anapc10;tubb6;masl;pole4;cables1;nek6;arpp19;psmd8;orc6;dctn3;hist1h4i;gtse1;dbf4;cntrl;e2f2;psmc4;psmf1;tubb4b;cep76;tubb2a;tuba1b;nup153;knctc1;nudc;hsp90aa1;h2afx;cdkn1a;cdk7;btrc;sec13;cenpf	3115.37568	3413.71	186.178	1486.03554	3109.35872	1497.91195	UP	0.837837838	0.162162162	
90Day	Signaling by Rho GTPases	0.0048127	0.99715	0.0096762	arhgef6;cenpu;fmnl2;rho;hist1h4h;tubb6;iqgap2;hist1h4i;hist1h3c;mapk14;wasf2;pin1;tubb4b;ywhaz;fgd4;vav1;tubb2a;tuba1b;tiam1;kntc1;sos1;rtkn;rock2;rock1;nudc;myo9b;h2afx;cdc42;ctnnb1;ar;sec13;cenpf	3399.93459	3912.96	137.958	1760.34923	3285.51236	1887.004	CONFLICT	0.59375	0.40625	
28Day	Fatty acyl-CoA biosynthesis	0.99744	0.010089	0.010089	hacd3;elovl2;hacd1;hsd17b3;acs1;elovl3;acly	3230.915	4155.33	411.194	1940.57679	2990.77125	2086.85335	CONFLICT	0.571428571	0.428571429	
28Day	RAF/MAP kinase cascade	0.0052703	0.99835	0.0101	ranbp9;map3k11;hbegf;fn1;fgf1	3061.3016	3156	919.738	1930.82326	2739.58196	1684.15141	DOWN	0.4	0.6	
28Day	Synthesis of bile acids and bile salts via 7alpha-hydroxycholesterol	0.99769	0.010474	0.010474	akr1c6;akr1c12;akr1c19;amacr;hsd17b4;akr1c14	3924.225	4373.23	702.63	2036.02025	3237.11114	1777.52258	DOWN	0.333333333	0.666666667	
90Day	RNA Polymerase II Pre-transcription Events	0.005158	0.99906	0.010493	eloa;cdk7	4445.455	4445.455	3130.16	1860.10803	4242.37403	1837.80252	UP	1	0	
90Day	MAPK family signaling cascades	0.0050676	0.99762	0.010791	klb;ranbp9;irs2;tln1;rasa1;tgifa;tek;nrg1;sos1;gfra1;fn1;fgf1;cdc42;areg	2357.87524	2148.075	74.8133	1925.27039	2446.17276	2054.34489	CONFLICT	0.428571429	0.571428571	
7Day	Cap-dependent Translation Initiation	0.99716	0.0079707	0.010827	eif3m;eif3j1;rps25;eif1ax;eif3b;rps3;eif2s3x;eif3l;eif5;rps12;eif4ebp1;eif4a2	3185.84438	3420.48	84.8066	1629.91973	3140.44345	1545.3292	UP	0.833333333	0.166666667	
28Day	Metabolism of amino acids and derivatives	0.99648	0.0069866	0.010909	phykpl;ndufab1;asrgl1;tdo2;serinc1;prodh2;txnr1;ahcy;sds;aldh4a1;sardh;otc;odc1;oat;hpd;gstz1;got2;glul;ddc;ass1;gm4737;aldh7a1;haao;aldh6a1	2751.13308	2763.68	726.832	1404.8189	2691.14141	1183.04341	DOWN	0.125	0.875	
28Day	Neuronal System	0.0064015	0.99707	0.01134	gria3;lin7c;slc22a1;slc1a2;ptprd;mdm2;jil1rap;gnb5;glul;slc6a13;epb41l3;adcy9	2791.34417	2159.59	151.142	1749.21816	2627.92103	1560.6028	DOWN	0.25	0.75	
7Day	Eukaryotic Translation Initiation	0.99668	0.0091338	0.011719	eif3m;eif3j1;rps25;eif1ax;eif3b;rps3;eif2s3x;eif3l;eif5;rps12;eif4ebp1;eif4a2	3185.84438	3420.48	84.8066	1629.91973	3140.44345	1545.3292	UP	0.833333333	0.166666667	
90Day	E3 ubiquitin ligases ubiquitinate target proteins	0.0073511	1	0.011932											
90Day	Chylomicron clearance	0.99927	0.011973	0.011973	apob;lipc;apoe	1672.98333	1749.82	175.96	1460.12207	2324.5335	1324.11035	DOWN	0	1	
90Day	Propionyl-CoA catabolism	0.99927	0.011973	0.011973	pccb;mut;pcca	1622.02567	1339.27	412.607	1372.81254	1859.85519	1369.88864	DOWN	0	1	
90Day	Transport of inorganic cations/anions and amino acids/oligopeptides	0.0054226	0.9985	0.012233	slc17a8;slc1a2;slc6a12;slc26a2	2689.32225	3008.81	777.189	1397.86912	3063.38493	929.405967	DOWN	0.25	0.75	
90Day	Collagen chain trimerization	0.0057811	1	0.012545											
7Day	Developmental Biology	0.0062483	0.99629	0.012789	ranbp9;gsk3b;kalrn;sdcbp;mapk3;tubb4b;yes1;pak2;vasp;uba52;tubb2a;tuba4a;rasa1;dsglc;sema4d;sema4a;reln;ptpn11;pfm2;pfm1;krts;krts;kras;hsp90aa1;gfra1;csnk2b;cdc42;ctnnb1;abl1;dsp	3184.11607	3381.94	54.5232	1578.02548	3131.41453	1822.62673	CONFLICT	0.566666667	0.433333333	
7Day	Neurotransmitter receptors and postsynaptic signal transmission	0.0056358	0.99824	0.013063	gria3;prkar2a;gna13;calm3;calm2	3336.17	3853.21	794.2	1568.57851	2915.53749	1584.96901	UP	0.6	0.4	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
7Day	Synthesis of bile acids and bile salts via 7alpha-hydroxycholesterol	0.99662	0.013068	0.013068	akr1c6;ncoa2;ncoa1;hsd17b4;baat;akr1c14;hsd3b7	2647.49451	3301.55	86.7986	1828.06574	2920.91192	1357.03567	UP	0.714285714	0.285714286	
7Day	Cardiac conduction	0.0056277	0.99843	0.013118	itpr2;dmpk;calm3;calm2	3890.9575	3798.475	3050.32	807.324813	3574.7767	786.454883	DOWN	0.25	0.75	
28Day	Transcriptional regulation by RUNX1	0.0068842	0.9983	0.013262	hist1h4;tal1;bmi1	3730.3	3918.46	1424.03	2218.18343	3823.03545	2379.05883	DOWN	0.333333333	0.666666667	
7Day	Alpha-oxidation of phytanate	0.99899	0.013412	0.013412	slc25a17;phyh;pecr	2478.42	2689.11	1604.15	790.277396	2367.9245	757.002727	DOWN	0.333333333	0.666666667	
7Day	Choline catabolism	0.99899	0.013412	0.013412	dmgdh;sardh;aldh7a1	1098.06733	408.564	233.368	1348.82647	1115.83937	1385.41342	DOWN	0	1	
7Day	Regulation of PTEN localization	0.99899	0.013412	0.013412	uba52;pten;xiap	4270.09	4761.56	3174.68	950.318197	4222.95249	979.246287	UP	0.666666667	0.333333333	
28Day	Proline catabolism	0.99968	0.013472	0.013472	prodh2;aldh4a1	2205.51	2205.51	1092.57	1573.93484	1975.64572	1539.99861	DOWN	0	1	
28Day	Beta oxidation of lauroyl-CoA to decanoyl-CoA-CoA	0.99968	0.013472	0.013472	echs1;acacdl	2016.1655	2016.1655	802.301	1716.66364	1538.10672	1577.92701	DOWN	0	1	
28Day	Biosynthesis of E-series 18(S)-resolvins	0.99968	0.013472	0.013472	gpx4;ita4h	4857.005	4857.005	3909.63	1339.79057	4832.85644	1339.35525	DOWN	0	1	
28Day	Keratinization	0.0067684	0.99805	0.013805	pkp4;pkp1;krt8;krt18	2676.64925	2807.215	856.847	1425.57491	2794.74322	1223.74793	UP	1	0	
7Day	SLC-mediated transmembrane transport	0.0063227	0.99712	0.013918	slc2a8;slc5a3;slc39a2;slc22a12;slc22a1;slc20a1;slc1a2;slc12a7;slc8b1;calm3;calm2;slc12a6	3720.52333	3445.645	1710.87	1322.53874	3757.00214	1300.02822	CONFLICT	0.416666667	0.583333333	
7Day	Activation of the mRNA upon binding of the cap-binding complex and eIFs, and subsequent binding to 43S	0.99679	0.0093065	0.014498	eif3m;eif3j1;rps25;eif1ax;eif3b;rps3;eif2s3x;eif3l;rps12;eif4ebp1;eif4a2	3166.42296	3441.48	84.8066	1708.01734	3102.15628	1658.7131	UP	0.818181818	0.181818182	
90Day	Metabolism of lipids	0.0080643	0.99453	0.014787	osbp10;acac10;osbp13;ndufab1;cyp4f16;dgat2;pcsb;ormdl2;tnfaip8l1;gpx4;hacl1;cyp3a25;cyp39a1;cyp3a41a;acaa2;acsl4;cyp2c54;agmo;cyp4a12a;pon3;slc27a5;slc27a2;tnfaip8l3;ppm11;scap;acer2;fitm2;pi4ka;sptlc2;slc25a17;slc10a1;scd1;psap;mut;amacr;hsd17b7;hsd11b1;hpgd;hdac3;gstm4;gm2a;acsl1;ephx2;cyp4a12b;cyp2e1;cyp2d9;cyp2c38;cyp2c37;cyp1a2;elovl3;pcaca;plekha1;osbp9;cyp2c69;cyp3a41b	3102.0314	3327.72	105.476	1472.79105	3064.34323	1368.45951	DOWN	0.381818182	0.618181818	
28Day	Cell junction organization	0.0062884	1	0.014873											
90Day	Purine catabolism	0.99665	0.015029	0.015029	pnp2;nudt5;dnph1;nudt15;nudt18;pnp	3648.29167	3600.91	2714.47	612.548675	3618.05393	423.693132	CONFLICT	0.5	0.5	
28Day	Formation of Fibrin Clot (Clotting Cascade)	0.99567	0.015564	0.015564	f12;a2m;proc;f7;f5;f2;serpinc1	2447.52357	2170.26	362.714	2004.60325	2068.01102	2112.87601	DOWN	0.142857143	0.857142857	
90Day	Golgi-to-ER retrograde transport	0.008227	0.99711	0.015588	tubb6;dctn3;tubb4b;tubb2a;tuba1b;kifc1	1779.45667	1751.94	713.489	1092.46087	1506.31085	1127.69973	UP	0.833333333	0.166666667	
90Day	Epigenetic regulation of gene expression	0.0082858	0.99761	0.016478	hist1h4h;hist1h4i;hist1h3c;h2afx	3214.00725	3979.26	811.859	1602.37406	2298.31583	1843.92338	CONFLICT	0.5	0.5	
7Day	Regulation of Complement cascade	0.99436	0.016933	0.016933	c8g;c1rb;c1s1;cfhr1;f2;cfh;c4b;c2;c1qb	2570.38667	1971.95	56.713	2036.81442	2209.89729	2181.8838	DOWN	0	1	
28Day	Retinoid metabolism and transport	0.99449	0.017403	0.017403	akr1c6;akr1c12;akr1c19;apob;lrp1;gpc4;apoe;akr1c14	3304.12688	3286.855	939.205	1587.30096	2770.81203	1466.02632	DOWN	0.25	0.75	
28Day	Intrinsic Pathway of Fibrin Clot Formation	0.99624	0.017932	0.017932	f12;a2m;proc;f2;serpinc1	2868.5328	2357.81	362.714	2225.23577	2689.94892	2345.22346	DOWN	0.2	0.8	
7Day	Peroxisomal protein import	0.9932	0.017045	0.018615	gstk1;peh14;decr2;peh6;uba52;peh7;phyh;hsd17b4;hao1;ephx2;baat;pecr	2289.21328	2985.61	49.8526	1767.76367	2628.16399	1537.73308	CONFLICT	0.416666667	0.583333333	
90Day	mTOR signalling	0.0093469	1	0.018812											
90Day	Class B/2 (Secretin family receptors)	0.0080143	0.99905	0.019003	gng11	4854.24	4854.24	4854.24		4854.24		UP	1	0	
7Day	Peptide hormone metabolism	0.011259	0.99858	0.019019	mme	2165.57	2165.57	2165.57		2165.57		DOWN	0	1	
7Day	Collagen biosynthesis and modifying enzymes	0.011259	0.99858	0.019019	p3h3	3788.93	3788.93	3788.93		3788.93		DOWN	0	1	
90Day	Organelle biogenesis and maintenance	0.0096732	0.99535	0.01929	haus7;cep89;tubb6;dctn3;cntrl1;ift52;tubb4b;cep76;tubb2a;tuba1b;exoc4;hsp90a1;atp5k	2333.235	1951.01	135.802	1719.06723	2342.66599	1539.02207	UP	0.769230769	0.230769231	
7Day	Collagen degradation	0.0094696	0.99884	0.019465	ctsb	3881.76	3881.76	3881.76		3881.76		UP	1	0	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
28Day	Metabolism of lipids	0.9921	0.011728	0.01968	echs1;akr1c6;acox3;fads1;crot;ndufab1;fitm1;pmvk;dgat2;pnpla8;pi4k2b;ormdl2;ormdl3;tnfaip8l1;gpx4;akr1c12;hacd3;hac11;fads2;cyp3a25;elovl2;acaa2;akr1c19;agmo;hacd1;acsf2;decr2;hsd17b13;phospho1;pla2g4c;pi4ka;etnk2;slc25a17;slc10a1;ptdss1;mapkapk2;amacr;ltta4h;phyh;hsd17b4;hsd17b3;hsd11b1;gstm4;gc;fdr;acs1;cyp4a12b;cyp3a11;cyp2e1;cyp2c37;cyp2c29;elovl3;aldh3a2;acox1;acdl;abhd4;akr1c14;acly;cyp3a59;cyp3a41b	3157.27265	3343.195	67.9262	1675.85824	2996.35377	1613.26151	DOWN	0.35	0.65
7Day	Class C/3 (Metabotropic glutamate/pheromone receptors)	0.01042	1	0.01969										
90Day	Transport of connexons to the plasma membrane	0.99589	0.020553	0.020553	tubb6;tubb4b;tubb2a;tuba1b;gjb2	1916.9702	1781.5	779.791	922.579865	1733.98302	1064.65299	UP	0.6	0.4
90Day	Biosynthesis of the N-glycan precursor (dolichol lipid-linked oligosaccharide, LLO) and transfer to a nascent protein	0.012219	0.99751	0.021009	st6galnac6;st3gal3	4683.725	4683.725	4143.19	764.431928	4469.98451	702.129746	DOWN	0	1
90Day	The role of GTSF1 in G2/M progression after G2 checkpoint	0.99384	0.021721	0.021721	tubb6;gtse1;tubb4b;tubb2a;tuba1b;hsp90aa1;cdkn1a	1386.23586	1722.38	426.32	664.868459	1289.25247	639.31966	UP	0.857142857	0.142857143
28Day	Metabolism of fat-soluble vitamins	0.99278	0.021803	0.021803	akr1c6;akr1c12;akr1c19;apob;lrp1;gpc4;apoe;akr1c14	3304.12688	3286.855	939.205	1587.30096	2770.81203	1466.02632	DOWN	0.25	0.75
90Day	Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell	0.012425	0.99581	0.02183	sh2d1b1;icam1;fcgr2b;cd1d1;c3	2316.7788	2931.68	639.57	1458.85717	1731.86105	1388.39031	DOWN	0.4	0.6
90Day	Alpha-oxidation of phytanate	0.99801	0.021952	0.021952	hac11;slc27a2;slc25a17	3683.26	3419.78	2910.82	932.527616	3761.45897	916.721686	DOWN	0.333333333	0.666666667
7Day	Initial triggering of complement	0.99526	0.02224	0.02224	c1rb;c1s1;c4b;c2;c1qb	2024.1086	1939.15	56.713	1811.39163	1363.19794	1399.09444	DOWN	0	1
90Day	Neddylation	0.010736	0.99445	0.022272	fbxo22;fbxo9;fbxw9;fbxo32;asb2;psmd8;keap1;ktbtd8;dcaf10;psmc4;wdtc1;psmf1;ube2m;fem1b;btrc;dcun1d2	2496.52815	2234.2	61.8554	1776.88051	2535.86014	1738.28033	UP	0.625	0.375
90Day	M Phase	0.012715	0.99265	0.022967	haus7;cenpu;smc4;hist1h4h;anapc10;tubb6;mastl;nek6;arpp19;dctn3;hist1h4i;cntrl;tubb4b;cep76;tubb2a;tuba1b;nup153;kntc1;nudc;hsp90aa1;h2afx;sec13;cenpf	3187.91661	3442.78	426.32	1395.97387	3224.94305	1447.49908	UP	0.869565217	0.130434783
7Day	Signaling by Receptor Tyrosine Kinases	0.011577	0.99319	0.023051	ranbp10;ranbp9;hgfac;nckap1;mapk3;polr2h;yes1;pak2;uba52;rasa1;stat1;ptpn11;ppp2cb;prkcz;pcsk5;kras;hsp90aa1;fgf1;cdc42;ctnnb1;calm3;calm2;atp6v	3378.37149	3629.67	54.5232	1564.98066	3325.71149	1661.08608	UP	0.64	0.36
7Day	Collagen formation	0.013014	0.99657	0.023576	p3h3;dst;ctsb	3551.01	3788.93	2982.34	494.665067	3542.51101	520.283197	UP	0.666666667	0.333333333
7Day	O-linked glycosylation	0.011254	0.99709	0.02407	c1galt1;large1;adamts7	3186.34333	3416.43	2525.28	581.242416	3214.36703	621.324607	DOWN	0.333333333	0.666666667
28Day	Cytokine Signaling in Immune system	0.011395	0.99427	0.024423	ube2n;map2k4;arih1;ube2m;tnfrsf1b;ppm1b;p4hb;sqtmt1;mapkapk2;lifr;il1ra;pi3kbkg;app;birc2	4008.77721	4948.59	727.581	1908.57018	3795.96088	2055.80587	CONFLICT	0.428571429	0.571428571
90Day	MAPK1/MAPK3 signaling	0.011593	0.99435	0.024694	klb;ranbp9;irs2;tln1;rasa1;tgifa;tekg;nrg1;sos1;gfra1;fn1;fgf1;areg	2527.21279	2162.51	74.8133	1892.25992	2550.28585	2041.691	DOWN	0.384615385	0.615384615
90Day	Deubiquitination	0.012722	0.99322	0.024698	babam1;tomm20;psmd8;mcrs1;keap1;tomm70a;usp18;psmc4;psmf1;yy1;ino80c;siah2;rad23a;nfkbia;mdm2;ikkbkg;ar	2829.23253	3031.27	143.029	1847.34956	2769.53306	1729.64448	UP	0.705882353	0.294117647
90Day	Synthesis of epoxy (EET) and dihydroxyeicosatrienoic acids (DHET)	0.99367	0.024729	0.024729	cyp2c54;ephx2;cyp2c38;cyp2c37;cyp1a2;cyp2c69	2656.36667	2368.37	928.37	1639.96321	2875.04451	1661.73435	DOWN	0.166666667	0.833333333
7Day	Proline catabolism	0.99917	0.02494	0.02494	prodh2;aldh4a1	1154.5437	1154.5437	84.5274	1513.23156	1587.65602	1383.72584	DOWN	0	1
7Day	VLDL assembly	0.99917	0.02494	0.02494	apob;apoc1	2882.07	2882.07	1999.21	1248.55259	3387.19612	1024.00135	DOWN	0	1
28Day	G2/M Transition	0.014424	0.99612	0.025215	dynl1;tubb4b;tubb2a	3684.67667	2903.04	2359.45	1844.72961	3931.15502	1868.40338	UP	1	0
28Day	Mitotic G2-G2/M phases	0.012997	0.99655	0.0254	dynl1;tubb4b;tubb2a	3684.67667	2903.04	2359.45	1844.72961	3931.15502	1868.40338	UP	1	0
28Day	Cell Cycle, Mitotic	0.013065	0.99256	0.025703	zwilch;psmd6;nek6;arpp19;pole3;psmd8;dynl1;set;cnep1r1;cenpt;hist1h4i;cdc6;cdc14a;psmf1;tubb4b;tubb2a;tfdp1;cdc27;rad21;psmb8;tp	3817.7681	3638.67	748.272	1660.67406	3936.11963	1582.40173	UP	0.80952381	0.19047619

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
28Day	Neurotransmitter uptake and metabolism in glial cells	0.99878	0.025721	0.025721	slc1a2;glul	1856.72	1856.72	1774.78	115.880659	1827.3371	108.174014	DOWN	0	1
28Day	Astrocytic Glutamate-Glutamine Uptake And Metabolism	0.99878	0.025721	0.025721	slc1a2;glul	1856.72	1856.72	1774.78	115.880659	1827.3371	108.174014	DOWN	0	1
28Day	Lysosomal oligosaccharide catabolism	0.99878	0.025721	0.025721	man2b2;man2b1	1624.9215	1624.9215	240.253	1958.21697	1298.07952	1902.88264	DOWN	0	1
28Day	Scavenging by Class B Receptors	0.99878	0.025721	0.025721	apob;scarb1	2108.7525	2108.7525	939.205	1653.98994	2000.86534	1646.93759	DOWN	0	1
28Day	Advanced glycosylation endproduct receptor signaling	0.99878	0.025721	0.025721	capza2;app	5033.45	5033.45	4630.47	569.899781	5168.55413	536.916667	DOWN	0	1
28Day	Resolution of AP sites via the single-nucleotide replacement pathway	0.99878	0.025721	0.025721	polb;lig3	5622.33	5622.33	5391.42	326.556054	5616.5595	326.454068	CONFLICT	0.5	0.5
28Day	Regulation of Complement cascade	0.99198	0.02576	0.02576	c8g;vtnf2;clui;c4b;c3;c2	1813.981	2305.72	447.762	1052.00591	1683.33373	944.640074	DOWN	0	1
90Day	Degradation of the extracellular matrix	0.015163	0.99395	0.025961	tmprrs6;plg;mmp2;fn1;ctsd;capn5;bm	3225.71843	3885.66	190.369	2242.46386	2534.03961	2382.64934	DOWN	0.285714286	0.714285714
90Day	Formation of TC-NER Pre-Incision Complex	0.016612	0.99779	0.026276	cdk7	3130.16	3130.16	3130.16		3130.16		UP	1	0
7Day	Translation initiation complex formation	0.99196	0.021558	0.027293	elf3m;elf3j1;rps25;elf1ax;elf3b;rps3;ei	3171.36726	3842.8	84.8066	1800.32538	3101.75382	1689.54617	UP	0.9	0.1
7Day	Pink/Parkin Mediated Mitophagy	0.99362	0.027905	0.027905	tomm20;mfn1;mtorf3;tomm7;uba52	4096.692	4048.88	2384.74	1205.41607	3628.23874	1042.88808	UP	0.6	0.4
7Day	G1/S DNA Damage Checkpoints	0.99362	0.027905	0.027905	cop1;uba52;cdkn1a;cdc25a;ccne2	4336.77	4598.19	2818.63	1165.22018	4198.65867	1079.35895	UP	1	0
90Day	Fanconi Anemia Pathway	0.017035	1	0.027972										
90Day	RNA Polymerase III Transcription	0.015109	1	0.028398										
90Day	RNA Polymerase III Transcription Initiation	0.015109	1	0.028398										
90Day	Translation	0.013037	0.99435	0.029248	elf3m;mrpl58;rps27l;mrps18b;mrpl54;mrps30;mrps31;mrpl22;rps12	3118.28833	3479.94	958.825	1389.80948	2899.04688	1530.79325	UP	0.777777778	0.222222222
7Day	Elastic fibre formation	0.018923	1	0.029507										
7Day	MET promotes cell motility	0.018923	1	0.029507										
7Day	L13a-mediated translational silencing of Ceruloplasmin expression	0.99069	0.024407	0.029599	elf3m;elf3j1;rps25;elf1ax;elf3b;rps3;ei	3171.36726	3842.8	84.8066	1800.32538	3101.75382	1689.54617	UP	0.9	0.1
28Day	Resolution of D-loop Structures through Synthesis-Dependent Strand Annealing (SDSA)	0.99281	0.029601	0.029601	rmi1;rad51d;rad51;brca1;blm	3513.5312	3769.36	692.086	1790.07678	3877.73216	1143.86555	UP	1	0
90Day	Macroautophagy	0.016192	0.99657	0.030007	gabrarpl1;atg13	2761.14	2761.14	841.06	2715.40318	2873.17968	2710.77639	CONFLICT	0.5	0.5
90Day	Collagen biosynthesis and modifying enzymes	0.016192	0.99657	0.030007	p4ha2;bmp1	2145.7695	2145.7695	190.369	2765.35391	1594.97401	2653.38103	CONFLICT	0.5	0.5
7Day	Transport of vitamins, nucleosides, and related molecules	0.015511	1	0.03008										
7Day	Cilium Assembly	0.014981	0.99339	0.030189	atat1;hspb11;cep89;rab11a;tubb4b;tub	2775.07956	3074.7	919.856	1351.62912	2688.13639	1362.55383	UP	0.888888889	0.111111111
90Day	RAF/MAP kinase cascade	0.016523	0.99171	0.030915	klb;ranbp9;irs2;tln1;rasa1;tgfa;tek;nrg	2527.21279	2162.51	74.8133	1892.25992	2550.28585	2041.691	DOWN	0.384615385	0.615384615
7Day	Amine ligand-binding receptors	0.014043	1	0.030975	1;sos1;gfra1;fn1;fgf1;areg									
7Day	Voltage gated Potassium channels	0.014043	1	0.030975										
7Day	Collagen chain trimerization	0.014043	1	0.030975										
90Day	Beta-catenin independent WNT signaling	0.018823	0.99484	0.031028	gng11;ctnnb1;ap2m1	3974.94333	4087.04	2983.55	940.369351	4048.13013	972.884127	UP	0.666666667	0.333333333
7Day	Biosynthesis of DHA-derived SPMs	0.9901	0.031269	0.031269	cyp3a25;gstt4;cyp3a11;cyp2e1;cyp2c	3229.52186	2813.51	529.743	1691.38457	3004.89739	1441.18311	CONFLICT	0.428571429	0.571428571
90Day	Clathrin-mediated endocytosis	0.017292	0.99264	0.031366	pacsin2;apob;trf;tgfa;fnbp1;sh3gl3;ar	3270.33713	3476.97	175.96	2233.63372	3101.83853	2159.25523	UP	0.625	0.375
28Day	Ion transport by P-type ATPases	0.019778	1	0.031599	eg;ap2m1									
28Day	Signaling by PDGF	0.018412	1	0.031667										
28Day	Signaling by Interleukins	0.016557	0.99258	0.031743	ube2n;map2k4;p4hb;sqstm1;mapkapk	4350.48344	5266.71	727.581	1708.00819	4616.0705	1618.62408	DOWN	0.333333333	0.666666667
90Day	Neurotransmitter receptors and postsynaptic signal transmission	0.015105	0.99365	0.031749	gng11;gria3;camkk2;mdm2;gna13;gabr	3313.27228	3683.79	98.0082	1910.30946	2834.02861	1761.68773	UP	0.75	0.25
90Day	Cell-Cell communication	0.013627	0.99583	0.031822	b3;epb41l1;ap2m1	4037.9335	4700.81	797.214	2295.03793	4190.02407	2312.13407	DOWN	0.25	0.75
90Day	CYP2E1 reactions	0.99	0.032075	0.032075	arhgef6;afdn;ctnnb1;actn1									
90Day	RHO GTPases activate IQGAPs	0.99	0.032075	0.032075	cyp2c54;cyp2f2;cyp2e1;cyp2d9;cyp2c3	3014.61429	3033.17	1493.96	1482.51701	3137.40638	1452.81272	CONFLICT	0.428571429	0.571428571
90Day					8;cyp2c37;cyp2c69									
90Day					tubb6;iqgap2;tubb4b;tubb2a;tuba1b;cd									
90Day					c42;ctnnb1	1826.00971	1781.5	156.487	1241.69399	1394.27274	939.491167	CONFLICT	0.571428571	0.428571429

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
7Day	Formation of the ternary complex, and subsequently, the 43S complex	0.9933	0.019565	0.032278	EIF3M;EIF3J1;RPS25;EIF1AX;EIF3B;RPS3;EIF3X;EIF3I;RPS12	3141.35473	4244.12	84.8066	1906.87819	3022.06387	1878.99333	UP	0.888888889	0.111111111
7Day	Formation of the cornified envelope	0.016975	0.99463	0.032346	DSP1C;KRT8;KRT18;DSP	1895.05825	2157.095	240.593	1294.67509	1764.83129	1510.73684	DOWN	0.25	0.75
7Day	Cytokine Signaling in Immune system	0.015231	0.99116	0.033182	UBE2N;FLNB;EIF4E2;MAPK3;MAP2K3;ARIH1;YWHAZ;YES1;UBA52;HSP90B1;STAT1;PTPN11;PRLR;PPP2CB;JAK1;IL1RAP;IFNG;GHR;EIF4A2;CSF1R;CSF1;BTRC	3311.8225	3628.355	131.024	1176.84533	3240.75029	1258.651	UP	0.772727273	0.227272727
28Day	G alpha (i) signalling events	0.01787	0.99016	0.033324	AKR1C6;AKR1C12;AKR1C19;APOB;RDH16F2;CX3CL1;CXCL9;IRP1;GPC4;GNB5;C3;APP;APOE;AGT;ADORA1;ADCY9;AKR1C14	3526.57288	3361.03	907.506	1788.0793	3033.72803	1754.35763	DOWN	0.294117647	0.705882353
90Day	Cellular Senescence	0.018706	0.9913	0.033465	HIST1H4H;ANAPC10;CBX6;HIST1H4I;HIST1H3C;MAPK14;TXN1;MDM2;H2AFX;CDKN1A	3184.5738	3979.26	744.949	1679.62346	2343.34957	1756.05903	UP	0.6	0.4
90Day	Phase I - Functionalization of compounds	0.98821	0.021181	0.033481	ALDH1B1;CYP4F16;CYP3A25;CYP39A1;FMO2;CYP3A41A;CYP2C54;CES3A;CYP4A12A;ADH4;ALDH1A7;CES2E;CES2C;CES3B;EPHX1;CYP4A12B;CYP2F2;CYP2E1;CYP2D9;CYP2C38;CYP2C37;CYP1A2;CBR3;CYP2C69;CYP3A41B	2739.95376	3047.49	343.937	1449.41888	2790.68439	1406.00101	CONFLICT	0.56	0.44
90Day	Cilium Assembly	0.018346	0.99095	0.034529	HAUS7;CEP89;TUBB6;DCTN3;CNTRL;IFT52;TUBB4B;CEP76;TUBB2A;TUBA1B;EXOC4;HSP90AA1	2516.35442	2032.085	154.682	1657.79703	2395.61575	1520.47541	UP	0.833333333	0.166666667
90Day	Transmission across Chemical Synapses	0.017635	0.9909	0.034877	GNG11;GRIA3;JLN7C;UNC13B;CAMKK2;SLC22A1;SLC1A2;MDM2;GNAI3;GLUL;SLC6A12;GABRB3;EPB41L1;AP2M1	2977.32694	3490.115	98.0082	1763.18318	2750.88314	1506.44157	CONFLICT	0.571428571	0.428571429
28Day	Chylomicron assembly	0.99508	0.035072	0.035072	APOB;P4HB;APOE	3294.26833	3212.68	939.205	2396.89917	2832.04742	2711.32472	DOWN	0	1
28Day	Gamma-carboxylation of protein precursors	0.99508	0.035072	0.035072	PROC;F7;F2	2700.24	2170.26	1340.75	1688.07416	1850.85737	1335.69078	DOWN	0	1
28Day	Transport of gamma-carboxylated protein precursors from the endoplasmic reticulum to the Golgi apparatus	0.99508	0.035072	0.035072	PROC;F7;F2	2700.24	2170.26	1340.75	1688.07416	1850.85737	1335.69078	DOWN	0	1
90Day	MASTL Facilitates Mitotic Progression	0.99857	0.035205	0.035205	MASTL;ARPP19	2369.5705	2369.5705	577.791	2533.95887	3023.16335	2359.36015	UP	1	0
90Day	STAT6-mediated induction of chemokines	0.99857	0.035205	0.035205	TMEM173;TBK1	2558.24	2558.24	1058.39	2121.10821	2553.28861	2121.09665	DOWN	0	1
90Day	Vitamins B6 activation to pyridoxal phosphate	0.99857	0.035205	0.035205	PDXK;AOX1	3825.07	3825.07	3196.71	888.635234	3853.28022	887.739233	CONFLICT	0.5	0.5
28Day	Estrogen-dependent gene expression	0.01453	0.99691	0.035289	HIST1H4I;POLR2A	5444.54	5444.54	5040.67	571.158431	5494.50555	566.770537	CONFLICT	0.5	0.5
7Day	Metabolism of RNA	0.98477	0.022287	0.035762	SF3B1;RPS25;SF3A3;FCF1;UTP14A;GM49336;DCP2;SNRPA1;DNAJC8;ZCRB1;FIP1L1;RIOK3;CRMK1;WDR61;PNO1;PPIH;SF3B6;UTP3;HBS1;ADAR;DDX21;NOP58;BYS1;HNRNPA2B1;CPSF2;PRPF19;RPS3;POLR2H;PCBP1;CNOT1;HNRNPUL1;PRPF38A;YWHAZ;UBA52;ZRSR2;UTP18;SNRPC;RPS12;UTP14B;NCL;HNRNPC;FBL;EIF4A2;DHX9;LSM10;PWP2;SRF1;TPR;CSF2;THOC5;SNRPD2;UTP15;XPO1;SF3B3	3495.79884	3404.94	84.8066	1271.25282	3331.61405	1190.08518	UP	0.962962963	0.037037037
7Day	Microtubule-dependent trafficking of connexons from Golgi to the plasma membrane	0.99287	0.036389	0.036389	TUBB4B;TUBB2A;TUBA4A;GJA1	2276.434	1954.85	919.856	1424.18025	1763.60227	985.706882	UP	0.75	0.25
7Day	Protein methylation	0.99287	0.036389	0.036389	PRMT3;ETFBKMT;CALM3;CALM2	3358.08	3253.69	2008.38	1204.86006	3326.34795	937.160808	UP	0.75	0.25
28Day	Pink/Parkin Mediated Mitophagy	0.99222	0.037302	0.037302	TOMM20;INTERF3;SQSTM1;ATG5	4818.665	4936.54	3654.44	1058.71114	5368.53606	825.784265	UP	1	0
90Day	Platelet activation, signaling and aggregation	0.017245	0.99031	0.037349	SPP2;GNG11;MAPK14;YWHAZ;VAV1;TRF;TLN1;SERPINA1E;SOS1;PSAP;PLG;GNAI3;FN1;ECM1;CDC42;ANXA5;AHSJ;ACTN1;SCCPDH	2864.74343	3112.61	82.4742	2024.71146	3226.11939	2006.99711	DOWN	0.263157895	0.736842105
28Day	G alpha (q) signalling events	0.021376	0.99105	0.037825	NTS;CYSLTR1;HBEFG;GNB5;F2;APP;AGT	3372.78514	4610.42	919.738	2192.42274	3223.5604	2239.60151	CONFLICT	0.571428571	0.428571429
28Day	Plasma lipoprotein assembly, remodeling, and clearance	0.98989	0.027121	0.038276	LMF1;NPC2;APOB;A2M;SCARB1;P4HB;CES3B;BMP1;APOE	2909.28044	3007.97	614.079	1893.95297	2560.18225	2078.39985	DOWN	0.222222222	0.777777778
90Day	Inositol phosphate metabolism	0.022604	0.99683	0.038377	MINPP1	3256.99	3256.99	3256.99		3256.99		UP	1	0
90Day	Aquaporin-mediated transport	0.022604	0.99683	0.038377	GNG11	4854.24	4854.24	4854.24		4854.24		UP	1	0

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
90Day	Phase II - Conjugation of compounds	0.9849	0.029403	0.038413	abhd14b;gstk1;sult1b1;ahcy;ugt2b35;b pnt1;ugdh;gstz1;gstp2;gstm4;gsta2;gs ta1;gclm;gclc;slc26a2;gm4737;gm106 39;gm3776	1928.25806	1651.995	444.891	1110.11588	1817.12238	1102.15486	UP	0.611111111	0.388888889
28Day	CYP2E1 reactions	0.98953	0.039535	0.039535	cyp2e1;cyp2c37;cyp2c29;cyp2a5;cyp2a 4	3205.078	2751.06	1326.21	1639.97523	3044.33339	1332.90059	UP	0.6	0.4
90Day	O-linked glycosylation	0.022915	0.99171	0.039618	galnt12;st3gal3;large1;adamts6;spon2 atat1;hspb11;cep89;rab11a;idh2;tubb4 b;tubb2a;tuba4a;nedd1;hsp90aa1;atp5 j	4039.772	3858.6	2622.31	1467.17891	3285.15745	1267.22913	DOWN	0.4	0.6
7Day	Organelle biogenesis and maintenance	0.01998	0.9903	0.040352		2968.22145	3074.7	919.856	1379.36573	2958.11122	1455.38031	UP	0.818181818	0.181818182
7Day	Class B/2 (Secretin family receptors)	0.022325	0.99684	0.040401	adgre1	2946.44	2946.44	2946.44		2946.44		DOWN	0	1
28Day	Peptide ligand-binding receptors	0.023615	0.9906	0.04093	nts;cx3cl1;cxcl9;f2;c3;agt	4497.39333	5577.235	1340.75	2013.82097	4077.79891	2113.96356	DOWN	0.333333333	0.666666667
28Day	Chylomicron clearance	0.9971	0.040936	0.040936	apob;apoE	2075.9425	2075.9425	939.205	1607.58959	1295.41266	1168.71324	DOWN	0	1
28Day	Synthesis of PIPs at the ER membrane	0.9971	0.040936	0.040936	pi4k2b;pi4ka	4418.385	4418.385	4173.55	346.248978	4399.97266	345.268484	CONFLICT	0.5	0.5
28Day	Biosynthesis of EPA-derived SPMs	0.9971	0.040936	0.040936	gpx4;ita4h	4857.005	4857.005	3909.63	1339.79057	4832.85644	1339.35525	DOWN	0	1
90Day	Rho GTPase cycle	0.021123	0.99082	0.040965	arhgef6;rho;fgd4;vav1;tiam1;sos1;my o9b;cdc42	4424.12838	4948.215	156.487	1937.7847	4628.92188	1600.97466	DOWN	0.375	0.625
90Day	Xenobiotics	0.99034	0.024355	0.040967	cyp3a25;cyp3a41a;cyp2c54;cyp2f2;cyp 2e1;cyp2d9;cyp2c38;cyp2c37;cyp1a2;cy p2c69;cyp3a41b	2462.65645	1703.57	343.937	1641.65669	2118.08842	1691.54269	DOWN	0.363636364	0.636363636
28Day	Mitotic Prometaphase	0.02168	0.99146	0.040976	zwilch;dynll1;cenpt;tubb4b;tubb2a;rad 21	3719.56667	3563.05	2359.45	1186.01958	3809.00797	1244.66079	UP	1	0
7Day	Regulation of insulin secretion	0.018837	0.99741	0.041757	itpr2	4098.21	4098.21	4098.21		4098.21		DOWN	0	1
90Day	Cellular responses to stress	0.02194	0.98647	0.042092	hist1h4h;anapc10;tubb6;dnaja2;dctn3; gm45902;txnr1;nox4;cbx6;hist1h4i;hi st1h3c;mapk14;tubb4b;txn1;tubb2a;tu ba1b;nup153;mdm2;hsp90aa1;h2afx;g stp2;gsr;cdkn1a;ar;prdx6;sec13	2595.55596	2450.705	190.561	1589.68108	2181.3073	1642.29523	UP	0.653846154	0.346153846
90Day	Protein ubiquitination	0.023445	0.99475	0.042432	ube2k;cdc34	2429.116	2429.116	569.072	2630.49945	1344.2356	2136.72563	UP	1	0
7Day	MAPK6/MAPK4 signaling	0.98693	0.042839	0.042839	kalrn;sept7;pak2;uba52;cdc42;xpo1	3485.07167	3161.305	2538.2	970.390702	3606.55949	978.996491	UP	0.833333333	0.166666667
90Day	Inactivation, recovery and regulation of the phototransduction cascade	0.027528	1	0.042907										
90Day	ROS, RNS production in phagocytes	0.027528	1	0.042907										
90Day	Negative regulation of MAPK pathway	0.027528	1	0.042907										
90Day	Transcription-Coupled Nucleotide Excision Repair (TC-NER)	0.024293	0.99311	0.042967	pole4;polk;cdk7	4212.22333	3652.71	3130.16	1445.45671	3760.17242	830.658559	UP	0.666666667	0.333333333
28Day	Synthesis of bile acids and bile salts	0.98645	0.043067	0.043067	akr1c6;akr1c12;akr1c19;amacr;hsd17b 4;akr1c14	3924.225	4373.23	702.63	2036.02025	3237.11114	1777.52258	DOWN	0.333333333	0.666666667
90Day	The phototransduction cascade	0.024416	1	0.043154										
28Day	HDACs deacetylate histones	0.021566	0.99693	0.043507	hist1h4i	5848.41	5848.41	5848.41		5848.41		DOWN	0	1
28Day	Synthesis of Prostaglandins (PG) and Thromboxanes (TX)	0.9902	0.044178	0.044178	akr1c6;akr1c12;akr1c19;akr1c14	4259.3975	4373.23	2669.87	1456.14239	3630.29862	1225.99018	CONFLICT	0.5	0.5
90Day	Lysosome Vesicle Biogenesis	0.021656	1	0.044245										
90Day	RAF activation	0.021656	1	0.044245										
28Day	Removal of aminoterminal propeptides from gamma-carboxylated proteins	0.99302	0.044436	0.044436	proc;f7;f2	2700.24	2170.26	1340.75	1688.07416	1850.85737	1335.69078	DOWN	0	1
28Day	Phenylalanine and tyrosine catabolism	0.99302	0.044436	0.044436	asrgl1;hpd;gstz1	3495.52	4526.39	726.97	2423.54016	2552.46734	2448.54772	DOWN	0.333333333	0.666666667
7Day	Protein ubiquitination	0.98815	0.028649	0.04453	ube2n;ube2v2;rraga;hist1h2bc;wdr61; pex14;ube2k;ube2a;ube2e3;uba52;cdc 34	3107.84909	3225.73	1018.89	955.142118	3165.74946	728.022569	UP	1	0
7Day	Activation of Matrix Metalloproteinases	0.028161	1	0.044944										
7Day	Complement cascade	0.98554	0.037255	0.044985	c8g;c1rb;c1s1;cfhr1;f2;cfh;c4b;c2;c1qb	2570.38667	1971.95	56.713	2036.81442	2209.89729	2181.8838	DOWN	0	1
7Day	Scavenging by Class A Receptors	0.9933	0.045455	0.045455	apob;hsp90b1;apoE	1321.822	1852.94	113.316	1049.14908	1545.13646	906.344871	DOWN	0.333333333	0.666666667
7Day	alpha-linolenic (omega3) and linoleic (omega6) acid metabolism	0.9933	0.045455	0.045455	fads1;elovl5;fads2	108.1313	56.7644	55.2305	90.301734	95.258529	83.000013	DOWN	0	1
7Day	Classical antibody-mediated complement activation	0.9933	0.045455	0.045455	c1rb;c1s1;c1qb	2315.66433	1939.15	56.713	2468.83611	1154.21203	1850.07688	DOWN	0	1

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
7Day	Biotin transport and metabolism	0.9933	0.045455	0.045455	mccc2;pccb;btd	1104.77653	199.112	77.8976	1674.72876	1310.70042	1721.84718	DOWN	0	1	
7Day	Prolactin receptor signaling	0.9933	0.045455	0.045455	prlr;ghr;btrc	4091.75333	4207.06	3805.67	249.302999	4180.66283	184.775987	UP	1	0	
28Day	MAPK family signaling cascades	0.02001	0.99125	0.045906	ranbp9;map3k11;sept7;cdc14a;hbegf;fn1;fgf1;cdc42	3036.8275	2809.745	748.272	1999.5176	3062.10703	1936.95559	UP	0.625	0.375	
7Day	Transport of connexons to the plasma membrane	0.99012	0.046029	0.046029	tubb4b;tubb2a;tuba4a;gja1	2276.434	1954.85	919.856	1424.18025	1763.60227	985.706882	UP	0.75	0.25	
7Day	Molecules associated with elastic fibres	0.023085	1	0.046043											
7Day	Fatty acids	0.023085	1	0.046043											
90Day	TBC/RABGAPs	0.019207	1	0.046173											
7Day	Lysosomal oligosaccharide catabolism	0.9969	0.046779	0.046779	man2c1;man2b1	1950.9045	1950.9045	420.579	2164.20708	1897.9567	2162.91131	DOWN	0	1	
7Day	Conjugation of benzoate with glycine	0.9969	0.046779	0.046779	acsm1;glyat	5641.24	5641.24	5478.46	230.205684	5548.95276	189.633298	UP	1	0	
7Day	Long-term potentiation	0.9969	0.046779	0.046779	calm3;calm2	3983.44	3983.44	3050.32	1319.63096	3556.9103	1173.69957	CONFLICT	0.5	0.5	
28Day	Epigenetic regulation of gene expression	0.026675	0.99378	0.047002	hist1h4i;polr1a	5855.735	5855.735	5848.41	10.3591143	5854.78856	10.27228	DOWN	0	1	
28Day	RNA Polymerase I Transcription	0.026675	0.99378	0.047002	hist1h4i;polr1a	5855.735	5855.735	5848.41	10.3591143	5854.78856	10.27228	DOWN	0	1	
28Day	RHO GTPase Effectors	0.02313	0.98824	0.047786	zwilch;dynl1;iqgap2;cenpt;hist1h4i;tubb4b;tubb2a;pf1n1;pdpk1;cdc42;mylk;brk1	3790.08567	3563.05	192.988	1713.23873	4051.71855	1407.6109	UP	0.666666667	0.333333333	
28Day	Semaphorin interactions	0.024512	1	0.048786											
28Day	Ion homeostasis	0.024512	1	0.048786											
90Day	Mitotic Spindle Checkpoint	0.026683	0.98938	0.048991	cenpu;anapc10;kntc1;nudc;sec13;cenpf	3803.32333	3370.595	2758.9	1092.35219	4013.06255	1256.89861	UP	1	0	
7Day	Biosynthesis of maresins	0.98414	0.049876	0.049876	cyp3a25;cyp3a11;cyp2e1;cyp2c37;cyp2c29;cyp3a41b	3329.52217	3098.075	529.743	1830.01027	3082.0157	1591.6575	DOWN	0.333333333	0.666666667	
7Day	Biosynthesis of maresin-like SPMs	0.98414	0.049876	0.049876	cyp3a25;cyp3a11;cyp2e1;cyp2c37;cyp2c29;cyp3a41b	3329.52217	3098.075	529.743	1830.01027	3082.0157	1591.6575	DOWN	0.333333333	0.666666667	
7Day	Signaling by Interleukins	0.02756	0.98488	0.050003	ube2n;mapk3;map2k3;ywhaz;yes1;uba52;hsp90b1;stat1;ptpn11;ppp2cb;jak1;il1rap;csf1r;csf1;btrc	3196.85567	3627.04	131.024	1352.57627	3093.02479	1434.87479	UP	0.733333333	0.266666667	
7Day	Sulfur amino acid metabolism	0.98625	0.050013	0.050013	bhmt2;txn2;ahcy;cdo1;gm4737	3841.228	3770.5	2019.09	1397.48618	4067.90229	1087.77839	DOWN	0.4	0.6	
7Day	Major pathway of rRNA processing in the nucleolus and cytosol	0.98176	0.035177	0.050016	rps25;fcf1;utp14a;riok3;pno1;utp3;ddx21;nop58;bysl;rps3;utp18;rps12;utp14b;ncf1;fbl;pwp2;utp15	3102.57074	3078.47	84.8066	1347.77261	3073.59348	1240.79203	UP	0.941176471	0.058823529	
7Day	rRNA processing	0.98176	0.035177	0.050016	rps25;fcf1;utp14a;riok3;pno1;utp3;ddx21;nop58;bysl;rps3;utp18;rps12;utp14b;ncf1;fbl;pwp2;utp15	3102.57074	3078.47	84.8066	1347.77261	3073.59348	1240.79203	UP	0.941176471	0.058823529	
7Day	rRNA processing in the nucleus and cytosol	0.98176	0.035177	0.050016	rps25;fcf1;utp14a;riok3;pno1;utp3;ddx21;nop58;bysl;rps3;utp18;rps12;utp14b;ncf1;fbl;pwp2;utp15	3102.57074	3078.47	84.8066	1347.77261	3073.59348	1240.79203	UP	0.941176471	0.058823529	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
7Day	Immune System	0.026219	0.97912	0.050692	ube2n;btbd1;rsn;faf2;rf6;cotl1;fbxo2;ist1;cul2;fuca1;fbxo9;trim69;ube2v2;tmem30a;c8g;arl8a;ndufc2;npc2;ilf2;pycard;c1rb;psmd6;9130409i23rik;golga7;iqgap2;sdcbb;ube2k;tax1bp1;hgsnat;c1s1;nckap1;cfhr1;flnb;eif4e2;ecsit;mapk3;map2k3;arih1;apob;mgam;tubb4b;ywaz;yes1;pak2;ube3a;ube2a;ube2e3;uba52;tubb2a;tuba4a;ttr;hsp90b1;cdc27;cdc34;tap2;nhr3;ds1c;stat1;sec22b;rab6a;rab18;rab10;ptpn11;pten;psmc2;prlr;ppp2cb;pa2g4;pgam1;neu1;meh9;mme;man2b1;lbp;lamp1;kras;kif2a;jak1;itpr2;kpn1;il1rap;cd74;igf2r;ifng;hsp90aa1;h2-t23;h2-q10;h2-ab1;h2-aa;trip12;gstp1;gstp2;gpi1;ghr;ftl1;ubox5;f2;ube2j2;eif4a2;dhx9;ddx3x;ctsb;csnk2b;csf1r;csf1;chil1;cfh;cdc42;cd34;cd1d1;cct2;ccnf;ctnnb1;casp9;capza2;calm3;calm2;cab39;c4b;c2;c1qb;btrc;atp6v1e1;arsb;ahsg;aga;ab11;dsp;mlec;atad3a;wwp1;qsox1;brk1;cd300d5	3279.47269	3395.925	34.2395	1366.28184	3196.67903	1377.65291	CONFLICT	0.567164179	0.432835821
28Day	IKK complex recruitment mediated by RIP1	0.98785	0.051715	0.051715	ube2n;ly96;ikkb;bir2	5276.735	5342.195	4560.3	540.392733	5309.42215	615.334604	UP	0.75	0.25
28Day	Common Pathway of Fibrin Clot Formation	0.98785	0.051715	0.051715	proc;f5;f2;serpinc1	1728.22875	980.2455	362.714	1952.05792	1110.89183	1146.81353	DOWN	0	1
90Day	Phosphate bond hydrolysis by NUDT proteins	0.99228	0.051747	0.051747	nudt5;nudt15;nudt18	3590.63333	3566.76	2714.47	888.340623	3657.31499	576.537187	UP	1	0
7Day	Formation of a pool of free 40S subunits	0.98754	0.03497	0.052102	eif3m;eif3j1;tps25;eif1ax;eif3b;tps3;eif3l;tps12	2913.68783	3791.07	84.8066	1903.28872	2870.95152	1872.08436	UP	0.875	0.125
7Day	E3 ubiquitin ligases ubiquitinate target proteins	0.98754	0.03497	0.052102	ube2n;ube2v2;rraga;hist1h2bc;wdr61;pex14;ube2a;uba52	3390.1375	3322.065	2423.08	715.376565	3236.66725	711.86911	UP	1	0
7Day	Adaptive Immune System	0.025479	0.98215	0.052709	ube2n;btbd1;rf6;fbxo22;cul2;fbxo9;trim69;ube2v2;ube2k;tubb4b;ywaz;yes1;pak2;ube3a;ube2a;ube2e3;uba52;tubb2a;tuba4a;cdc27;cdc34;tap2;sec22b;ptpn11;pten;ppp2cb;kras;kif2a;itpr2;cd74;h2-t23;h2-q10;h2-ab1;h2-aa;trip12;ubox5;ube2j2;ctsb;cdc42;cd34;cd1d1;ccnf;capza2;calm3;calm2;btrc;wwp1;cd300d5	3457.34388	3406.92	919.856	1060.09485	3503.7595	994.489345	UP	0.729166667	0.270833333
28Day	SLC-mediated transmembrane transport	0.024323	0.98869	0.052729	slc35d2;slc9a5;slc25a10;slc13a5;slc17a8;slc22a1;slc1a2;slc6a13;slco2b1	2711.97578	2439.34	151.142	1429.62145	3126.28699	1139.43816	CONFLICT	0.555555556	0.444444444
28Day	M Phase	0.028485	0.98488	0.052962	zwilch;nek6;arpp19;dynl1;set;cnep1r1;cenpt;hist1h4i;tubb4b;tubb2a;cdc27;rad21;tp	4083.04308	3638.67	2359.45	1315.31392	4033.02415	1271.14938	UP	0.923076923	0.076923077
90Day	COPI-mediated anterograde transport	0.03082	0.98844	0.053014	tubb6;dcn3;tubb4b;tubb2a;tuba1b	1992.6502	1781.5	779.791	1072.82446	1774.95351	1190.4266	UP	0.8	0.2
28Day	Gamma-carboxylation, transport, and amino-terminal cleavage of proteins	0.99046	0.054904	0.054904	proc;f7;f2	2700.24	2170.26	1340.75	1688.07416	1850.85737	1335.69078	DOWN	0	1
90Day	Ub-specific processing proteases	0.030835	0.98405	0.055005	tomm20;psmd8;keap1;tomm70a;usp18;psmc4;psmf1;siat2;nfkbia;mdm2;ikbkg;ar	2352.46525	2515.11	143.029	1666.82412	2357.30515	1496.66069	UP	0.75	0.25
90Day	Signaling by Interleukins	0.028367	0.98346	0.055418	irak3;tbk1;irs2;hist1h3c;mapk14;ywaz;vav1;stx3;sos1;nfkbia;ilfr;il1rap;il15a;ikkb;il18bp;csf1;crf1;btrc	3161.05565	3485.11	74.8133	1873.72768	3010.55942	2106.53889	DOWN	0.263157895	0.736842105
90Day	Phase 0 - rapid depolarisation	0.033923	0.99487	0.055974	scn3b	5870.91	5870.91	5870.91		5870.91		UP	1	0
90Day	Positive epigenetic regulation of rRNA expression	0.032716	0.98882	0.056631	hist1h4h;hist1h4i;hist1h3c;h2afx	3214.00725	3979.26	811.859	1602.37406	2298.31583	1843.92338	CONFLICT	0.5	0.5
90Day	B-WICH complex positively regulates rRNA expression	0.032716	0.98882	0.056631	hist1h4h;hist1h4i;hist1h3c;h2afx	3214.00725	3979.26	811.859	1602.37406	2298.31583	1843.92338	CONFLICT	0.5	0.5

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.														
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
7Day	p53-Dependent G1 DNA Damage Response	0.98673	0.056948	0.056948	cop1;uba52;cdkn1a;ccne2	3951.5225	4112.95	2818.63	906.024201	3955.42276	894.012085	UP	1	0
7Day	p53-Dependent G1/S DNA damage checkpoint	0.98673	0.056948	0.056948	cop1;uba52;cdkn1a;ccne2	3951.5225	4112.95	2818.63	906.024201	3955.42276	894.012085	UP	1	0
90Day	Synthesis of PIPs at the plasma membrane	0.027711	0.99597	0.057216	plekha1	2516.3	2516.3	2516.3		2516.3		UP	1	0
90Day	Class C/3 (Metabotropic glutamate/pheromone receptors)	0.027711	0.99597	0.057216	casr	5866.48	5866.48	5866.48		5866.48		UP	1	0
90Day	RAB GEFs exchange GTP for GDP on RABs	0.028006	0.99063	0.057278	trappc6b;st5;dennd1b;dennd1a	2873.6475	3095.14	1239.12	1313.98598	2663.10414	1396.8076	DOWN	0.25	0.75
7Day	Phospholipid metabolism	0.02631	0.98729	0.05765	hadha;pla1a;dgat2;cris1;tnfaip8l1;star d10;mtmr7;mtmr6;pten;ptdss1	3178.6217	3586.9	197.056	1571.67918	3422.43941	1330.86292	CONFLICT	0.5	0.5
7Day	NRAGE signals death through JNK	0.033995	0.99481	0.058402	kalrn	3395.83	3395.83	3395.83		3395.83		DOWN	0	1
28Day	Choline catabolism	0.9945	0.058652	0.058652	sardh;aldh7a1	3179.325	3179.325	2886.01	414.810051	3034.05808	360.364295	DOWN	0	1
28Day	Lipid particle organization	0.9945	0.058652	0.058652	fitm1;hsd17b13	2514.165	2514.165	1978.91	756.96488	2305.84445	697.281093	UP	1	0
28Day	Vitamin B2 (riboflavin) metabolism	0.9945	0.058652	0.058652	enpp1;acp5	1661.4965	1661.4965	201.213	2065.15273	1473.8792	2048.03694	DOWN	0	1
7Day	O-linked glycosylation of mucins	0.031268	0.9953	0.058786	c1galt1	3617.32	3617.32	3617.32		3617.32		UP	1	0
7Day	GABA receptor activation	0.031268	0.9953	0.058786	gna13	794.2	794.2	794.2		794.2		UP	1	0
90Day	RNA Polymerase II Promoter Escape	0.025032	0.99643	0.058865	cdk7	3130.16	3130.16	3130.16		3130.16		UP	1	0
90Day	RNA Polymerase II Transcription Pre-Initiation And Promoter Opening	0.025032	0.99643	0.058865	cdk7	3130.16	3130.16	3130.16		3130.16		UP	1	0
90Day	RNA Polymerase II Transcription Initiation	0.025032	0.99643	0.058865	cdk7	3130.16	3130.16	3130.16		3130.16		UP	1	0
90Day	RNA Polymerase II Transcription Initiation And Promoter Clearance	0.025032	0.99643	0.058865	cdk7	3130.16	3130.16	3130.16		3130.16		UP	1	0
7Day	Stimuli-sensing channels	0.032698	0.98875	0.058987	uba52;calm3;calm2;wwp1	3888.485	3905.94	2825.5	1103.27631	3548.17172	1016.84299	UP	0.75	0.25
7Day	Signaling by ROBO receptors	0.98285	0.059141	0.059141	vasp;uba52;pfm2;pfm1;abl1	3693.962	3557.63	3106.36	634.460751	3898.36452	786.373572	UP	0.6	0.4
7Day	Mitophagy	0.98285	0.059141	0.059141	tomm20;mfn1;mterf3;tomm7;uba52	4096.692	4048.88	2384.74	1205.41607	3628.23874	1042.88808	UP	0.6	0.4
28Day	Platelet degranulation	0.97624	0.04583	0.059523	spp2;cdc37l1;ola1;abcc4;a2m;trf;serp1na1e;serpina1b;itih4;fn1;f5;clu;app;an xa5;qsox1	2860.33287	3086.6	248.527	1738.11813	2807.32881	1831.76681	DOWN	0.2	0.8
90Day	Synthesis of substrates in N-glycan biosynthesis	0.030815	0.99279	0.060348	st6galnac6;st3gal3	4683.725	4683.725	4143.19	764.431928	4469.98451	702.129746	DOWN	0	1
90Day	Signaling by TGF-beta Receptor Complex	0.030815	0.99279	0.060348	ccnc;ube2m	2361.655	2361.655	678.11	2380.89217	2437.24834	2378.49087	UP	1	0
7Day	CS/DS degradation	0.98966	0.060503	0.060503	hyal1;bgn;arsb	2697.2565	2968.59	34.2395	2538.25052	3151.98547	2691.86356	DOWN	0	1
7Day	MAPK3 (ERK1) activation	0.98966	0.060503	0.060503	mapk3;ptpn11;jak1	3994.74333	3629.67	3554.32	698.597213	3930.59598	681.24112	UP	0.666666667	0.333333333
90Day	Regulation of insulin secretion	0.028144	0.99351	0.061417	gng11;kcns3	5349.345	5349.345	4854.24	700.184206	5679.2676	522.072862	UP	1	0
90Day	Opioid Signalling	0.026426	0.99241	0.061441	gng11;camkk2;gna13	3618.4394	4854.24	98.0082	3093.55588	2681.47556	3196.16742	UP	0.666666667	0.333333333
90Day	RNA polymerase II transcribes snRNA genes	0.026426	0.99241	0.061441	ints11;ints14;cdk7	3135.72	3130.16	3119.18	19.9109919	3137.13707	22.4959562	UP	0.666666667	0.333333333
90Day	mRNA Splicing - Major Pathway	0.032589	0.9835	0.061856	hnmpf;csf2t2;rbm17;cd2bp2;ppil3;srsf 6;u2surp;usp39;snrnp;prpf8;ddx5	4253.12818	3853.08	2671.37	1163.84413	4046.45743	1233.71041	UP	0.727272727	0.272727273
28Day	RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function	0.032968	0.99493	0.061995	hist1h4i	5848.41	5848.41	5848.41		5848.41		DOWN	0	1
28Day	Antimicrobial peptides	0.032968	0.99493	0.061995	clu	2374.31	2374.31	2374.31		2374.31		DOWN	0	1
7Day	Assembly of collagen fibrils and other multimeric structures	0.033275	0.99204	0.06253	dst;ctsb	3432.05	3432.05	2982.34	635.985981	3506.38147	627.238259	UP	1	0
7Day	Cell death signalling via NRAGE, NRIF and NADE	0.030877	0.99271	0.063183	kalrn;uba52	4078.695	4078.695	3395.83	965.716944	4279.32804	923.093701	CONFLICT	0.5	0.5
7Day	Histidine, lysine, phenylalanine, tyrosine, proline and tryptophan catabolism	0.98044	0.05064	0.063353	amdhd1;kyat1;prodh2;gcdh;uroc1;aldh 4a1;dld;aldh7a1	2910.94218	2817.09	84.5274	1574.94437	2781.21537	1295.61683	DOWN	0.125	0.875
28Day	Neurotransmitter receptors and postsynaptic signal transmission	0.027895	0.99052	0.063696	gria3;mdm2;gnb5;adcy9	2373.357	2159.59	953.648	1359.18843	1905.88243	938.033043	UP	0.75	0.25
90Day	Microtubule-dependent trafficking of connexons from Golgi to the plasma membrane	0.98493	0.063829	0.063829	tubb6;tubb4b;tubb2a;tuba1b	1558.67025	1751.94	779.791	528.216289	1311.72381	614.22224	UP	0.75	0.25
90Day	Toll Like Receptor 4 (TLR4) Cascade	0.035256	0.98549	0.064505	tbk1;irf7;mapk14;nfbk1a;ikbk;g;trc	3838.235	3931.53	1058.39	1639.93973	3671.64014	1885.92371	DOWN	0.333333333	0.666666667

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
28Day	Resolution of D-loop Structures through Holliday Junction Intermediates	0.98003	0.064836	0.064836	rmi1;rad51d;rad51;brca1;blm	3513.5312	3769.36	692.086	1790.07678	3877.73216	1143.86555	UP	1	0	
7Day	mRNA Splicing	0.97865	0.036516	0.064842	sf3b1;sf3a3;snrpa1;dnajc8;zcrb1;fip1l1;crnk1;ppih;sf3b6;hnrrpa2b1;cpsf2;prp f19;polr2h;pcbp1;hnrrpul1;prpf38a;zrs r2;snrnp;hnrrnp;dhx9;srsf1;ctsf2;snrpd 2;sf3b3	3686.87979	3515.895	730.51	1347.52896	3478.96033	1311.30014	UP	0.958333333	0.041666667	
28Day	ESR-mediated signaling	0.037651	0.9884	0.0649	ppid;hist1h4i;polr2a	5538.30333	5725.83	5040.67	435.299512	5566.6399	427.807411	UP	0.666666667	0.333333333	
28Day	Regulation of TP53 Activity	0.035848	0.98904	0.064932	meaf6;mdm2;ccng1	2083.91333	2266.61	1125.25	881.628529	2174.62481	822.305509	UP	0.666666667	0.333333333	
90Day	Neurotransmitter uptake and metabolism In glial cells	0.99477	0.065183	0.065183	slc1a2;glul	1166.9995	1166.9995	777.189	551.275296	1473.12635	341.287501	DOWN	0	1	
90Day	Astrocytic Glutamate-Glutamine Uptake And Metabolism	0.99477	0.065183	0.065183	slc1a2;glul	1166.9995	1166.9995	777.189	551.275296	1473.12635	341.287501	DOWN	0	1	
90Day	SOS-mediated signalling	0.99477	0.065183	0.065183	irs2;sos1	2984.87165	2984.87165	74.8133	4115.44399	2818.21844	4108.68989	DOWN	0	1	
90Day	Cell Cycle Checkpoints	0.031431	0.98232	0.065604	cenpu;hist1h4h;anapc10;babam1;orc6; hist1h4i;gtse1;dbf4;ywhaz;kntc1;nudc; mdm2;h2afx;cdkn1a;sec13;cenpf	3407.30362	3474.395	137.958	1484.96682	3335.48346	1502.62347	UP	0.875	0.125	
90Day	RNA Polymerase III Transcription Initiation From Type 1 Promoter	0.03945	1	0.066006											
90Day	RNA Polymerase III Transcription Initiation From Type 2 Promoter	0.03945	1	0.066006											
90Day	Insulin receptor recycling	0.03945	1	0.066006											
90Day	RNA Polymerase III Transcription Initiation From Type 3 Promoter	0.034992	1	0.067066											
90Day	Synthesis of IP3 and IP4 in the cytosol	0.034992	1	0.067066											
28Day	RNA Polymerase I Promoter Clearance	0.029733	0.99294	0.067702	hist1h4i;polr1a	5855.735	5855.735	5848.41	10.3591143	5854.78856	10.27228	DOWN	0	1	
7Day	Lysosome Vesicle Biogenesis	0.0419	1	0.068637											
7Day	G alpha (z) signalling events	0.0419	1	0.068637											
7Day	Glucagon-type ligand receptors	0.0419	1	0.068637											
28Day	Hydrolysis of LPE	1	0.068645	0.068645	pla2g4c	3475.05	3475.05	3475.05		3475.05		UP	1	0	
28Day	Metabolism of ingested MeSeO2H into MeSeH	1	0.068645	0.068645	txnr1	3178.52	3178.52	3178.52		3178.52		UP	1	0	
28Day	Mitophagy	0.98207	0.068745	0.068745	tomm20;mterf3;sqstm1;atg5	4818.665	4936.54	3654.44	1058.71114	5368.53606	825.784265	UP	1	0	
90Day	mRNA Splicing	0.036444	0.98085	0.069003	hnrrnpf;ctsf2t;rbm17;cd2bp2;ppil3;srsf 6;u2surp;usp39;zrsr1;snrnp;prpf8;ddx5	4254.3025	3986.9	2671.37	1109.68929	4054.34502	1207.21286	UP	0.75	0.25	
7Day	Striated Muscle Contraction	0.037939	1	0.069208											
90Day	Energy dependent regulation of mTOR by LKB1-AMPK	0.031037	1	0.069347											
90Day	DNA Double-Strand Break Repair	0.038624	0.9807	0.069444	hist1h4h;babam1;pole4;ppp4c;hist1h4i ;polk;rad51;h2afx;brca2;rad51c	4045.4582	4046.18	513.022	1470.8127	3606.13368	1521.5189	UP	0.7	0.3	
28Day	Ion channel transport	0.037393	0.98428	0.070119	atp6v0e2;ano8;clcn6;sgk3;clcn2;atp6v1 e1	3380.89167	3205.75	2316.49	1106.33568	3092.31363	862.148298	DOWN	0.333333333	0.666666667	
7Day	Metabolism of steroids	0.97615	0.043092	0.070347	akr1c6;cyp39a1;idi1;slc27a5;osbpl2;slc 10a2;slc10a1;ncoa2;ncoa1;kpnb1;hsd1 7b4;hsd17b2;hsd11b1;gc;ebp;baat;aca t2;akr1c14;hsd3b7	2531.59187	3113.35	41.196	1699.49847	2585.28128	1582.14086	CONFLICT	0.526315789	0.473684211	
90Day	COPI-dependent Golgi-to-ER retrograde traffic	0.041162	0.98396	0.070583	tubb6;tubb4b;tubb2a;tuba1b;kifc1	1389.634	1722.38	713.489	593.401723	1135.0221	585.08693	UP	0.8	0.2	
7Day	Amino acid transport across the plasma membrane	0.034351	1	0.070641											
90Day	Amplification of signal from the kinetochores	0.03565	0.98637	0.071014	cenpu;kntc1;nudc;sec13;cenpf	3685.894	3327.48	2758.9	1178.18473	3996.4277	1307.65387	UP	1	0	
90Day	Amplification of signal from unattached kinetochores via a MAD2 inhibitory signal	0.03565	0.98637	0.071014	cenpu;kntc1;nudc;sec13;cenpf	3685.894	3327.48	2758.9	1178.18473	3996.4277	1307.65387	UP	1	0	
90Day	Processing of Capped Intron-Containing Pre-mRNA	0.034152	0.98035	0.071077	hnrrnpf;ctsf2t;rbm17;cd2bp2;ppil3;srsf 6;u2surp;thoc7;wtap;usp39;zrsr1;nup1 53;snrnp;prpf8;nxf7;ddx5;sec13	4322.11	4120.72	2671.37	1161.73757	4241.09977	1205.1784	UP	0.823529412	0.176470588	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
28Day	Arachidonic acid metabolism	0.97806	0.049681	0.071247	akr1c6;gpx4;akr1c12;akr1c19;mapkapk2;ita4h;cyp4a12b;cyp2c37;cyp2c29;akr1c14	4519.911	5064.1	2669.87	1231.38753	4043.78048	1238.22292	DOWN	0.4	0.6
28Day	Resolution of D-Loop Structures	0.97696	0.072301	0.072301	rmi1;rad51d;rad51;brca1;blm	3513.5312	3769.36	692.086	1790.07678	3877.73216	1143.86555	UP	1	0
28Day	Plasma lipoprotein clearance	0.97696	0.072301	0.072301	npc2;apob;scarb1;ces3b;apoE	2145.8648	2685.06	614.079	1276.09083	1637.02007	1293.32598	DOWN	0	1
7Day	Activation of C3 and C5	0.99279	0.073159	0.073159	c4b;C2	1586.775	1586.775	1201.6	544.719709	1722.75787	509.643877	DOWN	0	1
7Day	VLDL clearance	0.99279	0.073159	0.073159	apob;apoc1	2882.07	2882.07	1999.21	1248.55259	3387.19612	1024.00135	DOWN	0	1
7Day	Autodegradation of the E3 ubiquitin ligase COP1	0.99279	0.073159	0.073159	cop1;uba52	4194.635	4194.635	3627.71	801.753024	4115.83314	793.970052	UP	1	0
7Day	Ubiquitin Mediated Degradation of Phosphorylated Cdc25A	0.99279	0.073159	0.073159	uba52;cdc25a	5319.66	5319.66	4761.56	789.272589	5256.30284	784.170237	UP	1	0
7Day	p53-Independent DNA Damage Response	0.99279	0.073159	0.073159	uba52;cdc25a	5319.66	5319.66	4761.56	789.272589	5256.30284	784.170237	UP	1	0
7Day	p53-Independent G1/S DNA damage checkpoint	0.99279	0.073159	0.073159	uba52;cdc25a	5319.66	5319.66	4761.56	789.272589	5256.30284	784.170237	UP	1	0
28Day	Class C/3 (Metabotropic glutamate/pheromone receptors)	0.037645	1	0.073531										
28Day	Extracellular matrix organization	0.03597	0.98094	0.074512	phylp;tmprss6;a2m;vtm;p4hb;fn1;dag1;ctss;col8a1;capn5;bmp1;app	3794.45175	4482.905	182.399	2111.69959	4236.00406	1783.26918	CONFLICT	0.416666667	0.583333333
28Day	Intracellular signaling by second messengers	0.034485	0.98403	0.074767	phlpp1;pdpk1;mdm2;il1rap;hbegf;fgf1;bmi1;adcyc9	2544.8045	2966.785	192.988	1545.1028	2305.79205	1239.28447	DOWN	0.375	0.625
90Day	Transcriptional Regulation by TP53	0.040542	0.97599	0.076145	trp53inp1;txnr1;eloa;mapk14;pin1;gata2b;whaz;txn1;plk2;pml;mdm2;hda2;gsr;cdkn1a;cdk7;cng1;btg2;bax	2834.12133	3114.78	137.958	1666.56665	2532.14033	1686.2547	UP	0.833333333	0.166666667
90Day	Transport to the Golgi and subsequent modification	0.038186	0.97936	0.076399	trapppc6b;lmn1;tubb6;stx17;dctn3;tubb4b;tubb2a;tuba1b;tfga;serpina1e;man1a;areg;sec13	2916.88077	2758.9	779.791	1508.82177	2494.78053	1441.67815	UP	0.692307692	0.307692308
90Day	Gene Silencing by RNA	0.044395	0.98415	0.076419	hist1h4h;hist1h4i;hist1h3c;h2afx	3214.00725	3979.26	811.859	1602.37406	2298.31583	1843.92338	CONFLICT	0.5	0.5
90Day	TRAF6 mediated induction of NFkB and MAP kinases upon TLR7/8 or 9 activation	0.044395	0.98415	0.076419	mapk14;nfbia;ikbk;btcr	4070.33	3931.53	3265.56	831.881085	4282.38479	1027.24106	DOWN	0.25	0.75
28Day	Cell-cell junction organization	0.03263	1	0.076553										
90Day	Cellular response to heat stress	0.038147	0.98668	0.077106	gm45902;nup153;hsp90aa1;sec13	1801.33125	1592.61	339.755	1680.72509	1453.56222	1669.59061	UP	1	0
7Day	Interleukin-6 signaling	0.98494	0.077544	0.077544	stat1;ptpn11;jak1	3700.28667	3629.67	3554.32	191.312992	3689.86935	200.012264	UP	1	0
7Day	Tetrahydrobiopterin (BH4) synthesis, recycling, salvage and regulation	0.98494	0.077544	0.077544	hsp90aa1;calm3;calm2	2990.83	3050.32	1005.61	1956.15357	2746.7427	1679.58489	UP	0.666666667	0.333333333
7Day	MET activates RAS signaling	0.98494	0.077544	0.077544	ranbp10;ranbp9;kras	2634.76333	2966.85	778.73	1714.28626	2764.00121	1370.47238	UP	0.666666667	0.333333333
7Day	Chylomicron remodeling	0.98494	0.077544	0.077544	apoA5;apob;apoE	1991.362	1999.21	113.316	1874.13432	2561.84919	1735.71019	DOWN	0	1
7Day	Growth hormone receptor signaling	0.98494	0.077544	0.077544	mapk3;prrl;ghr	4289.48	4262.53	3805.67	497.8324	4384.06501	412.716182	UP	0.666666667	0.333333333
7Day	Regulation of IFNG signaling	0.98494	0.077544	0.077544	stat1;jak1;ifng	3909.44667	3916.87	3554.32	351.473799	3908.88068	370.332739	UP	1	0
28Day	HDL assembly	0.99086	0.078456	0.078456	a2m;bmp1	3357.655	3357.655	1023.63	3300.80981	3295.67976	3299.64597	UP	1	0
28Day	Pyrimidine catabolism	0.99086	0.078456	0.078456	dpyd;dyps	1501.205	1501.205	744.72	1069.83135	1904.56626	905.062701	DOWN	0	1
28Day	APEX1-Independent Resolution of AP Sites via the Single Nucleotide Replacement Pathway	0.99086	0.078456	0.078456	polb;lig3	5622.33	5622.33	5391.42	326.556054	5616.5595	326.454068	CONFLICT	0.5	0.5
28Day	Complement cascade	0.9826	0.048344	0.078722	c8g;vtm;f2;clu;c4b;c3;c2	1813.981	2305.72	447.762	1052.00591	1683.33373	944.640074	DOWN	0	1
7Day	Clathrin-mediated endocytosis	0.03818	0.98306	0.079444	ubqln1;slc2a8;apob;picalm;uba52;ldlr;gfr2r	3609.88	3459.74	1999.21	993.723225	3580.2941	733.778551	CONFLICT	0.571428571	0.428571429
7Day	Plasma lipoprotein remodeling	0.97439	0.080039	0.080039	apoA5;angptl8;apob;pcsk5;apoE	2984.1052	3861.56	113.316	1899.27994	3554.8157	1538.66448	DOWN	0.2	0.8
90Day	Intracellular signaling by second messengers	0.038431	0.97801	0.080435	kib;cbx6;irs2;gata2b;vav1;tfga;nrng1;camlk2;pml;mdm2;il1rap;hdac2;gab1;fgf1;cdkn1a;areg	2088.97309	2423.43	74.8133	1676.16302	1953.69573	1554.09745	CONFLICT	0.5	0.5
90Day	TNF signaling	0.050596	0.99171	0.081519	ikbk	3265.56	3265.56	3265.56		3265.56		UP	1	0
90Day	DAP12 interactions	0.045813	0.99265	0.081616	sos1	5894.93	5894.93	5894.93		5894.93		DOWN	0	1
90Day	PCP/CE pathway	0.045813	0.99265	0.081616	ap2m1	2983.55	2983.55	2983.55		2983.55		UP	1	0
90Day	Vasopressin regulates renal water homeostasis via Aquaporins	0.045813	0.99265	0.081616	gng11	4854.24	4854.24	4854.24		4854.24		UP	1	0
90Day	SUMOylation of DNA replication proteins	0.045813	0.99265	0.081616	nup153	3680.35	3680.35	3680.35		3680.35		UP	1	0
90Day	trans-Golgi Network Vesicle Budding	0.04337	0.98657	0.081624	snap23;acbd3;ftl1	1950.35	1733.37	544.33	1526.12279	2829.99571	1312.61691	UP	1	0
90Day	Clathrin derived vesicle budding	0.04337	0.98657	0.081624	snap23;acbd3;ftl1	1950.35	1733.37	544.33	1526.12279	2829.99571	1312.61691	UP	1	0

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
90Day	Collagen degradation	0.04337	0.98657	0.081624	tmprss6;mmmp2;ctsd	4985.37667	5410.11	3885.66	960.566929	4770.14505	1031.26455	DOWN	0.333333333	0.666666667	
7Day	Regulation of PTEN stability and activity	0.97776	0.082518	0.082518	uba52;pten;csnk2b;xiap	3909.985	3968.12	2829.67	1058.66531	4009.38925	1028.42097	UP	0.75	0.25	
90Day	Metabolism of steroid hormones	0.041464	0.99348	0.08265	hsd11b1	2402.05	2402.05	2402.05		2402.05		DOWN	0	1	
28Day	Antigen processing: Ubiquitination & Proteasome degradation	0.044019	0.9768	0.083401	ube2n;btbd1;fbxo22;ube2v2;ube2g1;asb3;ube2k;arih2;ube2m;traip;cdc27	4026.69273	4043.68	1308.55	1279.87107	4058.69399	1282.071	UP	0.727272727	0.272727273	
90Day	O-linked glycosylation of mucins	0.048155	0.98783	0.084068	galnt12;st3gal3	3923.285	3923.285	2622.31	1839.85649	2887.75239	1113.7398	CONFLICT	0.5	0.5	
90Day	GABA receptor activation	0.048155	0.98783	0.084068	gnai3;gabrb3	5052.49	5052.49	4201.91	1202.90177	4597.44422	1016.28704	CONFLICT	0.5	0.5	
28Day	Bile acid and bile salt metabolism	0.9782	0.058006	0.084336	akr1c6;akr1c12;akr1c19;slc10a1;amacr;hsd17b4;akr1c14	3774.80714	3384.83	702.63	1900.2005	3180.23039	1613.96855	DOWN	0.285714286	0.714285714	
90Day	Cargo recognition for clathrin-mediated endocytosis	0.04626	0.98029	0.084492	apob;trf;tgifa;sh3gl3;areg;ap2m1	2487.8495	2573.03	175.96	2005.2704	2731.82978	2101.53961	UP	0.666666667	0.333333333	
90Day	Formation of RNA Pol II elongation complex	0.044085	0.98903	0.084585	eloa;cdk7	4445.455	4445.455	3130.16	1860.10803	4242.37403	1837.80252	UP	1	0	
90Day	RNA Polymerase II Transcription Elongation	0.044085	0.98903	0.084585	eloa;cdk7	4445.455	4445.455	3130.16	1860.10803	4242.37403	1837.80252	UP	1	0	
90Day	Voltage gated Potassium channels	0.037512	0.99422	0.084601	kcnk3	5844.45	5844.45	5844.45		5844.45		UP	1	0	
7Day	HDMs demethylate histones	0.047364	0.99227	0.084619	hist1h4h	3406.55	3406.55	3406.55		3406.55		DOWN	0	1	
28Day	Peroxisomal protein import	0.96752	0.075485	0.085152	acox3;crota;hacl1;decr2;amacr;phyh;hsd17b4;acox1	3167.76875	3416.51	702.63	1508.40439	3080.59607	1290.58284	DOWN	0.125	0.875	
90Day	Deadenylation-dependent mRNA decay	0.040338	0.99012	0.085816	exosc9;paip1	1508.701	1508.701	212.512	1833.08806	1967.17266	1714.59013	UP	1	0	
7Day	Chemokine receptors bind chemokines	0.040149	0.99366	0.086831	cxcr5	5913.54	5913.54	5913.54		5913.54		UP	1	0	
7Day	Nuclear Receptor transcription pathway	0.040149	0.99366	0.086831	rorc	3619.39	3619.39	3619.39		3619.39		DOWN	0	1	
7Day	ECM proteoglycans	0.040149	0.99366	0.086831	bgn	2968.59	2968.59	2968.59		2968.59		DOWN	0	1	
7Day	Integration of energy metabolism	0.037343	0.98862	0.087195	adipor2;prkar2a;itpr2	4454.89333	4098.21	4066.56	645.397401	4344.19833	587.600135	DOWN	0	1	
7Day	Macroautophagy	0.044736	0.98874	0.087793	rraga;atg4c	2173.4	2173.4	1121.07	1488.21936	1903.38488	1438.39512	UP	1	0	
28Day	Glycosaminoglycan metabolism	0.050344	0.98375	0.088142	hs2st1;hyal1;gpc4	3615.18667	3361.03	2376.85	1383.04188	3530.52442	1515.30949	DOWN	0	1	
90Day	Transcriptional regulation by RUNX1	0.043363	0.97806	0.088197	smarcd2;hist1h4h;cbx6;hist1h4i;hist1h3c;smarcb1;pml;h2afx;cdk7;cbfb	3413.5568	3961.185	744.949	1540.06894	3185.71409	1878.69661	UP	0.6	0.4	
28Day	PRC2 methylates histones and DNA	0.053101	0.991	0.088515	hist1h4i	5848.41	5848.41	5848.41		5848.41		DOWN	0	1	
28Day	Miscellaneous substrates	0.96992	0.088569	0.088569	cyp3a25;cyp4a12b;cyp3a11;cyp3a59;cyp3a41b	3316.883	3712.65	850.005	2173.66024	2761.60256	2036.23554	UP	0.6	0.4	
7Day	Chromatin modifying enzymes	0.047242	0.97441	0.088759	prmt3;hist1h4h;hist1h2bc;kmt5a;suz12;hist2h2ac;setd2;kmt5b;kat7;ncoa2;ncoa1;hist2h2aa1	3245.81155	3379.33	86.7986	1266.28832	3462.68653	875.789942	UP	0.75	0.25	
7Day	Chromatin organization	0.047242	0.97441	0.088759	prmt3;hist1h4h;hist1h2bc;kmt5a;suz12;hist2h2ac;setd2;kmt5b;kat7;ncoa2;ncoa1;hist2h2aa1	3245.81155	3379.33	86.7986	1266.28832	3462.68653	875.789942	UP	0.75	0.25	
28Day	RMTs methylate histone arginines	0.047179	0.9922	0.089	hist1h4i	5848.41	5848.41	5848.41		5848.41		DOWN	0	1	
28Day	Class I MHC mediated antigen processing & presentation	0.044183	0.97508	0.089031	ube2n;btbd1;fbxo22;ube2v2;ube2g1;asb3;ube2k;arih2;ube2m;traip;cdc27;tap1;h2-q7;h2-d1	3927.14	4039.16	1188.24	1453.58963	3938.47646	1379.20359	UP	0.642857143	0.357142857	
28Day	Signaling by NTRKs	0.04446	0.99274	0.08976	mapkapk2	5375	5375	5375		5375		DOWN	0	1	
28Day	Response to elevated platelet cytosolic Ca2+	0.96802	0.059452	0.09007	spp2;cdc37l1;ola1;abcc4;a2m;trf;serpina1e;serpina1b;itih4;fn1;f5;clu;app;anax5;qsox1	2860.33287	3086.6	248.527	1738.11813	2807.32881	1831.76681	DOWN	0.2	0.8	
7Day	Deactivation of the beta-catenin transactivating complex	0.97342	0.069179	0.09008	ywhaz;uba52;sox6;ctnnb1;btrc;xiap;xp01	2782.26174	2726.98	54.5232	2027.05359	2693.73177	2180.76333	CONFLICT	0.571428571	0.428571429	
7Day	ABC-family proteins mediated transport	0.97559	0.057572	0.091567	abcg8;abca3;abca8b;elf2s3x;abcc4;erln1;uba52;sel1l;abcb4	3839.74111	4054.31	2076.62	897.839237	3799.09245	727.748929	UP	0.777777778	0.222222222	
28Day	ABC-family proteins mediated transport	0.97306	0.06878	0.0916	abcb8;abca3;abca8b;abcc4;abcb3;abcb4;abcb1b	2657.01729	2494.49	870.176	1735.83727	2567.92033	1880.30238	UP	0.714285714	0.285714286	
7Day	Negative regulation of FGFR3 signaling	0.96928	0.091781	0.091781	mapk3;uba52;ptpn11;ppp2cb;fgf1	3893.254	3629.67	2647.76	903.905503	3770.28016	910.359639	UP	0.6	0.4	
28Day	Cell death signalling via NRAGE, NRIF and NADE	0.039465	0.99371	0.092288	sqstm1	5683.98	5683.98	5683.98		5683.98		UP	1	0	
28Day	Senescence-Associated Secretory Phenotype (SASP)	0.043248	0.98906	0.092915	hist1h4i;cdc27	5814.585	5814.585	5780.76	47.8357737	5810.29652	47.4497544	CONFLICT	0.5	0.5	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.														
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
90Day	Post-translational modification: synthesis of GPI-anchored proteins	0.050888	0.97958	0.093455	pigp;ceacam2;plaur;ly6d;gpld1	2543.714	3011.39	957.7	1198.12357	2837.1885	1182.21116	UP	0.6	0.4
90Day	Sulfur amino acid metabolism	0.96915	0.093461	0.093461	ahcy;tst;suox;cdo1;gm4737	2041.1644	1627.86	683.252	1216.09608	2221.12793	1306.03286	DOWN	0.2	0.8
90Day	Degradation of cysteine and homocysteine	0.98073	0.093577	0.093577	tst;suox;cdo1	2386.53067	2669.27	683.252	1580.98573	2390.34461	1507.50488	DOWN	0.333333333	0.666666667
7Day	Synthesis of CL	1	0.094226	0.094226	clrs1	4148.47	4148.47	4148.47		4148.47		UP	1	0
7Day	Metabolism of ingested MeSeO2H into MeSeH	1	0.094226	0.094226	txnrd1	2303.89	2303.89	2303.89		2303.89		UP	1	0
7Day	Respiratory electron transport	0.97248	0.063582	0.094851	ndufaf1;ndufaf4;ndufc2;coq10b;ndufa13;ndufa6;ndufa1;ecsf;ndufa2	3811.92444	3920.07	2874.39	543.291647	3626.07299	550.830133	CONFLICT	0.555555556	0.444444444
28Day	Signaling by Retinoic Acid	0.97021	0.074587	0.095831	akr1c6;akr1c12;akr1c19;adh4;aldh8a1;rdh16f2;akr1c14	3658.91614	3384.83	912.843	1735.94718	3406.08354	1417.35316	DOWN	0.285714286	0.714285714
28Day	Protein localization	0.97332	0.061121	0.096131	acox3;crota;hacl1;decr2;otc;amacr;phyh;hsd17b4;acox1	2896.55356	3304.47	702.63	1628.77023	2979.17912	1351.26373	DOWN	0.111111111	0.888888889
7Day	Biosynthesis of specialized proresolving mediators (SPMs)	0.96942	0.077367	0.09629	cyp3a25;gstm4;cyp3a11;cyp2e1;cyp2c37;cyp2c29;cyp3a41b	3229.52186	2813.51	529.743	1691.38457	3004.89739	1441.18311	CONFLICT	0.428571429	0.571428571
7Day	Creation of C4 and C2 activators	0.97907	0.096415	0.096415	clrb;clsl1;cltgb	2315.66433	1939.15	56.713	2468.83611	1154.21203	1850.07688	DOWN	0	1
7Day	Lysine catabolism	0.97907	0.096415	0.096415	gcdh;dlid;aldh7a1	3385.63	2652.27	2360.99	1529.42277	3078.93481	1351.60319	DOWN	0.333333333	0.666666667
7Day	Sodium/Calcium exchangers	0.97907	0.096415	0.096415	slc8b1;calm3;calm2	3614.55333	3050.32	2876.78	1130.90453	3353.96535	932.818439	DOWN	0.333333333	0.666666667
7Day	Spry regulation of FGF signaling	0.97907	0.096415	0.096415	mapk3;uba52;ppp2cb	4396.28	4761.56	3627.04	666.462054	4245.99731	706.330246	UP	0.666666667	0.333333333
7Day	eNOS activation	0.97907	0.096415	0.096415	hsp90aa1;calm3;calm2	2990.83	3050.32	1005.61	1956.15357	2746.7427	1679.58489	UP	0.666666667	0.333333333
28Day	Cytochrome P450 - arranged by substrate type	0.97128	0.060135	0.097005	cyp3a25;fdxr;cyp4a12b;cyp3a11;cyp2e1;cyp2c37;cyp2c29;cyp2a5;cyp2a4;cyp3a59;cyp3a41b	3430.53864	3712.65	850.005	1812.48495	3087.89317	1642.84983	CONFLICT	0.545454545	0.454545455
7Day	Aflatoxin activation and detoxification	0.97209	0.097081	0.097081	cyp3a25;cyp3a11;acy1;cyp3a41b	3841.9025	3960.035	1896.11	1766.87506	3524.50363	1681.78694	DOWN	0.25	0.75
7Day	LDL clearance	0.97209	0.097081	0.097081	npc2;apob;ldlr;ces3b	3506.2275	3545.22	1999.21	1199.64641	3611.77033	990.151608	DOWN	0.25	0.75
7Day	Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell	0.048382	0.9806	0.09709	h2-t23;h2-q10;cd34;cd1d1;cd300ld5	3924.828	3860.24	2584.12	940.924578	3546.12557	828.629454	DOWN	0	1
28Day	Nucleobase catabolism	0.96592	0.097358	0.097358	dpyd;dpy5;nudt5;pnp;entpd5	2268.334	2257.69	744.72	1776.9016	2216.14255	788.510641	DOWN	0.4	0.6
7Day	Hemostasis	0.050837	0.96385	0.098814	rbsn;tmx3;mf1n1;cdc37l1;f12;clec1b;m apk3;abcc4;apob;tubb4b;ywhaz;yes1;vps45;tubb2a;tuba4a;itpk1;sd3;serpinb8;sod1;ptpn11;flna;prkar2a;ppp2cb;lga ls3bp;kras;kif2a;kif1c;itpr2;cd74;gna13;f5;f2;ecm1;cdc42;cbx5;capza2;calm3;c alim2;serpincl1;ahsg;qsox1	3154.79004	3443.96	85.9375	1572.6713	2971.60322	1609.82206	CONFLICT	0.43902439	0.56097561
7Day	Vesicle-mediated transport	0.053146	0.96143	0.099614	rab3gap2;trappc6b;chmp5;trappc8;cog6;ubap1;trappc13;plin3;0610009b22rik;copz1;rab9;ubqln1;slc2a8;rab11a;den nd4c;ppp6r1;cog5;apob;picalm;tubb4b;ywhaz;vps45;uba52;tubb2a;tuba4a;hsp90b1;arcn1;sec22b;rab6a;rab18;rab10;rab1a;hps4;cyth1;lrp1;ldlr;kif2a;kif1c;igf2r;gja1;ftl1;f5;capza2;apoe;ap3b1;gbf1	3104.59324	3330.605	113.316	1364.54785	2985.00112	1255.31101	UP	0.673913043	0.326086957
28Day	Glutathione synthesis and recycling	0.98611	0.099978	0.099978	gclm;gclc	3489.155	3489.155	1604.65	2665.09253	3468.9264	2664.93899	CONFLICT	0.5	0.5
28Day	Terminal pathway of complement	0.98611	0.099978	0.099978	c8g;clu	2340.015	2340.015	2305.72	48.5004541	2340.47809	48.4960323	DOWN	0	1
90Day	RHO GTPases Activate ROCKs	0.98803	0.10066	0.10066	rock2;rock1	2068.101	2068.101	262.092	2554.08242	1087.57877	2144.87514	UP	1	0
90Day	Regulation of cytoskeletal remodeling and cell spreading by IPP complex components	0.98803	0.10066	0.10066	arhgef6;actn1	5633.74	5633.74	5314.58	451.360401	5440.61636	359.350429	DOWN	0	1
7Day	Mitotic Prometaphase	0.049565	0.97369	0.10071	clasp2;pd55a;cenpk;tubb4b;tubb2a;tub a4a;ppp2cb;nedd1;kif2a;hsp90aa1;xpo1	2843.69691	3074.7	919.856	1251.43972	2823.11876	1256.13876	UP	0.909090909	0.090909091
90Day	Trafficking and processing of endosomal TLR	0.063726	1	0.10162										
90Day	RAF-independent MAPK1/3 activation	0.063726	1	0.10162										
90Day	Miscellaneous transport and binding events	0.063726	1	0.10162										

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
		Fisher's Exact Left P- Value	Fisher's Exact Right P- Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
Study Day	Gene Set Name														
28Day	NCAM signaling for neurite out-growth	0.066671	1	0.10974											
7Day	RAF/MAP kinase cascade	0.056309	0.96894	0.11005	ranbp9;mapk3;pebp1;uba52;rasa1;ppp2cb;kras;jak1;gfra1;fgf1;calm3;calm2	3875.345	4115.2	778.73	1302.5301	3869.35753	1169.20014	CONFLICT	0.583333333	0.416666667	
90Day	Signaling by Hedgehog	0.05644	0.97531	0.11042	notum;tubb6;jift52;tubb4b;tubb2a;tuba1b	1737.39717	1751.94	154.682	1322.79012	1507.29711	1099.23869	CONFLICT	0.5	0.5	
28Day	Cell Cycle	0.053704	0.96428	0.11057	ube2n;ube2v2;zwilch;psmd6;cenpw;nek6;arpp19;pole3;psmd8;dynl1;set;cnepr1r1;cenpt;hist1h4i;cdc6;cdc14a;psmf1;tubb4b;tubb2a;tfdp1;cdc27;cenpx;rad21;mdm2;psmb8;brca1;tptr	3957.53704	4060.76	748.272	1598.51598	3945.41887	1554.10871	UP	0.740740741	0.259259259	
90Day	Dual incision in TC-NER	0.064637	0.97861	0.11114	pole4;polk;cdk7	4212.22333	3652.71	3130.16	1445.45671	3760.17242	830.658559	UP	0.666666667	0.333333333	
90Day	Regulation of HSF1-mediated heat shock response	0.064637	0.97861	0.11114	gm45902;nup153;sec13	2259.66833	2758.9	339.755	1725.34574	1626.35697	1830.96796	UP	1	0	
7Day	Neurexins and neuroligins	0.046275	1	0.11223											
7Day	G alpha (12/13) signalling events	0.046275	1	0.11223											
90Day	Aromatic amines can be N-hydroxylated or N-dealkylated by CYP1A2	1	0.11268	0.11268	cyp1a2	928.37	928.37	928.37		928.37		DOWN	0	1	
90Day	Synthesis of IPs in the ER lumen	1	0.11268	0.11268	minpp1	3256.99	3256.99	3256.99		3256.99		UP	1	0	
90Day	Metabolism of ingested MeSeO2H into MeSeH	1	0.11268	0.11268	txnr1	3099.4	3099.4	3099.4		3099.4		UP	1	0	
7Day	Cyclin E associated events during G1/S transition	0.96559	0.11275	0.11275	uba52;cdkn1a;cdc25a;ccne2	4514.035	4679.875	2818.63	1265.23972	4350.66448	1194.57246	UP	1	0	
7Day	Transcriptional Regulation by TP53	0.058571	0.96559	0.11358	rraga;kmt5a;txnr1;polr2h;taf10;cnot1;yywhaz;uba52;prdx2;ppp2cb;csnk2b;cdkn1a;ccnk;ccng1;ccne2	3177.14533	3225.73	1234.63	933.644194	3252.70841	970.863606	UP	0.933333333	0.066666667	
7Day	Post-translational protein modification	0.056421	0.95458	0.11405	dcaf8;c1galt1;ube2n;btbd1;trappc6b;dun1d5;plet1;usp16;fbxo22;prmt3;gm49336;cul2;fuca1;fbxo9;ube2v2;pigw;rnf168;hist1h4h;rraga;babam1;hist1h2bc;tomm20;cog6;psmd5;psmd6;wdr61;apoa5;O610009b22rik;ngly1;copz1;rab9;pex14;hdac7;nop58;gnpna1;rab11a;rab25;ube2k;suz12;uba2;etfbkmt;hist2h2ac;cop1;ppp6r1;dcaf10;taf10;fem1c;psmc4;cog5;apob;nae1;tubb4b;ino80c;vdac3;vdac2;ube2a;ube2e3;uba52;tubb2a;tuba4a;hsp90b1;top2b;tgfbr1;cdc34;arcn1;sel1l;sec22b;rab6a;rab18;rab10;rab1a;pten;psmc2;nucb1;neu1;ncoa1;commd1;ly6e;ly6d;large1;igfbp5;hnrnpcc;hist2h2aa1;gpaa1;gfpt1;f5;f2;csf1;cdc25a;ccnf;capza2;calm3;calm2;c4b;btrc;bmi1;serpinc1;asgr1;arsb;apoe;ahsg;afp;uhrf2;tptr;adamts7;gbf1;qsox1;alg9	3307.63049	3411.49	34.2395	1357.1012	3224.0202	1322.09714	UP	0.740740741	0.259259259	
90Day	RHO GTPase Effectors	0.055097	0.964	0.11439	cenpu;fmnl2;hist1h4h;tubb6;iggap2;hist1h4i;hist1h3c;mapk14;wasf2;pin1;tubb4b;yywhaz;tubb2a;tuba1b;kntc1;rtkn;rock2;rock1;nudc;h2afx;cdc42;ctnnb1;ar;sec13;cenpf	2942.45468	3327.48	137.958	1666.76604	2729.46778	1791.72597	UP	0.68	0.32	
7Day	Detoxification of Reactive Oxygen Species	0.97326	0.075011	0.11691	txn2;txnr1;prdx2;sod1;gstp1;gstp2	3067.77167	2364.315	1934.11	1407.64818	2638.24246	1004.62892	UP	0.666666667	0.333333333	
7Day	VEGFR2 mediated cell proliferation	0.97197	0.11693	0.11693	rasa1;prkc;kras	5247.51333	5786.08	4158.71	942.9494	5500.44753	766.132962	DOWN	0.333333333	0.666666667	
7Day	TGF-beta receptor signaling in EMT (epithelial to mesenchymal transition)	0.97197	0.11693	0.11693	uba52;tgfbr1;prkc	5403.78667	5652.05	4761.56	506.935327	5505.00175	513.773786	UP	0.666666667	0.333333333	
7Day	Attenuation phase	0.97197	0.11693	0.11693	hsbp1;ptges3;hsp90aa1	2555.69	3138.45	1005.61	1356.10936	2112.59176	1392.19616	UP	0.666666667	0.333333333	
7Day	Apoptotic cleavage of cell adhesion proteins	0.97197	0.11693	0.11693	dsg1c;ctnnb1;dsp	1106.8554	240.593	54.5232	1664.15427	1209.2455	1689.05741	DOWN	0	1	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
90Day	Nucleobase catabolism	0.95647	0.10353	0.11693	pnp2;dpys;nudt5;dnph1;nudt15;nudt18;pnp	3360.77571	3566.76	1635.68	944.106911	3216.17975	938.174015	CONFLICT	0.428571429	0.571428571	
28Day	Transcriptional Regulation by TP53	0.061662	0.96723	0.1172	meaf6;tmem219;e2f7;txnr1;cnot1;polr2a;mdm2;ccnk;ccng1;bnip3l	3457.676	3155.34	1125.25	1517.32818	3021.67977	1410.8717	UP	0.6	0.4	
90Day	Glucose metabolism	0.068194	0.98159	0.11762	pcpx;pfkfb3	2690.7375	2690.7375	410.825	3224.28318	1569.96174	2807.79725	CONFLICT	0.5	0.5	
90Day	Heparan sulfate/heparin (HS-GAG) metabolism	0.062565	0.98339	0.11811	sdca4;bgn	2581.783	2581.783	630.216	2759.93252	3403.41741	2503.40993	DOWN	0	1	
28Day	Amine ligand-binding receptors	0.046646	1	0.11817											
90Day	HDR through Single Strand Annealing (SSA)	0.067968	0.98812	0.11824	rad51	513.022	513.022	513.022		513.022		UP	1	0	
90Day	Base Excision Repair	0.067968	0.98812	0.11824	pole4	5853.8	5853.8	5853.8		5853.8		DOWN	0	1	
90Day	Resolution of Abasic Sites (AP sites)	0.067968	0.98812	0.11824	pole4	5853.8	5853.8	5853.8		5853.8		DOWN	0	1	
90Day	Chylomicron assembly	0.97238	0.11831	0.11831	apob;apoE;apoc3	2494.08667	1749.82	175.96	2766.39631	3075.73574	2798.82787	DOWN	0	1	
90Day	Chylomicron remodeling	0.97238	0.11831	0.11831	apob;apoE;apoc3	2494.08667	1749.82	175.96	2766.39631	3075.73574	2798.82787	DOWN	0	1	
28Day	Neddylation	0.053985	0.97174	0.1186	obs1;btbd1;fbxo22;psmd6;asb3;psmd8;uchl3;psmf1;ube2m;psmb8	3801.796	4283.805	1308.55	1505.91358	3880.67917	1590.21422	DOWN	0.4	0.6	
90Day	NCAM signaling for neurite out-growth	0.061629	0.98946	0.11928	sos1	5894.93	5894.93	5894.93		5894.93		DOWN	0	1	
90Day	GABA B receptor activation	0.061629	0.98946	0.11928	gna13	5903.07	5903.07	5903.07		5903.07		UP	1	0	
90Day	Activation of GABAB receptors	0.061629	0.98946	0.11928	gna13	5903.07	5903.07	5903.07		5903.07		UP	1	0	
90Day	Transcriptional activity of SMAD2/SMAD3:SMAD4 heterotrimer	0.061629	0.98946	0.11928	ccnc	4045.2	4045.2	4045.2		4045.2		UP	1	0	
90Day	Golgi Associated Vesicle Biogenesis	0.057368	0.98502	0.1195	acbd3;ftl1	2653.36	2653.36	1733.37	1301.06234	3063.20902	1164.8222	UP	1	0	
90Day	Formation of Fibrin Clot (Clotting Cascade)	0.055854	0.99065	0.12154	f7	3350.52	3350.52	3350.52		3350.52		DOWN	0	1	
90Day	Cargo trafficking to the periciliary membrane	0.055854	0.99065	0.12154	exoc4	2113.16	2113.16	2113.16		2113.16		UP	1	0	
28Day	Initial triggering of complement	0.96891	0.12189	0.12189	c4b;c3;c2	2076.44167	2572.88	520.995	1376.11119	1715.75301	1348.31746	DOWN	0	1	
28Day	Deposition of new CENPA-containing nucleosomes at the centromere	0.96891	0.12189	0.12189	cenpw;cenpt;cenpx	4594.13333	4682.29	3567.21	985.805758	4633.05174	1140.90633	DOWN	0.333333333	0.666666667	
28Day	Nucleosome assembly	0.96891	0.12189	0.12189	cenpw;cenpt;cenpx	4594.13333	4682.29	3567.21	985.805758	4633.05174	1140.90633	DOWN	0.333333333	0.666666667	
28Day	Endosomal Sorting Complex Required For Transport (ESCRT)	0.96046	0.12198	0.12198	vps36;ubap1;vps37a;hgs	3411.59	3333.065	2396.85	901.917258	3368.7906	1032.57673	UP	0.75	0.25	
28Day	RHO GTPases activate IQGAPs	0.96046	0.12198	0.12198	iqgap2;tubb4b;tubb2a;cdc42	2737.835	2683.265	2359.45	401.419857	2783.09066	384.123954	UP	0.75	0.25	
28Day	Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell	0.052807	0.98282	0.12262	h2-q7;h2-d1;c3	4023.66	3718.12	2572.88	1625.23494	3626.7901	1367.74163	DOWN	0.333333333	0.666666667	
7Day	Plasma lipoprotein clearance	0.96873	0.084731	0.12267	npc2;apob;ldlr;ces3b;apoE;apoc1	2983.85933	3545.22	113.316	1688.72845	3495.51574	1115.58326	DOWN	0.166666667	0.833333333	
28Day	Scavenging by Class A Receptors	0.98021	0.12289	0.12289	apob;apoE	2075.9425	2075.9425	939.205	1607.58959	1295.41266	1168.71324	DOWN	0	1	
28Day	mitochondrial fatty acid beta-oxidation of saturated fatty acids	0.98021	0.12289	0.12289	echs1;acadi	2016.1655	2016.1655	802.301	1716.66364	1538.10672	1577.92701	DOWN	0	1	
28Day	Urea cycle	0.98021	0.12289	0.12289	otc;ass1	899.061	899.061	726.832	243.568588	953.614934	231.026824	DOWN	0	1	
7Day	Hedgehog 'on' state	0.06055	0.98958	0.12381	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0	
7Day	HDR through Homologous Recombination (HRR)	0.055652	0.98542	0.12452	uba52;rad51ap1	4319.445	4319.445	3877.33	625.245029	4260.9519	619.748708	UP	1	0	
28Day	Fc gamma receptor (FCGR) dependent phagocytosis	0.07272	0.97971	0.12599	cdc42;brk1	3960.63	3960.63	2463.49	2117.27569	4417.2828	2016.38111	CONFLICT	0.5	0.5	
7Day	DNA Damage Bypass	0.055808	0.99057	0.12605	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0	
28Day	RNA Polymerase I Chain Elongation	0.0691	0.98092	0.12613	hist1h4i;polr1a	5855.735	5855.735	5848.41	10.3591143	5854.78856	10.27228	DOWN	0	1	
7Day	PIP, PP2A and IER3 Regulate PI3K/AKT Signaling	0.072147	0.96934	0.1265	mapk3;ptpn11;ppg2cb;il1rap;fgf1	2967.1468	3627.04	131.024	1759.27735	2795.99089	1795.89908	DOWN	0.4	0.6	
28Day	Positive epigenetic regulation of rRNA expression	0.065647	0.98205	0.1266	hist1h4i;polr1a	5855.735	5855.735	5848.41	10.3591143	5854.78856	10.27228	DOWN	0	1	
28Day	B-WICH complex positively regulates rRNA expression	0.065647	0.98205	0.1266	hist1h4i;polr1a	5855.735	5855.735	5848.41	10.3591143	5854.78856	10.27228	DOWN	0	1	
28Day	Regulation of PLK1 Activity at G2/M Transition	0.065647	0.98205	0.1266	dynl1;tubb4b	4075.495	4075.495	2359.45	2426.85411	4561.33816	2327.55961	UP	1	0	
28Day	Regulation of insulin secretion	0.075401	0.98617	0.12674	gnb5	953.648	953.648	953.648		953.648		UP	1	0	
28Day	PTEN Regulation	0.071153	0.98713	0.12686	bmi1	3918.46	3918.46	3918.46		3918.46		UP	1	0	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
7Day	Signaling by Rho GTPases	0.061713	0.95755	0.12707	clasp2;myh14;hist1h4h;hist1h2bc;cenp k;kalrn;iqgap2;nckap1;dlc1;hist2h2ac;mapk3;tubb4b;ywhaz;pak2;tubb2a;tuba4a;flna;ppp2cb;pfn2;pfn1;ncoa2;myh9;kif2a;hist2h2aa1;cdc42;ctnnb1;calm3;calm2;abl1;xpo1;brk1	3262.95283	3406.55	54.5232	1403.85221	3312.88593	1415.442	UP	0.612903226	0.387096774	
90Day	Glycosaminoglycan metabolism	0.061178	0.97137	0.12723	omd;sdca4;st3gal3;lum;hyal1;slc26a2;bgn	3214.985	3962.48	144.869	1997.4444	3545.10983	1689.16138	DOWN	0.285714286	0.714285714	
7Day	Cyclin A:Cdk2-associated events at S phase entry	0.95823	0.12945	0.12945	uba52;cdkn1a;cdc25a;ccne2	4514.035	4679.875	2818.63	1265.23972	4350.66448	1194.57246	UP	1	0	
7Day	Synaptic adhesion-like molecules	0.95823	0.12945	0.12945	gria3;ptprf;ptprd;flot2	3155.4775	3050.285	1019.97	1947.22982	3207.00014	1360.83163	DOWN	0.25	0.75	
7Day	Death Receptor Signalling	0.071486	0.96566	0.12966	kalrn;tax1bp1;lingo1;uba52;smpd2;prkci;xiap	4109.23286	3409.24	3247.44	1023.33552	4183.22777	1041.92089	CONFLICT	0.571428571	0.428571429	
28Day	PKMTs methylate histone lysines	0.059727	0.98962	0.12992	hist1h4i	5848.41	5848.41	5848.41		5848.41		DOWN	0	1	
28Day	p75 NTR receptor-mediated signalling	0.056218	0.98508	0.12999	arhgdia;sqstm1	5327.91	5327.91	4971.84	503.559023	5342.98982	503.107233	UP	1	0	
28Day	Synthesis of PS	0.99529	0.13259	0.13259	ptdss1	3854.48	3854.48	3854.48		3854.48		DOWN	0	1	
28Day	Biosynthesis of DHA-derived sulfido conjugates	0.99529	0.13259	0.13259	gstm4	792.488	792.488	792.488		792.488		UP	1	0	
28Day	Biosynthesis of maresin conjugates in tissue regeneration (MCTR)	0.99529	0.13259	0.13259	gstm4	792.488	792.488	792.488		792.488		UP	1	0	
28Day	Abasic sugar-phosphate removal via the single-nucleotide replacement pathway	0.99529	0.13259	0.13259	polb	5853.24	5853.24	5853.24		5853.24		UP	1	0	
28Day	TP53 Regulates Transcription of Death Receptors and Ligands	0.99529	0.13259	0.13259	tmem219	5589.83	5589.83	5589.83		5589.83		DOWN	0	1	
28Day	Transfer of LPS from LBP carrier to CD14	0.99529	0.13259	0.13259	lbp	5807.04	5807.04	5807.04		5807.04		DOWN	0	1	
28Day	Linoleic acid (LA) metabolism	0.99529	0.13259	0.13259	elovl2	829.671	829.671	829.671		829.671		DOWN	0	1	
7Day	Complex I biogenesis	0.96275	0.085569	0.13293	ndufaf1;ndufaf4;ndufc2;ndufa13;ndufa6;ndufa1;ecsf1;ndufa2	3765.34375	3870.965	2874.39	561.261806	3563.34922	546.182095	CONFLICT	0.5	0.5	
7Day	Interferon Signaling	0.95694	0.088503	0.13324	ube2n;flnb;eif4e2;mapk3;arih1;stat1;tpn11;jak1;ifng;eif4a2	3618.495	3591.995	2513.13	662.008597	3584.68031	664.910743	UP	0.8	0.2	
7Day	HSF1 activation	0.97816	0.13551	0.13551	ptges3;hsp90aa1	2072.03	2072.03	1005.61	1508.14563	1840.5494	1472.18772	UP	1	0	
7Day	Heme degradation	0.97816	0.13551	0.13551	ugt1a1;blvrb	2545.203	2545.203	178.786	3346.61902	2903.10937	3308.12105	CONFLICT	0.5	0.5	
7Day	Aryl hydrocarbon receptor signalling	0.97816	0.13551	0.13551	ptges3;arnt	3306.16	3306.16	3138.45	237.177757	3272.82664	232.445828	CONFLICT	0.5	0.5	
90Day	PI Metabolism	0.069124	0.97357	0.13757	tnfaip8l1;tnfaip8l3;pi4ka;plekha1	2755.15	2699.92	1984.74	693.540876	2789.32817	510.939159	DOWN	0.25	0.75	
28Day	LDL clearance	0.9627	0.13775	0.13775	npc2;apob;ces3b	1412.78133	939.205	614.079	1113.75333	1033.23597	853.388406	DOWN	0	1	
90Day	Mitotic Anaphase	0.067819	0.96392	0.13843	cenpu;anapc10;tubb6;tubb4b;tubb2a;tuba1b;kntc1;nudc;sec13;cenpf	2905.4621	2971.72	779.791	1448.96614	2908.06114	1718.42046	UP	0.9	0.1	
90Day	Mitotic Metaphase and Anaphase	0.064222	0.96605	0.13931	cenpu;anapc10;tubb6;tubb4b;tubb2a;tuba1b;kntc1;nudc;sec13;cenpf	2905.4621	2971.72	779.791	1448.96614	2908.06114	1718.42046	UP	0.9	0.1	
90Day	Fibronectin matrix formation	0.97805	0.14001	0.14001	ceacam2;fn1	2935.755	2935.755	2110.06	1167.70907	3438.7646	926.016822	CONFLICT	0.5	0.5	
90Day	Choline catabolism	0.97805	0.14001	0.14001	dmgdh;sardh	2153.1035	2153.1035	562.177	2249.90983	1709.48348	2160.67045	DOWN	0	1	
90Day	Activated NTRK2 signals through FRS2 and FRS3	0.97805	0.14001	0.14001	sos1;ntrk2	4819.635	4819.635	3744.34	1520.69677	5019.62489	1494.16424	DOWN	0	1	
7Day	RAB GEFs exchange GTP for GDP on RABs	0.9416	0.10767	0.14025	rab3gap2;trappc6b;trappc8;trappc13;0610009b22rik;rab9;dennd4c;rab6a;rab18;rab10;rab1a;hps4	3354.70917	3549.365	1046.66	987.765335	3158.49338	802.748125	UP	0.833333333	0.166666667	
7Day	p75 NTR receptor-mediated signalling	0.077514	0.96959	0.14053	kalrn;lingo1;uba52;prkci	3703.5175	3402.535	3247.44	709.16182	3635.7194	714.955261	UP	0.75	0.25	
90Day	Regulation of TP53 Activity	0.077647	0.96078	0.14176	trp53inp1;mapk14;pin1;gatad2b;pml;mdm2;hdac2;ccng1	2852.982	3338.28	202.162	1639.26752	2701.54097	1741.80736	UP	0.75	0.25	
7Day	mRNA Splicing - Minor Pathway	0.95332	0.10269	0.14284	sf3b1;zcrb1;sf3b6;polr2h;zrsr2;srsf1;snrpd2;sf3b3	4178.27875	3958.2	3209.5	845.527167	3976.3674	617.723557	UP	1	0	
90Day	Ethanol oxidation	0.96217	0.14514	0.14514	aldh1b1;adh4;aldh1a7	2948.69667	2828.04	2740.9	287.766466	2839.44943	213.108444	UP	1	0	
90Day	Phenylalanine and tyrosine catabolism	0.96217	0.14514	0.14514	asrgl1;hpd;gstz1	2010.449	1889.08	932.277	1143.69662	1847.96643	1180.88947	DOWN	0	1	
7Day	Cooperation of PDCL (PhLP1) and TRIC/CCT in G-protein beta folding	0.95214	0.11779	0.14595	tcp1;rgs9;gna13;cct7;cct4;cct2	3317.08333	3368.435	794.2	1639.67521	2488.37326	1531.66786	UP	0.833333333	0.166666667	
7Day	MAPK1/MAPK3 signaling	0.074403	0.95679	0.14615	ranbp9;mapk3;pebp1;uba52;rasa1;ptp n11;ppp2cb;kras;jak1;gfra1;fgf1;calm3;calm2	3856.44692	4071.69	778.73	1248.9377	3857.71942	1137.75892	UP	0.615384615	0.384615385	
28Day	Organic anion transporters	0.97315	0.1469	0.1469	slc25a10;slc17a8	3022.865	3022.865	2312.64	1004.40983	3208.50484	969.492034	UP	1	0	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.														
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
7Day	Metabolism of proteins	0.071932	0.94033	0.14698	elif3m;dcaf8;c1galt1;mrpl16;mrpl1;ube2n;btbd1;elf3j1;trappc6b;dcun1d5;plet1;rps25;mrpl47;usp16;fbxo22;prmt3;gm49336;cul2;fuca1;fbxo9;ube2v2;pigw;rnf168;hist1h4h;rraga;babam1;hist1h2bc;tomm20;cog6;psmd5;psmd6;wdr61;mrps17;elf1ax;mrps36;apoa5;0610009b22rik;ngly1;mrps31;copz1;rab9;pex14;hdac7;nop58;gnpnat1;rab11a;rab25;ube2k;suz12;uba2;etfbkmt;hist2h2ac;elf3b;abca3;mrpl2;msrb1;rps3;elf2s3x;cop1;ppp6r1;dcaf10;taf10;fem1c;psmc4;cog5;apob;nae1;tubb4b;ino80c;elf3l;vdac3;vdac2;ube2a;ube2e3;uba52;tubb2a;tuba4a;hsp90b1;top2b;tgfbr1;elf5;cdc34;tcp1;arcn1;sel1l;sec22b;rps12;rgs9;rab6a;rab18;rab10;rab1a;pten;psmc2;nucb1;neu1;ncoa1;commmd1;mme;ly6e;ly6d;large1;igfbp5;hnnpnc;hist2h2aa1;gspt1;gpaa1;gnai3;gfp1f5;f2;elf4ebp1;elf4a2;csf1;cdc25a;ctt7;cct4;cct2;ccnf;capza2;calm3;calm2;c4b;btcr;bmi1;serpinc1;asg1a;arsb;apoe;ahsg;afp;uhrf2;tpor;adamts7;gfb1;qsox1;alg9	3331.02157	3418.4	34.2395	1365.20864	3221.59993	1326.52158	UP	0.744525547	0.255474453
7Day	Glycerophospholipid biosynthesis	0.070324	0.96809	0.14754	hadha;pla1a;dgat2;cris1;stard10;ptdss1	2781.72283	3586.9	197.056	1878.288	3280.41818	1631.32008	DOWN	0.333333333	0.666666667
7Day	Regulation of TP53 Activity	0.066684	0.96997	0.14872	km15a;taf10;uba52;ppp2cb;csnk2b;ccng1	3216.805	3423.965	1234.63	1159.98087	3098.48255	1211.00302	UP	1	0
7Day	Cell Cycle, Mitotic	0.077549	0.9444	0.14877	clasp2;gm49336;pds5a;hist1h4h;hist1h2bc;km15a;psmd5;psmd6;cenpk;nek6;arpp19;hist2h2ac;gtse1;mapk3;psmc4;tubb4b;uba52;tubb2a;tuba4a;tfdp1;cdc27;rab1a;psmc2;prim2;ppp2cb;nedd1;kif2a;hsp90aa1;hist2h2aa1;cdkn1a;cdc25a;ccne2;btcr;abl1;tpor;xp01	3338.59217	3521.41	707.264	1286.77305	3294.11171	1260.15661	UP	0.861111111	0.138888889
90Day	Cap-dependent Translation Initiation	0.088041	0.96918	0.15091	elf3m;rps27l;rps12	2578.52	2517.83	1662.63	947.693586	2378.76706	980.623942	UP	1	0
90Day	Eukaryotic Translation Initiation	0.08157	0.97186	0.15108	elf3m;rps27l;rps12	2578.52	2517.83	1662.63	947.693586	2378.76706	980.623942	UP	1	0
90Day	Costimulation by the CD28 family	0.069891	0.97655	0.15399	vav1;h2-aa;cdc42	2439.569	3001.17	156.487	2060.5043	2705.98577	1639.34757	DOWN	0.333333333	0.666666667
90Day	Gap-filling DNA repair synthesis and ligation in TC-NER	0.069891	0.97655	0.15399	pole4;polk;cdk7	4212.22333	3652.71	3130.16	1445.45671	3760.17242	830.658559	UP	0.666666667	0.333333333
90Day	Cleavage of Growing Transcript in the Termination Region	0.069891	0.97655	0.15399	cstf2t;srsf6;thoc7	5120.03333	5843.41	3549.69	1361.36044	5319.43866	1251.94412	UP	0.666666667	0.333333333
90Day	RNA Polymerase II Transcription Termination	0.069891	0.97655	0.15399	cstf2t;srsf6;thoc7	5120.03333	5843.41	3549.69	1361.36044	5319.43866	1251.94412	UP	0.666666667	0.333333333
28Day	Glucose metabolism	0.94696	0.12572	0.154	slc25a10;pfkl;pcx;pcsk1;gpi1;bpgm	3791.51	3857.705	3056.49	619.406093	3535.2427	522.694369	DOWN	0.333333333	0.666666667
7Day	Chaperonin-mediated protein folding	0.94557	0.13006	0.15556	tcp1;rgs9;gnai3;cct7;cct4;cct2	3317.08333	3368.435	794.2	1639.67521	2488.37326	1531.66786	UP	0.833333333	0.166666667
7Day	Protein folding	0.94557	0.13006	0.15556	tcp1;rgs9;gnai3;cct7;cct4;cct2	3317.08333	3368.435	794.2	1639.67521	2488.37326	1531.66786	UP	0.833333333	0.166666667
7Day	Signaling by FGFR3	0.94557	0.13006	0.15556	mapk3;uba52;ptpn11;ppp2cb;kras;fgf1	3937.49667	3894.19	2647.76	815.708654	3810.92898	853.996178	UP	0.666666667	0.333333333
90Day	Unblocking of NMDA receptors, glutamate binding and activation	0.10292	1	0.15748										
90Day	Oxygen-dependent proline hydroxylation of Hypoxia-inducible Factor Alpha	0.10292	1	0.15748										
90Day	Lagging Strand Synthesis	0.091296	1	0.15755										
90Day	Downregulation of SMAD2/3-SMAD4 transcriptional activity	0.091296	1	0.15755										
90Day	Endosomal/Vacuolar pathway	0.091296	1	0.15755										
90Day	Synthesis of Prostaglandins (PG) and Thromboxanes (TX)	0.091296	1	0.15755										

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
28Day	Post-translational protein modification	0.081087	0.93575	0.15772	obs1;c1galt1;ube2n;btbd1;spp2;asxl2;fbxo22;ube2v2;tom20;nanp;ube2g1;lman2;psmd6;wdr61;asb3;ngly1;psmd8;dym11;rab9;pigp;rab11a;ube2k;ppp6r3;uchl3;gne;ano8;hist1h4i;pign;apob;psmf1;tubb4b;sbspon;rab29;ino80c;usp12;ube2m;tubb2a;trf;mgat2;sec22c;serpina1e;serpina1b;rad21;rab18;proc;polb;p4hb;mdm2;man1a;ly6d;psmb8;lgals1;itih2;ikbk;hgs;hcfcl;gfpt1;fn1;f7;f5;f2;dag1;capza2;c4b;c3;brca1;bmi1;blm;bet1;serpinc1;asgr1;app;apoe;birc2;tp;gbf1;qsox1;dnajc3	3694.92401	3767.265	185.394	1724.89683	3702.88491	1735.81921	CONFLICT	0.487179487	0.512820513
90Day	Death Receptor Signalling	0.072611	0.96227	0.15868	arhgef6;fgd4;vav1;tnfrsf10b;tiam1;sos1;psen2;nfbk1a;ikbk	4469.39778	4161.05	3135.19	1146.137	4336.11238	1140.0596	DOWN	0.333333333	0.666666667
7Day	Transcription-Coupled Nucleotide Excision Repair (TC-NER)	0.067874	0.97718	0.1597	prpf19;polr2h;uba52	3815.36333	3964.6	2719.93	1028.96402	3913.27434	885.21152	UP	1	0
90Day	CTLA4 inhibitory signaling	0.080986	1	0.16022										
90Day	NCAM1 interactions	0.080986	1	0.16022										
90Day	Metal ion SLC transporters	0.080986	1	0.16022										
90Day	Common Pathway of Fibrin Clot Formation	0.080986	1	0.16022										
7Day	DNA Double-Strand Break Repair	0.086304	0.95393	0.16049	ube2n;ube2v2;rnf168;hist1h4h;babam1;hist1h2bc;uba52;rad51ap1;abl1	3610.97889	3444.79	2423.08	647.933214	3488.58257	659.371908	UP	0.777777778	0.222222222
28Day	mRNA Splicing - Minor Pathway	0.94199	0.13475	0.16108	mpc3;sfb3b6;snrpd1;polr2a;prpf8;srsf1	3946.6835	4993.735	131.831	2170.39278	3775.10545	2384.96324	UP	0.666666667	0.333333333
90Day	RNA Polymerase I Chain Elongation	0.082007	0.96466	0.16141	hist1h4h;hist1h4i;hist1h3c;h2afx;cdk7	3197.2378	3951.81	811.859	1388.20317	2385.19446	1713.34211	UP	0.6	0.4
7Day	Role of phospholipids in phagocytosis	0.10238	1	0.16152										
7Day	Cobalamin (Cbl, vitamin B12) transport and metabolism	0.10238	1	0.16152										
7Day	G beta:gamma signalling through PI3Kgamma	0.092711	1	0.16186										
7Day	ADP signalling through P2Y purinoceptor 1	0.092711	1	0.16186										
7Day	Basigin interactions	0.092711	1	0.16186										
7Day	Activation of G protein gated Potassium channels	0.092711	1	0.16186										
7Day	G protein gated Potassium channels	0.092711	1	0.16186										
7Day	Inhibition of voltage gated Ca2+ channels via Gbeta/gamma subunits	0.092711	1	0.16186										
28Day	O-linked glycosylation	0.07683	0.97333	0.162	c1galt1;sbspon;dag1	5078.49333	5312.69	4256.3	733.685912	5100.20972	728.91463	UP	0.666666667	0.333333333
90Day	Mitotic Prometaphase	0.084425	0.9487	0.16285	haus7;cenpu;smc4;tubb6;dctn3;cntrl;tubb4b;cep76;tubb2a;tuba1b;kntc1;nudc;hsp90aa1;sec13;cenpf	3001.67807	3184.54	426.32	1482.71675	3068.64721	1625.21055	UP	0.933333333	0.066666667
28Day	PI3P, PP2A and IER3 Regulate PI3K/AKT Signaling	0.073366	0.97474	0.16325	il1rap;hbegf;fgf1	2030.93933	1467.57	919.738	1475.86252	1887.6209	1368.24713	DOWN	0.333333333	0.666666667
90Day	Nucleotide Excision Repair	0.073511	0.96474	0.16365	pole4;mcrs1;polk;yy1;ino80c;rad23a;cdk7	3814.86	3652.71	1252.26	1612.71329	3703.59993	1422.1654	CONFLICT	0.571428571	0.428571429
90Day	DNA Damage Bypass	0.08799	0.97497	0.16415	pole4;polk	4753.255	4753.255	3652.71	1556.40567	3884.77714	955.97646	CONFLICT	0.5	0.5
90Day	Toll Like Receptor 9 (TLR9) Cascade	0.071745	0.96972	0.16448	irf7;mapk14;nfbk1a;ikbk;bttrc	4394.204	4261.96	3265.56	1021.51429	4535.14678	1084.60939	DOWN	0.4	0.6
90Day	Processing of DNA double-strand break ends	0.071745	0.96972	0.16448	hist1h4h;babam1;ppp4c;hist1h4i;h2afx	4313.072	4006.71	3721.17	842.236755	4116.8701	738.037657	UP	0.6	0.4
28Day	Organelle biogenesis and maintenance	0.086545	0.95352	0.16513	atp5g2;atp5j2;dym11;rab11a;bbs9;tubb4b;tubb2a;exoc4;ttbk2	3784.97556	2903.04	2192.92	1616.78928	3801.04188	1646.66451	UP	0.666666667	0.333333333
90Day	CD28 dependent PI3K/Akt signaling	0.07184	1	0.1653										
90Day	mTORC1-mediated signalling	0.07184	1	0.1653										
90Day	Cellular hexose transport	0.07184	1	0.1653										
90Day	CD209 (DC-SIGN) signaling	0.07184	1	0.1653										
90Day	Transcriptional regulation by the AP-2 (TFAP2) family of transcription factors	0.07184	1	0.1653										
28Day	Transmission across Chemical Synapses	0.083771	0.9552	0.16537	gria3;lin7c;slc22a1;slc1a2;mdm2;gnb5;glul;slc6a13;adc9	2263.17889	1938.66	151.142	1586.36418	2350.06997	1505.23149	DOWN	0.333333333	0.666666667

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
90Day	Cell-cell junction organization	0.080873	0.9774	0.16571	afdn;ctnnb1	2442.127	2442.127	797.214	2326.25827	1451.95914	1857.58251	CONFLICT	0.5	0.5
7Day	Signaling by FGFR4	0.93847	0.14291	0.16599	mapk3;uba52;ptpn11;ppp2cb;kras;fgf1	3937.49667	3894.19	2647.76	815.708654	3810.92898	853.996178	UP	0.666666667	0.333333333
90Day	Detoxification of Reactive Oxygen Species	0.93844	0.1444	0.16606	bxnd1;nox4;txn1;gstp2;gsr;prdx6	3570.695	3583.44	1676.13	1519.56913	3616.58845	1660.04604	CONFLICT	0.5	0.5
7Day	Translation	0.9369	0.10073	0.16622	eif3m;mrpl16;mrpl1;eif3j1;rps25;mrpl47;mrps17;eif1ax;mrps36;mrps31;eif3b;mrpl2;rps3;eif2s3x;eif3l;eif5;rps12;g	3607.17663	3885.79	84.8066	1418.08335	3571.07351	1295.32571	UP	0.85	0.15
28Day	Digestion and absorption	0.10232	1	0.16716	spt1;eif4ebp1;eif4a2									
7Day	SUMOylation of intracellular receptors	0.076021	1	0.1678										
7Day	Integrin alphaIIb beta3 signaling	0.076021	1	0.1678										
7Day	Integrin signaling	0.076021	1	0.1678										
7Day	TNFs bind their physiological receptors	0.076021	1	0.1678										
7Day	Cytosolic sulfonation of small molecules	0.076021	1	0.1678										
7Day	Ion transport by P-type ATPases	0.097922	0.97125	0.1679	calm3;calm2	3983.44	3983.44	3050.32	1319.63096	3556.9103	1173.69957	CONFLICT	0.5	0.5
7Day	Histidine catabolism	0.96746	0.16983	0.16983	amdhd1;uroc1	3016.64	3016.64	2981.91	49.115637	3019.12941	48.9892991	DOWN	0	1
7Day	Mitochondrial protein import	0.96746	0.16983	0.16983	pitrm1;dhhd	3757.27	3757.27	3743.17	19.9404112	3753.77075	19.3165876	DOWN	0	1
7Day	alpha-linolenic acid (ALA) metabolism	0.96746	0.16983	0.16983	fads1;fads2	55.99745	55.99745	55.2305	1.08463109	56.0557676	1.08149097	DOWN	0	1
7Day	Synthesis of UDP-N-acetyl-glucosamine	0.96746	0.16983	0.16983	gnpnat1;gfpt1	3426.45	3426.45	3132.03	416.372757	3435.4841	416.176697	UP	1	0
7Day	Glutathione synthesis and recycling	0.96746	0.16983	0.16983	gss;gclc	2729.28	2729.28	2300.86	605.877374	2748.44746	605.270691	UP	1	0
7Day	Stabilization of p53	0.96746	0.16983	0.16983	cop1;uba52	4194.635	4194.635	3627.71	801.753024	4115.83314	793.970052	UP	1	0
7Day	SCF-beta-TrCP mediated degradation of Emi1	0.96746	0.16983	0.16983	uba52;btrc	4484.31	4484.31	4207.06	392.09071	4446.04923	388.339223	UP	1	0
28Day	RNA Polymerase III Transcription	0.082597	1	0.17117										
28Day	RNA Polymerase III Transcription Initiation	0.082597	1	0.17117										
28Day	Activation of NMDA receptors and postsynaptic events	0.082597	1	0.17117										
28Day	Rho GTPase cycle	0.080681	0.96483	0.17162	arhgap45;dlc1;a2m;arhgdia;cdc42	3661.188	4971.84	160.43	2311.53571	4076.2988	2025.40877	UP	0.8	0.2
28Day	Purine salvage	0.96493	0.17175	0.17175	hprt;adk	2990.7	2990.7	2420.29	806.681558	3160.53958	770.093613	CONFLICT	0.5	0.5
28Day	Tryptophan catabolism	0.96493	0.17175	0.17175	tdo2;haao	2669.151	2669.151	887.232	2520.01402	3576.30393	2169.01308	DOWN	0	1
28Day	Synthesis of PE	0.96493	0.17175	0.17175	phospho1;etnk2	3830.44	3830.44	2962.74	1227.11311	3824.40463	1227.08342	DOWN	0	1
28Day	Chylomicron remodeling	0.96493	0.17175	0.17175	apob;apoE	2075.9425	2075.9425	939.205	1607.58959	1295.41266	1168.71324	DOWN	0	1
28Day	Translocation of ZAP-70 to Immunological synapse	0.96493	0.17175	0.17175	h2-ab1;h2-aa	3461.14	3461.14	3245.73	304.635743	3292.13505	188.885132	DOWN	0	1
90Day	Metalloprotease DUBs	0.090885	0.98296	0.17186	babam1	5800.02	5800.02	5800.02		5800.02		UP	1	0
90Day	Amino acid transport across the plasma membrane	0.090885	0.98296	0.17186	slc6a12	3445.15	3445.15	3445.15		3445.15		DOWN	0	1
90Day	Gamma carboxylation, hypusine formation and arylsulfatase activation	0.090885	0.98296	0.17186	f7	3350.52	3350.52	3350.52		3350.52		DOWN	0	1
90Day	Separation of Sister Chromatids	0.079661	0.95679	0.17297	cenpu;anapc10;tubb6;tubb4b;tubb2a;tuba1b;kntc1;nudc;sec13;cenpf	2905.4621	2971.72	779.791	1448.96614	2908.06114	1718.42046	UP	0.9	0.1
7Day	Synthesis of Leukotrienes (LT) and Eoxins (EX)	0.068838	1	0.17319										
28Day	DNA Damage/Telomere Stress Induced Senescence	0.09833	0.97078	0.17338	acd;hist1h4i	5109.845	5109.845	4371.28	1044.48864	5169.31387	1041.09722	DOWN	0	1
90Day	GRB2 events in EGFR signaling	0.9501	0.17371	0.17371	tgfa;sos1;areg	4009.27667	3970.39	2162.51	1866.51383	3698.23096	2070.13409	UP	0.666666667	0.333333333
28Day	Activation of Matrix Metalloproteinases	0.076906	1	0.17426										
28Day	RHO GTPases activate PKNs	0.089004	0.97411	0.17434	hist1h4i;pdpk1	3020.699	3020.699	192.988	3998.98725	4607.8042	3309.69684	DOWN	0	1
28Day	Platelet homeostasis	0.089004	0.97411	0.17434	apob;ggnb5	946.4265	946.4265	939.205	10.2127432	947.355903	10.1278105	CONFLICT	0.5	0.5
90Day	Activation of NMDA receptors and postsynaptic events	0.08254	0.98489	0.17441	camkk2	98.0082	98.0082	98.0082		98.0082		DOWN	0	1
7Day	Dual Incision in GG-NER	0.10608	0.9791	0.17526	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	Cargo trafficking to the periciliary membrane	0.10608	0.9791	0.17526	rab11a	4542.35	4542.35	4542.35		4542.35		UP	1	0

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
7Day	DAPI2 interactions	0.090553	0.98287	0.17665	kras	4158.71	4158.71	4158.71		4158.71		UP	1	0
7Day	Homologous DNA Pairing and Strand Exchange	0.090553	0.98287	0.17665	rad51ap1	3877.33	3877.33	3877.33		3877.33		UP	1	0
28Day	Recruitment of mitotic centrosome proteins and complexes	0.080487	0.97708	0.17691	dynl1;tubb4b	4075.495	4075.495	2359.45	2426.85411	4561.33816	2327.55961	UP	1	0
28Day	Centrosome maturation	0.080487	0.97708	0.17691	dynl1;tubb4b	4075.495	4075.495	2359.45	2426.85411	4561.33816	2327.55961	UP	1	0
28Day	Gene Silencing by RNA	0.080487	0.97708	0.17691	hist1h4i;polr2a	5444.54	5444.54	5040.67	571.158431	5494.50555	566.770537	CONFLICT	0.5	0.5
28Day	Signaling by FGFR	0.080487	0.97708	0.17691	polr2a;fgf1	3254.12	3254.12	1467.57	2526.56324	2657.99173	2381.76069	CONFLICT	0.5	0.5
7Day	Synthesis of PS	0.99113	0.17958	0.17958	ptdss1	3684.01	3684.01	3684.01		3684.01		DOWN	0	1
7Day	Pre-NOTCH Transcription and Translation	0.99113	0.17958	0.17958	prkci	3409.24	3409.24	3409.24		3409.24		UP	1	0
7Day	Signaling by NOTCH4	0.99113	0.17958	0.17958	ywhaz	2726.98	2726.98	2726.98		2726.98		UP	1	0
7Day	Biosynthesis of DHA-derived sulfido conjugates	0.99113	0.17958	0.17958	gstm4	2629.52	2629.52	2629.52		2629.52		UP	1	0
7Day	Biosynthesis of maresin conjugates in tissue regeneration (MCTR)	0.99113	0.17958	0.17958	gstm4	2629.52	2629.52	2629.52		2629.52		UP	1	0
7Day	NOTCH4 Activation and Transmission of Signal to the Nucleus	0.99113	0.17958	0.17958	ywhaz	2726.98	2726.98	2726.98		2726.98		UP	1	0
7Day	mRNA Editing: A to I Conversion	0.99113	0.17958	0.17958	adar	3802.37	3802.37	3802.37		3802.37		UP	1	0
7Day	G6 deamination of adenosine	0.99113	0.17958	0.17958	adar	3802.37	3802.37	3802.37		3802.37		UP	1	0
7Day	Formation of editosomes by ADAR proteins	0.99113	0.17958	0.17958	adar	3802.37	3802.37	3802.37		3802.37		UP	1	0
7Day	Regulation of Glucokinase by Glucokinase Regulatory Protein	0.99113	0.17958	0.17958	gckr	3375.32	3375.32	3375.32		3375.32		DOWN	0	1
7Day	Synthesis of bile acids and bile salts via 24-hydroxycholesterol	0.99113	0.17958	0.17958	cyp39a1	3113.35	3113.35	3113.35		3113.35		DOWN	0	1
7Day	Biogenic amines are oxidatively deaminated to aldehydes by MAOA and MAOB	0.99113	0.17958	0.17958	maob	46.9364	46.9364	46.9364		46.9364		DOWN	0	1
7Day	Transfer of LPS from LBP carrier to CD14	0.99113	0.17958	0.17958	lbp	5240.82	5240.82	5240.82		5240.82		DOWN	0	1
7Day	Beta oxidation of myristoyl-CoA to lauroyl-CoA	0.99113	0.17958	0.17958	hadha	197.056	197.056	197.056		197.056		DOWN	0	1
7Day	Linoleic acid (LA) metabolism	0.99113	0.17958	0.17958	elovl5	212.399	212.399	212.399		212.399		DOWN	0	1
90Day	Cell surface interactions at the vascular wall	0.087018	0.95537	0.17982	ceacam2;apob;tnfrsf10b;tek;sdca4;sos1;cd74;fn1	2382.25025	2162.38	175.96	2004.49059	3360.58389	1812.67216	DOWN	0.25	0.75
7Day	Peroxisomal lipid metabolism	0.95716	0.11773	0.18006	decr2;slc25a17;phyh;hsd17b4;pecr	2226.2346	2689.11	185.683	1346.51069	2493.92571	1080.16661	DOWN	0.4	0.6
7Day	Synthesis of active ubiquitin: roles of E1 and E2 enzymes	0.95716	0.11773	0.18006	ube2k;ube2a;ube2e3;uba52;cdc34	2978.584	3066.12	1018.89	1374.41615	3333.18209	1060.44253	UP	1	0
7Day	Negative regulation of FGFR4 signaling	0.95716	0.11773	0.18006	mapk3;uba52;ptpn11;ppp2cb;fgf1	3893.254	3629.67	2647.76	903.905503	3770.28016	910.359639	UP	0.6	0.4
28Day	O-linked glycosylation of mucins	0.10632	0.97876	0.18091	c1galt1	4256.3	4256.3	4256.3		4256.3		UP	1	0
28Day	GABA receptor activation	0.10632	0.97876	0.18091	adcy9	4220.6	4220.6	4220.6		4220.6		DOWN	0	1
28Day	NoRC negatively regulates rRNA expression	0.10046	0.98022	0.18113	hist1h4i	5848.41	5848.41	5848.41		5848.41		DOWN	0	1
28Day	Regulation of TP53 Activity through Phosphorylation	0.10046	0.98022	0.18113	mdm2	2266.61	2266.61	2266.61		2266.61		UP	1	0
90Day	RUNX3 regulates p14-ARF	0.96476	0.18192	0.18192	brd2;cbfb	4716.23	4716.23	4070.59	913.072844	4385.61638	784.277557	UP	1	0
28Day	Signaling by NTRK1 (TRKA)	0.094894	0.98159	0.18193	mapkapk2	5375	5375	5375		5375		DOWN	0	1
90Day	The canonical retinoid cycle in rods (twilight vision)	0.95413	0.12548	0.18201	rdh7;ttr;rbp1;rdh11;abca4	4303.324	4135.51	2528.1	1361.66594	4808.5251	1316.78938	UP	0.8	0.2
7Day	Metabolism of amino acids and derivatives	0.92825	0.10769	0.18209	lias;mccc2;dmgdh;amdhd1;kyat1;lipt2;bhmt2;txn2;protdh2;txnr1;pdhx;gcdh;ahcy;uoc1;aldh4a1;sardh;nqo1;hao1;gnmt;dlld;cdol1;bckdha;amd1;gm4737;aldh7a1	2749.40854	2981.91	84.5274	1675.36876	2767.1782	1542.25177	DOWN	0.32	0.68
90Day	Toll Like Receptor 10 (TLR10) Cascade	0.091835	0.96316	0.1821	mapk14;nfbkbia;ikbk;btcr	4070.33	3931.53	3265.56	831.881085	4282.38479	1027.24106	DOWN	0.25	0.75
90Day	Toll Like Receptor 5 (TLR5) Cascade	0.091835	0.96316	0.1821	mapk14;nfbkbia;ikbk;btcr	4070.33	3931.53	3265.56	831.881085	4282.38479	1027.24106	DOWN	0.25	0.75
90Day	MyD88 cascade initiated on plasma membrane	0.091835	0.96316	0.1821	mapk14;nfbkbia;ikbk;btcr	4070.33	3931.53	3265.56	831.881085	4282.38479	1027.24106	DOWN	0.25	0.75

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
28Day	Presynaptic phase of homologous DNA pairing and strand exchange	0.95693	0.11619	0.18286	rmi1;rad51d;rad51;brca1;blm	3513.5312	3769.36	692.086	1790.07678	3877.73216	1143.86555	UP	1	0
28Day	SIRT1 negatively regulates rRNA expression	0.089621	0.98286	0.1833	hist1h4i	5848.41	5848.41	5848.41		5848.41		DOWN	0	1
28Day	RNA Polymerase I Promoter Opening	0.089621	0.98286	0.1833	hist1h4i	5848.41	5848.41	5848.41		5848.41		DOWN	0	1
90Day	Cell junction organization	0.085615	0.96607	0.1837	arhgef6;afdn;ctnnb1;actn1	4037.9335	4700.81	797.214	2295.03793	4190.02407	2312.13407	DOWN	0.25	0.75
90Day	Transcriptional regulation by small RNAs	0.085615	0.96607	0.1837	hist1h4h;hist1h4i;hist1h3c;h2afx	3214.00725	3979.26	811.859	1602.37406	2298.31583	1843.92338	CONFLICT	0.5	0.5
90Day	MyD88-MAL(TIRAP) cascade initiated on plasma membrane	0.085615	0.96607	0.1837	mapk14;nfkbia;ikbk;g;trc	4070.33	3931.53	3265.56	831.881085	4282.38479	1027.24106	DOWN	0.25	0.75
90Day	Toll Like Receptor TLR1:TLR2 Cascade	0.085615	0.96607	0.1837	mapk14;nfkbia;ikbk;g;trc	4070.33	3931.53	3265.56	831.881085	4282.38479	1027.24106	DOWN	0.25	0.75
90Day	Toll Like Receptor TLR6:TLR2 Cascade	0.085615	0.96607	0.1837	mapk14;nfkbia;ikbk;g;trc	4070.33	3931.53	3265.56	831.881085	4282.38479	1027.24106	DOWN	0.25	0.75
90Day	Toll Like Receptor 2 (TLR2) Cascade	0.085615	0.96607	0.1837	mapk14;nfkbia;ikbk;g;trc	4070.33	3931.53	3265.56	831.881085	4282.38479	1027.24106	DOWN	0.25	0.75
90Day	Synthesis of DNA	0.085615	0.96607	0.1837	gins1;anapc10;pole4;orc6	3885.0525	4279.405	1127.6	1984.54106	4057.44037	1374.34774	UP	0.75	0.25
90Day	Senescence-Associated Secretory Phenotype (SASP)	0.093851	0.9558	0.18376	hist1h4h;anapc10;hist1h4i;hist1h3c;h2afx;cdkn1a	3026.7015	3979.26	811.859	1683.31454	1966.58137	1670.51904	UP	0.666666667	0.333333333
28Day	Cellular responses to external stimuli	0.087259	0.94296	0.18445	hikeshi;dynl1;gm45902;bxnd1;acd;hist1h4i;map2k4;tubb4b;tubb2a;cdc27;p4hb;mdm2;mapkapk2;gstp1;gstp2;rb1cc1;capza2;bmi1;atg5;tptr	4149.3983	4262.915	691.166	1621.85619	4028.34302	1775.09832	UP	0.7	0.3
90Day	UCH proteinases	0.088232	0.95884	0.18485	psmd8;mcrcs1;psmc4;psmf1;yy1;ino80c	2661.14467	2213.18	186.178	2068.27993	2538.39981	2012.24745	UP	0.833333333	0.166666667
28Day	Negative epigenetic regulation of rRNA expression	0.084622	0.98404	0.18522	hist1h4i	5848.41	5848.41	5848.41		5848.41		DOWN	0	1
28Day	Class B/2 (Secretin family receptors)	0.084622	0.98404	0.18522	gnb5	953.648	953.648	953.648		953.648		UP	1	0
7Day	Transport of bile salts and organic acids, metal ions and amine compounds	0.10361	0.95725	0.1854	slc5a3;slc39a2;slc22a12;slc22a1	4744.3375	4897.26	3194.01	1274.2061	4760.1461	1346.31062	UP	0.75	0.25
7Day	Deubiquitination	0.09411	0.94029	0.18561	usp16;babam1;tomm20;psmd5;psmd6;hist2h2ac;taf10;psmc4;ino80c;vdac3;vdac2;uba52;tgfb1;pten;psmc2;hist2h2aa1;cdc25a	3774.16353	3567.39	1811.97	1174.89537	3578.1711	1272.52603	UP	0.941176471	0.058823529
7Day	Metabolism of cofactors	0.94305	0.18638	0.18638	hsp90aa1;calm3;calm2	2990.83	3050.32	1005.61	1956.15357	2746.7427	1679.58489	UP	0.666666667	0.333333333
7Day	Interleukin-4 and Interleukin-13 signaling	0.94305	0.18638	0.18638	hsp90b1;stat1;jak1	3108.04333	3554.32	1852.94	1101.96366	3490.72292	752.388279	UP	1	0
7Day	SCF(Skp2)-mediated degradation of p27/p21	0.94305	0.18638	0.18638	uba52;cdkn1a;ccne2	4059.46	4598.19	2818.63	1077.69047	4059.31666	1056.86455	UP	1	0
7Day	PD-1 signaling	0.94305	0.18638	0.18638	ptpn11;h2-ab1;h2-aa	2584.69667	2261.36	1863.06	926.627041	2807.18587	946.421592	DOWN	0.333333333	0.666666667
7Day	Metabolism of nitric oxide	0.94305	0.18638	0.18638	hsp90aa1;calm3;calm2	2990.83	3050.32	1005.61	1956.15357	2746.7427	1679.58489	UP	0.666666667	0.333333333
7Day	eNOS activation and regulation	0.94305	0.18638	0.18638	hsp90aa1;calm3;calm2	2990.83	3050.32	1005.61	1956.15357	2746.7427	1679.58489	UP	0.666666667	0.333333333
7Day	Negative regulation of the PI3K/AKT network	0.10099	0.95162	0.18741	mapk3;ptpn11;pten;ppp2cb;il1rap;fgf1	3001.73567	3400.86	131.024	1575.82479	2859.8929	1611.80192	CONFLICT	0.5	0.5
28Day	Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3	0.079886	0.98515	0.18767	hist1h4i	5848.41	5848.41	5848.41		5848.41		DOWN	0	1
28Day	Mitochondrial Fatty Acid Beta-Oxidation	0.95193	0.12621	0.18828	echs1;ndufab1;acaa2;acsf2;acacdl	2448.3922	2777.52	802.301	1178.11057	1949.93558	1216.2426	DOWN	0	1
7Day	VEGFR2 mediated vascular permeability	0.95012	0.13186	0.1883	pak2;hsp90aa1;ctnnb1;calm3;calm2	2313.04264	2538.2	54.5232	1883.00734	2084.58132	1819.40898	UP	0.6	0.4
7Day	Negative regulation of FGFR1 signaling	0.95012	0.13186	0.1883	mapk3;uba52;ptpn11;ppp2cb;fgf1	3893.254	3629.67	2647.76	903.905503	3770.28016	910.359639	UP	0.6	0.4
7Day	Mitotic Spindle Checkpoint	0.091239	0.95697	0.18866	clasp2;cenpk;cdc27;ppp2cb;kif2a;xpo1	3765.72	3796.245	2692.16	665.945287	3744.07612	688.039984	UP	0.833333333	0.166666667
90Day	Cytochrome P450 - arranged by substrate type	0.93537	0.11094	0.1888	cyp4f16;cyp3a25;cyp39a1;cyp3a41a;cyp2c54;cyp4a12a;cyp4a12b;cyp2f2;cyp2e1;cyp2d9;cyp2c38;cyp2c37;cyp1a2;cyp2c69;cyp3a41b	2806.3334	3465.22	343.937	1513.9795	2787.20665	1535.91861	CONFLICT	0.466666667	0.533333333
28Day	Synthesis of (16-20)-hydroxyeicosatetraenoic acids (HETE)	0.94009	0.18894	0.18894	cyp4a12b;cyp2c37;cyp2c29	4357.50333	4766.57	2751.06	1445.97832	3990.66484	1430.78399	UP	0.666666667	0.333333333
28Day	Glycolysis	0.94009	0.18894	0.18894	pfkl;gpi1;bpgm	4249.99333	3997.94	3982.32	450.16425	4205.69128	429.005103	DOWN	0.333333333	0.666666667

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
7Day	Plasma lipoprotein assembly, remodeling, and clearance	0.93114	0.13498	0.19063	npc2;apoA5;angptl8;apob;pcsk5;ldlr;ce s3b;apoE;apoC1	3412.35067	3764.93	113.316	1492.73573	3725.10131	1001.45029	DOWN	0.222222222	0.777777778	
28Day	Electron transport from NADPH to Ferredoxin	0.98653	0.19214	0.19214	fdxr	5126.12	5126.12	5126.12		5126.12		DOWN	0	1	
28Day	Activation of BIM and translocation to mitochondria	0.98653	0.19214	0.19214	dynll1	5791.54	5791.54	5791.54		5791.54		UP	1	0	
28Day	MASTL Facilitates Mitotic Progression	0.98653	0.19214	0.19214	arpp19	2388.34	2388.34	2388.34		2388.34		UP	1	0	
28Day	VLDL assembly	0.98653	0.19214	0.19214	apob	939.205	939.205	939.205		939.205		DOWN	0	1	
28Day	Threonine catabolism	0.98653	0.19214	0.19214	sds	3285.87	3285.87	3285.87		3285.87		DOWN	0	1	
28Day	Activation of NIMA Kinases NEK9, NEK6, NEK7	0.98653	0.19214	0.19214	nek6	3203.61	3203.61	3203.61		3203.61		UP	1	0	
28Day	Progressive trimming of alpha-1,2-linked mannose residues from Man9/8/7GlcNAc2 to produce Man5GlcNAc2	0.98653	0.19214	0.19214	man1a	185.394	185.394	185.394		185.394		DOWN	0	1	
28Day	Formation of the active cofactor, UDP-glucuronate	0.98653	0.19214	0.19214	ugdh	950.22	950.22	950.22		950.22		UP	1	0	
28Day	Activation of AMPA receptors	0.98653	0.19214	0.19214	grin3	2052.57	2052.57	2052.57		2052.57		UP	1	0	
28Day	Interleukin-33 signaling	0.98653	0.19214	0.19214	il1rap	3705.51	3705.51	3705.51		3705.51		DOWN	0	1	
28Day	Abacavir transmembrane transport	0.98653	0.19214	0.19214	slc22a1	1681.65	1681.65	1681.65		1681.65		DOWN	0	1	
28Day	Hemostasis	0.092971	0.93424	0.19294	spp2;cdc37l1;ola1;f12;abcc4;apob;a2m;tubb4b;tubb2a;trf;tnfrsf10b;serpina1e;serpina1b;proc;pdpk1;itih4;cd74;gmb5;fn1;f7;f5;f2;clu;cdc42;capza2;serpinc1;app;anxa5;jmjd1c;qsox1	2816.87093	2683.265	192.988	1800.84791	2779.45146	1813.3181	DOWN	0.3	0.7	
90Day	Plasma lipoprotein remodeling	0.94517	0.14315	0.19329	apob;pcsk5;lpc;apoE;apoC3	2867.376	3093.17	175.96	2035.57627	3179.0703	1745.69841	DOWN	0	1	
90Day	DNA Replication	0.10062	0.94544	0.19574	gins1;anapc10;pole4;psmd8;orc6;dbf4;e2f2;psmc4;psmf1	3041.22978	3031.27	186.178	1836.77776	2813.06537	1625.4728	UP	0.888888889	0.111111111	
90Day	Signaling by Retinoic Acid	0.92322	0.14852	0.19668	rdh7;pdh4;adh4;aldh1a7;aldh8a1;pdh1;rxrg;rarg;rdh11	3921.77556	3345.98	2740.9	1196.95376	3809.69662	1289.44478	UP	0.666666667	0.333333333	
28Day	Beta-oxidation of very long chain fatty acids	0.95556	0.19722	0.19722	decr2;acox1	2334.455	2334.455	1680.03	925.496711	1994.69491	790.993253	DOWN	0	1	
28Day	Ethanol oxidation	0.95556	0.19722	0.19722	adh4;aldh2	2764.9895	2764.9895	541.929	3143.88231	4119.97938	2492.38858	DOWN	0	1	
28Day	Lysine catabolism	0.95556	0.19722	0.19722	phfklp;aldh7a1	3903.99	3903.99	3472.64	610.02102	4099.52937	543.741075	CONFLICT	0.5	0.5	
28Day	Triglyceride biosynthesis	0.95556	0.19722	0.19722	dgat2;agmo	1526.6865	1526.6865	163.973	1927.16791	2004.73883	1804.69059	DOWN	0	1	
28Day	IRAK1 recruits IKK complex	0.95556	0.19722	0.19722	ube2n;ikkg	5342.195	5342.195	5266.71	106.751911	5380.12192	92.2987948	CONFLICT	0.5	0.5	
28Day	IRAK1 recruits IKK complex upon TLR7/8 or 9 stimulation	0.95556	0.19722	0.19722	ube2n;ikkg	5342.195	5342.195	5266.71	106.751911	5380.12192	92.2987948	CONFLICT	0.5	0.5	
90Day	PIP3 activates AKT signaling	0.092371	0.94333	0.19731	klb;cbx6;irs2;gatad2b;vav1;tfga;nrg1;pml;mdm2;il1rap;hdac2;gab1;fgf1;cdkn1a;areg	2221.70409	2684.35	74.8133	1645.65734	2027.86438	1539.35228	CONFLICT	0.533333333	0.466666667	
7Day	CLEC7A (Dectin-1) signaling	0.93674	0.1376	0.19815	ube2n;pycard;uba52;cdc34;calm3;calm2;btrc	3732.51571	4207.06	1018.89	1389.83645	3794.07644	919.371398	UP	0.714285714	0.285714286	
90Day	ER to Golgi Anterograde Transport	0.10211	0.93999	0.19837	trappc6b;man1;tubb6;stx17;dctn3;tubb4b;tubb2a;tuba1b;tfga;serpina1e;areg;sec13	2832.3325	2460.705	779.791	1543.41316	2462.75302	1445.0997	UP	0.75	0.25	
90Day	Metabolism of nucleotides	0.91896	0.13468	0.19897	pnp2;dpys;nudt5;txnrd1;dnph1;gmpp;txn1;tk1;nudt15;nudt18;pnp;gsr;ak2;adk;atic	3374.46733	3373.77	1635.68	1137.4905	3268.62436	1121.40488	CONFLICT	0.466666667	0.533333333	
28Day	Homologous DNA Pairing and Strand Exchange	0.9409	0.14737	0.20118	rmi1;rad51d;rad51;brca1;blm	3513.5312	3769.36	692.086	1790.07678	3877.73216	1143.86555	UP	1	0	
7Day	C-type lectin receptors (CLRs)	0.91838	0.15494	0.20307	ube2n;pycard;pak2;uba52;cdc34;kras;calm3;calm2;btrc	3647.16889	4158.71	1018.89	1281.22729	3782.27281	889.831821	UP	0.777777778	0.222222222	
90Day	mRNA 3'-end processing	0.11871	0.95592	0.20355	cstf2t;srsf6;thoc7	5120.03333	5843.41	3549.69	1361.36044	5319.43866	1251.94412	UP	0.666666667	0.333333333	
90Day	Signaling by PDGF	0.11027	0.95966	0.20367	rasa1;sos1;plg	2899.14333	2133.64	668.86	2695.82055	4599.05845	2543.65	DOWN	0.333333333	0.666666667	
90Day	SHC1 events in EGFR signaling	0.93617	0.20368	0.20368	tfga;sos1;areg	4009.27667	3970.39	2162.51	1866.51383	3698.23096	2070.13409	UP	0.666666667	0.333333333	
90Day	GRB2:SOS provides linkage to MAPK signaling for Integrins	0.93617	0.20368	0.20368	tin1;sos1;fn1	4161.30667	4478.93	2110.06	1912.32154	4694.64696	1722.82421	DOWN	0	1	
90Day	RNA Polymerase I Transcription	0.10472	0.94716	0.20466	hist1h4h;hist1h4i;hist1h3c;gatad2b;h2afx;hdac2;cdk7	2761.40443	3141.48	202.162	1599.6023	1901.73792	1742.50078	UP	0.714285714	0.285714286	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.																
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down		
7Day	COP1-independent Golgi-to-ER retrograde traffic	0.92975	0.14939	0.2052	rab3gap2;tubb4b;tubb2a;tuba4a;rab6a;rab18;capza2	2923.54371	3113.17	919.856	1449.40793	2603.01544	1111.87275	UP	1	0		
7Day	MAPK1 (ERK2) activation	0.95455	0.20537	0.20537	ptpn11;jak1	3591.995	3591.995	3554.32	53.280496	3575.77052	48.086838	UP	1	0		
7Day	Interleukin-9 signaling	0.95455	0.20537	0.20537	stat1;jak1	3735.595	3735.595	3554.32	256.361564	3703.94	252.422609	UP	1	0		
7Day	TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest	0.95455	0.20537	0.20537	cdkn1a;ccne2	3708.41	3708.41	2818.63	1258.33894	3837.98107	1244.92553	UP	1	0		
7Day	CLEC7A (Dectin-1) induces NFAT activation	0.95455	0.20537	0.20537	calm3;calm2	3983.44	3983.44	3050.32	1319.63096	3556.9103	1173.69957	CONFLICT	0.5	0.5		
7Day	Inhibition of replication initiation of damaged DNA by RB1/E2F1	0.95455	0.20537	0.20537	prim2;ppp2cb	3816.59	3816.59	3627.04	268.064181	3678.94216	184.294737	UP	1	0		
7Day	E2F mediated regulation of DNA replication	0.95455	0.20537	0.20537	prim2;ppp2cb	3816.59	3816.59	3627.04	268.064181	3678.94216	184.294737	UP	1	0		
7Day	Calcineurin activates NFAT	0.95455	0.20537	0.20537	calm3;calm2	3983.44	3983.44	3050.32	1319.63096	3556.9103	1173.69957	CONFLICT	0.5	0.5		
7Day	Processing of Capped Intron-Containing Pre-mRNA	0.90921	0.13102	0.20801	sf3b1;sf3a3;gm49336;snrpa1;dnajc8;zcrb1;fip1l1;crnkl1;ppih;sf3b6;hnrrnpa2b1;cpsf2;prpf19;polr2h;pcbp1;hnrrnpul1;prpf38a;zrsr2;snrpc;hnrrnpc;dhx9;srsf1;tpc;csf2;thoc5;snrpd2;sf3b3	3697.14907	3546.09	730.51	1304.08807	3486.45432	1271.82731	UP	0.962962963	0.037037037		
7Day	Negative regulation of FGFR2 signaling	0.93404	0.16225	0.20853	mapk3;uba52;ptpn11;ppp2cb;fgf1	3893.254	3629.67	2647.76	903.905503	3770.28016	910.359639	UP	0.6	0.4		
90Day	Signaling by FGFR	0.099793	0.95561	0.21093	hnmpf;klb;sos1;gab1;fgf1	2651.3294	3142.57	126.428	2468.68877	3600.8558	2042.44758	DOWN	0	1		
90Day	APC/C-mediated degradation of cell cycle proteins	0.099793	0.95561	0.21093	anapc10;psmd8;psmc4;psmf1;btrc	2831.1416	3031.27	186.178	2056.6518	2996.10829	2201.76413	UP	0.8	0.2		
90Day	Regulation of mitotic cell cycle	0.099793	0.95561	0.21093	anapc10;psmd8;psmc4;psmf1;btrc	2831.1416	3031.27	186.178	2056.6518	2996.10829	2201.76413	UP	0.8	0.2		
7Day	Interferon gamma signaling	0.93088	0.21151	0.21151	stat1;jak1;ifng	3909.44667	3916.87	3554.32	351.473799	3908.88068	370.332739	UP	1	0		
7Day	Platelet sensitization by LDL	0.93088	0.21151	0.21151	apob;ptpn11;ppp2cb	3085.30667	3627.04	1999.21	940.588224	3396.69474	696.103131	UP	0.666666667	0.333333333		
90Day	Metabolism of steroids	0.10327	0.9421	0.21231	osbpl3;cyp39a1;slc27a5;slc27a2;scap;slc10a1;amacr;hsd17b7;hsd11b1;osbpl9	3496.525	3510.085	263.79	1503.34531	3683.98216	1384.69135	DOWN	0.1	0.9		
90Day	Activation, translocation and oligomerization of BAX	0.98731	0.21268	0.21268	bax	1844.96	1844.96	1844.96		1844.96		UP	1	0		
90Day	RUNX2 regulates osteoblast differentiation	0.98731	0.21268	0.21268	ar	1998.95	1998.95	1998.95		1998.95		DOWN	0	1		
90Day	TICAM1-dependent activation of IRF3/IRF7	0.98731	0.21268	0.21268	irf7	5689.7	5689.7	5689.7		5689.7		UP	1	0		
90Day	Signaling by NOTCH4	0.98731	0.21268	0.21268	ywhaz	137.958	137.958	137.958		137.958		UP	1	0		
90Day	Biosynthesis of DHA-derived sulfido conjugates	0.98731	0.21268	0.21268	gstm4	793.669	793.669	793.669		793.669		UP	1	0		
90Day	Biosynthesis of maresin conjugates in tissue regeneration (MCTR)	0.98731	0.21268	0.21268	gstm4	793.669	793.669	793.669		793.669		UP	1	0		
90Day	Interleukin-37 signaling	0.98731	0.21268	0.21268	tbk1	1058.39	1058.39	1058.39		1058.39		DOWN	0	1		
90Day	NOTCH4 Activation and Transmission of Signal to the Nucleus	0.98731	0.21268	0.21268	ywhaz	137.958	137.958	137.958		137.958		UP	1	0		
90Day	mRNA Editing: A to I Conversion	0.98731	0.21268	0.21268	adar	5667.94	5667.94	5667.94		5667.94		UP	1	0		
90Day	C6 deamination of adenosine	0.98731	0.21268	0.21268	adar	5667.94	5667.94	5667.94		5667.94		UP	1	0		
90Day	Formation of editosomes by ADAR proteins	0.98731	0.21268	0.21268	adar	5667.94	5667.94	5667.94		5667.94		UP	1	0		
90Day	Synthesis of bile acids and bile salts via 24-hydroxycholesterol	0.98731	0.21268	0.21268	cyp39a1	4130.84	4130.84	4130.84		4130.84		DOWN	0	1		
90Day	DNA Damage Reversal	0.98731	0.21268	0.21268	fto	4107.48	4107.48	4107.48		4107.48		DOWN	0	1		
90Day	Reversal of alkylation damage by DNA dioxygenases	0.98731	0.21268	0.21268	fto	4107.48	4107.48	4107.48		4107.48		DOWN	0	1		
90Day	Biosynthesis of protectins	0.98731	0.21268	0.21268	cyp1a2	928.37	928.37	928.37		928.37		DOWN	0	1		
90Day	Toll Like Receptor 7/8 (TLR7/8) Cascade	0.093526	0.95884	0.21303	irf7;mapk14;nfbk1a;ikbkj;btrc	4394.204	4261.96	3265.56	1021.51429	4535.14678	1084.60939	DOWN	0.4	0.6		
90Day	MyD88 dependent cascade initiated on endosome	0.093526	0.95884	0.21303	irf7;mapk14;nfbk1a;ikbkj;btrc	4394.204	4261.96	3265.56	1021.51429	4535.14678	1084.60939	DOWN	0.4	0.6		
7Day	Cell-Cell communication	0.10563	0.95226	0.21434	vasp;flna;prkci;dst;ctnnb1	2974.30464	3409.24	54.5232	1777.63271	2180.24458	1910.18083	DOWN	0.4	0.6		
7Day	Amplification of signal from the kinetochores	0.10563	0.95226	0.21434	clasp2;cenok;ppp2cb;kif2a;xpo1	3744.748	3721.91	2692.16	742.330938	3727.2524	745.446361	UP	0.8	0.2		

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
7Day	Amplification of signal from unattached kinetochores via a MAD2 inhibitory signal	0.10563	0.95226	0.21434	clasp2;cenpk;ppp2cb;kif2a;xpo1	3744.748	3721.91	2692.16	742.330938	3727.2524	745.446361	UP	0.8	0.2	
28Day	COPI-dependent Golgi-to-ER retrograde traffic	0.11023	0.95899	0.21436	tubb4b;tubb2a;gbf1	3055.26667	2903.04	2359.45	783.106406	3042.68001	716.360849	UP	1	0	
28Day	Amplification of signal from the kinetochores	0.10086	0.96313	0.2165	zwilch;dynll1;cenpt	4305.88	3567.21	3558.89	1286.62603	4367.29213	1311.47892	UP	1	0	
28Day	Amplification of signal from unattached kinetochores via a MAD2 inhibitory signal	0.10086	0.96313	0.2165	zwilch;dynll1;cenpt	4305.88	3567.21	3558.89	1286.62603	4367.29213	1311.47892	UP	1	0	
28Day	Factors involved in megakaryocyte development and platelet production	0.11435	0.94722	0.21899	tubb4b;tubb2a;cdc42;capza2;jmjd1c	3799.026	2903.04	2359.45	1693.79969	3661.99495	1616.51991	UP	0.8	0.2	
7Day	Downstream TCR signaling	0.92499	0.17841	0.22031	ube2n;uba52;cdc34;pten;btrc	3321.396	3444.79	1018.89	1431.49909	3660.16961	864.444638	UP	1	0	
7Day	Retinoid metabolism and transport	0.91443	0.17431	0.22168	akr1c6;apob;ttr;sd3c3;lrp1;apoe;akr1c14	2956.06943	2842.81	113.316	1991.38668	3428.01601	1609.42615	DOWN	0.285714286	0.714285714	
7Day	HSP90 chaperone cycle for steroid hormone receptors (SHR)	0.91443	0.17431	0.22168	ptges3;tubb4b;tubb2a;tuba4a;stip1;hs p90aa1;capza2	1845.66129	1815.66	832.843	994.072057	1943.38865	1033.81072	UP	1	0	
28Day	Cell Cycle Checkpoints	0.10243	0.94208	0.2223	ube2n;ube2v2;zwilch;dynll1;cenpt;hist 1h4i;cdc6;cdc27;mdm2;brca1	4687.953	5455.01	2266.61	1364.22395	4423.32685	1463.98901	UP	0.8	0.2	
28Day	TRAF6 mediated NF-kB activation	0.9451	0.22309	0.22309	ikbk;app	5024.075	5024.075	4630.47	556.641529	5107.68148	543.939064	CONFLICT	0.5	0.5	
7Day	Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by uncoupling proteins.	0.92108	0.14606	0.22325	ndufaf1;ndufaf4;ndufc2;coq10b;ndufa 13;ndufa6;ndufa1;ecsi1;ndufa2;atp5j	3927.71	3976.805	2874.39	629.628907	3777.78755	683.205285	UP	0.6	0.4	
90Day	Regulation of RUNX1 Expression and Activity	0.94825	0.22531	0.22531	pml;cbfb	3837.085	3837.085	3603.58	330.225938	3844.42156	330.062903	CONFLICT	0.5	0.5	
90Day	Glutathione synthesis and recycling	0.94825	0.22531	0.22531	gclm;gclc	1985.395	1985.395	1419.33	800.5368	1562.90234	532.784267	UP	1	0	
90Day	SUMOylation of immune response proteins	0.94825	0.22531	0.22531	nfkbia;ikbk	3433.33	3433.33	3265.56	237.262609	3311.77597	163.5322	CONFLICT	0.5	0.5	
90Day	SUMOylation of ubiquitylation proteins	0.94825	0.22531	0.22531	pml;mdm2	3569.33	3569.33	3535.08	48.4368145	3563.16871	47.6466363	CONFLICT	0.5	0.5	
90Day	PLC beta mediated events	0.13279	0.95854	0.22653	camkk2;gna13	3000.5391	3000.5391	98.0082	4104.79856	1735.98836	3694.75224	CONFLICT	0.5	0.5	
90Day	Transport of vitamins, nucleosides, and related molecules	0.13279	0.95854	0.22653	slc29a1;slco2b1	1533.815	1533.815	1131.79	568.549207	1533.23698	568.54862	DOWN	0	1	
90Day	Antigen processing-Cross presentation	0.13279	0.95854	0.22653	tap2;snap23	2434.48	2434.48	544.33	2673.07576	3329.02624	2354.76285	CONFLICT	0.5	0.5	
90Day	Chromosome Maintenance	0.13279	0.95854	0.22653	cenpu;pole4	5799.32	5799.32	5744.84	77.0463549	5758.04583	50.2894335	CONFLICT	0.5	0.5	
90Day	TP53 Regulates Transcription of DNA Repair Genes	0.13279	0.95854	0.22653	elo4;cdk7	4445.455	4445.455	3130.16	1860.10803	4242.37403	1837.80252	UP	1	0	
90Day	Intra-Golgi traffic	0.12248	0.96249	0.22688	stx16;man1a	4890.04	4890.04	3931.46	1355.63684	5316.32153	1214.21552	CONFLICT	0.5	0.5	
90Day	Amine ligand-binding receptors	0.12248	0.96249	0.22688	gpr143;adra1b	3750.25	3750.25	2444.64	1846.41137	4324.10338	1658.49919	CONFLICT	0.5	0.5	
90Day	G-protein mediated events	0.12248	0.96249	0.22688	camkk2;gna13	3000.5391	3000.5391	98.0082	4104.79856	1735.98836	3694.75224	CONFLICT	0.5	0.5	
90Day	Switching of origins to a post-replicative state	0.12248	0.96249	0.22688	anapc10;orc6	4279.405	4279.405	4168.34	157.069629	4206.79823	118.858666	UP	1	0	
90Day	Ca2+ pathway	0.11288	0.96608	0.22858	gng11;ctnnb1	4470.64	4470.64	4087.04	542.492323	4551.11456	530.420221	CONFLICT	0.5	0.5	
90Day	Retrograde transport at the Trans-Golgi-Network	0.11288	0.96608	0.22858	scoc;stx16	5406.6	5406.6	4964.58	625.110679	5352.02708	620.328102	UP	1	0	
7Day	TNFR2 non-canonical NF-kB pathway	0.12015	0.96305	0.23207	uba52;btrc	4484.31	4484.31	4207.06	392.09071	4446.04923	388.339223	UP	1	0	
28Day	Membrane Trafficking	0.11555	0.91595	0.23273	pacs1n3;trappc8;vps36;ubap1;lman2;dynll1;rab9;rab11a;vps37a;ppp6r3;apob; picalm;tmf1;dennd1a;tubb4b;tubb2a;trf;sec22c;serpina1e;serpina1b;rab18; man1a;hgs;hbegf;ftl1;f5;cux1;capza2;b et1;app;gbf1;tbc1d10a	3387.70891	3377.52	185.394	1580.83635	3222.84678	1602.16108	CONFLICT	0.46875	0.53125	
7Day	Downstream signaling events of B Cell Receptor (BCR)	0.91527	0.19513	0.23307	uba52;kras;calm3;calm2;btrc	4218.842	4207.06	3050.32	733.237951	3970.29285	823.83106	UP	0.8	0.2	
90Day	Sphingolipid metabolism	0.12672	0.93737	0.23409	ormdl2;ppm1l;acer2;sptlc2;psap;gm2a	3886.44667	3669.21	3112.61	842.476455	3660.64044	555.904205	CONFLICT	0.5	0.5	
90Day	MyD88-independent TLR4 cascade	0.12672	0.93737	0.23409	tbk1;irf7;mapk14;nfkbia;ikbk;btrc	3838.235	3931.53	1058.39	1639.93973	3671.64014	1885.92371	DOWN	0.333333333	0.666666667	
90Day	TRIF(TICAM1)-mediated TLR4 signaling	0.12672	0.93737	0.23409	tbk1;irf7;mapk14;nfkbia;ikbk;btrc	3838.235	3931.53	1058.39	1639.93973	3671.64014	1885.92371	DOWN	0.333333333	0.666666667	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.														
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
90Day	Mitochondrial translation termination	0.12672	0.93737	0.23409	mrpl58;mrps18b;mrpl54;mrps30;mrps31;mrpl22	3388.1725	3632.435	958.825	1571.32063	3043.1093	1692.27602	UP	0.666666667	0.333333333
90Day	Mitochondrial translation	0.11947	0.94153	0.23465	mrpl58;mrps18b;mrpl54;mrps30;mrps31;mrpl22	3388.1725	3632.435	958.825	1571.32063	3043.1093	1692.27602	UP	0.666666667	0.333333333
90Day	DDX58/IFIH1-mediated induction of interferon-alpha/beta	0.91244	0.20178	0.23678	tbbk1;jrf7;pin1;nfkbia;ikbkg	3712.49	3601.1	1058.39	1781.25687	3302.05123	1944.70221	UP	0.6	0.4
28Day	Loss of Nlp from mitotic centrosomes	0.1318	0.95811	0.23725	dynl1;tubb4b	4075.495	4075.495	2359.45	2426.85411	4561.33816	2327.55961	UP	1	0
28Day	Loss of proteins required for interphase microtubule organization from the centrosome	0.1318	0.95811	0.23725	dynl1;tubb4b	4075.495	4075.495	2359.45	2426.85411	4561.33816	2327.55961	UP	1	0
7Day	Beta-catenin phosphorylation cascade	0.91748	0.23731	0.23731	gsk3b;ppp2cb;ctnnb1	2727.00107	3627.04	54.5232	2355.18023	2722.70432	2279.08261	UP	0.666666667	0.333333333
7Day	PKA-mediated phosphorylation of CREB	0.91748	0.23731	0.23731	prkar2a;calm3;calm2	4011.14667	4066.56	3050.32	934.353205	3661.3101	940.743026	DOWN	0.333333333	0.666666667
7Day	PKA activation	0.91748	0.23731	0.23731	prkar2a;calm3;calm2	4011.14667	4066.56	3050.32	934.353205	3661.3101	940.743026	DOWN	0.333333333	0.666666667
7Day	Processing of Intronless Pre-mRNAs	0.91748	0.23731	0.23731	fip1l1;cpsf2;ctsf2	4141.64667	3485.7	3207.13	1384.4062	3620.26137	835.420177	UP	1	0
28Day	Transcriptional regulation by small RNAs	0.1256	0.96054	0.23773	hist1h4;polr2a	5444.54	5444.54	5040.67	571.158431	5494.50555	566.770537	CONFLICT	0.5	0.5
28Day	Visual phototransduction	0.90524	0.16834	0.23838	akr1c6;akr1c12;akr1c19;apob;rdh16f2;rp1;gpc4;gnb5;apoe;akr1c14	3006.0593	2943.305	939.205	1587.10521	2423.77594	1397.55687	DOWN	0.3	0.7
90Day	DNA Double Strand Break Response	0.13803	0.94026	0.23848	hist1h4h;babam1;hist1h4i;h2afx	4461.0475	4046.18	3951.81	894.337005	4412.91487	861.771604	CONFLICT	0.5	0.5
90Day	PKMTs methylate histone lysines	0.13803	0.94026	0.23848	hist1h4h;atf7ip;hist1h4i;hist1h3c	2231.928	2381.8345	157.333	2035.38576	1872.37212	1795.00472	DOWN	0.25	0.75
90Day	SUMOylation of DNA damage response and repair proteins	0.13803	0.94026	0.23848	eid3;nup153;pml;sec13	3722.275	3641.965	2758.9	857.768881	3705.18542	766.87462	UP	0.75	0.25
90Day	PRC2 methylates histones and DNA	0.12082	0.94904	0.23937	hist1h4h;hist1h4i;hist1h3c;h2afx	3214.00725	3979.26	811.859	1602.37406	2298.31583	1843.92338	CONFLICT	0.5	0.5
90Day	Peptide hormone metabolism	0.12082	0.94904	0.23937	exoc4;mme;inhbc;ctsd	3065.9275	3132.445	2113.16	888.35815	2926.2467	859.013936	CONFLICT	0.5	0.5
90Day	Interferon Signaling	0.12082	0.94904	0.23937	usp18;abce1;ifngr2;ifnar1	2843.26675	3524.105	250.557	1794.46997	2303.69065	1986.68488	CONFLICT	0.5	0.5
28Day	AURKA Activation by TPX2	0.11397	0.96499	0.24014	dynl1;tubb4b	4075.495	4075.495	2359.45	2426.85411	4561.33816	2327.55961	UP	1	0
90Day	Axon guidance	0.13038	0.90883	0.24071	tubb6;pdlim7;ranbp9;irs2;mapk14;tubb4b;tubb2a;tuba1b;tln1;tiam1;rasa1;sos1;shah2;rock2;rock1;myo9b;msn;mmr2;hsp90aa1;gfra1;gab1;cdc42;ap2m1;itga9	2507.8766	2042.325	74.8133	1994.3986	2237.08825	2109.80424	CONFLICT	0.416666667	0.583333333
7Day	Nucleotide Excision Repair	0.11161	0.94567	0.24099	ube2n;ube2v2;prpf19;polr2h;ino80c;uba52	3622.83333	3704.695	2423.08	931.684013	3428.72673	879.959361	UP	1	0
90Day	Protein-protein interactions at synapses	0.11292	0.95298	0.24116	grisa3;ptprd;il1rap;epb41l1	2755.46	3045.76	1097.82	1202.43754	2533.97991	1186.68048	CONFLICT	0.5	0.5
90Day	Signaling by FGFR2	0.11292	0.95298	0.24116	hnrmpf;sos1;gab1;fgf1	2351.58925	1692.4995	126.428	2743.52655	3545.54798	2326.77262	DOWN	0	1
7Day	AKT phosphorylates targets in the cytosol	0.9395	0.24158	0.24158	cdkn1a;casp9	3233.65	3233.65	2818.63	586.926913	3260.0846	585.735115	CONFLICT	0.5	0.5
7Day	Golgi Cisternae Pericentriolar Stack Reorganization	0.9395	0.24158	0.24158	mapk3;rab1a	4176.96	4176.96	3553.68	881.451029	4087.79673	872.385087	CONFLICT	0.5	0.5
7Day	Degradation of cysteine and homocysteine	0.9395	0.24158	0.24158	txn2;cdo1	4345.35	4345.35	3081.26	1787.69322	3978.15605	1710.60932	CONFLICT	0.5	0.5
7Day	Interleukin-21 signaling	0.9395	0.24158	0.24158	stat1;jak1	3735.595	3735.595	3554.32	256.361564	3703.94	252.422609	UP	1	0
7Day	Degradation of DVL	0.9395	0.24158	0.24158	klhl12;uba52	4314.45	4314.45	3867.34	632.309026	4328.76951	631.984657	UP	1	0
28Day	Opioid Signalling	0.10853	0.96703	0.24204	gnb5;adcy9	2587.124	2587.124	953.648	2310.08391	1477.92173	1695.82674	CONFLICT	0.5	0.5
7Day	RNA Polymerase II Pre-transcription Events	0.12966	0.9442	0.2431	wdr61;polr2h;taf10;ccnk	3345.3475	3655.495	2105.8	873.384665	3595.5247	673.466686	UP	1	0
90Day	Resolution of Sister Chromatid Cohesion	0.1177	0.93478	0.24335	cenpu;tubb6;tubb4b;tubb2a;tuba1b;kntc1;nudc;sec13;cenpf	2740.46122	2758.9	779.791	1433.75598	2870.13302	1732.48579	UP	0.888888889	0.111111111
28Day	CLEC7A (Dectin-1) signaling	0.90725	0.20603	0.24368	ube2n;ube2m;ppp3cb;pdpk1;ikbkg	3581.4416	4095.87	192.988	2143.44278	3918.11922	1510.6886	UP	0.6	0.4
7Day	Global Genome Nucleotide Excision Repair (GG-NER)	0.12267	0.94776	0.24392	ube2n;ube2v2;ino80c;uba52	3763.1175	3933.915	2423.08	1053.47331	3364.60196	1010.9153	UP	1	0
28Day	Plasma lipoprotein remodeling	0.91171	0.24406	0.24406	lmf1;apob;apoe	2386.61833	3007.97	939.205	1257.6687	1733.49809	1264.85386	DOWN	0	1
90Day	Acyl chain remodelling of PG	0.14742	1	0.24444										
90Day	CRMPs in Sema3A signaling	0.14742	1	0.24444										
90Day	PKA activation in glucagon signalling	0.14742	1	0.24444										
7Day	Recruitment of mitotic centrosome proteins and complexes	0.11601	0.95112	0.24535	tubb4b;tuba4a;nedd1;hsp90aa1	1703.9565	1410.635	919.856	998.985626	1609.23265	1031.31055	UP	1	0
7Day	Centrosome maturation	0.11601	0.95112	0.24535	tubb4b;tuba4a;nedd1;hsp90aa1	1703.9565	1410.635	919.856	998.985626	1609.23265	1031.31055	UP	1	0
90Day	DAG and IP3 signaling	0.14573	0.96896	0.24614	camkk2	98.0082	98.0082	98.0082		98.0082		DOWN	0	1

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
90Day	Negative regulation of FGFR1 signaling	0.14573	0.96896	0.24614	fgf1	242.429	242.429	242.429		242.429		DOWN	0	1	
90Day	Ovarian tumor domain proteases	0.14573	0.96896	0.24614	ikbk	3265.56	3265.56	3265.56		3265.56		UP	1	0	
90Day	Recognition of DNA damage by PCNA-containing replication complex	0.14573	0.96896	0.24614	pole4	5853.8	5853.8	5853.8		5853.8		DOWN	0	1	
90Day	Nicotinate metabolism	0.14573	0.96896	0.24614	nmnat3	640.772	640.772	640.772		640.772		DOWN	0		
90Day	HS-GAG biosynthesis	0.14573	0.96896	0.24614	sdcc4	630.216	630.216	630.216		630.216		DOWN	0	1	
90Day	mRNA Capping	0.14573	0.96896	0.24614	cdk7	3130.16	3130.16	3130.16		3130.16		UP	1	0	
90Day	RNA Polymerase I Promoter Escape	0.14573	0.96896	0.24614	cdk7	3130.16	3130.16	3130.16		3130.16		UP	1	0	
7Day	Degradation of beta-catenin by the destruction complex	0.90489	0.21238	0.24673	gsk3b;uba52;ppp2cb;ctnnb1;btrc	3429.92464	4207.06	54.5232	1933.47127	3287.62365	1938.69249	UP	0.8	0.2	
	Formation of Senescence-Associated Heterochromatin Foci (SAHF)	0.13078	1	0.24688											
90Day	Translesion Synthesis by POLH	0.13078	1	0.24688											
90Day	ABC transporters in lipid homeostasis	0.13078	1	0.24688											
90Day	Synthesis, secretion, and deacylation of Ghrelin	0.13078	1	0.24688											
90Day	Activation of SMO	0.13078	1	0.24688											
90Day	Regulation of TNFR1 signaling	0.13278	0.97247	0.24697	ikbk	3265.56	3265.56	3265.56		3265.56		UP	1	0	
90Day	DAP12 signaling	0.13278	0.97247	0.24697	sos1	5894.93	5894.93	5894.93		5894.93		DOWN	0	1	
90Day	MET activates PTK2 signaling	0.13278	0.97247	0.24697	fn1	2110.06	2110.06	2110.06		2110.06		DOWN	0	1	
90Day	Inwardly rectifying K+ channels	0.13278	0.97247	0.24697	kcnj8	2260.22	2260.22	2260.22		2260.22		UP	1	0	
90Day	RNA Polymerase I Transcription Termination	0.13278	0.97247	0.24697	cdk7	3130.16	3130.16	3130.16		3130.16		UP	1	0	
90Day	Ca-dependent events	0.13278	0.97247	0.24697	camkk2	98.0082	98.0082	98.0082		98.0082		DOWN	0	1	
7Day	HDACs deacetylate histones	0.10966	0.95428	0.24738	hist1h4h;hist1h2bc;hist2h2ac;hist2h2aa1	4100.405	3802.835	3406.55	933.741438	4060.85571	1011.0164	CONFLICT	0.5	0.5	
28Day	Release of apoptotic factors from the mitochondria	0.97428	0.24762	0.24762		211.182	211.182	211.182		211.182		UP	1	0	
28Day	Mitochondrial ABC transporters	0.97428	0.24762	0.24762	abcb8	3799.52	3799.52	3799.52		3799.52		UP	1	0	
28Day	Axonal growth stimulation	0.97428	0.24762	0.24762	arhgdia	4971.84	4971.84	4971.84		4971.84		UP	1	0	
28Day	The NLRP1 inflammasome	0.97428	0.24762	0.24762	bcl2l1	2151.36	2151.36	2151.36		2151.36		UP	1	0	
28Day	Biquinol biosynthesis	0.97428	0.24762	0.24762	coq3	1252.61	1252.61	1252.61		1252.61		DOWN	0	1	
28Day	Alternative complement activation	0.97428	0.24762	0.24762	c3	2572.88	2572.88	2572.88		2572.88		DOWN	0	1	
28Day	mRNA Editing: C to U Conversion	0.97428	0.24762	0.24762	a1cf	1306.69	1306.69	1306.69		1306.69		DOWN	0	1	
28Day	Formation of the Editosome	0.97428	0.24762	0.24762	a1cf	1306.69	1306.69	1306.69		1306.69		DOWN	0	1	
28Day	Conjugation of benzoate with glycine	0.97428	0.24762	0.24762	glyat	3673.59	3673.59	3673.59		3673.59		UP	1	0	
28Day	Selenoamino acid metabolism	0.97428	0.24762	0.24762	txnrd1	3178.52	3178.52	3178.52		3178.52		UP	1	0	
28Day	Activation of AKT2	0.97428	0.24762	0.24762	pdprk1	192.988	192.988	192.988		192.988		DOWN	0	1	
28Day	Fructose catabolism	0.97428	0.24762	0.24762	khk	3680.34	3680.34	3680.34		3680.34		DOWN	0	1	
28Day	Reuptake of GABA	0.97428	0.24762	0.24762	slc6a13	151.142	151.142	151.142		151.142		DOWN	0	1	
28Day	Synthesis of IP3 in the nucleus	0.97428	0.24762	0.24762	iprk	4371.1	4371.1	4371.1		4371.1		UP	1	0	
28Day	Scavenging by Class H Receptors	0.97428	0.24762	0.24762	apob	939.205	939.205	939.205		939.205		DOWN	0	1	
28Day	Transport of inorganic cations/anions and amino acids/oligopeptides	0.13846	0.93913	0.24877	slc9a5;slc25a10;slc17a8;slc1a2	2877.15	3000.365	1774.78	987.277084	3012.78763	996.593412	UP	0.75	0.25	
28Day	Formation of ATP by chemiosmotic coupling	0.93357	0.2492	0.2492	atp5g2;atp5j2	5554.105	5554.105	5480.89	103.541646	5551.28634	103.464887	CONFLICT	0.5	0.5	
28Day	Cristae formation	0.93357	0.2492	0.2492	atp5g2;atp5j2	5554.105	5554.105	5480.89	103.541646	5551.28634	103.464887	CONFLICT	0.5	0.5	
28Day	TP53 Regulates Transcription of Cell Death Genes	0.93357	0.2492	0.2492	tmem219;bnip3l	3715.515	3715.515	1841.2	2650.68169	2387.84735	1871.01861	DOWN	0	1	
28Day	Synthesis of PIPs at the Golgi membrane	0.93357	0.2492	0.2492	pi4k2b;pi4ka	4418.385	4418.385	4173.55	346.248978	4399.97266	345.268484	CONFLICT	0.5	0.5	
28Day	Microtubule-dependent trafficking of connexons from Golgi to the plasma membrane	0.93357	0.2492	0.2492	tubb4b;tubb2a	2631.245	2631.245	2359.45	384.376175	2702.45657	370.948608	UP	1	0	
28Day	Methylation	0.93357	0.2492	0.2492	ahcy;gm4737	2386.29	2386.29	2114.57	384.270109	2337.94463	378.13882	DOWN	0	1	
7Day	G beta-gamma signalling through PLC beta	0.15225	1	0.24933											
7Day	RHO GTPases Activate NADPH Oxidases	0.15225	1	0.24933											

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.														
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
90Day	Activation of kainate receptors upon glutamate binding	0.12089	0.97558	0.24976	gng11	4854.24	4854.24	4854.24		4854.24		UP	1	0
90Day	Neurexins and neuroligins	0.12089	0.97558	0.24976	epb41l1	3832.5	3832.5	3832.5		3832.5		UP	1	0
90Day	Transferrin endocytosis and recycling	0.12089	0.97558	0.24976	trf	368.457	368.457	368.457		368.457		DOWN	0	1
90Day	Negative regulation of FGFR2 signaling	0.12089	0.97558	0.24976	fgf1	242.429	242.429	242.429		242.429		DOWN	0	1
90Day	Glucagon signaling in metabolic regulation	0.12089	0.97558	0.24976	gng11	4854.24	4854.24	4854.24		4854.24		UP	1	0
90Day	Thrombin signalling through proteinase activated receptors (PARs)	0.12089	0.97558	0.24976	gng11	4854.24	4854.24	4854.24		4854.24		UP	1	0
90Day	Disassembly of the destruction complex and recruitment of AXIN to the membrane	0.12089	0.97558	0.24976	ctnnb1	4087.04	4087.04	4087.04		4087.04		DOWN	0	1
90Day	Formation of the Early Elongation Complex	0.12089	0.97558	0.24976	cdk7	3130.16	3130.16	3130.16		3130.16		UP	1	0
90Day	Smooth Muscle Contraction	0.12089	0.97558	0.24976	tlr1	4478.93	4478.93	4478.93		4478.93		DOWN	0	1
28Day	Negative regulation of the PI3K/AKT network	0.12292	0.94719	0.25016	phlpp1;il1rap;hbegf;fgf1	2439.9445	2567.265	919.738	1456.45266	2065.97653	1370.40565	DOWN	0.25	0.75
7Day	Cell Cycle	0.12597	0.90428	0.25054	ube2n;clasp2;gm49336;pds5a;ube2v2;rnf168;hist1h4h;babam1;hist1h2bc;km15a;psmd5;psmd6;cenpk;nek6;arpp19;hist2h2ac;gtse1;mapk3;cop1;psmc4;tu1bb4b;whaz;uba52;tubb2a;tuba4a;tfdp1;cdc27;rab1a;psmc2;prim2;ppp2cb;nedd1;kif2a;hsp90aa1;hist2h2aa1;cdkn1a	3338.35543	3521.41	707.264	1210.81998	3295.05526	1159.72514	UP	0.880952381	0.119047619
7Day	Presynaptic function of Kainate receptors	0.13787	1	0.25062	cdc25a;cne2;btrc;abl1;tpr;ppo1									
7Day	Phase I - Functionalization of compounds	0.90818	0.14317	0.25084	bphl;cyp3a25;ptges3;cyp39a1;ces2c;nqo2;ncoa2;ncoa1;ces3b;cyp3a11;cyp2e1;cyp2c37;cyp2c29;arnt;aldh2;maob;ces2a;cyp3a41b	2586.41444	3125.9	46.9364	1865.00344	2351.21285	1793.97063	DOWN	0.388888889	0.611111111
7Day	Platelet Aggregation (Plug Formation)	0.13406	0.97184	0.25186	f2	156.627	156.627	156.627		156.627		DOWN	0	1
90Day	Regulation of PTEN stability and activity	0.11601	1	0.25267										
90Day	Signaling by NOTCH1	0.11601	1	0.25267										
90Day	Nicotinamide salvaging	0.11601	1	0.25267										
90Day	DARPP-32 events	0.11601	1	0.25267										
90Day	Ephrin signaling	0.11601	1	0.25267										
90Day	PKA-mediated phosphorylation of CREB	0.11601	1	0.25267										
90Day	PKA activation	0.11601	1	0.25267										
28Day	Mitotic Spindle Checkpoint	0.11341	0.95201	0.25268	zwilch;dynll1;cenpt;cdc27	4674.6	4673.985	3558.89	1283.51942	4611.45147	1282.74646	UP	1	0
28Day	Formation of the cornified envelope	0.11341	0.95201	0.25268	pkp4;pkp1;krt8;krt18	2676.64925	2807.215	856.847	1425.57491	2794.74322	1223.74793	UP	1	0
28Day	COPI-independent Golgi-to-ER retrograde traffic	0.89949	0.2186	0.25364	dynll1;tubb4b;tubb2a;rab18;capza2	4334.282	5180.95	2359.45	1581.42285	4391.93484	1559.12644	UP	0.6	0.4
7Day	Adherens junctions interactions	0.12406	0.9745	0.25412	ctnnb1	54.5232	54.5232	54.5232		54.5232		DOWN	0	1
7Day	O-glycosylation of TSR domain-containing proteins	0.12406	0.9745	0.25412	adamts7	3416.43	3416.43	3416.43		3416.43		DOWN	0	1
7Day	HDR through Single Strand Annealing (SSA)	0.12406	0.9745	0.25412	abl1	3368.05	3368.05	3368.05		3368.05		DOWN	0	1
7Day	Translesion synthesis by Y family DNA polymerases bypasses lesions on DNA template	0.12406	0.9745	0.25412	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	Activation of ATR in response to replication stress	0.12406	0.9745	0.25412	cdc25a	5877.76	5877.76	5877.76		5877.76		UP	1	0
90Day	Digestion and absorption	0.10999	0.97834	0.25439	mgam	2596.25	2596.25	2596.25		2596.25		DOWN	0	1
90Day	G alpha (z) signalling events	0.10999	0.97834	0.25439	gng11	4854.24	4854.24	4854.24		4854.24		UP	1	0
90Day	Glucagon-type ligand receptors	0.10999	0.97834	0.25439	gng11	4854.24	4854.24	4854.24		4854.24		UP	1	0

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
90Day	HSP90 chaperone cycle for steroid hormone receptors (SHR)	0.90593	0.18125	0.25553	tubb6;dnaja2;dctn3;tubb4b;tubb2a;tuba1b;hsp90aa1;ar	1572.38525	1751.94	190.561	1127.05582	1474.4089	1168.2909	UP	0.625	0.375
28Day	Digestion	0.15699	1	0.25595										
28Day	SUMOylation of intracellular receptors	0.15699	1	0.25595										
28Day	RNA Polymerase III Transcription Initiation From Type 1 Promoter	0.14618	1	0.25638										
28Day	RNA Polymerase III Transcription Initiation From Type 2 Promoter	0.14618	1	0.25638										
28Day	Platelet calcium homeostasis	0.14618	1	0.25638										
7Day	Inositol transporters	0.97506	0.2569	0.2569	slc5a3	5988.82	5988.82	5988.82		5988.82		UP	1	0
7Day	MASTL Facilitates Mitotic Progression	0.97506	0.2569	0.2569	arpp19	1931.08	1931.08	1931.08		1931.08		UP	1	0
7Day	SMAC (DIABLO) binds to IAPs	0.97506	0.2569	0.2569	xiap	4874.03	4874.03	4874.03		4874.03		DOWN	0	1
7Day	SMAC(DIABLO)-mediated dissociation of IAP:caspase complexes	0.97506	0.2569	0.2569	xiap	4874.03	4874.03	4874.03		4874.03		DOWN	0	1
7Day	SUMO is conjugated to E1 (UBA2:SAE1)	0.97506	0.2569	0.2569	uba2	2542.64	2542.64	2542.64		2542.64		UP	1	0
7Day	NOTCH2 Activation and Transmission of Signal to the Nucleus	0.97506	0.2569	0.2569	mdk	4385.8	4385.8	4385.8		4385.8		DOWN	0	1
7Day	Activation of NIMA Kinases NEK9, NEK6, NEK7	0.97506	0.2569	0.2569	nek6	770.098	770.098	770.098		770.098		UP	1	0
7Day	Formation of the active cofactor, UDP-glucuronate	0.97506	0.2569	0.2569	ugdh	654.44	654.44	654.44		654.44		UP	1	0
7Day	c-src mediated regulation of Cx43 function and closure of gap junctions	0.97506	0.2569	0.2569	gja1	4276.18	4276.18	4276.18		4276.18		DOWN	0	1
7Day	Regulation of gap junction activity	0.97506	0.2569	0.2569	gja1	4276.18	4276.18	4276.18		4276.18		DOWN	0	1
7Day	Activation of AMPA receptors	0.97506	0.2569	0.2569	gria3	3853.21	3853.21	3853.21		3853.21		UP	1	0
7Day	Interleukin-33 signaling	0.97506	0.2569	0.2569	il1rap	131.024	131.024	131.024		131.024		DOWN	0	1
7Day	Abacavir transmembrane transport	0.97506	0.2569	0.2569	slc22a1	4237.04	4237.04	4237.04		4237.04		DOWN	0	1
28Day	Inositol phosphate metabolism	0.1487	0.96737	0.25729	ippk	4371.1	4371.1	4371.1		4371.1		UP	1	0
7Day	GABA B receptor activation	0.11474	0.97692	0.25765	gnai3	794.2	794.2	794.2		794.2		UP	1	0
7Day	Activation of GABAB receptors	0.11474	0.97692	0.25765	gnai3	794.2	794.2	794.2		794.2		UP	1	0
90Day	Anchoring of the basal body to the plasma membrane	0.13119	0.93144	0.25766	haus7;cep89;dctn3;cntrl;tubb4b;cep76;hsp90aa1	3353.60429	4147.42	426.32	1613.41073	3557.04342	1441.36283	UP	1	0
28Day	Signaling by PTK6	0.1407	0.96962	0.2577	hbegf	919.738	919.738	919.738		919.738		UP	1	0
28Day	Signaling by Non-Receptor Tyrosine Kinases	0.1407	0.96962	0.2577	hbegf	919.738	919.738	919.738		919.738		UP	1	0
28Day	HDMs demethylate histones	0.1407	0.96962	0.2577	hist1h4i	5848.41	5848.41	5848.41		5848.41		DOWN	0	1
28Day	RNA Polymerase III Transcription Initiation From Type 3 Promoter	0.13612	1	0.2581										
28Day	Synthesis of IP3 and IP4 in the cytosol	0.13612	1	0.2581										
28Day	Laminin interactions	0.13612	1	0.2581										
7Day	CD28 dependent PI3K/Akt signaling	0.11306	1	0.26016										
7Day	Adrenaline,noradrenaline inhibits insulin secretion	0.11306	1	0.26016										
7Day	Thromboxane signalling through TP receptor	0.11306	1	0.26016										
7Day	Dopamine Neurotransmitter Release Cycle	0.11306	1	0.26016										
90Day	RNA Polymerase I Promoter Clearance	0.11734	0.93975	0.26052	hist1h4h;hist1h4i;hist1h3c;gatad2b;h2afx;hdac2;cdk7	2761.40443	3141.48	202.162	1599.6023	1901.73792	1742.50078	UP	0.714285714	0.285714286
90Day	Plasma lipoprotein clearance	0.92913	0.16074	0.26075	ces3a;apob;lipc;ces3b;apoe;ap2m1	2386.01167	3015.52	175.96	1213.11723	2683.76947	1023.04019	DOWN	0.166666667	0.833333333
28Day	Downstream signal transduction	0.12674	1	0.26101										
90Day	Aflatoxin activation and detoxification	0.94544	0.15854	0.26146	cyp3a25;cyp3a41a;cyp1a2;cyp3a41b	1496.73025	871.037	343.937	1622.60806	933.270479	1101.72823	DOWN	0.25	0.75
90Day	Plasma lipoprotein assembly	0.94544	0.15854	0.26146	apob;bmp1;apoe;apoc3	1918.15725	970.0945	175.96	2535.49688	1662.93345	2515.46435	DOWN	0	1
90Day	LDL clearance	0.94544	0.15854	0.26146	ces3a;apob;ces3b;ap2m1	2368.27	3015.52	175.96	1466.53733	2640.00097	1351.10864	DOWN	0.25	0.75
7Day	Cell surface interactions at the vascular wall	0.13971	0.92586	0.26162	apob;yes1;sd3;ptpn11;kras;cd74;f2	2984.82957	3629.67	156.627	1444.9241	2799.96363	1715.23029	CONFLICT	0.428571429	0.571428571
28Day	Inwardly rectifying K+ channels	0.11802	1	0.26505										
7Day	HSF1-dependent transactivation	0.94086	0.16562	0.268	hspb8;hsbp1;ptges3;hsp90aa1	2848.82	3330.73	1005.61	1252.88568	2463.28688	1392.96486	UP	0.75	0.25
7Day	Transcriptional Regulation by E2F6	0.94086	0.16562	0.268	pcgf6;suz12;tfdp1;bmi1	3451.9685	4064.915	707.264	2009.25089	3529.23604	1701.83142	UP	1	0

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
90Day	Cytosolic sensors of pathogen-associated DNA	0.91902	0.17783	0.26872	tmem173;tbk1;irf7;nfkbia;ikbkj;ctnnb1	3626.64667	3829.595	1058.39	1508.72615	3285.24843	1672.16356	DOWN	0.333333333	0.666666667	
90Day	Recycling pathway of L1	0.91902	0.17783	0.26872	tubb6;tubb4b;tubb2a;tuba1b;msn;ap2m1	2247.1185	1866.255	779.791	1212.01981	1561.1871	977.049086	UP	0.666666667	0.333333333	
90Day	RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function	0.14539	0.93088	0.26926	hist1h4h;hist1h4i;hist1h3c;h2afx;cbfb	3385.3238	4006.71	811.859	1439.60021	2670.8166	1780.268	UP	0.6	0.4	
90Day	Scavenging by Class A Receptors	0.92872	0.26931	0.26931	apob;apoe	962.89	962.89	175.96	1112.88708	1105.17513	1094.54444	DOWN	0	1	
90Day	EGFR interacts with phospholipase C-gamma	0.92872	0.26931	0.26931	tgfa;areg	3066.45	3066.45	2162.51	1278.36421	2568.896	1067.28398	UP	1	0	
90Day	Keratan sulfate degradation	0.92872	0.26931	0.26931	omd;lum	4004.86	4004.86	3651.14	500.235621	4146.75069	458.22455	UP	1	0	
90Day	Regulation of RUNX3 expression and activity	0.92872	0.26931	0.26931	mdm2;cbfb	3802.835	3802.835	3535.08	378.662752	3762.85478	374.417741	UP	1	0	
90Day	IRF3-mediated induction of type I IFN	0.92872	0.26931	0.26931	tmem173;tbk1	2558.24	2558.24	1058.39	2121.10821	2553.28861	2121.09665	DOWN	0	1	
7Day	TCR signaling	0.89225	0.2004	0.2694	ube2n;pak2;uba52;cdc34;pten;h2-ab1;h2-aa;bttrc	2908.7	2856.44	1018.89	1236.24032	3402.87357	962.286555	UP	0.75	0.25	
90Day	Signaling by Insulin receptor	0.13676	0.93571	0.27001	klb;irs2;sos1;gab1;fgf1	2037.77806	242.429	74.8133	2687.59133	2592.91452	2898.02513	DOWN	0	1	
90Day	Transport of Mature mRNA derived from an Intron-Containing Transcript	0.13676	0.93571	0.27001	srsf6;thoc7;nup153;nxf7;sec13	4365.538	3680.35	2758.9	1461.99618	4679.90767	1460.69593	UP	1	0	
90Day	Transport of Mature Transcript to Cytoplasm	0.13676	0.93571	0.27001	srsf6;thoc7;nup153;nxf7;sec13	4365.538	3680.35	2758.9	1461.99618	4679.90767	1460.69593	UP	1	0	
28Day	Disassembly of the destruction complex and recruitment of AXIN to the membrane	0.10989	1	0.27014											
28Day	Cellular Senescence	0.12037	0.93722	0.27076	acd;hist1h4i;map2k4;cdc27;mdm2;mapkapk2;bmi1	4311.00286	4371.28	2266.61	1464.26899	3999.04543	1655.86208	CONFLICT	0.571428571	0.428571429	
90Day	mRNA Splicing - Minor Pathway	0.15826	0.93744	0.27248	srsf6;zrsr1;prpf8	4512.93667	4267.22	3549.69	1106.75498	4550.21269	1147.36315	UP	0.666666667	0.333333333	
90Day	Translation initiation complex formation	0.14745	0.94263	0.27257	eif3m;rps27l;rps12	2578.52	2517.83	1662.63	947.693586	2378.76706	980.623942	UP	1	0	
90Day	Interleukin-17 signaling	0.14745	0.94263	0.27257	mapk14;ikbkj;bttrc	4226.74	4261.96	3265.56	944.062859	4326.22256	1102.6478	DOWN	0.333333333	0.666666667	
90Day	TNFR2 non-canonical NF-kB pathway	0.14745	0.94263	0.27257	eda2r;ube2m;bttrc	2527.68333	1752.24	678.11	2335.9095	2635.86595	2417.95822	UP	0.666666667	0.333333333	
90Day	L13a-mediated translational silencing of Ceruloplasmin expression	0.13727	0.94743	0.27383	eif3m;rps27l;rps12	2578.52	2517.83	1662.63	947.693586	2378.76706	980.623942	UP	1	0	
90Day	Activation of the mRNA upon binding of the cap-binding complex and eIFs, and subsequent binding to 43S	0.13727	0.94743	0.27383	eif3m;rps27l;rps12	2578.52	2517.83	1662.63	947.693586	2378.76706	980.623942	UP	1	0	
90Day	ABC-family proteins mediated transport	0.13727	0.94743	0.27383	abcb8;rnf5;abca4	4273.66	3718.83	3667.8	1005.5108	4488.51838	1066.58349	UP	1	0	
90Day	Iron uptake and transport	0.13727	0.94743	0.27383	abcg2;trff;ftl1	2195.09567	1733.37	368.457	2095.99746	2551.60144	2268.40089	UP	0.666666667	0.333333333	
7Day	Recruitment of NuMA to mitotic centrosomes	0.14413	0.93118	0.27403	tubb4b;tubb2a;tuba4a;nedd1;hsp90aa1	1781.9732	1815.66	919.856	882.560048	1726.78849	899.616232	UP	1	0	
28Day	mRNA 3'-end processing	0.91933	0.17373	0.27418	cpsf2;u2af2;papola;srsf1;thoc5;bc005561	3815.70217	4120.91	983.533	1557.90855	4079.59666	1475.43623	CONFLICT	0.5	0.5	
7Day	Post-translational modification: synthesis of GPI-anchored proteins	0.137	0.93519	0.27484	plet1;plgw;ly6e;ly6d;gpaa1	4689.798	4464.3	3178.98	1065.1948	4804.57437	1109.31416	UP	0.8	0.2	
28Day	snRNP Assembly	0.92104	0.27539	0.27539	snrpd1;smn1	1756.176	1756.176	961.122	1124.37615	1914.56475	1101.83834	CONFLICT	0.5	0.5	
28Day	Metabolism of non-coding RNA	0.92104	0.27539	0.27539	snrpd1;smn1	1756.176	1756.176	961.122	1124.37615	1914.56475	1101.83834	CONFLICT	0.5	0.5	
28Day	Phosphorylation of CD3 and TCR zeta chains	0.92104	0.27539	0.27539	h2-ab1;h2-aa	3461.14	3461.14	3245.73	304.635743	3292.13505	188.885132	DOWN	0	1	
28Day	Caspase activation via Death Receptors in the presence of ligand	0.92104	0.27539	0.27539	tnfrsf10b;ly96	4300.525	4300.525	4040.75	367.377328	4219.52756	349.062933	UP	1	0	
28Day	Transport of connexons to the plasma membrane	0.92104	0.27539	0.27539	tubb4b;tubb2a	2631.245	2631.245	2359.45	384.376175	2702.45657	370.948608	UP	1	0	
28Day	Regulation of necroptotic cell death	0.92104	0.27539	0.27539	tnfrsf10b;birc2	4951.5	4951.5	4040.75	1287.995	4749.40037	1255.8832	UP	1	0	
28Day	Amino acid synthesis and interconversion (transamination)	0.93516	0.17388	0.2762	serinc1;oat;got2;glul	2322.7925	2161.54	1574.09	787.273072	2374.14146	914.935891	DOWN	0	1	
28Day	Detoxification of Reactive Oxygen Species	0.93516	0.17388	0.2762	txnrd1;p4hb;gstp1;gstp2	2875.8315	2540.62	691.166	2157.37958	2467.7214	2357.58858	UP	0.75	0.25	
7Day	Gap-filling DNA repair synthesis and ligation in TC-NER	0.15164	0.94019	0.27718	prpf19;polr2h;uba52	3815.36333	3964.6	2719.93	1028.96402	3913.27434	885.21152	UP	1	0	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
7Day	Regulation of Hypoxia-inducible Factor (HIF) by oxygen	0.93085	0.18492	0.27763	cul2;uba52;arnt;egln1	4260.7	4403.685	3473.87	556.456084	4323.49865	509.372912	CONFLICT	0.5	0.5	
7Day	Cellular response to hypoxia	0.93085	0.18492	0.27763	cul2;uba52;arnt;egln1	4260.7	4403.685	3473.87	556.456084	4323.49865	509.372912	CONFLICT	0.5	0.5	
7Day	Dual incision in TC-NER	0.14296	0.94435	0.27794	prpf19;polr2h;uba52	3815.36333	3964.6	2719.93	1028.96402	3913.27434	885.21152	UP	1	0	
7Day	Chylomicron assembly	0.92246	0.27804	0.27804	apob;apoE	1056.263	1056.263	113.316	1333.52844	1337.47219	1272.84755	DOWN	0	1	
7Day	Interleukin-27 signaling	0.92246	0.27804	0.27804	stat1;jak1	3735.595	3735.595	3554.32	256.361564	3703.94	252.422609	UP	1	0	
7Day	Assembly of active LPL and LIPC lipase complexes	0.92246	0.27804	0.27804	angptl8;pcsk5	4473.22	4473.22	4393.36	112.939095	4482.15982	112.229223	CONFLICT	0.5	0.5	
7Day	p75NTR recruits signalling complexes	0.92246	0.27804	0.27804	uba52;prkci	4085.4	4085.4	3409.24	956.234642	4275.2759	917.757582	UP	1	0	
7Day	Translocation of ZAP-70 to Immunological synapse	0.92246	0.27804	0.27804	h2-ab1;h2-aa	2062.21	2062.21	1863.06	281.640631	2105.93651	274.767957	DOWN	0	1	
90Day	Programmed Cell Death	0.14928	0.91712	0.27834	hmgb2;ywhaz;tfnrsf10b;rock1;bmf;dsg2;ctnnb1;bax	2260.36	2106.36	137.958	1594.54742	2319.13546	1448.3806	UP	0.625	0.375	
7Day	The citric acid (TCA) cycle and respiratory electron transport	0.8789	0.18873	0.28029	ndufaf1;ndufaf4;ndufc2;coq10b;ndufa13;ndufa6;sdha;ndufa1;pdhx;idh2;ecsit;ndufa2;idh3b;dld;atp5j	3707.30533	3920.07	114.56	1234.07401	3744.00079	925.90502	CONFLICT	0.466666667	0.533333333	
28Day	Vesicle-mediated transport	0.14225	0.89335	0.28169	pacsin3;trappc8;vps36;ubap1;lman2;dynll1;rab9;rab11a;vps37a;ppp6r3;apob;picalm;tmf1;dennd1a;tubb4b;tubb2a;trf;sec22c;scarb1;serpina1e;serpina1b;rab18;man1a;lrp1;hgs;hbgef;ftl1;f5;cux1;capza2;bet1;app;apoE;gbf1;tbc1d10a	3336.57643	3278.3	185.394	1530.92697	3185.30924	1559.82158	CONFLICT	0.428571429	0.571428571	
28Day	Sphingolipid metabolism	0.14304	0.94378	0.28444	ormdl2;ormdl3;aladh3a2	3690.26	3444.81	2456.59	1372.94999	3564.34119	1439.47386	UP	0.666666667	0.333333333	
28Day	Signaling by TGF-beta family members	0.14304	0.94378	0.28444	ube2m;tfpdp1;ccnk	4577.73667	5090.85	2933.96	1456.65483	4832.41634	1309.22256	UP	0.666666667	0.333333333	
28Day	Recruitment of NuMA to mitotic centrosomes	0.13128	0.94935	0.28722	dynll1;tubb4b;tubb2a	3684.67667	2903.04	2359.45	1844.72961	3931.15502	1868.40338	UP	1	0	
7Day	Processing of Capped Intronless Pre-mRNA	0.91996	0.20489	0.28884	fip1l1;cpsf2;lsml10;cstf2	3832.545	3346.415	2905.24	1288.3694	3400.92865	758.313332	UP	1	0	
28Day	Post-translational modification: synthesis of GPI-anchored proteins	0.12572	0.95194	0.28919	pigp;pign;ly6d	3866.46567	5041.89	781.797	2696.48077	4764.57849	2265.4523	UP	1	0	
90Day	Mitochondrial translation elongation	0.1423	0.92826	0.29874	mrpl58;mrps18b;mrpl54;mrps30;mrps31;mrpl22	3388.1725	3632.435	958.825	1571.32063	3043.1093	1692.27602	UP	0.666666667	0.333333333	
28Day	SMAC, XIAP-regulated apoptotic response	0.95906	0.29929	0.29929	4-Sep	211.182	211.182	211.182		211.182		UP	1	0	
28Day	Sodium-coupled sulphate, di- and tri-carboxylate transporters	0.95906	0.29929	0.29929	slc13a5	4810.3	4810.3	4810.3		4810.3		UP	1	0	
28Day	Extrinsic Pathway of Fibrin Clot Formation	0.95906	0.29929	0.29929	f7	2170.26	2170.26	2170.26		2170.26		DOWN	0	1	
28Day	HDL clearance	0.95906	0.29929	0.29929	scarb1	3278.3	3278.3	3278.3		3278.3		DOWN	0	1	
28Day	Serotonin and melatonin biosynthesis	0.95906	0.29929	0.29929	ddc	5580.16	5580.16	5580.16		5580.16		DOWN	0	1	
28Day	JNK (c-Jun kinases) phosphorylation and activation mediated by activated human TAK1	0.95906	0.29929	0.29929	map2k4	2616.5	2616.5	2616.5		2616.5		UP	1	0	
28Day	Adenosine P1 receptors	0.95906	0.29929	0.29929	adora1	907.506	907.506	907.506		907.506		UP	1	0	
28Day	Leukotriene receptors	0.95906	0.29929	0.29929	cysltr1	4610.42	4610.42	4610.42		4610.42		UP	1	0	
28Day	Abacavir transport and metabolism	0.95906	0.29929	0.29929	slc22a1	1681.65	1681.65	1681.65		1681.65		DOWN	0	1	
28Day	Pre-NOTCH Processing in Golgi	0.95906	0.29929	0.29929	notch1	908.573	908.573	908.573		908.573		UP	1	0	
28Day	VLDL clearance	0.95906	0.29929	0.29929	apob	939.205	939.205	939.205		939.205		DOWN	0	1	
28Day	N-glycan trimming and elongation in the cis-Golgi	0.95906	0.29929	0.29929	man1a	185.394	185.394	185.394		185.394		DOWN	0	1	
28Day	Synthesis of 15-eicosatetraenoic acid derivatives	0.95906	0.29929	0.29929	gpx4	3909.63	3909.63	3909.63		3909.63		DOWN	0	1	
28Day	TRAIL signaling	0.95906	0.29929	0.29929	tfnrsf10b	4040.75	4040.75	4040.75		4040.75		UP	1	0	
28Day	Fructose metabolism	0.95906	0.29929	0.29929	khk	3680.34	3680.34	3680.34		3680.34		DOWN	0	1	
28Day	Metabolism of steroids	0.87553	0.20158	0.29972	akr1c6;pmvk;akr1c12;akr1c19;slc10a1;amacr;hsl17b4;hsl17b3;hsl11b1;gc;fdxr;akr1c14	3381.83435	3383.375	67.9262	2102.09252	3010.03351	1961.85968	DOWN	0.25	0.75	
90Day	RUNX2 regulates bone development	0.96479	0.30141	0.30141	ar	1998.95	1998.95	1998.95		1998.95		DOWN	0	1	
90Day	CREB3 factors activate genes	0.96479	0.30141	0.30141	creb3	3847.29	3847.29	3847.29		3847.29		UP	1	0	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
90Day	SUMO is conjugated to E1 (UBA2:SAE1)	0.96479	0.30141	0.30141	sae1	3998.58	3998.58	3998.58		3998.58		UP	1	0
90Day	VLDL assembly	0.96479	0.30141	0.30141	apob	175.96	175.96	175.96		175.96		DOWN	0	1
90Day	Activation of NIMA Kinases NEK9, NEK6, NEK7	0.96479	0.30141	0.30141	nek6	3442.78	3442.78	3442.78		3442.78		UP	1	0
90Day	Progressive trimming of alpha-1,2-linked mannose residues from Man9/8/7GlcNAc2 to produce Man5GlcNAc2	0.96479	0.30141	0.30141	man1a	3931.46	3931.46	3931.46		3931.46		DOWN	0	1
90Day	Biosynthesis of E-series 18(S)-resolvins	0.96479	0.30141	0.30141	gpx4	2353.96	2353.96	2353.96		2353.96		UP	1	0
90Day	Formation of the active cofactor, UDP-glucuronate	0.96479	0.30141	0.30141	ugdh	444.891	444.891	444.891		444.891		UP	1	0
90Day	RUNX1 and FOXP3 control the development of regulatory T lymphocytes (Tregs)	0.96479	0.30141	0.30141	cbfb	4070.59	4070.59	4070.59		4070.59		UP	1	0
90Day	RUNX1 regulates estrogen receptor mediated transcription	0.96479	0.30141	0.30141	cbfb	4070.59	4070.59	4070.59		4070.59		UP	1	0
90Day	RUNX1 regulates transcription of genes involved in differentiation of myeloid cells	0.96479	0.30141	0.30141	cbfb	4070.59	4070.59	4070.59		4070.59		UP	1	0
90Day	RUNX1 regulates transcription of genes involved in interleukin signaling	0.96479	0.30141	0.30141	cbfb	4070.59	4070.59	4070.59		4070.59		UP	1	0
90Day	Activation of BMF and translocation to mitochondria	0.96479	0.30141	0.30141	bmf	1597.1	1597.1	1597.1		1597.1		DOWN	0	1
90Day	betaKlotho-mediated ligand binding	0.96479	0.30141	0.30141	klb	3850.29	3850.29	3850.29		3850.29		DOWN	0	1
90Day	FMO oxidises nucleophiles	0.96479	0.30141	0.30141	fmo2	4634.02	4634.02	4634.02		4634.02		DOWN	0	1
90Day	Activation of AMPA receptors	0.96479	0.30141	0.30141	gria3	1097.82	1097.82	1097.82		1097.82		UP	1	0
90Day	Interleukin-33 signaling	0.96479	0.30141	0.30141	il1rap	2684.35	2684.35	2684.35		2684.35		DOWN	0	1
90Day	Abacavir transmembrane transport	0.96479	0.30141	0.30141	slc22a1	1050.57	1050.57	1050.57		1050.57		DOWN	0	1
7Day	Endogenous sterols	0.90822	0.22546	0.30148	cyp39a1;ncoa2;ncoa1;arnt	2493.89215	3207.45	86.7986	1611.46881	3047.88667	868.85147	CONFLICT	0.5	0.5
28Day	Metabolism of Angiotensinogen to Angiotensins	0.90758	0.30153	0.30153	mme;agt	3209.989	3209.989	776.548	3441.40527	2561.91124	3317.11631	DOWN	0	1
28Day	mRNA decay by 3' to 5' exoribonuclease	0.90758	0.30153	0.30153	exosc3;wdr61	4156.29	4156.29	2805.79	1909.89542	4910.83867	1583.98646	CONFLICT	0.5	0.5
28Day	Acyl chain remodelling of PE	0.90758	0.30153	0.30153	pnpla8;abhd4	4366.025	4366.025	4305.66	85.3690017	4370.65129	85.1179265	UP	1	0
28Day	PD-1 signaling	0.90758	0.30153	0.30153	h2-ab1;h2-aa	3461.14	3461.14	3245.73	304.635743	3292.13505	188.885132	DOWN	0	1
28Day	Syndecan interactions	0.90758	0.30153	0.30153	vtg;fn1	1801.881	1801.881	447.762	1915.01345	2418.97549	1704.60122	DOWN	0	1
7Day	Signaling by Hedgehog	0.15638	0.91939	0.30156	tubb4b;tuba52;tubb2a;tuba4a;sel1l;prk ar2a	2980.59933	3080.3	919.856	1567.90875	2665.52182	1597.68307	UP	0.833333333	0.166666667
7Day	Retrograde transport at the Trans-Golgi-Network	0.88453	0.23056	0.30176	cog6;plin3;rab9;cog5;rab6a;igf2r	3323.49833	3535.83	1046.66	1169.77215	3128.60678	1189.09328	DOWN	0.333333333	0.666666667
28Day	Clathrin-mediated endocytosis	0.14051	0.92844	0.31051	pacs1n3;apob;picalm;trf;hgs;hbegf	2887.5755	3153.66	919.738	1670.43485	2099.89084	1545.313	CONFLICT	0.5	0.5
90Day	PTEN Regulation	0.16767	0.92447	0.31115	cbx6;gatad2b;pm1;hdac2	1923.04275	1943.2145	202.162	1698.8359	1425.49987	1661.38348	UP	0.75	0.25
90Day	Autodegradation of Cdh1 by Cdh1:APC/C	0.17863	0.91843	0.31115	anapc10;psmd8;psmc4;psmf1	2250.752	2213.18	186.178	1842.30153	1652.9232	1457.31364	UP	1	0
90Day	Molecules associated with elastic fibres	0.18207	0.93837	0.3112	vtg;fn1	1077.79535	1077.79535	45.5307	1459.84267	655.289482	1331.96028	DOWN	0	1
90Day	Metabolism of polyamines	0.18207	0.93837	0.3112	slc6a12;arg2	3788.58	3788.58	3445.15	485.683364	3774.75555	485.289706	CONFLICT	0.5	0.5
90Day	Dual Incision in GG-NER	0.16847	0.94415	0.31147	pole4;polk	4753.255	4753.255	3652.71	1556.40567	3884.77714	955.97646	CONFLICT	0.5	0.5
90Day	AKT phosphorylates targets in the cytosol	0.90642	0.31325	0.31325	mdm2;cdkn1a	2224.395	2224.395	913.71	1853.5885	2056.00777	1838.2279	UP	1	0
90Day	Erythropoietin activates RAS	0.90642	0.31325	0.31325	irs2;vav1	2117.93165	2117.93165	74.8133	2889.40568	1233.22113	2604.46535	DOWN	0	1
90Day	CS/DS degradation	0.90642	0.31325	0.31325	hyal1;bgn	2339.1095	2339.1095	144.869	3103.12467	3096.28811	2912.51504	DOWN	0	1
90Day	HDL remodeling	0.90642	0.31325	0.31325	apoE;apoc3	3653.15	3653.15	1749.82	2691.7151	3933.46099	2662.36393	DOWN	0	1
90Day	Signaling by NTRK2 (TRKB)	0.90642	0.31325	0.31325	sos1;ntrk2	4819.635	4819.635	3744.34	1520.69677	5019.62489	1494.16424	DOWN	0	1
90Day	Glycosphingolipid metabolism	0.15575	0.9494	0.31331	psap;gpm2a	3480.875	3480.875	3112.61	520.805358	3533.31507	515.498106	CONFLICT	0.5	0.5
90Day	Elastic fibre formation	0.15575	0.9494	0.31331	vtg;fn1	1077.79535	1077.79535	45.5307	1459.84267	655.289482	1331.96028	DOWN	0	1
90Day	MAP2K and MAPK activation	0.15575	0.9494	0.31331	tltn1;fn1	3294.495	3294.495	2110.06	1675.04404	3616.30164	1612.03397	DOWN	0	1
90Day	MET promotes cell motility	0.15575	0.9494	0.31331	gab1;fn1	1118.244	1118.244	126.428	1402.63964	1214.48427	1396.02062	DOWN	0	1
90Day	Signaling by SCF-KIT	0.15575	0.9494	0.31331	vav1;sos1	5027.99	5027.99	4161.05	1226.03831	5362.02772	1131.37418	DOWN	0	1

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.														
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
90Day	Recruitment and ATM-mediated phosphorylation of repair and signaling proteins at DNA double strand breaks	0.14738	0.93536	0.31414	hist1h4h;babam1;hist1h4i;h2afx	4461.0475	4046.18	3951.81	894.337005	4412.91487	861.771604	CONFLICT	0.5	0.5
7Day	ER Quality Control Compartment (ERQC)	0.90358	0.31436	0.31436	uba52;sel1l	4493.74	4493.74	4225.92	378.754676	4638.58379	318.583834	UP	1	0
7Day	Dectin-1 mediated noncanonical NF-kB signaling	0.90358	0.31436	0.31436	uba52;btrc	4484.31	4484.31	4207.06	392.09071	4446.04923	388.339223	UP	1	0
7Day	NIK->noncanonical NF-kB signaling	0.90358	0.31436	0.31436	uba52;btrc	4484.31	4484.31	4207.06	392.09071	4446.04923	388.339223	UP	1	0
7Day	Regulation of TP53 Activity through Methylation	0.90358	0.31436	0.31436	kmt5a;uba52	4125.35	4125.35	3489.14	899.736811	3982.64921	876.812007	UP	1	0
7Day	Interleukin-35 Signalling	0.90358	0.31436	0.31436	stat1;jak1	3735.595	3735.595	3554.32	256.361564	3703.94	252.422609	UP	1	0
7Day	MAP3K8 (TPL2)-dependent MAPK1/3 activation	0.90358	0.31436	0.31436	uba52;btrc	4484.31	4484.31	4207.06	392.09071	4446.04923	388.339223	UP	1	0
7Day	Ionotropic activity of kainate receptors	0.90358	0.31436	0.31436	calm3;calm2	3983.44	3983.44	3050.32	1319.63096	3556.9103	1173.69957	CONFLICT	0.5	0.5
7Day	Activation of Ca-permeable Kainate Receptor	0.90358	0.31436	0.31436	calm3;calm2	3983.44	3983.44	3050.32	1319.63096	3556.9103	1173.69957	CONFLICT	0.5	0.5
7Day	CD28 dependent Vav1 pathway	0.90358	0.31436	0.31436	pak2;cdc42	3567.05	3567.05	2538.2	1455.01362	4188.77837	1159.29819	UP	1	0
7Day	IRAK1 recruits IKK complex	0.90358	0.31436	0.31436	ube2n;uba52	4103.175	4103.175	3444.79	931.096996	3863.51066	867.216021	UP	1	0
7Day	TRAF6 mediated IRF7 activation in TLR7/8 or 9 signaling	0.90358	0.31436	0.31436	ube2n;uba52	4103.175	4103.175	3444.79	931.096996	3863.51066	867.216021	UP	1	0
7Day	IRAK1 recruits IKK complex upon TLR7/8 or 9 stimulation	0.90358	0.31436	0.31436	ube2n;uba52	4103.175	4103.175	3444.79	931.096996	3863.51066	867.216021	UP	1	0
7Day	GP1b-IX-V activation signalling	0.90358	0.31436	0.31436	ywhaz;flna	3797.385	3797.385	2726.98	1513.78127	3602.54505	1488.49203	CONFLICT	0.5	0.5
7Day	PECAM1 interactions	0.90358	0.31436	0.31436	yes1;ptpn11	3825.31	3825.31	3629.67	276.676741	3856.08221	273.232797	UP	1	0
7Day	Negative regulators of DDX58/IFIH1 signaling	0.90358	0.31436	0.31436	tax1bp1;uba52	4021.115	4021.115	3280.67	1047.14736	4201.81454	1015.48656	UP	1	0
7Day	AURKA Activation by TPX2	0.16979	0.92281	0.31585	tubb4b;tuba4a;nedd1;hsp90aa1	1703.9565	1410.635	919.856	998.985626	1609.23265	1031.31055	UP	1	0
7Day	Synthesis of PIPs at the plasma membrane	0.17837	0.93945	0.31597	mtmr6;pten	3141.54	3141.54	3108.4	46.8670375	3155.24331	42.6726796	UP	1	0
90Day	Homology Directed Repair	0.16007	0.90459	0.31634	hist1h4h;babam1;pole4;ppp4c;hist1h4i;polk;rad51;h2afx;brca2;rad51c	4045.4582	4046.18	513.022	1470.8127	3606.13368	1521.5189	UP	0.7	0.3
7Day	RUNX1 regulates genes involved in megakaryocyte differentiation and platelet function	0.16104	0.9276	0.3166	hist1h4h;hist1h2bc;hist2h2ac;hist2h2a	4100.405	3802.835	3406.55	933.741438	4060.85571	1011.0164	CONFLICT	0.5	0.5
7Day	PI Metabolism	0.16104	0.9276	0.3166	tnfrsf8l1;mtmr7;mtmr6;pten	3773.97	3510.64	3108.4	861.939561	3673.74135	722.775577	UP	0.75	0.25
7Day	RNA Polymerase II Promoter Escape	0.16724	0.94419	0.31663	polr2h;taf10	3661.695	3661.695	3358.79	428.372359	3731.6441	416.793865	UP	1	0
7Day	RNA Polymerase II Transcription Pre-Initiation And Promoter Opening	0.16724	0.94419	0.31663	polr2h;taf10	3661.695	3661.695	3358.79	428.372359	3731.6441	416.793865	UP	1	0
7Day	RNA Polymerase II Transcription Initiation	0.16724	0.94419	0.31663	polr2h;taf10	3661.695	3661.695	3358.79	428.372359	3731.6441	416.793865	UP	1	0
7Day	RNA Polymerase II Transcription Initiation And Promoter Clearance	0.16724	0.94419	0.31663	polr2h;taf10	3661.695	3661.695	3358.79	428.372359	3731.6441	416.793865	UP	1	0
90Day	Formation of Incision Complex in GG-NER	0.14387	0.95419	0.31664	rad23a;cdk7	2921.59	2921.59	2713.02	294.962523	2994.07751	276.57551	CONFLICT	0.5	0.5
7Day	Signaling by Insulin receptor	0.15266	0.93213	0.31803	mapk3;ptpn11;fgf1;atp6v1e1	3715.1475	3706.295	2647.76	881.029951	3601.78694	1028.41317	CONFLICT	0.5	0.5
7Day	Transport of Mature mRNA derived from an Intron-Containing Transcript	0.15266	0.93213	0.31803	gm49336;srsf1;tp;thoc5	3646.2575	3708.43	2535	938.48001	3502.21235	1031.06433	UP	1	0
7Day	Transport of Mature Transcript to Cytoplasm	0.15266	0.93213	0.31803	gm49336;srsf1;tp;thoc5	3646.2575	3708.43	2535	938.48001	3502.21235	1031.06433	UP	1	0
28Day	Protein ubiquitination	0.86907	0.25107	0.3182	ube2n;ube2v2;ube2g1;wdr61;ube2k;uc	4568.95833	4655.195	3288.55	901.493696	4499.53987	938.691394	CONFLICT	0.5	0.5
28Day	Cleavage of Growing Transcript in the Termination Region	0.86907	0.25107	0.3182	cpsf2;u2af2;papola;srsf1;thoc5;bc0055	3815.70217	4120.91	983.533	1557.90855	4079.59666	1475.43623	CONFLICT	0.5	0.5
28Day	RNA Polymerase II Transcription Termination	0.86907	0.25107	0.3182	cpsf2;u2af2;papola;srsf1;thoc5;bc0055	3815.70217	4120.91	983.533	1557.90855	4079.59666	1475.43623	CONFLICT	0.5	0.5
7Day	Cell-cell junction organization	0.15671	0.94858	0.31834	prkci;ctnnb1	1731.8816	1731.8816	54.5232	2372.143	959.953496	2106.01909	CONFLICT	0.5	0.5
7Day	IRS-related events triggered by IGF1R	0.15671	0.94858	0.31834	ptpn11;fgf1	3138.715	3138.715	2647.76	694.31522	2984.26892	659.064823	CONFLICT	0.5	0.5
7Day	Neurotransmitter release cycle	0.15671	0.94858	0.31834	slc22a1;slc1a2	2973.955	2973.955	1710.87	1786.27194	2632.70664	1719.84492	DOWN	0	1
7Day	Aquaporin-mediated transport	0.15671	0.94858	0.31834	rab11a;prkar2a	4304.455	4304.455	4066.56	336.434335	4288.10382	335.638705	CONFLICT	0.5	0.5
28Day	Cargo concentration in the ER	0.89343	0.24705	0.31866	lman2;serpina1e;serpina1b;f5	3322.35775	3403.785	619.741	2143.6356	2388.59316	2035.76691	DOWN	0	1

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
28Day	HDR through Single Strand Annealing (SSA)	0.89343	0.24705	0.31866	rmi1;rad51;brca1;blm	3449.574	3731.45	692.086	2060.39551	3948.89403	1514.9493	UP	1	0
28Day	Binding and Uptake of Ligands by Scavenger Receptors	0.89343	0.24705	0.31866	apob;scarb1;lrp1;apoE	2328.17375	2547.595	939.205	1127.37772	2051.38533	1157.35972	DOWN	0	1
7Day	IGF1R signaling cascade	0.14676	0.95264	0.32107	ptpn11;fgf1	3138.715	3138.715	2647.76	694.31522	2984.26892	659.064823	CONFLICT	0.5	0.5
28Day	Cellular responses to stress	0.16828	0.88446	0.32111	hikeshi;dynl1;gm45902;txnrd1;acd;hist1h4i;map2k4;tubb4b;tubb2a;cdc27;p4hb;mdm2;mapkapk2;gstp1;gstp2;capz a2;bmi1;tpor	3964.21589	4036.505	691.166	1605.06154	3782.47702	1758.58395	UP	0.666666667	0.333333333
7Day	Transcriptional regulation by RUNX1	0.158	0.90562	0.32113	pcgf5;hist1h4h;hist1h2bc;hist2h2ac;ub a52;ptpn11;hist2h2aa1;csnk2b;bmi1;a bl1	4031.764	3908.47	2829.67	827.425176	4093.68811	851.726114	UP	0.7	0.3
90Day	S Phase	0.17168	0.90615	0.32132	esco2;gins1;anapc10;pole4;cables1;orc 6;cdkn1a	3442.09	4071.91	913.71	1798.40239	2966.13615	1623.11377	UP	0.714285714	0.285714286
28Day	Signaling by Hedgehog	0.17448	0.91956	0.32185	tubb4b;tubb2a;p4hb;adcy9	3803.5025	3561.82	2359.45	1503.88706	3496.76486	1471.76062	CONFLICT	0.5	0.5
28Day	Collagen formation	0.18117	0.9158	0.32186	p4hb;ctss;col8a1;bmp1	4192.9125	4983.815	1023.63	2230.98048	3878.77064	2323.26474	CONFLICT	0.5	0.5
28Day	Stimuli-sensing channels	0.168	0.92317	0.3222	ano8;clcn6;sgk3;clcn2	3151.355	3205.75	2316.49	647.347601	3143.31625	644.169192	DOWN	0.25	0.75
28Day	Signaling by VEGF	0.16171	0.92663	0.3229	pdpk1;mapkapk2;cdc42;brk1	3372.312	3919.245	192.988	2536.00426	4213.88679	1981.66272	DOWN	0.25	0.75
7Day	M Phase	0.16288	0.88324	0.32466	clasp2;gm49336;pds5a;hist1h4h;hist1 h2bc;kmt5a;cenpk;nek6;arpp19;hist2h 2ac;mapk3;tubb4b;uba52;tubb2a;tuba 4a;cdc27;rab1a;ppp2cb;nedd1;kif2a;hs p90aa1;hist2h2aa1;tpor;pxo1	3251.11808	3521.41	770.098	1294.16242	3190.92806	1264.84947	UP	0.833333333	0.166666667
7Day	Signaling by Type 1 Insulin-like Growth Factor 1 Receptor (IGF1R)	0.13737	0.95639	0.32477	ptpn11;fgf1	3138.715	3138.715	2647.76	694.31522	2984.26892	659.064823	CONFLICT	0.5	0.5
7Day	Glycosaminoglycan metabolism	0.17429	0.90399	0.32583	hs3st3b1;hgsnat;sdcc3;hyal1;ext1;bgn;a rsb	3466.58564	3370.58	34.2395	1859.25257	3868.38892	1587.24792	DOWN	0.142857143	0.857142857
28Day	Signaling by FGFR2	0.15204	0.94994	0.32647	polr2a;fgf1	3254.12	3254.12	1467.57	2526.56324	2657.99173	2381.76069	CONFLICT	0.5	0.5
7Day	Role of ABL in ROBO-SLIT signaling	0.95322	0.32694	0.32694	abl1	3368.05	3368.05	3368.05		3368.05		DOWN	0	1
7Day	Neurotransmitter uptake and metabolism in glial cells	0.95322	0.32694	0.32694	slc1a2	1710.87	1710.87	1710.87		1710.87		DOWN	0	1
7Day	Astrocytic Glutamate-Glutamine Uptake And Metabolism	0.95322	0.32694	0.32694	slc1a2	1710.87	1710.87	1710.87		1710.87		DOWN	0	1
7Day	Scavenging by Class B Receptors	0.95322	0.32694	0.32694	apob	1999.21	1999.21	1999.21		1999.21		DOWN	0	1
7Day	Phosphorylation of proteins involved in G1/S transition by active Cyclin E:Cdk2 complexes	0.95322	0.32694	0.32694	ccne2	4598.19	4598.19	4598.19		4598.19		UP	1	0
7Day	Ubiquitin-dependent degradation of Cyclin D1	0.95322	0.32694	0.32694	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	Ubiquitin-dependent degradation of Cyclin D	0.95322	0.32694	0.32694	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	Selenoamino acid metabolism	0.95322	0.32694	0.32694	txnrd1	2303.89	2303.89	2303.89		2303.89		UP	1	0
7Day	Glycine degradation	0.95322	0.32694	0.32694	dld	5143.63	5143.63	5143.63		5143.63		UP	1	0
7Day	Cholesterol biosynthesis via desmosterol	0.95322	0.32694	0.32694	ebp	2966.55	2966.55	2966.55		2966.55		DOWN	0	1
7Day	Organic anion transport	0.95322	0.32694	0.32694	slc22a12	3194.01	3194.01	3194.01		3194.01		UP	1	0
7Day	CLEC7A/inflammasome pathway	0.95322	0.32694	0.32694	pycard	4728.43	4728.43	4728.43		4728.43		DOWN	0	1
7Day	Amine Oxidase reactions	0.95322	0.32694	0.32694	maob	46.9364	46.9364	46.9364		46.9364		DOWN	0	1
7Day	Advanced glycosylation endproduct receptor signaling	0.95322	0.32694	0.32694	capza2	3113.17	3113.17	3113.17		3113.17		UP	1	0
7Day	NGF processing	0.95322	0.32694	0.32694	pcsk5	4553.08	4553.08	4553.08		4553.08		DOWN	0	1
7Day	Expression and Processing of Neurotrophins	0.95322	0.32694	0.32694	pcsk5	4553.08	4553.08	4553.08		4553.08		DOWN	0	1
7Day	Neurofascin interactions	0.95322	0.32694	0.32694	sdcbp	3244.26	3244.26	3244.26		3244.26		UP	1	0
7Day	Caspase activation via Dependence Receptors in the absence of ligand	0.95322	0.32694	0.32694	casp9	3648.67	3648.67	3648.67		3648.67		DOWN	0	1
7Day	LRR FLII-interacting protein 1 (LRRFIP1) activates type I IFN production	0.95322	0.32694	0.32694	ctnnb1	54.5232	54.5232	54.5232		54.5232		DOWN	0	1
7Day	Reelin signalling pathway	0.95322	0.32694	0.32694	reln	3928.43	3928.43	3928.43		3928.43		DOWN	0	1
7Day	Scavenging by Class H Receptors	0.95322	0.32694	0.32694	apob	1999.21	1999.21	1999.21		1999.21		DOWN	0	1

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
28Day	ABC transporters in lipid homeostasis	0.89325	0.3275	0.3275	abca3;abcb3	1989.92	1989.92	1485.35	713.569737	1670.93402	552.881235	DOWN	0	1
28Day	Synthesis of glycosylphosphatidylinositol (GPI)	0.89325	0.3275	0.3275	pigp;pign	5408.8	5408.8	5041.89	518.889098	5603.60631	439.712292	UP	1	0
28Day	RIPK1-mediated regulated necrosis	0.89325	0.3275	0.3275	tnfrsf10b;birc2	4951.5	4951.5	4040.75	1287.995	4749.40037	1255.8832	UP	1	0
28Day	Regulated Necrosis	0.89325	0.3275	0.3275	tnfrsf10b;birc2	4951.5	4951.5	4040.75	1287.995	4749.40037	1255.8832	UP	1	0
7Day	Metabolism of fat-soluble vitamins	0.89731	0.20088	0.32938	akr1c6;apob;ttr;sdcb3;lrp1;apoe;akr1c14	2956.06943	2842.81	113.316	1991.38668	3428.01601	1609.42615	DOWN	0.285714286	0.714285714
7Day	Xenobiotics	0.89731	0.20088	0.32938	cyp3a25;cyp3a11;cyp2e1;cyp2c37;cyp2c29;arnt;cyp3a41b	3350.14329	3382.64	529.743	1671.45384	3114.36428	1507.72766	DOWN	0.285714286	0.714285714
7Day	Synthesis of IP3 and IP4 in the cytosol	0.88227	0.26798	0.33032	itpk1;pten;calm3;calm2	3684.875	3386.31	3050.32	853.925176	3438.70794	788.233521	CONFLICT	0.5	0.5
28Day	Transport of small molecules	0.1761	0.86409	0.3335	lmf1;atp6v0e2;abcb8;slc35d2;micu2;npc2;rab11a;ano8;slc9a5;abca3;abca8b;slc25a10;clcn6;abcc4;apob;slc13a5;a2m;trf;slc17a8;scarb1;slc22a1;slc1a2;abcb3;abcb4;abcb1b;p4hb;sgk3;gmb5;slc6a13;ftl1;ces3b;clcn2;bmp1;azgp1;atp6v1e1;apoe;adc9y;slco2b1	2786.96053	2846.515	151.142	1606.28246	2694.95041	1574.5074	CONFLICT	0.447368421	0.552631579
90Day	RHO GTPases Activate Formins	0.16072	0.90187	0.33396	cenpu;fmln2;tubb6;tubb4b;tubb2a;tuba1b;kntc1;nudc;cdc42;sec13;cenpf	2685.02709	2758.9	156.487	1642.73646	2833.25496	1787.93511	UP	0.909090909	0.090909091
90Day	Apoptosis	0.19162	0.88912	0.34359	hmgb2;ylwaz;tnfrsf10b;rock1;bmf;dsgr2;ctnnb1;bax	2260.36	2106.36	137.958	1594.54742	2319.13546	1448.3806	UP	0.625	0.375
7Day	Downstream signal transduction	0.86814	0.28976	0.3462	rasa1;stat1;ptpn11;kras	4372.8325	4037.79	3629.67	966.662513	4569.74061	1058.51347	UP	0.75	0.25
7Day	ER-Phagosome pathway	0.86814	0.28976	0.3462	tap2;sec22b;h2-t23;h2-q10	3670.8125	3724.57	2584.12	941.890827	3414.68027	934.619277	DOWN	0.25	0.75
28Day	Regulation of ornithine decarboxylase (ODC)	0.94135	0.34741	0.34741	odc1	2869.35	2869.35	2869.35		2869.35		DOWN	0	1
28Day	Fibronectin matrix formation	0.94135	0.34741	0.34741	fn1	3156	3156	3156		3156		DOWN	0	1
28Day	FGFR1b ligand binding and activation	0.94135	0.34741	0.34741	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1
28Day	Glucocorticoid biosynthesis	0.94135	0.34741	0.34741	hsd11b1	67.9262	67.9262	67.9262		67.9262		DOWN	0	1
28Day	TP53 Regulates Transcription of Genes Involved in Cytochrome C Release	0.94135	0.34741	0.34741	bnip3l	1841.2	1841.2	1841.2		1841.2		DOWN	0	1
28Day	mRNA Editing	0.94135	0.34741	0.34741	a1cf	1306.69	1306.69	1306.69		1306.69		DOWN	0	1
28Day	Regulation of expression of SLITs and ROBOs	0.94135	0.34741	0.34741	dag1	5666.49	5666.49	5666.49		5666.49		DOWN	0	1
28Day	Amino Acid conjugation	0.94135	0.34741	0.34741	glyat	3673.59	3673.59	3673.59		3673.59		UP	1	0
28Day	Conjugation of carboxylic acids	0.94135	0.34741	0.34741	glyat	3673.59	3673.59	3673.59		3673.59		UP	1	0
28Day	activated TAK1 mediates p38 MAPK activation	0.94135	0.34741	0.34741	mapkapk2	5375	5375	5375		5375		DOWN	0	1
28Day	PTK6 promotes HIF1A stabilization	0.94135	0.34741	0.34741	hbegf	919.738	919.738	919.738		919.738		UP	1	0
28Day	AMPK inhibits chREBP transcriptional activation activity	0.94135	0.34741	0.34741	adipor2	2864.86	2864.86	2864.86		2864.86		DOWN	0	1
28Day	Synthesis of 12-eicosatetraenoic acid derivatives	0.94135	0.34741	0.34741	gpx4	3909.63	3909.63	3909.63		3909.63		DOWN	0	1
90Day	Response to elevated platelet cytosolic Ca2+	0.18291	0.88388	0.34823	spp2;trf;tltn1;serpina1e;psap;plg;fn1;ecm1;anxa5;ahsg;actn1;scppdh	2421.70252	2481.665	82.4742	1669.5291	2984.03278	1802.70421	DOWN	0.083333333	0.916666667
7Day	DNA Replication	0.16887	0.9039	0.34942	psmd5;psmd6;psmc4;uba52;cdc27;psmc2;prim2;cne2	3685.25375	3897.135	2309.23	862.418796	3751.9907	969.75616	UP	1	0
7Day	ERKs are inactivated	0.88307	0.35026	0.35026	mapk3;ppp2cb	4213.64	4213.64	3627.04	829.577676	4084.83206	809.330679	CONFLICT	0.5	0.5
7Day	Glycogen breakdown (glycogenolysis)	0.88307	0.35026	0.35026	calm3;calm2	3983.44	3983.44	3050.32	1319.63096	3556.9103	1173.69957	CONFLICT	0.5	0.5
28Day	COPII-mediated vesicle transport	0.86649	0.24396	0.35248	lman2;ppp6r3;sec22c;serpina1e;serpin a1b;f5;bet1	3734.47014	3497.94	619.741	1768.65464	2866.68484	1722.46541	DOWN	0.285714286	0.714285714
90Day	APC/C:Cdh1 mediated degradation of Cdc20 and other APC/C:Cdh1 targeted proteins in late mitosis/early G1	0.20979	0.94986	0.35294	anapc10	4390.47	4390.47	4390.47		4390.47		UP	1	0
90Day	Cdc20:Phospho-APC/C mediated degradation of Cyclin A	0.20979	0.94986	0.35294	anapc10	4390.47	4390.47	4390.47		4390.47		UP	1	0
90Day	CDK-mediated phosphorylation and removal of Cdc6	0.20979	0.94986	0.35294	anapc10	4390.47	4390.47	4390.47		4390.47		UP	1	0
90Day	Cholesterol biosynthesis	0.20979	0.94986	0.35294	hsd17b7	5001.13	5001.13	5001.13		5001.13		DOWN	0	1
90Day	Processing of Capped Intronless Pre-mRNA	0.20979	0.94986	0.35294	cstf2t	5843.41	5843.41	5843.41		5843.41		DOWN	0	1

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
90Day	WNT ligand biogenesis and trafficking	0.20979	0.94986	0.35294	tmed5	3479.95	3479.95	3479.95		3479.95		UP	1	0
7Day	Signaling by TGF-beta family members	0.15928	0.92249	0.35301	uba52;tgfbr1;tfdp1;prkc2;ccnk	3804.8848	4761.56	707.264	2279.30374	4710.02856	1911.5824	UP	0.8	0.2
28Day	Acyl chain remodelling of PC	0.87811	0.3532	0.3532	pnpla8;pla2g4c	3890.355	3890.355	3475.05	587.329964	3736.74096	545.675674	UP	1	0
28Day	Metabolism of porphyrins	0.87811	0.3532	0.3532	ugt1a1;fech	2693.2965	2693.2965	309.913	3370.61327	2866.03689	3361.74885	DOWN	0	1
28Day	Processing of Intronless Pre-mRNAs	0.87811	0.3532	0.3532	cpsf2;papola	3117.8765	3117.8765	983.533	3018.41752	4045.49974	2718.43238	DOWN	0	1
90Day	Formation of the beta-catenin:TCF transactivating complex	0.19177	0.95552	0.35358	ctnnb1	4087.04	4087.04	4087.04		4087.04		DOWN	0	1
90Day	ISG15 antiviral mechanism	0.19177	0.95552	0.35358	usp18	4074.3	4074.3	4074.3		4074.3		UP	1	0
90Day	Interleukin receptor SHC signaling	0.19177	0.95552	0.35358	sos1	5894.93	5894.93	5894.93		5894.93		DOWN	0	1
90Day	Digestion	0.19177	0.95552	0.35358	mgam	2596.25	2596.25	2596.25		2596.25		DOWN	0	1
90Day	Endogenous sterols	0.19177	0.95552	0.35358	cyp39a1	4130.84	4130.84	4130.84		4130.84		DOWN	0	1
90Day	TNFs bind their physiological receptors	0.19177	0.95552	0.35358	eda2r	1752.24	1752.24	1752.24		1752.24		UP	1	0
90Day	Beta defensins	0.19177	0.95552	0.35358	defb30	5550.64	5550.64	5550.64		5550.64		UP	1	0
90Day	Defensins	0.19177	0.95552	0.35358	defb30	5550.64	5550.64	5550.64		5550.64		UP	1	0
90Day	APC:Cdc20 mediated degradation of cell cycle proteins prior to satisfaction of the cell cycle checkpoint	0.19177	0.95552	0.35358	anapc10	4390.47	4390.47	4390.47		4390.47		UP	1	0
90Day	Negative regulation of FGFR3 signaling	0.19177	0.95552	0.35358	fgf1	242.429	242.429	242.429		242.429		DOWN	0	1
28Day	SUMOylation	0.18145	0.8949	0.35381	hist1h4i;rad21;mdm2;ikbk;brca1;bmi1;blm;tpo	3945.312	4027.865	692.086	1781.08975	3897.46085	1655.95085	UP	0.875	0.125
90Day	Deadenylation of mRNA	0.17514	0.96055	0.35653	paip1	212.512	212.512	212.512		212.512		UP	1	0
90Day	RNA Pol II CTD phosphorylation and interaction with CE	0.17514	0.96055	0.35653	cdk7	3130.16	3130.16	3130.16		3130.16		UP	1	0
90Day	Platelet calcium homeostasis	0.17514	0.96055	0.35653	p2rx4	185.907	185.907	185.907		185.907		DOWN	0	1
90Day	Sema4D induced cell migration and growth-cone collapse	0.88169	0.35657	0.35657	rock2;rock1	2068.101	2068.101	262.092	2554.08242	1087.57877	2144.87514	UP	1	0
90Day	MET activates RAS signaling	0.88169	0.35657	0.35657	ranbp9;sos1	4628.24	4628.24	3361.55	1791.37018	5369.66555	1452.4405	CONFLICT	0.5	0.5
90Day	STING mediated induction of host immune responses	0.88169	0.35657	0.35657	tmem173;tbk1	2558.24	2558.24	1058.39	2121.10821	2553.28861	2121.09665	DOWN	0	1
90Day	CDC6 association with the ORC:origin complex	0.88169	0.35657	0.35657	orc6;e2f2	4208.98	4208.98	4168.34	57.4736392	4203.70416	56.9872814	UP	1	0
90Day	Assembly of active LPL and LIPC lipase complexes	0.88169	0.35657	0.35657	pcsk5;lpl	3427.31	3427.31	3093.17	472.54532	3265.76421	413.648394	DOWN	0	1
90Day	Signal attenuation	0.88169	0.35657	0.35657	irs2;sos1	2984.87165	2984.87165	74.8133	4115.44399	2818.21844	4108.68989	DOWN	0	1
28Day	Metabolism of water-soluble vitamins and cofactors	0.17087	0.91508	0.35675	nudt12;enpp1;pcx;acp5;cyb5a	3447.1046	3121.78	201.213	2170.0831	2762.25847	2129.24585	DOWN	0.2	0.8
7Day	ROS, RNS production in phagocytes	0.21115	0.94889	0.35787	atp6v1e1	3782.92	3782.92	3782.92		3782.92		UP	1	0
7Day	DAP12 signaling	0.21115	0.94889	0.35787	kras	4158.71	4158.71	4158.71		4158.71		UP	1	0
7Day	EPH-ephrin mediated repulsion of cells	0.21115	0.94889	0.35787	yes1	4020.95	4020.95	4020.95		4020.95		UP	1	0
7Day	Termination of translesion DNA synthesis	0.21115	0.94889	0.35787	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	G-protein beta:gamma signalling	0.19604	0.95372	0.35829	cdc42	4595.9	4595.9	4595.9		4595.9		UP	1	0
7Day	Transferrin endocytosis and recycling	0.19604	0.95372	0.35829	atp6v1e1	3782.92	3782.92	3782.92		3782.92		UP	1	0
7Day	Signal amplification	0.19604	0.95372	0.35829	gna13	794.2	794.2	794.2		794.2		UP	1	0
7Day	Sialic acid metabolism	0.19604	0.95372	0.35829	neu1	3613.22	3613.22	3613.22		3613.22		DOWN	0	1
7Day	Glucagon signaling in metabolic regulation	0.19604	0.95372	0.35829	prkar2a	4066.56	4066.56	4066.56		4066.56		DOWN	0	1
7Day	Formation of the Early Elongation Complex	0.19604	0.95372	0.35829	polr2h	3964.6	3964.6	3964.6		3964.6		UP	1	0
7Day	Amino acid synthesis and interconversion (transamination)	0.1819	0.9581	0.36031	kyat1	4788.28	4788.28	4788.28		4788.28		DOWN	0	1
7Day	Resolution of D-loop Structures through Holliday Junction Intermediates	0.1819	0.9581	0.36031	rad51ap1	3877.33	3877.33	3877.33		3877.33		UP	1	0
7Day	Digestion and absorption	0.1819	0.9581	0.36031	mgam	132.859	132.859	132.859		132.859		DOWN	0	1
7Day	Activation of the pre-replicative complex	0.1819	0.9581	0.36031	prim2	4006.14	4006.14	4006.14		4006.14		UP	1	0

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
90Day	MAPK6/MAPK4 signaling	0.15982	0.96501	0.36161	cdc42	156.487	156.487	156.487		156.487		UP	1	0	
90Day	MAPK targets/ Nuclear events mediated by MAP kinases	0.15982	0.96501	0.36161	mapk14	4261.96	4261.96	4261.96		4261.96		DOWN	0	1	
90Day	Gluconeogenesis	0.15982	0.96501	0.36161	pcx	410.825	410.825	410.825		410.825		DOWN	0	1	
90Day	Endosomal Sorting Complex Required For Transport (ESCRT)	0.15982	0.96501	0.36161	ubap1	4451.86	4451.86	4451.86		4451.86		UP	1	0	
90Day	TNFR1-induced NFKappaB signaling pathway	0.15982	0.96501	0.36161	ikbkg	3265.56	3265.56	3265.56		3265.56		UP	1	0	
90Day	APC/C-Cdc20 mediated degradation of mitotic proteins	0.15982	0.96501	0.36161	anapc10	4390.47	4390.47	4390.47		4390.47		UP	1	0	
90Day	Activation of APC/C and APC/C-Cdc20 mediated degradation of mitotic proteins	0.15982	0.96501	0.36161	anapc10	4390.47	4390.47	4390.47		4390.47		UP	1	0	
90Day	Calmodulin induced events	0.15982	0.96501	0.36161	camkk2	98.0082	98.0082	98.0082		98.0082		DOWN	0	1	
90Day	CaM pathway	0.15982	0.96501	0.36161	camkk2	98.0082	98.0082	98.0082		98.0082		DOWN	0	1	
90Day	Signaling by PTK6	0.18188	0.92571	0.36313	gpnmb;rasa1;nrg1	3532.88667	3912.34	2133.64	1253.36637	4185.38166	823.865612	UP	1	0	
90Day	Signaling by Non-Receptor Tyrosine Kinases	0.18188	0.92571	0.36313	gpnmb;rasa1;nrg1	3532.88667	3912.34	2133.64	1253.36637	4185.38166	823.865612	UP	1	0	
90Day	HDMs demethylate histones	0.18188	0.92571	0.36313	hist1h4h;hist1h4i;hist1h3c	2923.45967	3951.81	811.859	1828.90583	2005.0795	1880.81489	DOWN	0.333333333	0.666666667	
90Day	Negative regulation of the PI3K/AKT network	0.20117	0.87896	0.36375	klb;irs2;vav1;tgfa;nrg1;il1rap;gab1;fgf1;areg	2353.84448	2684.35	74.8133	1778.57928	2322.93121	1581.92848	DOWN	0.333333333	0.666666667	
90Day	Mitotic Prophase	0.20117	0.87896	0.36375	smc4;hist1h4h;mastl;nek6;arpp19;hist1h4i;nup153;h2afx;sec13	3275.56122	3680.35	577.791	1139.1806	3412.99082	939.1085	UP	0.777777778	0.222222222	
7Day	Resolution of D-Loop Structures	0.16868	0.96206	0.36381	rad51ap1	3877.33	3877.33	3877.33		3877.33		UP	1	0	
28Day	Regulation of PTEN gene transcription	0.20594	0.9499	0.36442	bmi1	3918.46	3918.46	3918.46		3918.46		UP	1	0	
28Day	PLC beta mediated events	0.20594	0.9499	0.36442	adcy9	4220.6	4220.6	4220.6		4220.6		DOWN	0	1	
28Day	G-protein mediated events	0.19521	0.95335	0.36513	adcy9	4220.6	4220.6	4220.6		4220.6		DOWN	0	1	
28Day	Collagen chain trimerization	0.19521	0.95335	0.36513	col8a1	4236.71	4236.71	4236.71		4236.71		UP	1	0	
28Day	RNA Polymerase I Transcription Initiation	0.19521	0.95335	0.36513	polr1a	5863.06	5863.06	5863.06		5863.06		DOWN	0	1	
90Day	Estrogen-dependent gene expression	0.17492	0.89714	0.36535	hist1h4h;hist1h4i;hist1h3c;nr5a2;yy1;hsp90aa1;h2afx;ddx5;cbfb	2963.50756	3951.81	174.249	1923.75546	2558.29556	1937.36612	CONFLICT	0.555555556	0.444444444	
90Day	Ribosomal scanning and start codon recognition	0.16973	0.93181	0.36571	elf3m;rps27l;rps12	2578.52	2517.83	1662.63	947.693586	2378.76706	980.623942	UP	1	0	
28Day	Signaling by ERBB2	0.18498	0.95657	0.36666	hbegf	919.738	919.738	919.738		919.738		UP	1	0	
28Day	Phase 0 - rapid depolarisation	0.18498	0.95657	0.36666	scn7a	3855.8	3855.8	3855.8		3855.8		UP	1	0	
7Day	Synthesis of substrates in N-glycan biosynthesis	0.18039	0.92593	0.36844	gnpnat1;neu1;gfpt1	3488.70667	3613.22	3132.03	313.545553	3454.676	347.044078	UP	0.666666667	0.333333333	
7Day	Fanconi Anemia Pathway	0.15633	0.96565	0.36871	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0	
7Day	Glucagon-like Peptide-1 (GLP1) regulates insulin secretion	0.15633	0.96565	0.36871	ltp2	4098.21	4098.21	4098.21		4098.21		DOWN	0	1	
28Day	TP53 Regulates Metabolic Genes	0.17523	0.95957	0.36895	txnrd1	3178.52	3178.52	3178.52		3178.52		UP	1	0	
7Day	Neddylation	0.17947	0.87622	0.36957	dcaf8;btbd1;dcun1d5;fbxo22;cul2;fbxo9;psmd5;psmd6;cop1;dcaf10;fem1c;psmc4;nae1;uba52;psmc2;commd1;ccnf;btcr	3494.13889	3634.375	1001.32	964.08138	3461.56237	1079.97456	UP	0.833333333	0.166666667	
28Day	Synthesis of PIPs at the plasma membrane	0.16595	0.96236	0.37198	pi4k2b	4173.55	4173.55	4173.55		4173.55		UP	1	0	
28Day	Signaling by FGFR1	0.16595	0.96236	0.37198	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1	
28Day	Beta-catenin independent WNT signaling	0.20751	0.911	0.37249	ppp3cb;pf1n1;gnb5	3293.566	4095.87	953.648	2059.51023	2775.44284	2099.86753	UP	1	0	
28Day	Integrin cell surface interactions	0.20751	0.911	0.37249	vtn;fn1;col8a1	2613.49067	3156	447.762	1951.86296	3375.185	1506.1754	DOWN	0.333333333	0.666666667	
90Day	RHO GTPases activate PKNs	0.20935	0.88659	0.37295	hist1h4h;hist1h4i;hist1h3c;ywhaz;h2afx;ar	2498.82283	2975.38	137.958	1764.78432	2050.81594	1694.68636	CONFLICT	0.5	0.5	
90Day	Integrin cell surface interactions	0.20935	0.88659	0.37295	vtn;tnclum;icam1;fn1;itga9	3345.66678	3833.35	45.5307	2012.35797	3331.92876	2418.50495	CONFLICT	0.5	0.5	
90Day	Recruitment of mitotic centrosome proteins and complexes	0.18811	0.90021	0.3737	haus7;dctn3;cntrl;tubb4b;cep76;hsp90aa1	3221.30167	3997.375	426.32	1725.30565	3467.98166	1544.87279	UP	1	0	
90Day	Centrosome maturation	0.18811	0.90021	0.3737	haus7;dctn3;cntrl;tubb4b;cep76;hsp90aa1	3221.30167	3997.375	426.32	1725.30565	3467.98166	1544.87279	UP	1	0	
7Day	RHO GTPases Activate WASPs and WAVES	0.89386	0.23009	0.37489	nckap1;mapk3;cdc42;abl1;brk1	3771.484	3468.74	2624.49	909.396614	4035.8468	882.276231	UP	0.6	0.4	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
90Day	HDACs deacetylate histones	0.17813	0.90647	0.37522	hist1h4h;hist1h4i;hist1h3c;gatad2b;hdac3;hdac2	2918.02017	3546.645	202.162	2012.29586	1830.19513	1944.61876	CONFLICT	0.5	0.5	
28Day	RNA Polymerase II Promoter Escape	0.15711	0.96495	0.3757	polr2a	5040.67	5040.67	5040.67		5040.67		UP	1	0	
28Day	RNA Polymerase II Transcription Pre-Initiation And Promoter Opening	0.15711	0.96495	0.3757	polr2a	5040.67	5040.67	5040.67		5040.67		UP	1	0	
28Day	RNA Polymerase II Transcription Initiation	0.15711	0.96495	0.3757	polr2a	5040.67	5040.67	5040.67		5040.67		UP	1	0	
28Day	RNA Polymerase II Transcription Initiation And Promoter Clearance	0.15711	0.96495	0.3757	polr2a	5040.67	5040.67	5040.67		5040.67		UP	1	0	
28Day	DNA Damage Bypass	0.15711	0.96495	0.3757	pole3	805.318	805.318	805.318		805.318		UP	1	0	
28Day	Mitotic G1-G1/S phases	0.1764	0.92728	0.3759	pole3;cdc6;tfdp1	4127.086	5708.4	805.318	2877.83571	4917.81429	2323.3286	UP	1	0	
28Day	Transport of bile salts and organic acids, metal ions and amine compounds	0.1764	0.92728	0.3759	slc13a5;slc22a1;slc6a13	2214.364	1681.65	151.142	2374.82136	3682.83861	2229.861	DOWN	0.333333333	0.666666667	
90Day	Gap junction assembly	0.88581	0.24465	0.37742	tubb6;tubb4b;tubb2a;tuba1b;gjb2	1916.9702	1781.5	779.791	922.579865	1733.98302	1064.65299	UP	0.6	0.4	
90Day	Mitotic G1-G1/S phases	0.16856	0.9124	0.37746	pole4;cables1;orc6;dbf4;e2f2;cdkn1a	3704.34667	4120.125	913.71	1649.0418	2970.33065	1677.04064	UP	0.666666667	0.333333333	
90Day	SUMO E3 ligases SUMOylate target proteins	0.18105	0.88134	0.37761	hist1h4h;eid3;park7;hist1h4i;nr5a2;nu p153;pml;nfkbia;mdm2;ikbk;hdac2;dd x5;ar;sec13	2821.69924	3568.09	25.9884	1590.20729	2400.75322	1744.05489	CONFLICT	0.5	0.5	
28Day	G beta:gamma signalling through CDC42	0.86225	0.37855	0.37855	gnb5;cdc42	1708.569	1708.569	953.648	1067.61952	1507.0508	1028.87913	UP	1	0	
28Day	Caspase activation via extrinsic apoptotic signalling pathway	0.86225	0.37855	0.37855	tnfrsf10b;ly96	4300.525	4300.525	4040.75	367.377328	4219.52756	349.062933	UP	1	0	
28Day	Conversion from APC/C:Cdc20 to APC/C:Cdh1 in late anaphase	0.86225	0.37855	0.37855	cdc14a;cdc27	3264.516	3264.516	748.272	3558.50639	3689.73493	3507.32739	UP	1	0	
28Day	Purine catabolism	0.86225	0.37855	0.37855	nudt5;pnp	3241.65	3241.65	2482	1074.30733	2885.35398	948.81112	CONFLICT	0.5	0.5	
7Day	Class I MHC mediated antigen processing & presentation	0.1981	0.8541	0.37928	ube2n;btbd1;rnf6;fbxo22;cul2;fbxo9;trm69;ube2v2;ube2k;ube3a;ube2a;ube2e3;uba52;cdc27;cdc34;tap2;sec22b;h2-t23;h2-q10;trip12;ubox5;ube2j2;ccnf;btrc;ww p1	3567.1704	3369.05	1018.89	1053.55378	3616.27808	996.188047	UP	0.8	0.2	
7Day	Anchoring of the basal body to the plasma membrane	0.17955	0.90508	0.37981	cep89;rab11a;tubb4b;tuba4a;nedd1;hs p90aa1	2550.90267	2445.18	919.856	1534.84908	2426.2675	1534.52335	UP	1	0	
90Day	Release of apoptotic factors from the mitochondria	0.93482	0.38016	0.38016	bax	1844.96	1844.96	1844.96		1844.96		UP	1	0	
90Day	Lysosomal oligosaccharide catabolism	0.93482	0.38016	0.38016	man2b1	677.096	677.096	677.096		677.096		DOWN	0	1	
90Day	Mitochondrial ABC transporters	0.93482	0.38016	0.38016	abc8	3667.8	3667.8	3667.8		3667.8		UP	1	0	
90Day	SLIT2:ROBO1 increases RHOA activity	0.93482	0.38016	0.38016	myo9b	5309.89	5309.89	5309.89		5309.89		DOWN	0	1	
90Day	Ubiquinol biosynthesis	0.93482	0.38016	0.38016	pdss1	5691.78	5691.78	5691.78		5691.78		UP	1	0	
90Day	ATF6 (ATF6-alpha) activates chaperones	0.93482	0.38016	0.38016	mbtps2	3467.51	3467.51	3467.51		3467.51		UP	1	0	
90Day	TRAF6 mediated IRF7 activation	0.93482	0.38016	0.38016	irf7	5689.7	5689.7	5689.7		5689.7		UP	1	0	
90Day	Scavenging by Class B Receptors	0.93482	0.38016	0.38016	apob	175.96	175.96	175.96		175.96		DOWN	0	1	
90Day	Sulfide oxidation to sulfate	0.93482	0.38016	0.38016	suox	3807.07	3807.07	3807.07		3807.07		DOWN	0	1	
90Day	Alternative complement activation	0.93482	0.38016	0.38016	c3	639.57	639.57	639.57		639.57		DOWN	0	1	
90Day	ATP sensitive Potassium channels	0.93482	0.38016	0.38016	kcnj8	2260.22	2260.22	2260.22		2260.22		UP	1	0	
90Day	Interleukin-18 signaling	0.93482	0.38016	0.38016	il18bp	3115.46	3115.46	3115.46		3115.46		DOWN	0	1	
90Day	Selenoamino acid metabolism	0.93482	0.38016	0.38016	txnr1	3099.4	3099.4	3099.4		3099.4		UP	1	0	
90Day	Unwinding of DNA	0.93482	0.38016	0.38016	gins1	1127.6	1127.6	1127.6		1127.6		UP	1	0	
90Day	NGF processing	0.93482	0.38016	0.38016	pcsk5	3761.45	3761.45	3761.45		3761.45		DOWN	0	1	
90Day	Expression and Processing of Neurotrophins	0.93482	0.38016	0.38016	pcsk5	3761.45	3761.45	3761.45		3761.45		DOWN	0	1	
90Day	Activated NTRK2 signals through PLCG1	0.93482	0.38016	0.38016	ntrk2	3744.34	3744.34	3744.34		3744.34		DOWN	0	1	
90Day	LRR FLII-interacting protein 1 (LRRFIP1) activates type I IFN production	0.93482	0.38016	0.38016	ctnnb1	4087.04	4087.04	4087.04		4087.04		DOWN	0	1	
90Day	RUNX1 regulates transcription of genes involved in BCR signaling	0.93482	0.38016	0.38016	cbfb	4070.59	4070.59	4070.59		4070.59		UP	1	0	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.														
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
90Day	TRAF3-dependent IRF activation pathway	0.93482	0.38016	0.38016	irf7	5689.7	5689.7	5689.7		5689.7		UP	1	0
90Day	Fructose catabolism	0.93482	0.38016	0.38016	tkfc	1863.37	1863.37	1863.37		1863.37		UP	1	0
90Day	Reuptake of GABA	0.93482	0.38016	0.38016	slc6a12	3445.15	3445.15	3445.15		3445.15		DOWN	0	1
90Day	Scavenging by Class H Receptors	0.93482	0.38016	0.38016	apob	175.96	175.96	175.96		175.96		DOWN	0	1
90Day	HDR through Homologous Recombination (HRR) or Single Strand Annealing (SSA)	0.2097	0.86965	0.38215	hist1h4h;babam1;pole4;ppp4c;hist1h4i;polk;rad51;h2afx;brca2;rad51c	4045.4582	4046.18	513.022	1470.8127	3606.13368	1521.5189	UP	0.7	0.3
7Day	Recruitment and ATM-mediated phosphorylation of repair and signaling proteins at DNA double strand breaks	0.86502	0.23928	0.38224	ube2n;ube2v2;rnf168;hist1h4h;babam1;hist1h2bc;uba52;abl1	3577.685	3431.595	2423.08	684.390117	3444.78005	685.408558	UP	0.75	0.25
90Day	Beta-oxidation of very long chain fatty acids	0.23799	1	0.38313										
90Day	Regulation of TP53 Activity through Methylation	0.23799	1	0.38313										
90Day	Interleukin-35 Signalling	0.23799	1	0.38313										
90Day	Zinc transporters	0.23799	1	0.38313										
90Day	Pregnenolone biosynthesis	0.23799	1	0.38313										
90Day	Interleukin-2 signaling	0.23799	1	0.38313										
90Day	Sodium/Calcium exchangers	0.23799	1	0.38313										
90Day	Ionotropic activity of kainate receptors	0.23799	1	0.38313										
90Day	Activation of Ca-permeable Kainate Receptor	0.23799	1	0.38313										
90Day	Activation of the TFAP2 (AP-2) family of transcription factors	0.23799	1	0.38313										
90Day	Synthesis of IP2, IP, and Ins in the cytosol	0.23799	1	0.38313										
28Day	Death Receptor Signalling	0.20873	0.88565	0.38317	tax1bp1;tnfrsf10b;arhgdia;sqstm1;ikbk g;birc2	5157.53167	5194.76	4040.75	657.083981	5090.48747	657.56748	UP	0.833333333	0.166666667
90Day	ERKs are inactivated	0.21114	1	0.38485										
90Day	FGFRL1 modulation of FGFR1 signaling	0.21114	1	0.38485										
90Day	Notch-HLH transcription pathway	0.21114	1	0.38485										
90Day	Synthesis of PIPs at the early endosome membrane	0.21114	1	0.38485										
90Day	mRNA decay by 5' to 3' exonibonuclease	0.21114	1	0.38485										
90Day	Glycogen breakdown (glycogenolysis)	0.21114	1	0.38485										
90Day	Glycogen synthesis	0.21114	1	0.38485										
28Day	Interleukin-1 signaling	0.883	0.24439	0.38509	ube2n;sqstm1;il1rap;ikbk g;app	4940.87	5266.71	3705.51	791.86401	5097.48088	859.756978	DOWN	0.4	0.6
7Day	PTK6 Regulates RHO GTPases, RAS GTPase and MAP kinases	0.8611	0.38548	0.38548	rasa1;kras	4972.395	4972.395	4158.71	1150.72436	5283.81236	1063.11101	CONFLICT	0.5	0.5
7Day	KSRP (KHSRP) binds and destabilizes mRNA	0.8611	0.38548	0.38548	dcp2;ywhaz	3109.105	3109.105	2726.98	540.406358	3045.31761	532.823957	UP	1	0
7Day	Cell-extracellular matrix interactions	0.8611	0.38548	0.38548	vasp;flna	4212.71	4212.71	3557.63	926.42302	4355.77345	904.060458	DOWN	0	1
7Day	p75NTR signals via NF-kB	0.8611	0.38548	0.38548	uba52;prkci	4085.4	4085.4	3409.24	956.234642	4275.2759	917.757582	UP	1	0
7Day	Other semaphorin interactions	0.8611	0.38548	0.38548	sema4d;sema4a	5652.975	5652.975	5514.77	195.451385	5725.74518	166.163307	DOWN	0	1
7Day	Downregulation of TGF-beta receptor signaling	0.8611	0.38548	0.38548	uba52;tgfb1	5206.805	5206.805	4761.56	629.671518	5273.58539	622.548776	UP	1	0
7Day	Methylation	0.8611	0.38548	0.38548	ahcy;gm4737	2894.795	2894.795	2019.09	1238.43389	3236.60399	1140.19811	DOWN	0	1
7Day	Reduction of cytosolic Ca++ levels	0.8611	0.38548	0.38548	calm3;calm2	3983.44	3983.44	3050.32	1319.63096	3556.9103	1173.69957	CONFLICT	0.5	0.5
7Day	DNA Double Strand Break Response	0.85521	0.25277	0.38748	ube2n;ube2v2;rnf168;hist1h4h;babam1;hist1h2bc;uba52;abl1	3577.685	3431.595	2423.08	684.390117	3444.78005	685.408558	UP	0.75	0.25
7Day	WNT5A-dependent internalization of FZD4	0.22635	1	0.38847										
7Day	SUMOylation of transcription factors	0.22635	1	0.38847										
7Day	Insulin processing	0.22635	1	0.38847										
7Day	Anchoring fibril formation	0.22635	1	0.38847										

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
28Day	Regulation of RAS by GAPs	0.22423	1	0.39558										
28Day	NCAM1 interactions	0.22423	1	0.39558										
28Day	Metal ion SLC transporters	0.22423	1	0.39558										
7Day	SHC1 events in ERBB2 signaling	0.18564	1	0.39715										
7Day	G beta:gamma signalling through BTK	0.18564	1	0.39715										
7Day	Synthesis, secretion, and deacylation of Ghrelin	0.18564	1	0.39715										
7Day	Visual phototransduction	0.83015	0.26206	0.39773	akr1c6;metap2;apob;ttr;rdh16f2;sdca3;rgs9;lrp1;calm3;calm2;apoe;akr1c14	3329.32883	3349.655	113.316	1742.98114	3338.017	1322.70907	DOWN	0.333333333	0.666666667
28Day	Cellular hexose transport	0.2088	1	0.39775										
28Day	CD209 (DC-SIGN) signaling	0.2088	1	0.39775										
28Day	Transcriptional regulation by the AP-2 (TFAP2) family of transcription factors	0.2088	1	0.39775										
90Day	p75 NTR receptor-mediated signalling	0.22127	0.87328	0.39817	arhgef6;fgd4;vav1;tiam1;sos1;psen2;nfbia	4733.14714	4586.54	3135.19	1166.20331	4863.56928	1187.56504	DOWN	0.142857143	0.857142857
90Day	Factors involved in megakaryocyte development and platelet production	0.19989	0.87392	0.39958	tubb6;hist1h3c;tubb4b;tubb2a;tuba1b;hdac2;cdc42;cbx5;rad51c;dock9;kifc1	1840.02618	1722.38	156.487	1550.4745	1737.85424	1637.55179	UP	0.818181818	0.181818182
90Day	Import of palmitoyl-CoA into the mitochondrial matrix	0.16617	1	0.40088										
90Day	Translesion synthesis by POLI	0.16617	1	0.40088										
90Day	Asymmetric localization of PCP proteins	0.16617	1	0.40088										
90Day	Processive synthesis on the lagging strand	0.16617	1	0.40088										
28Day	Cobalamin (Cbl, vitamin B12) transport and metabolism	0.19443	1	0.40141										
90Day	Signaling by NTRK1 (TRKA)	0.22836	0.88973	0.40228	irs2;mapk14;sos1;ap2m1	3303.81333	3622.755	74.8133	2460.41598	2955.19946	3083.33332	DOWN	0.25	0.75
90Day	CDT1 association with the CDC6:ORC:origin complex	0.22836	0.88973	0.40228	psmd8;orc6;psmc4;psmf1	2195.2195	2213.18	186.178	1757.71062	2242.33342	1753.93797	UP	1	0
90Day	SIRT1 negatively regulates rRNA expression	0.21502	0.89763	0.40235	hist1h4h;hist1h4i;hist1h3c;h2afx	3214.00725	3979.26	811.859	1602.37406	2298.31583	1843.92338	CONFLICT	0.5	0.5
90Day	RNA Polymerase I Promoter Opening	0.21502	0.89763	0.40235	hist1h4h;hist1h4i;hist1h3c;h2afx	3214.00725	3979.26	811.859	1602.37406	2298.31583	1843.92338	CONFLICT	0.5	0.5
90Day	Nonhomologous End-Joining (NHEJ)	0.21502	0.89763	0.40235	hist1h4h;babam1;hist1h4i;h2afx	4461.0475	4046.18	3951.81	894.337005	4412.91487	861.771604	CONFLICT	0.5	0.5
7Day	Transport of inorganic cations/anions and amino acids/oligopeptides	0.20647	0.88273	0.40294	slc20a1;slc1a2;slc12a7;slc8b1;calm3;calm2;slc12a6	3204.57857	3050.32	1710.87	1160.4099	3133.06323	998.250535	DOWN	0.285714286	0.714285714
90Day	Negative epigenetic regulation of rRNA expression	0.2023	0.90504	0.40346	hist1h4h;hist1h4i;hist1h3c;h2afx	3214.00725	3979.26	811.859	1602.37406	2298.31583	1843.92338	CONFLICT	0.5	0.5
7Day	Prostacyclin signalling through prostacyclin receptor	0.16812	1	0.40543										
28Day	DNA strand elongation	0.18105	1	0.40642										
28Day	Activation of G protein gated Potassium channels	0.18105	1	0.40642										
28Day	G protein gated Potassium channels	0.18105	1	0.40642										
28Day	Inhibition of voltage gated Ca2+ channels via Gbeta/gamma subunits	0.18105	1	0.40642										
28Day	Regulation of Hypoxia-inducible Factor (HIF) by oxygen	0.18105	1	0.40642										
28Day	Cellular response to hypoxia	0.18105	1	0.40642										
7Day	RMTs methylate histone arginines	0.21949	0.89434	0.40686	prmt3;hist1h4h;hist2h2ac;hist2h2aa1	3747.9	3796.91	2008.38	1417.74679	3847.08019	1329.43276	CONFLICT	0.5	0.5
7Day	Signaling by NTRKs	0.20873	0.90068	0.40753	mapk3;ppp2cb;pcsk5;kras	4284.7675	4355.895	3627.04	511.924296	4177.70071	574.511106	CONFLICT	0.5	0.5
7Day	Biosynthesis of the N-glycan precursor (dolichol lipid-linked oligosaccharide, LLO) and transfer to a nascent protein	0.20873	0.90068	0.40753	gnpnat1;neu1;gfpt1;alg9	3673.235	3667.045	3132.03	449.158509	3575.95319	442.141891	CONFLICT	0.5	0.5
7Day	Loss of Nlp from mitotic centrosomes	0.19839	0.90669	0.4089	tubb4b;tuba4a;nedd1;hsp90aa1	1703.9565	1410.635	919.856	998.985626	1609.23265	1031.31055	UP	1	0
7Day	Loss of proteins required for interphase microtubule organization from the centrosome	0.19839	0.90669	0.4089	tubb4b;tuba4a;nedd1;hsp90aa1	1703.9565	1410.635	919.856	998.985626	1609.23265	1031.31055	UP	1	0
7Day	Synthesis of DNA	0.18846	0.91237	0.41095	uba52;cdc27;prim2;ccne2	4309.1175	4302.165	3870.58	436.798058	4459.0906	388.783432	UP	1	0
7Day	Rab regulation of trafficking	0.84065	0.24469	0.41158	rab3gap2;trappc6b;trappc8;trappc13;0610009b22rik;rab9;rab11a;dennd4c;rab6a;rab18;rab10;rab1a;hps4	3446.06615	3553.68	1046.66	1001.43544	3219.80464	836.314437	UP	0.846153846	0.153846154

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
90Day	RA biosynthesis pathway	0.83926	0.31261	0.41263	rdh7;adh4;aldh1a7;aldh8a1;rdh11	3741.732	3277.15	2740.9	1218.47664	3770.57211	1434.78885	UP	0.8	0.2	
28Day	Effects of PIP2 hydrolysis	0.16859	1	0.41265											
28Day	VEGFA-VEGFR2 Pathway	0.21772	0.89454	0.41296	pdpk1;mapkapk2;cdc42;brk1	3372.312	3919.245	192.988	2536.00426	4213.88679	1981.66272	DOWN	0.25	0.75	
90Day	Regulation of pyruvate dehydrogenase (PDH) complex	0.90297	0.26647	0.41389	pdck4;pdck1;gstz1	4115.21	3345.98	3209.99	1451.70948	3914.67407	1357.04203	DOWN	0.333333333	0.666666667	
90Day	Syndecan interactions	0.90297	0.26647	0.41389	vtg;sdca4;fn1	928.602233	630.216	45.5307	1064.11751	649.620371	1014.84371	DOWN	0	1	
90Day	Platelet degranulation	0.22429	0.8532	0.41458	spp2;trf;tlm1;serpina1e;psap;plg;fn1;ecm1;anxa5;ahsg;actn1;scppdh	2421.70252	2481.665	82.4742	1669.5291	2984.03278	1802.70421	DOWN	0.083333333	0.916666667	
28Day	Anchoring of the basal body to the plasma membrane	0.19516	0.9078	0.41582	dynl1;rab11a;ubb4b;ttbk2	3168.02	2343.81	2192.92	1750.5057	3398.35091	1878.93645	UP	0.75	0.25	
7Day	Plasma lipoprotein assembly	0.90292	0.2636	0.41585	apob;apo;apoec1	1959.152	1999.21	113.316	1826.13655	3047.84336	1482.79348	DOWN	0	1	
7Day	Oxygen-dependent proline hydroxylation of Hypoxia-inducible Factor Alpha	0.90292	0.2636	0.41585	cul2;uba52;egl1	4522.97667	4498.76	4308.61	227.443973	4513.18547	247.67794	UP	0.666666667	0.333333333	
7Day	Post NMDA receptor activation events	0.90292	0.2636	0.41585	prkar2a;calm3;calm2	4011.14667	4066.56	3050.32	934.353205	3661.3101	940.743026	DOWN	0.333333333	0.666666667	
28Day	ISG15 antiviral mechanism	0.90104	0.26299	0.41998	ube2n;arih1;ppm1b	4090.57	5266.71	1290.26	2435.46398	2838.72879	2524.17867	DOWN	0.333333333	0.666666667	
28Day	TAK1 activates NFkB by phosphorylation and activation of IKKs complex	0.90104	0.26299	0.41998	ube2n;ikkb;app	5104.95333	5266.71	4630.47	417.790391	5134.26949	435.986687	DOWN	0.333333333	0.666666667	
28Day	Interconversion of nucleotide di- and triphosphates	0.90104	0.26299	0.41998	nme4;txnr1;guk1	4741.02333	5240	3178.52	1382.2958	4869.76023	1349.71028	UP	0.666666667	0.333333333	
28Day	Cytosolic sulfonation of small molecules	0.90104	0.26299	0.41998	sult2a8;abhd14b;sult2a7	3437.08	4127.93	1389.09	1804.62818	3827.35854	1658.62082	DOWN	0.333333333	0.666666667	
7Day	RNA polymerase II transcribes snRNA genes	0.84443	0.25988	0.42092	rprd2;ints13;rprd1b;ssu72;zc3h8;phax;polr2h;ell2;ccnk	3273.98444	3652.28	1662.33	983.667799	3432.99013	705.824778	UP	1	0	
90Day	G2/M Checkpoints	0.21089	0.87589	0.42125	hist1h4h;babam1;orc6;hist1h4i;gtse1;dbf4;ywhaz;h2afx	3406.016	3979.26	137.958	1687.57608	3339.52629	1447.23226	UP	0.75	0.25	
28Day	Apoptosis	0.85263	0.24727	0.42176	dnm1;dynl1;tnfrsf10b;sept4;pkp1;ly96;kpna1;bcl2l1;birc2	4098.76578	4560.3	211.182	1937.78356	4222.81278	1594.84798	UP	1	0	
90Day	Oxidative Stress Induced Senescence	0.20109	0.88266	0.42251	hist1h4h;cbx6;hist1h4i;hist1h3c;mapk14;txn1;mdm2;h2afx	3317.69475	3979.26	744.949	1631.71413	2616.77139	1797.82337	CONFLICT	0.5	0.5	
90Day	Plasma lipoprotein assembly, remodeling, and clearance	0.83324	0.27593	0.42331	ces3a;apob;pcsk5;lpc;ces3b;bmp1;apo e;apoc3;ap2m1	2647.15211	3047.49	175.96	1714.24418	2494.70359	1796.92696	DOWN	0.111111111	0.888888889	
90Day	GPVI-mediated activation cascade	0.24608	0.90912	0.42391	vav1;cdc42	2158.7685	2158.7685	156.487	2831.65365	2296.14268	2824.98125	CONFLICT	0.5	0.5	
90Day	Degradation of beta-catenin by the destruction complex	0.24608	0.90912	0.42391	ctnnb1;btrc	4619.87	4619.87	4087.04	753.535412	5033.38781	475.206971	DOWN	0	1	
90Day	Glucagon-like Peptide-1 (GLP1) regulates insulin secretion	0.24608	0.90912	0.42391	gng11;kcns3	5349.345	5349.345	4854.24	700.184206	5679.2676	522.072862	UP	1	0	
90Day	RHO GTPases Activate WASPs and WAVes	0.22856	0.91746	0.42418	wasf2;cdc42	2729.3135	2729.3135	156.487	3638.52613	2386.31403	3606.04702	CONFLICT	0.5	0.5	
90Day	SUMOylation of transcription cofactors	0.22856	0.91746	0.42418	park7;ddx5	1939.5342	1939.5342	25.9884	2706.16242	669.441381	2024.11549	CONFLICT	0.5	0.5	
90Day	Activation of Matrix Metalloproteinases	0.21208	0.92508	0.42611	plg;mmp2	3039.485	3039.485	668.86	3352.57003	3567.16565	3268.4602	DOWN	0	1	
90Day	Cooperation of PDCL (PhLP1) and TRiC/CCT in G-protein beta folding	0.21208	0.92508	0.42611	gng11;gna13	5378.655	5378.655	4854.24	741.634805	5266.80756	724.570551	UP	1	0	
7Day	Receptor-type tyrosine-protein phosphatases	0.88725	0.29022	0.42809	ptprf;ptprd;il1rap	1132.78467	1019.97	131.024	1062.66875	894.670977	1177.96202	DOWN	0	1	
7Day	FRS-mediated FGFR3 signaling	0.88725	0.29022	0.42809	ptpn11;kras;fgf1	3478.71333	3629.67	2647.76	766.702949	3262.18888	788.939216	UP	0.666666667	0.333333333	
7Day	Citric acid cycle (TCA cycle)	0.88725	0.29022	0.42809	sdha;idh2;idh3b	2119.2	2704.94	114.56	1785.35012	2865.72033	1459.09968	DOWN	0	1	
7Day	Synthesis of Prostaglandins (PG) and Thromboxanes (TX)	0.88725	0.29022	0.42809	akr1c6;ptges3;akr1c14	3632.50667	3138.45	2842.81	1121.54702	3231.69332	834.302096	UP	1	0	
28Day	Synthesis of Leukotrienes (LT) and Eoxins (EX)	0.8898	0.28209	0.42827	mapkapk2;ita4h;cyp4a12b	5315.31667	5375	4766.57	521.472889	5169.46224	585.253197	DOWN	0.333333333	0.666666667	
7Day	Interleukin-2 family signaling	0.24385	0.90945	0.42852	stat1;jak1	3735.595	3735.595	3554.32	256.361564	3703.94	252.422609	UP	1	0	
7Day	PCP/CE pathway	0.24385	0.90945	0.42852	uba52;pfn1	3933.96	3933.96	3106.36	1170.40314	4147.24454	1130.86822	UP	1	0	
7Day	Vasopressin regulates renal water homeostasis via Aquaporins	0.24385	0.90945	0.42852	rab11a;prkar2a	4304.455	4304.455	4066.56	336.434335	4288.10382	335.638705	CONFLICT	0.5	0.5	
7Day	Metabolism of steroid hormones	0.22937	0.91639	0.42893	hsd17b2;hsd11b1	2230.17	2230.17	119.56	2984.85329	2092.72536	2978.5176	CONFLICT	0.5	0.5	
7Day	Chromosome Maintenance	0.22937	0.91639	0.42893	cenpk;prim2	3958.635	3958.635	3911.13	67.1822153	3938.19452	60.6450649	UP	1	0	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
7Day	TP53 Regulates Transcription of DNA Repair Genes	0.22937	0.91639	0.42893	polr2h;ccnk	3035.2	3035.2	2105.8	1314.37008	3590.43465	1054.03875	UP	1	0
90Day	Signaling by Erythropoietin	0.8839	0.2987	0.42948	irs2;vav1;gab1	1454.0971	126.428	74.8133	2344.43203	1038.75826	2111.79854	DOWN	0	1
90Day	GAB1 signalosome	0.8839	0.2987	0.42948	tgfa;gab1;areg	2086.44267	2162.51	126.428	1923.10963	2211.30125	1359.24692	UP	0.666666667	0.333333333
90Day	Adherens junctions interactions	0.19659	0.93203	0.42961	afdn;ctnnb1	2442.127	2442.127	797.214	2326.25827	1451.95914	1857.58251	CONFLICT	0.5	0.5
90Day	O-glycosylation of TSR domain-containing proteins	0.19659	0.93203	0.42961	adamts5;spon2	3255.88	3255.88	2653.16	852.374798	3005.16209	775.128281	CONFLICT	0.5	0.5
90Day	Cyclin D associated events in G1	0.19659	0.93203	0.42961	e2f2;cdkn1a	2581.665	2581.665	913.71	2358.84458	2049.72117	2235.66976	UP	1	0
90Day	G1 Phase	0.19659	0.93203	0.42961	e2f2;cdkn1a	2581.665	2581.665	913.71	2358.84458	2049.72117	2235.66976	UP	1	0
90Day	Binding and Uptake of Ligands by Scavenger Receptors	0.19659	0.93203	0.42961	apob;apoE	962.89	962.89	175.96	1112.88708	1105.17513	1094.54444	DOWN	0	1
90Day	Regulation of mRNA stability by proteins that bind AU-rich elements	0.19659	0.93203	0.42961	exosc9;ywhaz	1471.424	1471.424	137.958	1885.8057	1856.1388	1805.61685	UP	1	0
90Day	Chaperonin-mediated protein folding	0.19659	0.93203	0.42961	gng11;gna13	5378.655	5378.655	4854.24	741.634805	5266.80756	724.570551	UP	1	0
90Day	Protein folding	0.19659	0.93203	0.42961	gng11;gna13	5378.655	5378.655	4854.24	741.634805	5266.80756	724.570551	UP	1	0
90Day	Translesion synthesis by Y family DNA polymerases bypasses lesions on DNA template	0.19659	0.93203	0.42961	pole4;polk	4753.255	4753.255	3652.71	1556.40567	3884.77714	955.97646	CONFLICT	0.5	0.5
90Day	Activation of ATR in response to replication stress	0.19659	0.93203	0.42961	orc6;dbf4	3568.52	3568.52	2968.7	848.273579	3583.49623	848.009133	UP	1	0
7Day	PI3K Cascade	0.21561	0.92283	0.43047	ptpn11;fgf1	3138.715	3138.715	2647.76	694.31522	2984.26892	659.064823	CONFLICT	0.5	0.5
7Day	RNA Polymerase I Transcription Initiation	0.21561	0.92283	0.43047	polr2h;ubtf	2970.455	2970.455	1976.31	1405.93334	3441.15761	1238.35644	UP	1	0
28Day	SUMO E3 ligases SUMOylate target proteins	0.2156	0.87133	0.43085	hist1h4i;rad21;mdm2;ikbkg;brca1;bmi1;blm;tptr	3945.312	4027.865	692.086	1781.08975	3897.46085	1655.95085	UP	0.875	0.125
7Day	IRS-mediated signalling	0.20253	0.9288	0.43309	ptpn11;fgf1	3138.715	3138.715	2647.76	694.31522	2984.26892	659.064823	CONFLICT	0.5	0.5
7Day	Phase 0 - rapid depolarisation	0.20253	0.9288	0.43309	calm3;calm2	3983.44	3983.44	3050.32	1319.63096	3556.9103	1173.69957	CONFLICT	0.5	0.5
28Day	Mitochondrial protein import	0.90002	0.43399	0.43399	otc	726.832	726.832	726.832		726.832		DOWN	0	1
28Day	Synthesis of UDP-N-acetyl-glucosamine	0.90002	0.43399	0.43399	gfpt1	5852.61	5852.61	5852.61		5852.61		UP	1	0
28Day	HuR (ELAVL1) binds and stabilizes mRNA	0.90002	0.43399	0.43399	set	4060.76	4060.76	4060.76		4060.76		UP	1	0
28Day	Vitamin C (ascorbate) metabolism	0.90002	0.43399	0.43399	cyb5a	5740.08	5740.08	5740.08		5740.08		UP	1	0
28Day	Stabilization of p53	0.90002	0.43399	0.43399	mdm2	2266.61	2266.61	2266.61		2266.61		UP	1	0
28Day	Activated NOTCH1 Transmits Signal to the Nucleus	0.90002	0.43399	0.43399	notch1	908.573	908.573	908.573		908.573		UP	1	0
28Day	SUMOylation of immune response proteins	0.90002	0.43399	0.43399	ikbkg	5417.68	5417.68	5417.68		5417.68		UP	1	0
28Day	Association of Tric/CCT with target proteins during biosynthesis	0.90002	0.43399	0.43399	cct4	5836.87	5836.87	5836.87		5836.87		UP	1	0
28Day	p38MAPK events	0.90002	0.43399	0.43399	mapkapk2	5375	5375	5375		5375		DOWN	0	1
28Day	SUMOylation of ubiquitylation proteins	0.90002	0.43399	0.43399	mdm2	2266.61	2266.61	2266.61		2266.61		UP	1	0
28Day	Phosphate bond hydrolysis by NUDT proteins	0.90002	0.43399	0.43399	nudt5	2482	2482	2482		2482		UP	1	0
28Day	Receptor Mediated Mitophagy	0.90002	0.43399	0.43399	atg5	5747.14	5747.14	5747.14		5747.14		UP	1	0
28Day	Telomere C-strand synthesis initiation	0.90002	0.43399	0.43399	pole3	805.318	805.318	805.318		805.318		UP	1	0
28Day	DNA replication initiation	0.90002	0.43399	0.43399	pole3	805.318	805.318	805.318		805.318		UP	1	0
28Day	CDT1 association with the CDC6;ORC;origin complex	0.81587	0.33942	0.43432	psmd6;psmd8;cdc6;psmf1;psmb8	3966.316	4413.43	1415.14	1680.76279	4053.96174	1828.75774	DOWN	0.4	0.6
28Day	Signaling by the B Cell Receptor (BCR)	0.22957	0.91538	0.43521	ppp3cb;ikbkg	4756.775	4756.775	4095.87	934.660814	4545.37184	885.555333	UP	1	0
90Day	C-type lectin receptors (CLRs)	0.24422	0.87082	0.43594	ube2m;cdc34;nfkbia;ikbkg;btrc	2653.3084	3265.56	569.072	1985.29402	2657.76128	2167.87416	UP	0.6	0.4
90Day	HATs acetylate histones	0.24422	0.87082	0.43594	msl1;hist1h4h;mcrs1;hist1h4i;hist1h3c	3183.1678	3951.81	811.859	2119.24618	2113.0481	1882.23775	UP	0.6	0.4
90Day	Assembly of the pre-replicative complex	0.24422	0.87082	0.43594	psmd8;orc6;e2f2;psmc4;psmf1	2606.0996	3031.27	186.178	1777.9967	2622.61858	1763.81664	UP	1	0
28Day	Cap-dependent Translation Initiation	0.21959	0.92011	0.4363	eif3m;eif1ax	2737.81	2737.81	1517.45	1725.84966	2423.68091	1667.69388	CONFLICT	0.5	0.5
90Day	Toll Like Receptor 3 (TLR3) Cascade	0.21876	0.88708	0.43697	irf7;mapk14;nfkbia;ikbkg;btrc	4394.204	4261.96	3265.56	1021.51429	4535.14678	1084.60939	DOWN	0.4	0.6
28Day	MAPK6/MAPK4 signaling	0.87802	0.3013	0.43742	sept7;cdc14a;cdc42	2996.03733	2463.49	748.272	2555.99239	3546.69811	2573.36962	UP	1	0
28Day	Gluconeogenesis	0.87802	0.3013	0.43742	slc25a10;pcx;pck1	3333.02667	3209.5	3056.49	354.811243	3331.76336	350.089935	DOWN	0.333333333	0.666666667

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
28Day	Synthesis of active ubiquitin: roles of E1 and E2 enzymes	0.87802	0.3013	0.43742	ube2g1;ube2k;uchl3	4450.56667	4043.68	4034.64	712.591585	4474.78803	724.761299	UP	0.666666667	0.333333333	
28Day	DDX58/IFIH1-mediated induction of interferon-alpha/beta	0.87802	0.3013	0.43742	tax1bp1;ikbk;app	5005.61333	4968.69	4630.47	394.901754	5021.48956	301.863796	DOWN	0.333333333	0.666666667	
28Day	EGFR downregulation	0.87802	0.3013	0.43742	hgs;hbegf;cdc42	2201.316	2463.49	919.738	1172.68109	2028.69886	1124.36761	UP	1	0	
28Day	Pyruvate metabolism	0.87802	0.3013	0.43742	me1;ldha;gstz1	5509.17333	5449.12	5233.2	310.388148	5608.35417	296.13799	DOWN	0	1	
28Day	Programmed Cell Death	0.81693	0.2938	0.43779	dnm1;dynl1;tnfrsf10b;sept4;pkp1;ly9	4098.76578	4560.3	211.182	1937.78356	4222.81278	1594.84798	UP	1	0	
28Day	Eukaryotic Translation Initiation	0.20997	0.9246	0.43796	eif3m;eif1ax	2737.81	2737.81	1517.45	1725.84966	2423.68091	1667.69388	CONFLICT	0.5	0.5	
90Day	RMTs methylate histone arginines	0.2068	0.89453	0.43878	smarcd2;hist1h4h;hist1h4i;hist1h3c;smarcb1	3700.1278	3970.56	811.859	1789.86064	3394.25997	2201.30818	DOWN	0.4	0.6	
28Day	Regulation of actin dynamics for phagocytic cup formation	0.2007	0.92885	0.44015	cdc42;brk1	3960.63	3960.63	2463.49	2117.27569	4417.2828	2016.38111	CONFLICT	0.5	0.5	
7Day	Beta-catenin independent WNT signaling	0.24384	0.87034	0.44033	uba52;pfn1;ctnnb1;calm3;calm2	3177.86464	3106.36	54.5232	1956.25886	2843.19005	1975.40546	UP	0.6	0.4	
90Day	Mitochondrial Fatty Acid Beta-Oxidation	0.85699	0.2724	0.44087	acad10;ndufab1;pccb;acaa2;mut;pcca	1850.32883	2143.53	105.476	1410.64201	2371.80545	1194.37732	DOWN	0.166666667	0.833333333	
7Day	Gene Silencing by RNA	0.22262	0.88399	0.44117	hist1h4h;hist1h2bc;hist2h2ac;polr2h;hist2h2aa1	4073.244	3964.6	3406.55	810.921331	4033.48029	829.513011	UP	0.6	0.4	
7Day	Signaling by FGFR1	0.8624	0.26295	0.44131	mapk3;uba52;ptpn11;ppp2cb;kras;fgf1	3937.49667	3894.19	2647.76	815.708654	3810.92898	853.996178	UP	0.666666667	0.333333333	
7Day	CTLA4 inhibitory signaling	0.87055	0.31702	0.44187	yes1;ptpn11;ppp2cb	3759.22	3629.67	3627.04	226.668643	3744.87584	220.142069	UP	1	0	
7Day	Regulation of RAS by GAPs	0.87055	0.31702	0.44187	uba52;rasa1;kras	4902.11667	4761.56	4158.71	822.739577	5136.80433	831.742073	UP	0.666666667	0.333333333	
7Day	Synthesis of epoxy (EET) and dihydroxyeicosatrienoic acids (DHET)	0.87055	0.31702	0.44187	ephx2;cyp2c37;cyp2c29	2023.18057	2593.25	93.6517	1717.00186	2278.23391	1552.8981	DOWN	0.333333333	0.666666667	
7Day	Common Pathway of Fibrin Clot Formation	0.87055	0.31702	0.44187	f5;f2;serpinc1	162.215167	156.627	85.9375	79.2197094	194.700484	66.2186001	DOWN	0	1	
28Day	EPH-Ephrin signaling	0.19178	0.93287	0.44285	epha7;cdc42	4147.25	4147.25	2463.49	2381.19623	4157.06877	2381.15574	UP	1	0	
28Day	HDR through Homologous Recombination (HRR)	0.86085	0.26285	0.44604	rmi1;pole3;rad51d;rad51;brca1;blm	3062.16233	3608.735	692.086	1945.73971	3555.697	1478.95115	UP	1	0	
90Day	Eicosanoids	0.86335	0.33111	0.44712	cyp4f16;cyp4a12a;cyp4a12b	3624.98	3568.65	3465.22	194.153566	3583.99801	170.385902	UP	1	0	
7Day	PIP3 activates AKT signaling	0.21866	0.85238	0.44713	rraga;suz12;mapk3;uba52;ptpn11;pten;ppp2cb;il1rap;fgf1;csnk2b;cdkn1a;casp9;bmi1;xiap	3449.89529	3426.385	131.024	1256.33563	3350.39421	1322.94503	UP	0.642857143	0.357142857	
28Day	ER-Phagosome pathway	0.86573	0.32057	0.44732	tap1;h2-q7;h2-d1	3562.11333	3718.12	1188.24	2299.84187	3462.70475	1959.38094	DOWN	0.333333333	0.666666667	
28Day	Glyoxylate metabolism and glycine degradation	0.86573	0.32057	0.44732	ndufab1;prodh2;got2	2474.68	2384.42	1721.17	802.45623	2449.32669	832.107975	DOWN	0	1	
7Day	Vasopressin-like receptors	0.89697	0.44786	0.44786	avpr1a	836.92	836.92	836.92		836.92		UP	1	0	
7Day	Degradation of GLI1 by the proteasome	0.89697	0.44786	0.44786	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0	
7Day	Regulation of ornithine decarboxylase (ODC)	0.89697	0.44786	0.44786	nqo1	1137.09	1137.09	1137.09		1137.09		UP	1	0	
7Day	FGFR1b ligand binding and activation	0.89697	0.44786	0.44786	fgf1	2647.76	2647.76	2647.76		2647.76		DOWN	0	1	
7Day	Molybdenum cofactor biosynthesis	0.89697	0.44786	0.44786	mocs1	3839.03	3839.03	3839.03		3839.03		DOWN	0	1	
7Day	Glucocorticoid biosynthesis	0.89697	0.44786	0.44786	hsd11b1	119.56	119.56	119.56		119.56		DOWN	0	1	
7Day	MET Receptor Activation	0.89697	0.44786	0.44786	hgfac	186.634	186.634	186.634		186.634		DOWN	0	1	
7Day	Attachment of GPI anchor to uPAR	0.89697	0.44786	0.44786	gpaa1	5658.97	5658.97	5658.97		5658.97		DOWN	0	1	
7Day	Interleukin-10 signaling	0.89697	0.44786	0.44786	jak1	3554.32	3554.32	3554.32		3554.32		UP	1	0	
7Day	Lipid particle organization	0.89697	0.44786	0.44786	fitm1	3812.67	3812.67	3812.67		3812.67		UP	1	0	
7Day	Eukaryotic Translation Termination	0.89697	0.44786	0.44786	gspt1	5370.24	5370.24	5370.24		5370.24		DOWN	0	1	
7Day	mRNA Editing	0.89697	0.44786	0.44786	adar	3802.37	3802.37	3802.37		3802.37		UP	1	0	
7Day	Regulation of expression of SLITs and ROBOs	0.89697	0.44786	0.44786	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0	
7Day	activated TAK1 mediates p38 MAPK activation	0.89697	0.44786	0.44786	map2k3	2894.34	2894.34	2894.34		2894.34		DOWN	0	1	
7Day	TNFR1-mediated ceramide production	0.89697	0.44786	0.44786	smpd2	5795.86	5795.86	5795.86		5795.86		DOWN	0	1	
7Day	CREB1 phosphorylation through the activation of Adenylate Cyclase	0.89697	0.44786	0.44786	prkar2a	4066.56	4066.56	4066.56		4066.56		DOWN	0	1	
7Day	AMPK inhibits chREBP transcriptional activation activity	0.89697	0.44786	0.44786	adipor2	5199.91	5199.91	5199.91		5199.91		DOWN	0	1	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
7Day	Negative feedback regulation of MAPK pathway	0.89697	0.44786	0.44786	mapk3	4800.24	4800.24	4800.24		4800.24		DOWN	0	1
7Day	Protein repair	0.89697	0.44786	0.44786	msrb1	2837.64	2837.64	2837.64		2837.64		DOWN	0	1
90Day	Gap junction trafficking	0.84244	0.29267	0.44841	tubb6;tubb4b;tubb2a;tuba1b;gjb2;ap2m1	2094.7335	1866.255	779.791	933.017487	1798.35123	1060.01907	UP	0.666666667	0.333333333
90Day	GRB7 events in ERBB2 signaling	0.89934	0.45003	0.45003	nrg1	3912.34	3912.34	3912.34		3912.34		UP	1	0
90Day	Extrinsic Pathway of Fibrin Clot Formation	0.89934	0.45003	0.45003	f7	3350.52	3350.52	3350.52		3350.52		DOWN	0	1
90Day	Activation of C3 and C5	0.89934	0.45003	0.45003	c3	639.57	639.57	639.57		639.57		DOWN	0	1
90Day	MET activates PTPN11	0.89934	0.45003	0.45003	gab1	126.428	126.428	126.428		126.428		DOWN	0	1
90Day	Adenosine P1 receptors	0.89934	0.45003	0.45003	adora1	1587.43	1587.43	1587.43		1587.43		DOWN	0	1
90Day	Abacavir transport and metabolism	0.89934	0.45003	0.45003	slc22a1	1050.57	1050.57	1050.57		1050.57		DOWN	0	1
90Day	Condensation of Prometaphase Chromosomes	0.89934	0.45003	0.45003	smc4	2814.71	2814.71	2814.71		2814.71		UP	1	0
90Day	Synthesis of Lipoxins (LX)	0.89934	0.45003	0.45003	hpgd	5817.8	5817.8	5817.8		5817.8		DOWN	0	1
90Day	SUMO is transferred from E1 to E2 (UBE2I, UBC9)	0.89934	0.45003	0.45003	sae1	3998.58	3998.58	3998.58		3998.58		UP	1	0
90Day	VLDL clearance	0.89934	0.45003	0.45003	apob	175.96	175.96	175.96		175.96		DOWN	0	1
90Day	Regulation of cholesterol biosynthesis by SREBP (SREBF)	0.89934	0.45003	0.45003	scap	4410.99	4410.99	4410.99		4410.99		DOWN	0	1
90Day	N-glycan trimming and elongation in the cis-Golgi	0.89934	0.45003	0.45003	man1a	3931.46	3931.46	3931.46		3931.46		DOWN	0	1
90Day	Transcriptional Regulation by MECP2	0.89934	0.45003	0.45003	hdac2	202.162	202.162	202.162		202.162		UP	1	0
90Day	Synthesis of PIPs at the ER membrane	0.89934	0.45003	0.45003	pi4ka	3636.02	3636.02	3636.02		3636.02		DOWN	0	1
90Day	Synthesis of 15-eicosatetraenoic acid derivatives	0.89934	0.45003	0.45003	gpx4	2353.96	2353.96	2353.96		2353.96		UP	1	0
90Day	Biosynthesis of EPA-derived SPMs	0.89934	0.45003	0.45003	gpx4	2353.96	2353.96	2353.96		2353.96		UP	1	0
90Day	TRAIL signaling	0.89934	0.45003	0.45003	tnfrsf10b	3826.99	3826.99	3826.99		3826.99		UP	1	0
90Day	Activated NTRK2 signals through FYN	0.89934	0.45003	0.45003	ntrk2	3744.34	3744.34	3744.34		3744.34		DOWN	0	1
90Day	NTRK2 activates RAC1	0.89934	0.45003	0.45003	ntrk2	3744.34	3744.34	3744.34		3744.34		DOWN	0	1
90Day	RUNX3 regulates WNT signaling	0.89934	0.45003	0.45003	ctnnb1	4087.04	4087.04	4087.04		4087.04		DOWN	0	1
90Day	Fructose metabolism	0.89934	0.45003	0.45003	tkfc	1863.37	1863.37	1863.37		1863.37		UP	1	0
90Day	Regulation of MECP2 expression and activity	0.89934	0.45003	0.45003	hdac2	202.162	202.162	202.162		202.162		UP	1	0
90Day	OAS antiviral response	0.89934	0.45003	0.45003	abce1	3026.26	3026.26	3026.26		3026.26		UP	1	0
7Day	Intra-Golgi and retrograde Golgi-to-ER traffic	0.81193	0.2591	0.45174	rab3gap2;cog6;plin3;copz1;rab9;cog5;tubb4b;vps45;tubb2a;tuba4a;arcn1;sec22b;rab6a;rab18;rab1a;cyth1;kif2a;kif1c;jgf2r;capza2;gbf1	3014.27314	3251.9	919.856	1251.48482	2885.62196	1189.24013	UP	0.714285714	0.285714286
7Day	Platelet activation, signaling and aggregation	0.23938	0.82446	0.45536	tmx3;cdc3711;clec1b;mapk3;abcc4;ywhaz;tuba4a;sod1;ptpn11;flna;lgals3bp;itpr2;gna13;f5;f2;ecm1;cdc42;calm3;calm2;ahsg;qsox1	3246.81448	3443.96	156.627	1742.4818	2837.08229	1884.89995	CONFLICT	0.428571429	0.571428571
7Day	Antigen processing: Ubiquitination & Proteasome degradation	0.23938	0.82446	0.45536	ube2n;ubtbd1;rnf6;fbxo2;cui2;fbxo9;trtm69;ube2v2;ube2k;ube3a;ube2a;ube2e3;uba52;cdc27;cdc34;trip12;ubox5;ub	3547.42905	3369.05	1018.89	1093.773	3640.32488	1015.82497	UP	0.904761905	0.095238095
7Day	mTORC1-mediated signalling	0.8529	0.34384	0.45691	rps6kb1;rrrag;elf4ebp1	3455.34333	3225.73	3116.98	494.878532	3686.05963	493.949394	UP	0.666666667	0.333333333
7Day	N-glycan trimming in the ER and Calnexin/Calreticulin cycle	0.8529	0.34384	0.45691	ngly1;uba52;sel1l	4695.51	4761.56	4225.92	440.296435	4822.82749	349.287811	UP	1	0
7Day	Glycolysis	0.8529	0.34384	0.45691	pfkfb3;gckr;gpi1	3112.06	3375.32	1853.98	1149.29064	3116.61725	1080.45298	DOWN	0	1
7Day	FRS-mediated FGFR4 signaling	0.8529	0.34384	0.45691	ptpn11;kras;fgf1	3478.71333	3629.67	2647.76	766.702949	3262.18888	788.939216	UP	0.666666667	0.333333333
28Day	Antiviral mechanism by IFN-stimulated genes	0.85296	0.33985	0.45787	ube2n;arih1;ppm1b	4090.57	5266.71	1290.26	2435.46398	2838.72879	2524.17867	DOWN	0.333333333	0.666666667
28Day	Regulation of TNFR1 signaling	0.85296	0.33985	0.45787	tax1bp1;ikkg;birc2	5416.20667	5417.68	4968.69	446.781822	5309.28907	473.741883	UP	0.666666667	0.333333333
90Day	ESR-mediated signaling	0.22849	0.85592	0.45935	hist1h4h;ppid;hist1h4i;hist1h3c;nr5a2;yy1;hsp90aa1;h2afx;ddx5;cbfb	2972.2308	3902.445	174.249	1813.9438	2612.30985	1823.93818	UP	0.6	0.4
90Day	Signaling by MET	0.24453	0.86324	0.46451	ranbp9;jhgfac;sos1;sh3gl3;gab1;fn1	3111.65133	2735.805	126.428	2182.12293	4302.86563	2073.75712	DOWN	0.333333333	0.666666667
90Day	Fc epsilon receptor (FCER1) signaling	0.23235	0.87143	0.46537	vav1;cdc34;sos1;nfbia;ikkg;btrc	3774.06867	3881.075	569.072	1849.80726	3950.01751	1961.11201	DOWN	0.333333333	0.666666667
90Day	Activation of NF-kappaB in B cells	0.84146	0.36346	0.46638	nfbia;ikkg;btrc	4006.45333	3601.1	3265.56	1006.7561	4283.92049	1129.74967	DOWN	0.333333333	0.666666667

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
90Day	G beta:gamma signalling through CDC42	0.84146	0.36346	0.46638	arhgef6;gng11;cdc42	3654.54233	4854.24	156.487	3078.80769	3619.71528	3169.47674	UP	0.666666667	0.333333333	
90Day	Gap junction trafficking and regulation	0.81143	0.33399	0.46679	tubb6;tubb4b;tubb2a;tuba1b;gjb2;ap2m1	2094.7335	1866.255	779.791	933.017487	1798.35123	1060.01907	UP	0.666666667	0.333333333	
28Day	Phospholipid metabolism	0.24214	0.84447	0.46782	dgat2;pnpla8;pi4k2b;tnfaip81;phospho1;pla2g4c;pi4ka;etnk2;ptdss1;abhd4	3808.807	4014.015	2639.44	769.146816	3817.56261	672.152485	DOWN	0.4	0.6	
28Day	Intra-Golgi and retrograde Golgi-to-ER traffic	0.2303	0.85333	0.46857	dynl1;rab9;tmf1;tubb4b;tubb2a;rab18;man1a;cux1;capza2;gbf1	3731.9494	4064.745	185.394	1694.77939	4137.04061	1320.52339	CONFLICT	0.5	0.5	
28Day	G-protein beta:gamma signalling	0.83975	0.3591	0.46899	pdpk1;gnb5;cdc42	1203.37533	953.648	192.988	1155.66762	1408.50452	956.075532	UP	0.666666667	0.333333333	
28Day	NOD1/2 Signaling Pathway	0.83975	0.3591	0.46899	ube2n;ikbk;bir2	5515.54667	5417.68	5266.71	309.597135	5632.53274	300.031601	UP	0.666666667	0.333333333	
28Day	Transferrin endocytosis and recycling	0.83975	0.3591	0.46899	atp6v0e2;trf;atp6v1e1	3588.84333	3086.6	2385.58	1518.03228	2996.26029	1240.9233	DOWN	0.333333333	0.666666667	
28Day	Reactions specific to the complex N-glycan synthesis pathway	0.87711	0.47288	0.47288	mgat2	3478.56	3478.56	3478.56		3478.56		UP	1	0	
28Day	Apoptotic factor-mediated response	0.87711	0.47288	0.47288	4-Sep	211.182	211.182	211.182		211.182		UP	1	0	
28Day	Transport of nucleotide sugars	0.87711	0.47288	0.47288	slc35d2	3816.75	3816.75	3816.75		3816.75		UP	1	0	
28Day	EGFR interacts with phospholipase C-gamma	0.87711	0.47288	0.47288	hbegf	919.738	919.738	919.738		919.738		UP	1	0	
28Day	FGFR2b ligand binding and activation	0.87711	0.47288	0.47288	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1	
28Day	Axonal growth inhibition (RHOA activation)	0.87711	0.47288	0.47288	arhgdia	4971.84	4971.84	4971.84		4971.84		UP	1	0	
28Day	Androgen biosynthesis	0.87711	0.47288	0.47288	hsd17b3	5151.17	5151.17	5151.17		5151.17		UP	1	0	
28Day	Acyl chain remodelling of PI	0.87711	0.47288	0.47288	pla2g4c	3475.05	3475.05	3475.05		3475.05		UP	1	0	
28Day	TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest	0.87711	0.47288	0.47288	e2f7	4451.79	4451.79	4451.79		4451.79		UP	1	0	
28Day	TRIF-mediated programmed cell death	0.87711	0.47288	0.47288	ly96	4560.3	4560.3	4560.3		4560.3		UP	1	0	
28Day	Regulation of RUNX3 expression and activity	0.87711	0.47288	0.47288	mdm2	2266.61	2266.61	2266.61		2266.61		UP	1	0	
28Day	Serine biosynthesis	0.87711	0.47288	0.47288	serinc1	1574.09	1574.09	1574.09		1574.09		DOWN	0	1	
28Day	CLEC7A (Dectin-1) induces NFAT activation	0.87711	0.47288	0.47288	ppp3cb	4095.87	4095.87	4095.87		4095.87		UP	1	0	
28Day	Phosphate bond hydrolysis by NTPDase proteins	0.87711	0.47288	0.47288	entpd5	1855.96	1855.96	1855.96		1855.96		UP	1	0	
28Day	Biotin transport and metabolism	0.87711	0.47288	0.47288	pccx	3056.49	3056.49	3056.49		3056.49		DOWN	0	1	
28Day	Sodium/Proton exchangers	0.87711	0.47288	0.47288	slc9a5	3688.09	3688.09	3688.09		3688.09		UP	1	0	
28Day	Calcineurin activates NFAT	0.87711	0.47288	0.47288	ppp3cb	4095.87	4095.87	4095.87		4095.87		UP	1	0	
28Day	EGFR Transactivation by Gastrin	0.87711	0.47288	0.47288	hbegf	919.738	919.738	919.738		919.738		UP	1	0	
28Day	Role of LAT2/NTAL/LAB on calcium mobilization	0.87711	0.47288	0.47288	pdpk1	192.988	192.988	192.988		192.988		DOWN	0	1	
7Day	Generation of second messenger molecules	0.83438	0.37058	0.47296	pak2;h2-ab1;h2-aa	2220.87333	2261.36	1863.06	339.386038	2208.54305	306.463493	DOWN	0.333333333	0.666666667	
7Day	Branched-chain amino acid catabolism	0.83438	0.37058	0.47296	mccc2;dlid;bckdha	3122.99067	4026.23	199.112	2593.05718	3005.23722	2577.26557	DOWN	0.333333333	0.666666667	
7Day	FRS-mediated FGFR1 signaling	0.83438	0.37058	0.47296	ptpn11;kras;fgf1	3478.71333	3629.67	2647.76	766.702949	3262.18888	788.939216	UP	0.666666667	0.333333333	
7Day	RAF-independent MAPK1/3 activation	0.83438	0.37058	0.47296	mapk3;ptpn11;jak1	3994.74333	3629.67	3554.32	698.597213	3930.59598	681.24112	UP	0.666666667	0.333333333	
7Day	SMAD2/SMAD3:SMAD4 heterotrimer regulates transcription	0.83438	0.37058	0.47296	uba52;tfdp1;ccnk	2524.87467	2105.8	707.264	2059.38017	3053.07053	2186.83839	UP	1	0	
7Day	Cyclin A/B1/B2 associated events during G2/M transition	0.83438	0.37058	0.47296	ppp2cb;cdc25a;xpo1	4065.65333	3627.04	2692.16	1637.46697	3841.17985	1373.84347	UP	1	0	
7Day	Intrinsic Pathway of Fibrin Clot Formation	0.83438	0.37058	0.47296	f12;f2;serpinc1	849.784833	156.627	85.9375	1262.29842	372.869706	816.971643	DOWN	0	1	
7Day	VEGFA-VEGFR2 Pathway	0.8279	0.26961	0.47491	nckap1,pak2,rasa1,prkc,kras,hsp90aa1,cdc42,ctnnb1,calm3,calm2,brk1	3454.26211	3468.74	54.5232	1846.95429	3559.80325	2027.96172	UP	0.636363636	0.363636364	
90Day	The citric acid (TCA) cycle and respiratory electron transport	0.24554	0.83993	0.47517	ndufab1,ndufc2,sdha,etfdh,ndufaf3,ndufb9,pdk4,pdk1,suclg2,gstz1,atp5k	3140.79345	3209.99	105.476	1841.10037	3749.80618	1710.82178	DOWN	0.272727273	0.727272727	
90Day	RNA Polymerase I Transcription Initiation	0.27037	0.87752	0.47531	gatat2b;hdac2;cdk7	2157.934	3130.16	202.162	1693.75769	1207.98838	1704.99046	UP	1	0	
90Day	Formation of the ternary complex, and subsequently, the 43S complex	0.25368	0.88712	0.4755	eif3m;rps27l;rps12	2578.52	2517.83	1662.63	947.693586	2378.76706	980.623942	UP	1	0	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
90Day	Interleukin-3, Interleukin-5 and GM-CSF signaling	0.25368	0.88712	0.4755	ywhaz;vav1;sos1	3397.97933	4161.05	137.958	2953.36914	4245.68398	2762.84474	DOWN	0.333333333	0.666666667	
28Day	DNA Repair	0.2232	0.84452	0.47622	ube2n;usp45;rm1;ube2v2;pole3;hist1h4i;prpf19;ino80c;cenpx;polr2a;rad51d;rads1;polb;lig3;brca1;blm	4090.84338	4527.73	692.086	1739.90034	4395.59369	1381.79209	UP	0.625	0.375	
28Day	Neutrophil degranulation	0.79216	0.26058	0.47625	arhgap45;ndufc2;npc2;cmtm6;ormdl3;psmd6;serpinb1a;golga7;dynll1;hebp2;methig1;iqgap2;clec12a;tubb4b;tnfrsf1b;serpina1e;serpina1b;s100a11;rab18;pnppa2g4;pkp1;pfkl;mme;man2b1;ita4h;anpep;h2-q7;h2-d1;gstp1;gstp2;gpi1;gaa;ftl1;ctss;c3;atad3a;acly;qsox1;dnajc3	2977.4934	3122.575	160.43	1934.38527	2908.55852	2001.74707	DOWN	0.3	0.7	
28Day	Golgi-to-ER retrograde transport	0.22222	0.87673	0.47692	dynll1;tubb4b;tubb2a;rab18;capza2;gbf1	4262.45333	4542.13	2359.45	1425.36828	4325.76478	1432.18749	UP	0.666666667	0.333333333	
90Day	MAP kinase activation	0.23778	0.89605	0.47695	mapk14;ikbk;btcr	4226.74	4261.96	3265.56	944.062859	4326.22256	1102.6478	DOWN	0.333333333	0.666666667	
90Day	Nuclear Envelope Breakdown	0.23778	0.89605	0.47695	nek6;nup153;sec13	3294.01	3442.78	2758.9	478.400366	3382.9906	363.640364	UP	1	0	
90Day	Chondroitin sulfate/dermatan sulfate metabolism	0.22267	0.90433	0.47961	sdca4;hyal1;bgn	1769.47833	630.216	144.869	2405.85336	2565.87271	2556.11563	DOWN	0	1	
90Day	Nucleotide-binding domain, leucine rich repeat containing receptor (NLR) signaling pathways	0.22267	0.90433	0.47961	mapk14;txn1;ikbk	4223.68667	4261.96	3265.56	939.574827	3938.62375	1035.73316	DOWN	0.333333333	0.666666667	
90Day	Signaling by FGFR1	0.22267	0.90433	0.47961	sos1;gab1;fgf1	2087.929	242.429	126.428	3297.46971	3907.43024	3338.39856	DOWN	0	1	
90Day	Arachidonic acid metabolism	0.80291	0.30205	0.48018	cyp4f16;gpx4;cyp2c54;cyp4a12a;pon3;ephx2;cyp4a12b;cyp2c38;cyp2c37;cyp1a2;cyp2c69	3044.3	3376.53	928.37	1324.45459	3281.65304	1143.95283	CONFLICT	0.545454545	0.454545455	
28Day	Downstream TCR signaling	0.82612	0.37826	0.48058	ube2n;pdpk1;ikbk	3625.79267	5266.71	192.988	2973.85422	4348.16829	2537.13387	DOWN	0.333333333	0.666666667	
28Day	FCERI mediated NF-kB activation	0.82612	0.37826	0.48058	ube2n;pdpk1;ikbk	3625.79267	5266.71	192.988	2973.85422	4348.16829	2537.13387	DOWN	0.333333333	0.666666667	
7Day	Intracellular signaling by second messengers	0.25612	0.81682	0.48106	rraga;suz12;mapk3;uba52;ptpn11;pten;prkar2a;ppp2cb;il1rap;fgf1;csnk2b;cdk1a;casp9;calm3;calm2;bmi1;xiap	3548.93965	3627.04	131.024	1200.08345	3402.72598	1247.39608	CONFLICT	0.588235294	0.411764706	
7Day	Regulation of TP53 Activity through Phosphorylation	0.22554	0.90208	0.48367	taf10;uba52;csnk2b	3650.00667	3358.79	2829.67	998.326151	3713.93443	980.911573	UP	1	0	
7Day	Formation of RNA Pol II elongation complex	0.22554	0.90208	0.48367	wdr61;polr2h;ccnk	3340.86667	3952.2	2105.8	1069.61708	3683.32669	810.404723	UP	1	0	
7Day	RNA Polymerase II Transcription Elongation	0.22554	0.90208	0.48367	wdr61;polr2h;ccnk	3340.86667	3952.2	2105.8	1069.61708	3683.32669	810.404723	UP	1	0	
28Day	Synthesis of DNA	0.27232	0.8744	0.48541	pole3;cdc6;cdc27	4151.206	5780.76	805.318	2897.94886	4893.04993	2396.93088	UP	1	0	
7Day	Signaling by NTRK1 (TRKA)	0.21349	0.90862	0.48662	mapk3;ppp2cb;kras	4195.33	4158.71	3627.04	587.456661	4099.43077	628.875162	UP	0.666666667	0.333333333	
28Day	PI Metabolism	0.24287	0.89147	0.48683	pi4k2b;tnfraip8l1;pi4ka	3825.40333	4173.55	2639.44	1055.85318	4197.62456	743.017577	DOWN	0.333333333	0.666666667	
90Day	Keratan sulfate biosynthesis	0.81839	0.39555	0.48685	omd;st3gal3;lum	4411.32667	4358.58	3651.14	787.885329	4239.33949	529.843763	UP	0.666666667	0.333333333	
90Day	PI-3K cascade:FGFR4	0.81839	0.39555	0.48685	klb;gab1;fgf1	1406.38233	242.429	126.428	2117.2807	2186.59517	2243.99506	DOWN	0	1	
90Day	SHC-mediated cascade:FGFR4	0.81839	0.39555	0.48685	klb;sos1;fgf1	3329.21633	3850.29	242.429	2862.05	4571.98571	2172.73633	DOWN	0	1	
28Day	Signaling by MET	0.23362	0.89668	0.48817	ranbp9;hgs;fn1	4005.54667	3220.72	3156	1415.7787	3669.94431	1199.45955	UP	0.666666667	0.333333333	
90Day	Regulation of PLK1 Activity at G2/M Transition	0.25567	0.84934	0.48905	haus7;dctn3;cntrl;tubb4b;cep76;hsp90aa1;btcr	3497.21571	4266.18	426.32	1735.93382	4002.25491	1517.09734	UP	0.857142857	0.142857143	
7Day	Interleukin-20 family signaling	0.81508	0.3971	0.48981	stat1;ptpn11;jak1	3700.28667	3629.67	3554.32	191.312992	3689.86935	200.012264	UP	1	0	
7Day	Regulation of IFNA signaling	0.81508	0.3971	0.48981	stat1;ptpn11;jak1	3700.28667	3629.67	3554.32	191.312992	3689.86935	200.012264	UP	1	0	
7Day	MAPK family signaling cascades	0.23858	0.8294	0.49208	ranbp9;kalrn;mapk3;pepb1;sept7;pak2;uba52;rasa1;ptpn11;ppp2cb;kras;jak1;gfra1;fgf1;cdc42;calm3;calm2;xpo1	3682.37111	3628.355	778.73	1160.35694	3754.56617	1087.58131	UP	0.666666667	0.333333333	
28Day	Intrinsic Pathway for Apoptosis	0.81211	0.39729	0.49256	dynll1;sept4;bcl2l1	2718.02733	2151.36	211.182	2833.00772	3821.84553	2491.98211	UP	1	0	
7Day	Apoptosis	0.26269	0.84362	0.49302	ywhaz;dsgr1c;kpnbl1;ctnnb1;casp9;xiap;dsp	2684.62517	3025.45	54.5232	1875.07698	2538.12877	1960.56129	DOWN	0.285714286	0.714285714	
7Day	RNA Polymerase I Transcription	0.25264	0.85078	0.49338	hist1h4h;hist1h2bc;hist2h2ac;mapk3;polr2h;ubtf;hist2h2aa1	3877.53857	3964.6	1976.31	1102.11348	3992.99121	990.713071	CONFLICT	0.571428571	0.428571429	
90Day	Retinoid metabolism and transport	0.81875	0.31223	0.49411	apob;ttr;sdca4;rpb1;rdh11;apoae;apoc3	2947.38943	2528.1	175.96	2285.35174	3535.38245	2360.67997	CONFLICT	0.428571429	0.571428571	
7Day	SUMO E3 ligases SUMOylate target proteins	0.23894	0.84149	0.49508	gm49336;rnf168;hist1h4h;hdac7;nop58;suz12;top2b;ncoa1;hnnpcc;bmi1;uhrf2;tpr	3370.48792	3258.095	852.825	1076.86867	3176.03835	1053.06744	UP	0.916666667	0.083333333	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
7Day	Cargo recognition for clathrin-mediated endocytosis	0.23337	0.86432	0.49543	ubqln1;slc2a8;apob;picalm;uba52;ldlr;g2r	3609.88	3459.74	1999.21	993.723225	3580.2941	733.778551	CONFLICT	0.571428571	0.428571429
28Day	Separation of Sister Chromatids	0.26035	0.8444	0.49829	zwilch;dynll1;cenpt;tubb4b;tubb2a;cdc27;rad21	4014.02286	3567.21	2359.45	1333.84151	4025.91847	1335.86752	UP	1	0
7Day	GLI3 is processed to GLI3R by the proteasome	0.86449	0.49992	0.49992	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	Beta-oxidation of pristanoyl-CoA	0.86449	0.49992	0.49992	hsd17b4	185.683	185.683	185.683		185.683		DOWN	0	1
7Day	Pyrimidine catabolism	0.86449	0.49992	0.49992	dpys	395.538	395.538	395.538		395.538		DOWN	0	1
7Day	Synthesis of PIPs at the late endosome membrane	0.86449	0.49992	0.49992	mtmr7	4966.2	4966.2	4966.2		4966.2		UP	1	0
7Day	Pre-NOTCH Expression and Processing	0.86449	0.49992	0.49992	prkci	3409.24	3409.24	3409.24		3409.24		UP	1	0
7Day	Frs2-mediated activation	0.86449	0.49992	0.49992	mapk3	4800.24	4800.24	4800.24		4800.24		DOWN	0	1
7Day	Acyl chain remodeling of DAG and TAG	0.86449	0.49992	0.49992	dgat2	623.511	623.511	623.511		623.511		DOWN	0	1
7Day	Regulation of gene expression by Hypoxia-inducible Factor	0.86449	0.49992	0.49992	arnt	3473.87	3473.87	3473.87		3473.87		DOWN	0	1
7Day	Interleukin-36 pathway	0.86449	0.49992	0.49992	il1rap	131.024	131.024	131.024		131.024		DOWN	0	1
7Day	RUNX3 regulates p14-ARF	0.86449	0.49992	0.49992	kras	4158.71	4158.71	4158.71		4158.71		UP	1	0
7Day	PTK6 Regulates RTKs and Their Effectors AKT1 and DOK1	0.86449	0.49992	0.49992	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	Synthesis of Ketone Bodies	0.86449	0.49992	0.49992	hmgcs2	3736.33	3736.33	3736.33		3736.33		UP	1	0
7Day	DEX/H-box helicases activate type I IFN and inflammatory cytokines production	0.86449	0.49992	0.49992	dhx9	3100.35	3100.35	3100.35		3100.35		UP	1	0
7Day	FGFR3b ligand binding and activation	0.86449	0.49992	0.49992	fgf1	2647.76	2647.76	2647.76		2647.76		DOWN	0	1
28Day	Mitotic Anaphase	0.23911	0.85949	0.5	zwilch;dynll1;cenpt;tubb4b;tubb2a;cdc27;rad21	4014.02286	3567.21	2359.45	1333.84151	4025.91847	1335.86752	UP	1	0
28Day	Mitotic Metaphase and Anaphase	0.23231	0.86426	0.50102	zwilch;dynll1;cenpt;tubb4b;tubb2a;cdc27;rad21	4014.02286	3567.21	2359.45	1333.84151	4025.91847	1335.86752	UP	1	0
90Day	Regulation of RAS by GAPs	0.29749	0.91901	0.50319	rasa1	2133.64	2133.64	2133.64		2133.64		UP	1	0
90Day	Acyl chain remodelling of PS	0.29749	0.91901	0.50319	osbp10	3327.72	3327.72	3327.72		3327.72		UP	1	0
90Day	PCNA-Dependent Long Patch Base Excision Repair	0.29749	0.91901	0.50319	pole4	5853.8	5853.8	5853.8		5853.8		DOWN	0	1
90Day	IKK complex recruitment mediated by RIP1	0.29749	0.91901	0.50319	ikbkg	3265.56	3265.56	3265.56		3265.56		UP	1	0
90Day	APC/C:Cdc20 mediated degradation of Cyclin B	0.29749	0.91901	0.50319	anapc10	4390.47	4390.47	4390.47		4390.47		UP	1	0
90Day	Nuclear Events (kinase and transcription factor activation)	0.27306	0.92816	0.50371	mapk14	4261.96	4261.96	4261.96		4261.96		DOWN	0	1
90Day	Telomere C-strand (Lagging Strand) Synthesis	0.27306	0.92816	0.50371	pole4	5853.8	5853.8	5853.8		5853.8		DOWN	0	1
90Day	Adrenaline,noradrenaline inhibits insulin secretion	0.27306	0.92816	0.50371	gng11	4854.24	4854.24	4854.24		4854.24		UP	1	0
90Day	Thromboxane signalling through TP receptor	0.27306	0.92816	0.50371	gng11	4854.24	4854.24	4854.24		4854.24		UP	1	0
90Day	Glycolysis	0.27306	0.92816	0.50371	pfkfb3	4970.65	4970.65	4970.65		4970.65		UP	1	0
90Day	Mitochondrial biogenesis	0.27306	0.92816	0.50371	atp5k	135.802	135.802	135.802		135.802		DOWN	0	1
28Day	Gamma carboxylation, hypusine formation and arylsulfatase activation	0.79775	0.41617	0.50488	proc;f7;f2	2700.24	2170.26	1340.75	1688.07416	1850.85737	1335.69078	DOWN	0	1
7Day	G2/M DNA damage checkpoint	0.7996	0.33507	0.50541	ube2n;ube2v2;rfn168;hist1h4h;babam1;hist1h2bc;ywhaz	3316.97857	3418.4	2423.08	588.946245	3285.99154	576.827592	UP	0.857142857	0.142857143
90Day	Signaling by ROBO receptors	0.25036	0.93627	0.50663	myo9b	5309.89	5309.89	5309.89		5309.89		DOWN	0	1
90Day	Generation of second messenger molecules	0.25036	0.93627	0.50663	h2-aa	3001.17	3001.17	3001.17		3001.17		DOWN	0	1
90Day	Role of phospholipids in phagocytosis	0.25036	0.93627	0.50663	fcgr2b	3055.31	3055.31	3055.31		3055.31		DOWN	0	1
90Day	SMAD2/SMAD3:SMAD4 heterotrimer regulates transcription	0.25036	0.93627	0.50663	ccnc	4045.2	4045.2	4045.2		4045.2		UP	1	0
90Day	Cobalamin (Cbl, vitamin B12) transport and metabolism	0.25036	0.93627	0.50663	mut	1339.27	1339.27	1339.27		1339.27		DOWN	0	1
90Day	Cyclin A/B1/B2 associated events during G2/M transition	0.25036	0.93627	0.50663	cdk7	3130.16	3130.16	3130.16		3130.16		UP	1	0

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
90Day	HSF1-dependent transactivation	0.25036	0.93627	0.50663	hsp90aa1	426.32	426.32	426.32		426.32		UP	1	0	
90Day	APC-Cdc20 mediated degradation of Nek2A	0.25036	0.93627	0.50663	anapc10	4390.47	4390.47	4390.47		4390.47		UP	1	0	
90Day	Transcriptional Regulation by E2F6	0.25036	0.93627	0.50663	pcgf6	2798.08	2798.08	2798.08		2798.08		UP	1	0	
7Day	CDO in myogenesis	0.79511	0.42331	0.50726	cdc42;ctnnb1;abl1	2672.8244	3368.05	54.5232	2349.15512	2310.38278	2623.74558	DOWN	0.333333333	0.666666667	
7Day	Myogenesis	0.79511	0.42331	0.50726	cdc42;ctnnb1;abl1	2672.8244	3368.05	54.5232	2349.15512	2310.38278	2623.74558	DOWN	0.333333333	0.666666667	
7Day	FRS-mediated FGFR2 signaling	0.79511	0.42331	0.50726	ptpn11;kras;fgf1	3478.71333	3629.67	2647.76	766.702949	3262.18888	788.939216	UP	0.666666667	0.333333333	
7Day	Carboxyterminal post-translational modifications of tubulin	0.79511	0.42331	0.50726	tubb4b;tubb2a;tuba4a	1609.852	1815.66	919.856	613.550908	1582.39232	663.092821	UP	1	0	
7Day	CDK-mediated phosphorylation and removal of Cdc6	0.79511	0.42331	0.50726	uba52;cdc27;ccne2	4410.11	4598.19	3870.58	474.333116	4498.87719	394.432252	UP	1	0	
7Day	Downstream signaling of activated FGFR3	0.79511	0.42331	0.50726	ptpn11;kras;fgf1	3478.71333	3629.67	2647.76	766.702949	3262.18888	788.939216	UP	0.666666667	0.333333333	
7Day	Glycogen metabolism	0.79511	0.42331	0.50726	uba52;calm3;calm2	4242.81333	4761.56	3050.32	1035.63339	3855.87886	1087.62143	UP	0.666666667	0.333333333	
7Day	Cholesterol biosynthesis	0.79511	0.42331	0.50726	idi1;ebp;acat2	2228.13533	2966.55	41.196	1926.93845	1932.68892	2106.7444	DOWN	0.333333333	0.666666667	
7Day	Formation of the beta-catenin:TCF transactivating complex	0.28225	0.92398	0.50771	ctnnb1	54.5232	54.5232	54.5232		54.5232		DOWN	0	1	
7Day	Interleukin receptor SHC signaling	0.28225	0.92398	0.50771	jak1	3554.32	3554.32	3554.32		3554.32		UP	1	0	
7Day	Netrin-1 signaling	0.28225	0.92398	0.50771	cdc42	4595.9	4595.9	4595.9		4595.9		UP	1	0	
7Day	Digestion	0.28225	0.92398	0.50771	mgam	132.859	132.859	132.859		132.859		DOWN	0	1	
7Day	Trafficking of AMPA receptors	0.28225	0.92398	0.50771	gria3	3853.21	3853.21	3853.21		3853.21		UP	1	0	
7Day	Glutamate binding, activation of AMPA receptors and synaptic plasticity	0.28225	0.92398	0.50771	gria3	3853.21	3853.21	3853.21		3853.21		UP	1	0	
7Day	Resolution of D-loop Structures through Synthesis-Dependent Strand Annealing (SDSA)	0.28225	0.92398	0.50771	rad51ap1	3877.33	3877.33	3877.33		3877.33		UP	1	0	
90Day	Metabolism of fat-soluble vitamins	0.7888	0.35024	0.50849	apob;ttr;sdca4;rbp1;rdh11;apoae;apoc3	2947.38943	2528.1	175.96	2285.35174	3535.38245	2360.67997	CONFLICT	0.428571429	0.571428571	
90Day	Bile acid and bile salt metabolism	0.7888	0.35024	0.50849	osbpl3;cyp39a1;slc27a5;slc27a2;slc10a1;amacr;osbpl9	3307.29714	3419.78	263.79	1622.33452	3906.606	1438.56267	DOWN	0.142857143	0.857142857	
28Day	AKT phosphorylates targets in the cytosol	0.8531	0.5091	0.5091	mdm2	2266.61	2266.61	2266.61		2266.61		UP	1	0	
28Day	CS/DS degradation	0.8531	0.5091	0.5091	hyal1	2376.85	2376.85	2376.85		2376.85		DOWN	0	1	
28Day	p75NTR regulates axonogenesis	0.8531	0.5091	0.5091	arhgdia	4971.84	4971.84	4971.84		4971.84		UP	1	0	
28Day	HDR through MMEJ (alt-NHEJ)	0.8531	0.5091	0.5091	lig3	5391.42	5391.42	5391.42		5391.42		DOWN	0	1	
28Day	PI3K events in ERBB4 signaling	0.8531	0.5091	0.5091	hbegf	919.738	919.738	919.738		919.738		UP	1	0	
28Day	HDL remodeling	0.8531	0.5091	0.5091	apoae	3212.68	3212.68	3212.68		3212.68		DOWN	0	1	
28Day	Interleukin-12 signaling	0.8531	0.5091	0.5091	p4hb	5730.92	5730.92	5730.92		5730.92		DOWN	0	1	
28Day	Synthesis of pyrophosphates in the cytosol	0.8531	0.5091	0.5091	lppk	4371.1	4371.1	4371.1		4371.1		UP	1	0	
28Day	Cohesin Loading onto Chromatin	0.8531	0.5091	0.5091	rad21	4137.27	4137.27	4137.27		4137.27		UP	1	0	
28Day	Adenylate cyclase activating pathway	0.8531	0.5091	0.5091	adcy9	4220.6	4220.6	4220.6		4220.6		DOWN	0	1	
28Day	Vitamin D (calciferol) metabolism	0.8531	0.5091	0.5091	gc	431.226	431.226	431.226		431.226		DOWN	0	1	
28Day	Regulation by c-FLIP	0.8531	0.5091	0.5091	tnfrsf10b	4040.75	4040.75	4040.75		4040.75		UP	1	0	
28Day	CASP8 activity is inhibited	0.8531	0.5091	0.5091	tnfrsf10b	4040.75	4040.75	4040.75		4040.75		UP	1	0	
28Day	Dimerization of procaspase-8	0.8531	0.5091	0.5091	tnfrsf10b	4040.75	4040.75	4040.75		4040.75		UP	1	0	
7Day	Insulin receptor recycling	0.26279	0.93116	0.5093	atp6v1e1	3782.92	3782.92	3782.92		3782.92		UP	1	0	
7Day	G-protein activation	0.26279	0.93116	0.5093	gnai3	794.2	794.2	794.2		794.2		UP	1	0	
7Day	RNA Pol II CTD phosphorylation and interaction with CE	0.26279	0.93116	0.5093	polr2h	3964.6	3964.6	3964.6		3964.6		UP	1	0	
7Day	PTEN Regulation	0.78694	0.35088	0.51165	rraga;suz12;uba52;pten;csnk2b;bmi1;xiap	3856.5	3225.73	2829.67	946.764064	3870.44666	926.251147	UP	0.857142857	0.142857143	
7Day	Regulation of actin dynamics for phagocytic cup formation	0.78694	0.35088	0.51165	nckap1;mapk3;myh9;hsp90aa1;cdc42;abl1;brk1	3145.07714	3368.05	1005.61	1343.65458	3031.74508	1474.85132	CONFLICT	0.571428571	0.428571429	
7Day	RAB geranylgeranylation	0.78694	0.35088	0.51165	rab9;rab11a;rab25;rab6a;rab18;rab10;rab1a	3525.11714	3553.68	1046.66	1329.4585	3611.40244	1330.92078	UP	0.857142857	0.142857143	
90Day	G beta:gamma signalling through PI3kgamma	0.22929	0.94347	0.51173	gng11	4854.24	4854.24	4854.24		4854.24		UP	1	0	
90Day	Surfactant metabolism	0.22929	0.94347	0.51173	ctsh	1857.39	1857.39	1857.39		1857.39		DOWN	0	1	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
90Day	Resolution of AP sites via the multiple-nucleotide patch replacement pathway	0.22929	0.94347	0.51173	pole4	5853.8	5853.8	5853.8		5853.8		DOWN	0	1
90Day	Telomere Maintenance	0.22929	0.94347	0.51173	pole4	5853.8	5853.8	5853.8		5853.8		DOWN	0	1
90Day	Extension of Telomeres	0.22929	0.94347	0.51173	pole4	5853.8	5853.8	5853.8		5853.8		DOWN	0	1
90Day	DNA strand elongation	0.22929	0.94347	0.51173	gins1	1127.6	1127.6	1127.6		1127.6		UP	1	0
90Day	FGFR2 alternative splicing	0.22929	0.94347	0.51173	hnmpf	3142.57	3142.57	3142.57		3142.57		DOWN	0	1
90Day	Orc1 removal from chromatin	0.22929	0.94347	0.51173	orc6	4168.34	4168.34	4168.34		4168.34		UP	1	0
90Day	FGFR1b ligand binding and activation	0.85999	0.51204	0.51204	fgf1	242.429	242.429	242.429		242.429		DOWN	0	1
90Day	RHO GTPases Activate Rhotekin and RhoGTPases	0.85999	0.51204	0.51204	rtkn	3994.23	3994.23	3994.23		3994.23		UP	1	0
90Day	Glucocorticoid biosynthesis	0.85999	0.51204	0.51204	hsd11b1	2402.05	2402.05	2402.05		2402.05		DOWN	0	1
90Day	MET Receptor Activation	0.85999	0.51204	0.51204	hgf	1910.71	1910.71	1910.71		1910.71		DOWN	0	1
90Day	MET activates PI3K/AKT signaling	0.85999	0.51204	0.51204	gab1	126.428	126.428	126.428		126.428		DOWN	0	1
90Day	Attachment of GPI anchor to uPAR	0.85999	0.51204	0.51204	plaur	1622.23	1622.23	1622.23		1622.23		DOWN	0	1
90Day	Synthesis of 5-eicosatetraenoic acids	0.85999	0.51204	0.51204	pon3	4320.2	4320.2	4320.2		4320.2		UP	1	0
90Day	Lipid particle organization	0.85999	0.51204	0.51204	fitm2	3161.07	3161.07	3161.07		3161.07		UP	1	0
90Day	mRNA Editing	0.85999	0.51204	0.51204	adar	5667.94	5667.94	5667.94		5667.94		UP	1	0
90Day	activated TAK1 mediates p38 MAPK activation	0.85999	0.51204	0.51204	mapk14	4261.96	4261.96	4261.96		4261.96		DOWN	0	1
90Day	Release of Hh-Np from the secreting cell	0.85999	0.51204	0.51204	notum	4035.02	4035.02	4035.02		4035.02		DOWN	0	1
90Day	PTK6 promotes HIF1A stabilization	0.85999	0.51204	0.51204	gpmmb	4552.68	4552.68	4552.68		4552.68		UP	1	0
90Day	CaMK IV-mediated phosphorylation of CREB	0.85999	0.51204	0.51204	camkk2	98.0082	98.0082	98.0082		98.0082		DOWN	0	1
90Day	CREB1 phosphorylation through the activation of CaMKII/CaMKK/CaMKIV cascade	0.85999	0.51204	0.51204	camkk2	98.0082	98.0082	98.0082		98.0082		DOWN	0	1
90Day	Activation of RAC1 downstream of NMDARs	0.85999	0.51204	0.51204	camkk2	98.0082	98.0082	98.0082		98.0082		DOWN	0	1
90Day	Transport and synthesis of PAPS	0.85999	0.51204	0.51204	slc26a2	3962.48	3962.48	3962.48		3962.48		DOWN	0	1
90Day	Protein repair	0.85999	0.51204	0.51204	txn1	5143.54	5143.54	5143.54		5143.54		DOWN	0	1
90Day	Vitamin B2 (riboflavin) metabolism	0.85999	0.51204	0.51204	slc52a3	5271	5271	5271		5271		UP	1	0
90Day	SHC-related events triggered by IGF1R	0.85999	0.51204	0.51204	sos1	5894.93	5894.93	5894.93		5894.93		DOWN	0	1
90Day	Synthesis of 12-eicosatetraenoic acid derivatives	0.85999	0.51204	0.51204	gpx4	2353.96	2353.96	2353.96		2353.96		UP	1	0
90Day	Regulation of PTEN localization	0.85999	0.51204	0.51204	pml	3603.58	3603.58	3603.58		3603.58		DOWN	0	1
90Day	IRS activation	0.85999	0.51204	0.51204	irs2	74.8133	74.8133	74.8133		74.8133		DOWN	0	1
90Day	Assembly of the ORC complex at the origin of replication	0.85999	0.51204	0.51204	orc6	4168.34	4168.34	4168.34		4168.34		UP	1	0
7Day	Gluconeogenesis	0.24448	0.93767	0.51246	pgam1	4274.34	4274.34	4274.34		4274.34		UP	1	0
7Day	RNA Polymerase III Transcription Initiation From Type 3 Promoter	0.24448	0.93767	0.51246	polr2h	3964.6	3964.6	3964.6		3964.6		UP	1	0
28Day	SUMOylation of transcription cofactors	0.29651	0.9174	0.51344	bmi1	3918.46	3918.46	3918.46		3918.46		UP	1	0
28Day	RUNX1 interacts with co-factors whose precise effect on RUNX1 targets is not known	0.29651	0.9174	0.51344	bmi1	3918.46	3918.46	3918.46		3918.46		UP	1	0
28Day	DNA Damage Recognition in GG-NER	0.2818	0.92309	0.51366	ino80c	5465.53	5465.53	5465.53		5465.53		DOWN	0	1
28Day	O-glycosylation of TSR domain-containing proteins	0.2677	0.92839	0.51475	sbspon	5312.69	5312.69	5312.69		5312.69		UP	1	0
28Day	Cyclin D associated events in G1	0.2677	0.92839	0.51475	tfdp1	5708.4	5708.4	5708.4		5708.4		UP	1	0
28Day	G1 Phase	0.2677	0.92839	0.51475	tfdp1	5708.4	5708.4	5708.4		5708.4		UP	1	0
28Day	EPHB-mediated forward signaling	0.2677	0.92839	0.51475	cdc42	2463.49	2463.49	2463.49		2463.49		UP	1	0
28Day	Translesion synthesis by Y family DNA polymerases bypasses lesions on DNA template	0.2677	0.92839	0.51475	pole3	805.318	805.318	805.318		805.318		UP	1	0
28Day	Signaling by FGFR3	0.2677	0.92839	0.51475	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1
28Day	Activation of ATR in response to replication stress	0.2677	0.92839	0.51475	cdc6	5867.54	5867.54	5867.54		5867.54		UP	1	0
90Day	Semaphorin interactions	0.28799	0.85255	0.51484	tln1;rock2;rock1;hsp90aa1	2260.363	2150.215	262.092	2227.33171	2108.65317	2313.26435	UP	0.75	0.25

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.														
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
28Day	GABA B receptor activation	0.25421	0.93333	0.51666	adcy9	4220.6	4220.6	4220.6		4220.6		DOWN	0	1
28Day	Activation of GABAB receptors	0.25421	0.93333	0.51666	adcy9	4220.6	4220.6	4220.6		4220.6		DOWN	0	1
28Day	Signaling by FGFR4	0.25421	0.93333	0.51666	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1
7Day	Recognition of DNA damage by PCNA-containing replication complex	0.22728	0.94356	0.51705	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	Interleukin-7 signaling	0.22728	0.94356	0.51705	jak1	3554.32	3554.32	3554.32		3554.32		UP	1	0
7Day	mRNA Capping	0.22728	0.94356	0.51705	polr2h	3964.6	3964.6	3964.6		3964.6		UP	1	0
90Day	NoRC negatively regulates rRNA expression	0.24231	0.88129	0.51835	hist1h4h;hist1h4i;hist1h3c;h2afx	3214.00725	3979.26	811.859	1602.37406	2298.31583	1843.92338	CONFLICT	0.5	0.5
90Day	Regulation of TP53 Activity through Phosphorylation	0.24231	0.88129	0.51835	trp53inp1;mapk14;pin1;mdm2	3753.1775	3898.52	2267.97	1145.88415	3622.70918	1133.0118	UP	0.75	0.25
7Day	Costimulation by the CD28 family	0.77397	0.36677	0.51842	yes1;pak2;ptpn11;ppp2cb;h2-ab1;h2-aa;cdc42	3219.45429	3627.04	1863.06	1007.7416	3600.30516	855.55687	UP	0.714285714	0.285714286
90Day	CDO in myogenesis	0.85685	0.30897	0.51876	mapk14;mef2a;cdc42;ctnnb1	3134.22675	4059.23	156.487	1987.58858	2980.93174	2048.77964	DOWN	0.25	0.75
90Day	Myogenesis	0.85685	0.30897	0.51876	mapk14;mef2a;cdc42;ctnnb1	3134.22675	4059.23	156.487	1987.58858	2980.93174	2048.77964	DOWN	0.25	0.75
90Day	Carboxyterminal post-translational modifications of tubulin	0.85685	0.30897	0.51876	tubb6;tubb4b;tubb2a;tuba1b	1558.67025	1751.94	779.791	528.216289	1311.72381	614.22224	UP	0.75	0.25
7Day	Regulation of HSF1-mediated heat shock response	0.27969	0.85704	0.51897	gm49336;dnajb6;hsp1;tptr	2911.057	3210.97	589.118	1774.90285	2760.63037	1688.7125	UP	1	0
28Day	mTOR signalling	0.2413	0.93792	0.51932	stradb	5007.07	5007.07	5007.07		5007.07		DOWN	0	1
28Day	Dual Incision in GG-NER	0.2413	0.93792	0.51932	pole3	805.318	805.318	805.318		805.318		UP	1	0
28Day	Deactivation of the beta-catenin transactivating complex	0.2413	0.93792	0.51932	pygo2	3936.43	3936.43	3936.43		3936.43		DOWN	0	1
7Day	SUMOylation of DNA damage response and repair proteins	0.26678	0.86529	0.51956	gm49336;rnf168;hdac7;tptr	3653.6175	3723.15	2535	955.277026	3456.68876	933.956694	UP	1	0
28Day	Toll Like Receptor 9 (TLR9) Cascade	0.77285	0.36599	0.52167	ube2n;map2k4;ee1;mapkapk2;ly96;ikbkg;app	4767.72571	5266.71	2616.5	1022.82226	4879.47107	988.613786	CONFLICT	0.428571429	0.571428571
28Day	MAP2K and MAPK activation	0.22896	0.9422	0.5227	fn1	3156	3156	3156		3156		DOWN	0	1
28Day	MET promotes cell motility	0.22896	0.9422	0.5227	fn1	3156	3156	3156		3156		DOWN	0	1
7Day	Interleukin-1 family signaling	0.24227	0.88058	0.52272	ube2n;uba52;il1rap;bttrc	3136.1085	3825.925	131.024	2074.83709	2895.88682	2054.23699	UP	0.75	0.25
7Day	Inactivation, recovery and regulation of the phototransduction cascade	0.85328	0.31177	0.52292	metap2;rgs9;calm3;calm2	4272.6525	4282.775	3050.32	1116.94268	3771.99798	1052.02681	CONFLICT	0.5	0.5
7Day	Negative regulation of MAPK pathway	0.85328	0.31177	0.52292	mapk3;pebp1;uba52;kras	4517.91	4556.345	4158.71	314.067806	4543.01794	302.022236	UP	0.75	0.25
7Day	Gap junction assembly	0.85328	0.31177	0.52292	tubb4b;tubb2a;tuba4a;gja1	2276.434	1954.85	919.856	1424.18025	1763.60227	985.706882	UP	0.75	0.25
7Day	Metabolism of vitamins and cofactors	0.78622	0.29132	0.52387	akr1c6;mccc2;nudt12;qprt;pccb;mocs1;btd;naxe;apob;ttr;sd3;lrp1;hsp90aa1;calm3;calm2;apoe;cyb5a;shmt2;aldh1l1;akr1c14	2456.08094	2783.725	77.8976	1883.49191	2618.45487	1697.27921	DOWN	0.3	0.7
28Day	RAB GEFs exchange GTP for GDP on RABs	0.28761	0.85075	0.52428	trappc8;rab9;dennd1a;rab18	3404.915	2992.42	2453.87	1213.23951	3862.04186	1278.52857	DOWN	0.25	0.75
28Day	PCP/CE pathway	0.21718	0.94619	0.52674	pfn1	4831.18	4831.18	4831.18		4831.18		UP	1	0
28Day	Signaling by NOTCH	0.21718	0.94619	0.52674	notch1	908.573	908.573	908.573		908.573		UP	1	0
28Day	SUMOylation of DNA replication proteins	0.21718	0.94619	0.52674	tptr	3638.67	3638.67	3638.67		3638.67		UP	1	0
90Day	Interconversion of nucleotide di- and triphosphates	0.83819	0.33573	0.5275	txnrd1;txn1;gsr;ak2	3060.2	2620.955	1855.35	1487.24137	2797.06582	1575.60934	CONFLICT	0.5	0.5
90Day	Trafficking of AMPA receptors	0.83819	0.33573	0.5275	gria3;mdm2;epb41l1;ap2m1	2862.2375	3259.315	1097.82	1227.7367	2584.40324	1386.19776	UP	1	0
90Day	Glutamate binding, activation of AMPA receptors and synaptic plasticity	0.83819	0.33573	0.5275	gria3;mdm2;epb41l1;ap2m1	2862.2375	3259.315	1097.82	1227.7367	2584.40324	1386.19776	UP	1	0
90Day	Cytosolic sulfonation of small molecules	0.83819	0.33573	0.5275	abhd14b;sult1b1;bpnt1;slc26a2	3219.905	3036.205	2844.73	516.097522	3077.28766	434.41209	DOWN	0.25	0.75
90Day	Signaling by VEGF	0.27335	0.8263	0.52936	mapk14;wasf2;vav1;rasa1;rock2;rock1;hsp90aa1;cdc42;ctnnb1	2740.53767	3874.11	156.487	2016.69226	2197.99008	2124.70017	CONFLICT	0.555555556	0.444444444
90Day	PI3P, PP2A and IER3 Regulate PI3K/AKT Signaling	0.27335	0.8263	0.52936	klb;irs2;vav1;tgifa;nrg1;il1rap;gab1;fgf1;areg	2353.84448	2684.35	74.8133	1778.57928	2322.93121	1581.92848	DOWN	0.333333333	0.666666667
7Day	The phototransduction cascade	0.83775	0.33392	0.52996	metap2;rgs9;calm3;calm2	4272.6525	4282.775	3050.32	1116.94268	3771.99798	1052.02681	CONFLICT	0.5	0.5
7Day	Disassembly of the destruction complex and recruitment of AXIN to the membrane	0.83775	0.33392	0.52996	gsk3b;ppp2cb;lrp5;ctnnb1	3235.2933	4063.24	54.5232	2175.16894	3178.95783	2131.91975	CONFLICT	0.5	0.5

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.														
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
90Day	Visual phototransduction	0.26209	0.83476	0.53006	rdh7;apob;tr;sdca4;rbp1;rdh11;apoe;apoc3;abca4	3292.12178	3563.02	175.96	2145.67605	4076.34615	2043.87414	CONFLICT	0.444444444	0.555555556
28Day	S Phase	0.23385	0.8848	0.53012	pole3;cdc6;cdc27;rad21	4147.722	4959.015	805.318	2366.17559	4745.67586	2056.85116	UP	1	0
28Day	Chromosome Maintenance	0.84152	0.32546	0.53139	cenpw;pole3;cenpt;cenpx	3646.9295	4124.75	805.318	2058.31381	4051.51676	1870.37166	CONFLICT	0.5	0.5
28Day	UCH proteinases	0.81294	0.30655	0.53223	asxl2;psmd6;psmd8;uchl3;psmf1;ino80c;psmb8;hcfcl	3618.15388	4041.425	572.861	1783.86457	3604.51854	1890.72941	DOWN	0.375	0.625
7Day	MHC class II antigen presentation	0.28504	0.81669	0.53298	tubb4b;tubb2a;tuba4a;kif2a;cd74;h2-ab1;h2-aa;ctsb;capza2	2649.55511	2261.36	919.856	1184.67475	2821.27362	1222.39151	UP	0.666666667	0.333333333
7Day	Homology Directed Repair	0.25685	0.83802	0.53452	ube2n;ube2v2;rnf168;hist1h4h;babam1;hist1h2bc;uba52;rad51ap1;abl1	3610.97889	3444.79	2423.08	647.933214	3488.58257	659.371908	UP	0.777777778	0.222222222
28Day	mRNA Splicing - Major Pathway	0.75772	0.34394	0.53629	phf5a;ccar1;sf3b6;cpsf2;prpf19;hnnpul1;prpf38a;u2af2;snrpd1;polr2a;prpf8;papola;srsf1	4273.981	4946.8	983.533	1347.689	4407.52389	1232.15325	UP	0.615384615	0.384615385
90Day	Downstream signaling of activated FGFR4	0.81861	0.36257	0.53771	kib;sos1;gab1;fgf1	2528.51925	2046.3595	126.428	2832.90488	3890.50542	2640.67822	DOWN	0	1
7Day	FCER1 mediated NF-kB activation	0.82159	0.35614	0.53804	ube2n;uba52;cdc34;btrc	3358.075	3825.925	1018.89	1650.23752	3816.68588	959.204428	UP	1	0
7Day	RAF activation	0.82159	0.35614	0.53804	ppp2cb;kras;calm3;calm2	3938.1575	3892.875	3050.32	793.927869	3662.8258	731.819469	UP	0.75	0.25
7Day	Golgi-to-ER retrograde transport	0.78569	0.30849	0.53909	rab3gap2;copz1;tubb4b;tubb2a;tuba4a;arcn1;sec22b;rab6a;rab18;rab1a;kif2a;kif1c;capza2;gbf1	3009.42471	3164.9	919.856	1239.06258	2905.56928	1095.93066	UP	0.928571429	0.071428571
28Day	RHO GTPases activate KTN1	0.82825	0.54283	0.54283	cdc42	2463.49	2463.49	2463.49		2463.49		UP	1	0
28Day	Mitochondrial iron-sulfur cluster biogenesis	0.82825	0.54283	0.54283	fdxr	5126.12	5126.12	5126.12		5126.12		DOWN	0	1
28Day	NOTCH1 Intracellular Domain Regulates Transcription	0.82825	0.54283	0.54283	notch1	908.573	908.573	908.573		908.573		UP	1	0
28Day	MET activates RAS signaling	0.82825	0.54283	0.54283	ranbp9	5639.92	5639.92	5639.92		5639.92		UP	1	0
28Day	RUNX3 regulates NOTCH signaling	0.82825	0.54283	0.54283	notch1	908.573	908.573	908.573		908.573		UP	1	0
28Day	Establishment of Sister Chromatid Cohesion	0.82825	0.54283	0.54283	rad21	4137.27	4137.27	4137.27		4137.27		UP	1	0
28Day	CDC6 association with the ORC:origin complex	0.82825	0.54283	0.54283	cdc6	5867.54	5867.54	5867.54		5867.54		UP	1	0
28Day	DCC mediated attractive signaling	0.82825	0.54283	0.54283	cdc42	2463.49	2463.49	2463.49		2463.49		UP	1	0
28Day	Assembly of active LPL and LIPC lipase complexes	0.82825	0.54283	0.54283	lmf1	3007.97	3007.97	3007.97		3007.97		DOWN	0	1
28Day	p75NTR recruits signalling complexes	0.82825	0.54283	0.54283	sqstm1	5683.98	5683.98	5683.98		5683.98		UP	1	0
28Day	NF-kB is activated and signals survival	0.82825	0.54283	0.54283	sqstm1	5683.98	5683.98	5683.98		5683.98		UP	1	0
28Day	Heme biosynthesis	0.82825	0.54283	0.54283	fech	5076.68	5076.68	5076.68		5076.68		DOWN	0	1
28Day	FGFR1c ligand binding and activation	0.82825	0.54283	0.54283	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1
28Day	mRNA Splicing	0.78556	0.30738	0.54294	phf5a;ccar1;rnpc3;sf3b6;cpsf2;prpf19;hnnpul1;prpf38a;u2af2;snrpd1;polr2a;prpf8;papola;srsf1	3978.11314	4859.02	131.831	1703.54981	3970.57701	1778.01563	UP	0.642857143	0.357142857
7Day	Downregulation of ERBB2:ERBB3 signaling	0.83017	0.54708	0.54708	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	Negative regulation of TCF-dependent signaling by WNT ligand antagonists	0.83017	0.54708	0.54708	lrp5	4760.17	4760.17	4760.17		4760.17		DOWN	0	1
7Day	Sema4D mediated inhibition of cell attachment and migration	0.83017	0.54708	0.54708	sema4d	5514.77	5514.77	5514.77		5514.77		DOWN	0	1
7Day	Regulation of RUNX1 Expression and Activity	0.83017	0.54708	0.54708	ptpn11	3629.67	3629.67	3629.67		3629.67		UP	1	0
7Day	WNT mediated activation of DVL	0.83017	0.54708	0.54708	csnk2b	2829.67	2829.67	2829.67		2829.67		UP	1	0
7Day	HuR (ELAVL1) binds and stabilizes mRNA	0.83017	0.54708	0.54708	xpo1	2692.16	2692.16	2692.16		2692.16		UP	1	0
7Day	Vitamin C (ascorbate) metabolism	0.83017	0.54708	0.54708	cyb5a	2724.64	2724.64	2724.64		2724.64		UP	1	0
7Day	Signaling by NOTCH2	0.83017	0.54708	0.54708	mdk	4385.8	4385.8	4385.8		4385.8		DOWN	0	1
7Day	The activation of arylsulfatases	0.83017	0.54708	0.54708	arsb	34.2395	34.2395	34.2395		34.2395		DOWN	0	1
7Day	Activated NOTCH1 Transmits Signal to the Nucleus	0.83017	0.54708	0.54708	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	IRAK2 mediated activation of TAK1 complex	0.83017	0.54708	0.54708	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	Degradation of AXIN	0.83017	0.54708	0.54708	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
7Day	FBXL7 down-regulates AURKA during mitotic entry and in early mitosis	0.83017	0.54708	0.54708	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	Regulation of RUNX2 expression and activity	0.83017	0.54708	0.54708	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	p38MAPK events	0.83017	0.54708	0.54708	kras	4158.71	4158.71	4158.71		4158.71		UP	1	0
7Day	Transcriptional activation of mitochondrial biogenesis	0.83017	0.54708	0.54708	idh2	2704.94	2704.94	2704.94		2704.94		DOWN	0	1
7Day	Zinc influx into cells by the SLC39 gene family	0.83017	0.54708	0.54708	slc39a2	5557.48	5557.48	5557.48		5557.48		UP	1	0
7Day	Recycling of eIF2:GDP	0.83017	0.54708	0.54708	eif2s3x	4962.69	4962.69	4962.69		4962.69		UP	1	0
7Day	Terminal pathway of complement	0.83017	0.54708	0.54708	c8g	2794.51	2794.51	2794.51		2794.51		DOWN	0	1
7Day	Phosphate bond hydrolysis by NUDT proteins	0.83017	0.54708	0.54708	nudt5	1880.13	1880.13	1880.13		1880.13		UP	1	0
7Day	Estrogen biosynthesis	0.83017	0.54708	0.54708	hsd17b2	4340.78	4340.78	4340.78		4340.78		UP	1	0
7Day	SLBP independent Processing of Histone Pre-mRNAs	0.83017	0.54708	0.54708	lsm10	2905.24	2905.24	2905.24		2905.24		UP	1	0
7Day	Formyl peptide receptors bind formyl peptides and many other ligands	0.83017	0.54708	0.54708	hebp1	790.154	790.154	790.154		790.154		DOWN	0	1
7Day	Telomere C-strand synthesis initiation	0.83017	0.54708	0.54708	prim2	4006.14	4006.14	4006.14		4006.14		UP	1	0
7Day	DNA replication initiation	0.83017	0.54708	0.54708	prim2	4006.14	4006.14	4006.14		4006.14		UP	1	0
90Day	HDR through Homologous Recombination (HRR)	0.27178	0.85262	0.54771	pole4;polk;rad51;brca2;rad51c	3777.8444	4249.95	513.022	1994.74231	3346.62459	1844.20396	UP	0.8	0.2
90Day	Major pathway of rRNA processing in the nucleolus and cytosol	0.25884	0.83323	0.54798	nop14;riok1;rps27l;rc1l;exosc9;utp4;rp s12;emg1;fbl;tsr1	2846.4009	2776.515	591.419	1480.39943	2670.58313	1277.5984	UP	0.8	0.2
90Day	rRNA processing	0.25884	0.83323	0.54798	nop14;riok1;rps27l;rc1l;exosc9;utp4;rp s12;emg1;fbl;tsr1	2846.4009	2776.515	591.419	1480.39943	2670.58313	1277.5984	UP	0.8	0.2
90Day	rRNA processing in the nucleus and cytosol	0.25884	0.83323	0.54798	nop14;riok1;rps27l;rc1l;exosc9;utp4;rp s12;emg1;fbl;tsr1	2846.4009	2776.515	591.419	1480.39943	2670.58313	1277.5984	UP	0.8	0.2
90Day	EGFR downregulation	0.79822	0.38937	0.54919	tgifa;sh3gl3;cdc42;areg	2888.90425	3066.45	156.487	2222.23924	3335.44859	2016.78896	UP	1	0
7Day	Opioid Signalling	0.29061	0.83896	0.55049	prkar2a;ppp2cb;gna13;calm3;calm2	3290.936	3627.04	794.2	1553.12577	2908.54515	1523.23127	UP	0.6	0.4
28Day	Nucleotide-binding domain, leucine rich repeat containing receptor (NLR) signaling pathways	0.79397	0.38928	0.55523	ube2n;ikbk;bel2l1;birc2	4674.5	5342.195	2151.36	1700.98155	4096.41432	2007.10901	UP	0.75	0.25
28Day	Cargo recognition for clathrin-mediated endocytosis	0.28114	0.84438	0.55604	apob;picalm;trf;hgs;hbegf	2458.9746	3086.6	919.738	1452.65283	1857.20336	1315.60072	UP	0.6	0.4
7Day	Metalloprotease DUBs	0.78762	0.40047	0.5568	babam1;hist2h2ac;uba52;hist2h2aa1	4476.405	4474.415	3567.39	779.910371	4363.95684	884.124588	UP	0.75	0.25
90Day	MHC class II antigen presentation	0.2761	0.81636	0.56197	tubb6;dctn3;tubb4b;tubb2a;tuba1b;cd7 4;h2-aa;ctsh;ctsd;ap2m1;sec13	2424.05645	2214.7	779.791	937.752913	2264.1907	1084.33865	UP	0.636363636	0.363636364
7Day	Mitotic Metaphase and Anaphase	0.30271	0.79461	0.56466	clasp2;pds5a;cenpk;tubb4b;uba52;tubb 2a;tuba4a;cdc27;ppp2cb;kif2a;xpo1	3257.49964	3647.06	919.856	1227.93386	3222.5988	1220.34245	UP	0.909090909	0.090909091
90Day	TP53 Regulates Transcription of Genes Involved in G2 Cell Cycle Arrest	0.81808	0.56706	0.56706	bax	1844.96	1844.96	1844.96		1844.96		UP	1	0
90Day	HDL assembly	0.81808	0.56706	0.56706	bmp1	190.369	190.369	190.369		190.369		DOWN	0	1
90Day	HSF1 activation	0.81808	0.56706	0.56706	hsp90aa1	426.32	426.32	426.32		426.32		UP	1	0
90Day	Pyrimidine catabolism	0.81808	0.56706	0.56706	dpys	1635.68	1635.68	1635.68		1635.68		DOWN	0	1
90Day	BH3-only proteins associate with and inactivate anti-apoptotic BCL-2 members	0.81808	0.56706	0.56706	bmf	1597.1	1597.1	1597.1		1597.1		DOWN	0	1
90Day	Heme degradation	0.81808	0.56706	0.56706	blvrb	3840.4	3840.4	3840.4		3840.4		UP	1	0
90Day	Acyl chain remodeling of DAG and TAG	0.81808	0.56706	0.56706	dgat2	2903.14	2903.14	2903.14		2903.14		DOWN	0	1
90Day	Interleukin-36 pathway	0.81808	0.56706	0.56706	il1rap	2684.35	2684.35	2684.35		2684.35		DOWN	0	1
90Day	DEX/H-box helicases activate type I IFN and inflammatory cytokines production	0.81808	0.56706	0.56706	irf7	5689.7	5689.7	5689.7		5689.7		UP	1	0
90Day	FGFR3b ligand binding and activation	0.81808	0.56706	0.56706	fgf1	242.429	242.429	242.429		242.429		DOWN	0	1
28Day	Neurotransmitter release cycle	0.76861	0.42096	0.56966	lin7c;slc22a1;slc1a2;slc6a13	2234.1305	1728.215	151.142	2193.39816	3178.351	2203.82829	DOWN	0	1
90Day	CD28 co-stimulation	0.32705	0.86722	0.5717	vav1;cdc42	2158.7685	2158.7685	156.487	2831.65365	2296.14268	2824.98125	CONFLICT	0.5	0.5
90Day	Antiviral mechanism by IFN-stimulated genes	0.32705	0.86722	0.5717	usp18;abce1	3550.28	3550.28	3026.26	741.076191	3605.64422	736.928441	UP	1	0
90Day	FCERI mediated Ca+2 mobilization	0.32705	0.86722	0.5717	vav1;sos1	5027.99	5027.99	4161.05	1226.03831	5362.02772	1131.37418	DOWN	0	1

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
90Day	EPH-ephrin mediated repulsion of cells	0.32705	0.86722	0.5717	tiam1;mmp2	4998.325	4998.325	4586.54	582.351932	4881.4162	558.389146	DOWN	0	1
90Day	Termination of translesion DNA synthesis	0.32705	0.86722	0.5717	pole4;polk	4753.255	4753.255	3652.71	1556.40567	3884.77714	955.97646	CONFLICT	0.5	0.5
90Day	NOD1/2 Signaling Pathway	0.30513	0.87911	0.57205	mapk14;ikbk	3763.76	3763.76	3265.56	704.561197	3420.95379	511.247768	CONFLICT	0.5	0.5
90Day	Sialic acid metabolism	0.30513	0.87911	0.57205	st6galnac6;st3gal3	4683.725	4683.725	4143.19	764.431928	4469.98451	702.129746	DOWN	0	1
90Day	Loss of Nlp from mitotic centrosomes	0.31214	0.8156	0.57259	haus7;dctn3;cntrl;tubb4b;cep76;hsp90aa1	3221.30167	3997.375	426.32	1725.30565	3467.98166	1544.87279	UP	1	0
90Day	Loss of proteins required for interphase microtubule organization from the centrosome	0.31214	0.8156	0.57259	haus7;dctn3;cntrl;tubb4b;cep76;hsp90aa1	3221.30167	3997.375	426.32	1725.30565	3467.98166	1544.87279	UP	1	0
90Day	Cell death signalling via NRAGE, NRIF and NADE	0.29772	0.82606	0.57281	arhgef6;fgd4;vav1;tiam1;sos1;psen2	4921.82167	5193.43	3135.19	1154.56154	4931.17678	1191.79698	DOWN	0.166666667	0.833333333
90Day	Regulation of APC/C activators between G1/S and early anaphase	0.28434	0.89001	0.57394	anapc10;btrc	4771.585	4771.585	4390.47	538.978002	5062.49481	348.195709	CONFLICT	0.5	0.5
28Day	RIP-mediated NFkB activation via ZBP1	0.80278	0.57425	0.57425	ikbk	5417.68	5417.68	5417.68		5417.68		UP	1	0
28Day	Dectin-1 mediated noncanonical NF-kB signaling	0.80278	0.57425	0.57425	ube2m	2933.96	2933.96	2933.96		2933.96		UP	1	0
28Day	NIK-->noncanonical NF-kB signaling	0.80278	0.57425	0.57425	ube2m	2933.96	2933.96	2933.96		2933.96		UP	1	0
28Day	Apoptosis induced DNA fragmentation	0.80278	0.57425	0.57425	kpn1	5384.85	5384.85	5384.85		5384.85		UP	1	0
28Day	Activation of DNA fragmentation factor	0.80278	0.57425	0.57425	kpn1	5384.85	5384.85	5384.85		5384.85		UP	1	0
28Day	Purine ribonucleoside monophosphate biosynthesis	0.80278	0.57425	0.57425	adss	3213.44	3213.44	3213.44		3213.44		UP	1	0
28Day	MAP3K8 (TPL2)-dependent MAPK1/3 activation	0.80278	0.57425	0.57425	ikbk	5417.68	5417.68	5417.68		5417.68		UP	1	0
28Day	Pregnenolone biosynthesis	0.80278	0.57425	0.57425	fdxr	5126.12	5126.12	5126.12		5126.12		DOWN	0	1
28Day	CD28 dependent Vav1 pathway	0.80278	0.57425	0.57425	cdc42	2463.49	2463.49	2463.49		2463.49		UP	1	0
28Day	TRAF6 mediated IRF7 activation in TLR7/8 or 9 signaling	0.80278	0.57425	0.57425	ube2n	5266.71	5266.71	5266.71		5266.71		DOWN	0	1
28Day	Organic cation transport	0.80278	0.57425	0.57425	slc22a1	1681.65	1681.65	1681.65		1681.65		DOWN	0	1
28Day	Negative regulators of DDX58/IFIH1 signaling	0.80278	0.57425	0.57425	tax1bp1	4968.69	4968.69	4968.69		4968.69		DOWN	0	1
90Day	Protein localization	0.27022	0.84555	0.57529	gstk1;hacl1;slc27a2;amacr;ephx2;agxt	3428.52667	3398.155	2157.32	816.22512	3062.66676	947.203112	DOWN	0	1
90Day	Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by uncoupling proteins.	0.27022	0.84555	0.57529	ndufab1;ndufc2;etfdh;ndufaf3;ndufb9;atp5k	2794.408	3310.375	105.476	2268.6022	4306.21778	2218.58014	DOWN	0.333333333	0.666666667
90Day	AURKA Activation by TPX2	0.27022	0.84555	0.57529	haus7;dctn3;cntrl;tubb4b;cep76;hsp90aa1	3221.30167	3997.375	426.32	1725.30565	3467.98166	1544.87279	UP	1	0
7Day	RET signaling	0.32742	0.86594	0.57562	ptpn11;gfra1	3850.68	3850.68	3629.67	312.555339	3903.39421	303.534619	CONFLICT	0.5	0.5
7Day	DNA Damage Recognition in GG-NER	0.32742	0.86594	0.57562	ino80c;uba52	4592.3	4592.3	4423.04	239.369788	4648.50109	225.789217	UP	1	0
7Day	Cargo concentration in the ER	0.30917	0.87594	0.57583	sec22b;f5	1730.3555	1730.3555	244.081	2101.90956	868.772233	1712.70906	CONFLICT	0.5	0.5
7Day	Regulation of PLK1 Activity at G2/M Transition	0.31092	0.81559	0.57627	tubb4b;uba52;tuba4a;nedd1;hsp90aa1	2630.741	2445.18	919.856	1640.41495	2578.74438	1683.29047	UP	1	0
7Day	Metabolism of polyamines	0.2917	0.88526	0.57711	btrc	1683.855	1683.855	1137.09	773.242478	1840.19108	740.96018	UP	1	0
7Day	Non-integrin membrane-ECM interactions	0.2917	0.88526	0.57711	ttr;cdc3	4752.175	4752.175	3803.05	1342.26545	4518.7704	1301.04616	DOWN	0	1
7Day	NCAM signaling for neurite out-growth	0.2917	0.88526	0.57711	mapk3;kras	4479.475	4479.475	4158.71	453.630213	4552.01512	441.878074	CONFLICT	0.5	0.5
28Day	HSP90 chaperone cycle for steroid hormone receptors (SHR)	0.75561	0.43666	0.57736	dynl1;tubb4b;tubb2a;capza2	4122.615	4169.735	2359.45	1742.36759	4179.60212	1734.13634	UP	0.75	0.25
28Day	Ribosomal scanning and start codon recognition	0.32314	0.8669	0.58071	eif3m;eif1ax	2737.81	2737.81	1517.45	1725.84966	2423.68091	1667.69388	CONFLICT	0.5	0.5
28Day	Signaling by Type 1 Insulin-like Growth Factor 1 Receptor (IGF1R)	0.32314	0.8669	0.58071	pdpk1;fgf1	830.279	830.279	192.988	901.265575	1273.10558	648.142632	DOWN	0	1
28Day	Chemokine receptors bind chemokines	0.31007	0.87412	0.58099	cx3cl1;cxcl9	5958.13	5958.13	5937.6	29.0338044	5963.10667	28.1678407	CONFLICT	0.5	0.5
28Day	Condensation of Prophase Chromosomes	0.31007	0.87412	0.58099	set;hist1h4i	4954.585	4954.585	4060.76	1264.05944	4946.81076	1264.01162	CONFLICT	0.5	0.5

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
28Day	Cell surface interactions at the vascular wall	0.31652	0.81032	0.58099	apob;tnfrsf10b;proc;cd74;fn1;f2	3287.43083	3598.375	939.205	1854.98409	2882.27048	1899.80049	DOWN	0.166666667	0.833333333
28Day	Insulin receptor signalling cascade	0.31007	0.87412	0.58099	pdpk1;fgf1	830.279	830.279	192.988	901.265575	1273.10558	648.142632	DOWN	0	1
28Day	Heparan sulfate/heparin (HS-GAG) metabolism	0.31007	0.87412	0.58099	hs2st1;gpc4	4234.355	4234.355	3361.03	1235.06806	4554.00819	1149.36364	DOWN	0	1
28Day	Formation of TC-NER Pre-Incision Complex	0.31007	0.87412	0.58099	prpf19;polr2a	4295.465	4295.465	3550.26	1053.87902	3967.52849	946.348921	UP	1	0
28Day	Translation initiation complex formation	0.29739	0.88098	0.58181	eif3m;eif1ax	2737.81	2737.81	1517.45	1725.84966	2423.68091	1667.69388	CONFLICT	0.5	0.5
28Day	Golgi Associated Vesicle Biogenesis	0.29739	0.88098	0.58181	picalm;ftl1	2328.2885	2328.2885	527.967	2546.03908	979.680637	1686.66199	UP	1	0
28Day	L13a-mediated translational silencing of Ceruloplasmin expression	0.28512	0.8875	0.58315	eif3m;eif1ax	2737.81	2737.81	1517.45	1725.84966	2423.68091	1667.69388	CONFLICT	0.5	0.5
28Day	Activation of the mRNA upon binding of the cap-binding complex and eIFs, and subsequent binding to 43S	0.28512	0.8875	0.58315	eif3m;eif1ax	2737.81	2737.81	1517.45	1725.84966	2423.68091	1667.69388	CONFLICT	0.5	0.5
28Day	Resolution of Sister Chromatid Cohesion	0.27443	0.84082	0.58339	zwilch;dynl1;cenpt;tubb4b;tubb2a;rad21	3719.56667	3563.05	2359.45	1186.01958	3809.00797	1244.66079	UP	1	0
28Day	Kinesins	0.27324	0.89368	0.58499	tubb4b;tubb2a	2631.245	2631.245	2359.45	384.376175	2702.45657	370.948608	UP	1	0
90Day	Mitotic G2-G2/M phases	0.30784	0.78447	0.58722	haus7;tubb6;dctn3;gtse1;cntrl;tubb4b;cep76;tubb2a;tuba1b;hsp90aa1;cdkn1a;cdk7;btrc	2700.50008	2128.94	426.32	1618.52744	2593.60842	1735.8006	UP	0.846153846	0.153846154
28Day	G1/S Transition	0.26175	0.89954	0.58731	pole3;cdc6	3336.429	3336.429	805.318	3579.5315	4404.50906	3245.22045	UP	1	0
28Day	Homology Directed Repair	0.76921	0.34573	0.58937	ube2n;rm1;ube2v2;pole3;hist1h4i;rad51d;rad51;lig3;brca1;blm	3816.8064	3892.075	692.086	1865.9087	4049.79857	1462.97446	UP	0.7	0.3
28Day	The citric acid (TCA) cycle and respiratory electron transport	0.76921	0.34573	0.58937	ndufab1;ndufaf1;ndufc2;atp5g2;etfdh;atp5j2;suclg2;me1;ldha;gstz1	4115.695	5341.16	1023.12	1938.77223	4052.10752	2107.143	DOWN	0.2	0.8
7Day	Neutrophil degranulation	0.74091	0.31019	0.58967	faf2;cotl1;ist1;fuca1;tmem30a;arl8a;ndufc2;npc2;ilf2;pycard;psmd6;9130409i23rik;golga7;igap2;sdcbp;hgsnat;mgam;tubb4b;ttr;nhlrc3;dsg1c;rab6a;rab18;rab10;psmc2;pa2g4;pgam1;neu1;mme;man2b1;lamp1;kpnb1;igf2r;hsp90aa1;h2-t23;h2-q10;gstp1;gstp2;gpi1;ftl1;ddx3x;ctsb;csnk2b;chil1;cct2;cab39;arsb;ahsg;aga;dsip;mlec;atad3a;qsox1	3282.41918	3422.8	34.2395	1455.3462	3167.92101	1410.26461	CONFLICT	0.528301887	0.471698113
7Day	Regulation of localization of FOXO transcription factors	0.79463	0.58979	0.58979	ywhaz	2726.98	2726.98	2726.98		2726.98		UP	1	0
7Day	Reactions specific to the complex N-glycan synthesis pathway	0.79463	0.58979	0.58979	fuca1	2644.02	2644.02	2644.02		2644.02		DOWN	0	1
7Day	Apoptotic factor-mediated response	0.79463	0.58979	0.58979	xiap	4874.03	4874.03	4874.03		4874.03		DOWN	0	1
7Day	Tight junction interactions	0.79463	0.58979	0.58979	prkci	3409.24	3409.24	3409.24		3409.24		UP	1	0
7Day	FGFR2b ligand binding and activation	0.79463	0.58979	0.58979	fgf1	2647.76	2647.76	2647.76		2647.76		DOWN	0	1
7Day	Axonal growth inhibition (RHOA activation)	0.79463	0.58979	0.58979	lingo1	3247.44	3247.44	3247.44		3247.44		UP	1	0
7Day	Josephin domain DUBs	0.79463	0.58979	0.58979	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	Regulation of RUNX3 expression and activity	0.79463	0.58979	0.58979	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	Phosphate bond hydrolysis by NTPDase proteins	0.79463	0.58979	0.58979	entpd5	821.082	821.082	821.082		821.082		UP	1	0
7Day	mitochondrial fatty acid beta-oxidation of saturated fatty acids	0.79463	0.58979	0.58979	hadha	197.056	197.056	197.056		197.056		DOWN	0	1
7Day	Translocation of SLC2A4 (GLUT4) to the plasma membrane	0.79463	0.58979	0.58979	ywhaz	2726.98	2726.98	2726.98		2726.98		UP	1	0
7Day	SLBP Dependent Processing of Replication-Dependent Histone Pre-mRNAs	0.79463	0.58979	0.58979	lsm10	2905.24	2905.24	2905.24		2905.24		UP	1	0
7Day	EGFR Transactivation by Gastrin	0.79463	0.58979	0.58979	kras	4158.71	4158.71	4158.71		4158.71		UP	1	0
7Day	SUMOylation	0.2828	0.80419	0.59186	gm49336;rnf168;hist1h4h;hdac7;nop58;suz12;uba2;top2b;ncoa1;hnnpbc;mbi1;uhrf2;tptr	3306.80731	3214.64	852.825	1056.2797	3114.72341	1016.19186	UP	0.923076923	0.076923077

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
7Day	COPI-dependent Golgi-to-ER retrograde traffic	0.7418	0.37947	0.59396	copz1;tubb4b;tubb2a;tuba4a;arcn1;sec22b;rab1a;kif2a;kif1c;gbf1	2649.6696	2888.645	919.856	1184.96711	2687.56923	1231.98217	UP	0.9	0.1	
90Day	Global Genome Nucleotide Excision Repair (GG-NER)	0.32085	0.80149	0.59459	pole4;mcrs1;polky;y1;ino80c;rad23a;cdk7	3814.86	3652.71	1252.26	1612.71329	3703.59993	1422.1654	CONFLICT	0.571428571	0.428571429	
90Day	RET signaling	0.78597	0.38264	0.59472	pdlim7;irs2;sos1;gfra1;gab1	1573.00986	218.188	74.8133	2492.60036	1678.27136	2433.76832	DOWN	0	1	
90Day	DNA Replication Pre-Initiation	0.29361	0.82187	0.59566	pole4;psmd8;orc6;cbf4;e2f2;psmc4;psmf1	3121.85686	3031.27	186.178	1891.29969	2809.12655	1647.18856	UP	0.857142857	0.142857143	
90Day	Fcgamma receptor (FCGR) dependent phagocytosis	0.28057	0.83144	0.59705	wasf2;vav1;myo9b;myo10;hsp90aa1;fcgr2b;cdc42	2644.57429	3055.31	100.823	2388.05593	3312.00806	2193.71301	DOWN	0.285714286	0.714285714	
7Day	Metabolism of nucleotides	0.28359	0.82846	0.6003	dpys;nudt5;txnrd1;entpd5;ak1;adk;atichist1h4h;hist1h2bc;hist2h2ac;mapk3;pplr2h;ubtf;hist2h2aa1	2189.216	1880.13	124.762	2094.21117	2234.18323	2040.5626	UP	0.714285714	0.285714286	
7Day	RNA Polymerase I Promoter Clearance	0.273	0.83618	0.60179	olr2h;ubtf;hist2h2aa1	3877.53857	3964.6	1976.31	1102.11348	3992.99121	990.713071	CONFLICT	0.571428571	0.428571429	
90Day	EPHB-mediated forward signaling	0.76698	0.40602	0.60261	tiam1;rasa1;rock2;rock1;cdc42	2202.5738	2133.64	156.487	2026.94479	1983.44718	2199.56514	UP	0.8	0.2	
7Day	Interleukin-3, Interleukin-5 and GM-CSF signaling	0.76944	0.40096	0.60349	ywhaz;yes1;uba52;ptpn11;jak1	3738.696	3629.67	2726.98	740.838803	3785.22967	622.632352	UP	1	0	
28Day	Nonsense-Mediated Decay (NMD)	0.77691	0.60352	0.60352	smg5	4382.44	4382.44	4382.44		4382.44		UP	1	0	
	Nonsense Mediated Decay (NMD) enhanced by the Exon Junction Complex (EJC)	0.77691	0.60352	0.60352	smg5	4382.44	4382.44	4382.44		4382.44		UP	1	0	
28Day	VEGFR2 mediated cell proliferation	0.77691	0.60352	0.60352	pdpk1	192.988	192.988	192.988		192.988		DOWN	0	1	
28Day	ZBP1(DAI) mediated induction of type I IFNs	0.77691	0.60352	0.60352	ikbkg	5417.68	5417.68	5417.68		5417.68		UP	1	0	
28Day	GRB2 events in EGFR signaling	0.77691	0.60352	0.60352	hbegf	919.738	919.738	919.738		919.738		UP	1	0	
28Day	Depolymerisation of the Nuclear Lamina	0.77691	0.60352	0.60352	cnepr1r1	5841.61	5841.61	5841.61		5841.61		UP	1	0	
28Day	ERBB2 Activates PTK6 Signaling	0.77691	0.60352	0.60352	hbegf	919.738	919.738	919.738		919.738		UP	1	0	
28Day	Oncogene Induced Senescence	0.77691	0.60352	0.60352	mdm2	2266.61	2266.61	2266.61		2266.61		UP	1	0	
28Day	Trafficking of GluR2-containing AMPA receptors	0.77691	0.60352	0.60352	gria3	2052.57	2052.57	2052.57		2052.57		UP	1	0	
28Day	IRAK2 mediated activation of TAK1 complex upon TLR7/8 or 9 stimulation	0.77691	0.60352	0.60352	ly96	4560.3	4560.3	4560.3		4560.3		UP	1	0	
28Day	Notch-HLH transcription pathway	0.77691	0.60352	0.60352	notch1	908.573	908.573	908.573		908.573		UP	1	0	
28Day	BBSome-mediated cargo-targeting to cilium	0.77691	0.60352	0.60352	bbs9	4941.88	4941.88	4941.88		4941.88		DOWN	0	1	
28Day	Apoptotic cleavage of cell adhesion proteins	0.77691	0.60352	0.60352	pkp1	3208.19	3208.19	3208.19		3208.19		UP	1	0	
28Day	Glycogen breakdown (glycogenolysis)	0.77691	0.60352	0.60352	gaa	3036.96	3036.96	3036.96		3036.96		DOWN	0	1	
28Day	Signalling to RAS	0.77691	0.60352	0.60352	mapkapk2	5375	5375	5375		5375		DOWN	0	1	
28Day	FGFR3 ligand binding and activation	0.77691	0.60352	0.60352	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1	
28Day	FGFR3c ligand binding and activation	0.77691	0.60352	0.60352	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1	
28Day	FGFR2c ligand binding and activation	0.77691	0.60352	0.60352	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1	
28Day	Phospholipase C-mediated cascade; FGFR3	0.77691	0.60352	0.60352	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1	
28Day	RHO GTPases Activate Formins	0.29062	0.82228	0.60405	zwilch;dynl11;cenpt;tubb4b;tubb2a;pfn1;cdc42	3639.25714	3558.89	2359.45	1266.6887	3715.75771	1282.08584	UP	1	0	
28Day	TCR signaling	0.77201	0.39514	0.60511	ube2n;pdpk1;ikbkj;h2-ab1;h2-aa	3559.9316	3676.55	192.988	2110.26973	3695.28288	1546.16292	DOWN	0.2	0.8	
28Day	Autodegradation of Cdh1 by Cdh1:APC/C	0.77201	0.39514	0.60511	psmd6;psmd8;psmf1;cdc27;psmb8	3948.96	4413.43	1415.14	1656.49498	3909.29906	1781.98522	DOWN	0.4	0.6	
7Day	Signaling by VEGF	0.74868	0.36551	0.60838	nckap1;pak2;rasa1;prckc2;kras;hsp90aa1;cdc42;ctnnb1;calm3;calm2;brk1	3454.26211	3468.74	54.5232	1846.95429	3559.80325	2027.96172	UP	0.636363636	0.363636364	
90Day	Mitochondrial protein import	0.38412	1	0.60943											
90Day	XBP1(S) activates chaperone genes	0.38412	1	0.60943											
90Day	Phase 3 - rapid repolarisation	0.38412	1	0.60943											
90Day	Synthesis of UDP-N-acetyl-glucosamine	0.38412	1	0.60943											
90Day	WNT mediated activation of DVL	0.38412	1	0.60943											
90Day	HuR (ELAVL1) binds and stabilizes mRNA	0.38412	1	0.60943											
90Day	Degradation of AXIN	0.38412	1	0.60943											

[illegible]

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
90Day	Triglyceride catabolism	0.26825	1	0.62482											
90Day	Mismatch Repair	0.26825	1	0.62482											
90Day	p75NTR recruits signalling complexes	0.26825	1	0.62482											
90Day	Growth hormone receptor signaling	0.26825	1	0.62482											
90Day	Heme biosynthesis	0.26825	1	0.62482											
90Day	Signaling by EGFR	0.79506	0.35492	0.62529	tgfa;sos1;sh3gl3;gab1;cdc42;areg	2929.49583	3066.45	126.428	2508.88906	3628.85041	2226.41237	UP	0.666666667	0.333333333	
28Day	Formation of Senescence-Associated Heterochromatin Foci (SAHF)	0.29818	1	0.62569											
28Day	Translesion Synthesis by POLH	0.29818	1	0.62569											
28Day	Synthesis, secretion, and deacylation of Ghrelin	0.29818	1	0.62569											
28Day	Interferon gamma signaling	0.29818	1	0.62569											
28Day	Macroautophagy	0.32716	0.84063	0.62613	dynll1;rb1cc1;atg5	5807.87333	5791.54	5747.14	70.3369983	5786.29948	55.9545375	UP	1	0	
28Day	Peptide hormone metabolism	0.32716	0.84063	0.62613	exoc4;mme;agt	2953.18267	2439.57	776.548	2473.759	2533.74323	2521.18437	DOWN	0.333333333	0.666666667	
28Day	Interferon Signaling	0.32716	0.84063	0.62613	ube2n;arih1;ppm1b	4090.57	5266.71	1290.26	2435.46398	2838.72879	2524.17867	DOWN	0.333333333	0.666666667	
28Day	Collagen biosynthesis and modifying enzymes	0.32716	0.84063	0.62613	p4hb;col8a1;bmp1	3663.75333	4236.71	1023.63	2405.38028	3386.85404	2424.23445	UP	0.666666667	0.333333333	
28Day	L1CAM interactions	0.32716	0.84063	0.62613	ranbp9;tubb4b;tubb2a	3634.13667	2903.04	2359.45	1758.19442	2994.52802	1118.88605	UP	1	0	
7Day	TRAF6 mediated NF-kB activation	0.27598	1	0.62624											
7Day	LGI-ADAM interactions	0.27598	1	0.62624											
7Day	cGMP effects	0.27598	1	0.62624											
7Day	BBSome-mediated cargo-targeting to cilium	0.27598	1	0.62624											
7Day	Insulin receptor signalling cascade	0.27915	0.8715	0.62708	mapk3;ptpn11;fgf1	3692.55667	3629.67	2647.76	1077.61709	3582.43453	1145.05081	DOWN	0.333333333	0.666666667	
7Day	Formation of TC-NER Pre-Incision Complex	0.27915	0.8715	0.62708	prpf19;polr2h;uba52	3815.36333	3964.6	2719.93	1028.96402	3913.27434	885.21152	UP	1	0	
28Day	Collagen degradation	0.30436	0.85499	0.62791	phykpl1;tmprss6;col8a1	2918.14967	4236.71	182.399	2369.74276	3669.8463	1804.74723	UP	0.666666667	0.333333333	
28Day	ER to Golgi Anterograde Transport	0.74133	0.36731	0.62837	lman2;dynll1;ppp6r3;tubb4b;tubb2a;se c22c;serpina1e;serpina1b;f5;capza2;bet1;gbf1	3877.92175	3700.625	619.741	1602.85433	3499.22612	1690.42867	CONFLICT	0.5	0.5	
28Day	Biosynthesis of the N-glycan precursor (dolichol lipid-linked oligosaccharide, LLO) and transfer to a nascent protein	0.29339	0.86173	0.62935	nanp;gne;gfpt1	5085.35667	5755.83	3647.63	1246.04778	5180.06702	1205.69221	DOWN	0.333333333	0.666666667	
28Day	Unfolded Protein Response (UPR)	0.27768	1	0.63088											
28Day	DARPP-32 events	0.27768	1	0.63088											
28Day	Ephrin signaling	0.27768	1	0.63088											
28Day	Assembly of collagen fibrils and other multimeric structures	0.28271	0.8682	0.63112	ctss;col8a1;bmp1	3680.24333	4236.71	1023.63	2426.71234	3369.41807	2436.78186	UP	0.666666667	0.333333333	
7Day	TCF dependent signaling in response to WNT	0.71383	0.39986	0.6321	gsk3b;klhl12;ywhaz;uba52;sox6;ppp2c b;lrp5;csnk2b;ctnnb1;btrc;xiap;xpo1	3254.95768	3747.19	54.5232	1671.32215	3246.91196	1784.39588	UP	0.666666667	0.333333333	
7Day	HDR through Homologous Recombination (HRR) or Single Strand Annealing (SSA)	0.31514	0.79329	0.63373	ube2n;ube2v2;rfn168;hist1h4h;babam 1;hist1h2bc;uba52;rad51ap1;abl1	3610.97889	3444.79	2423.08	647.933214	3488.58257	659.371908	UP	0.777777778	0.222222222	
7Day	Eicosanoid ligand-binding receptors	0.24994	1	0.63543											
7Day	GRB2:SOS provides linkage to MAPK signaling for Integrins	0.24994	1	0.63543											
7Day	p130Cas linkage to MAPK signaling for integrins	0.24994	1	0.63543											
7Day	Synthesis of PIPs at the Golgi membrane	0.24994	1	0.63543											
7Day	Resolution of Sister Chromatid Cohesion	0.29486	0.80912	0.63556	clasp2;pds5a;cenpk;tubb4b;tubb2a;tub a4a;ppp2cb;kif2a;xpo1	3022.26178	3627.04	919.856	1221.78757	3036.17958	1202.74898	UP	0.888888889	0.111111111	
90Day	RIP-mediated NFkB activation via ZBP1	0.85486	0.39885	0.63684	nfkbia;ikbkg	3433.33	3433.33	3265.56	237.262609	3311.77597	163.5322	CONFLICT	0.5	0.5	
90Day	Erythropoietin activates Phosphoinositide-3-kinase (PI3K)	0.85486	0.39885	0.63684	irs2;gab1	100.62065	100.62065	74.8133	36.4971044	86.6473692	30.6844174	DOWN	0	1	
90Day	Dectin-1 mediated noncanonical NF-kB signaling	0.85486	0.39885	0.63684	ube2m;btrc	2915.405	2915.405	678.11	3164.01293	2982.75275	3162.57907	CONFLICT	0.5	0.5	
90Day	NIK->noncanonical NF-kB signaling	0.85486	0.39885	0.63684	ube2m;btrc	2915.405	2915.405	678.11	3164.01293	2982.75275	3162.57907	CONFLICT	0.5	0.5	
90Day	Reversible hydration of carbon dioxide	0.85486	0.39885	0.63684	car5a;car3	2229.49	2229.49	859.92	1936.86447	1474.33408	1615.83509	CONFLICT	0.5	0.5	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
90Day	Purine ribonucleoside monophosphate biosynthesis	0.85486	0.39885	0.63684	gmps;atic	3841.07	3841.07	2515.37	1874.82292	3607.96146	1845.6115	UP	1	0	
90Day	MAP3K8 (TPL2)-dependent MAPK1/3 activation	0.85486	0.39885	0.63684	ikbkg;btrc	4209.13	4209.13	3265.56	1334.40949	4331.39024	1323.16044	CONFLICT	0.5	0.5	
90Day	Triglyceride biosynthesis	0.85486	0.39885	0.63684	dgat2;agmo	3065.025	3065.025	2903.14	228.939963	3009.70495	215.157829	DOWN	0	1	
90Day	CD28 dependent Vav1 pathway	0.85486	0.39885	0.63684	vav1;cdc42	2158.7685	2158.7685	156.487	2831.65365	2296.14268	2824.98125	CONFLICT	0.5	0.5	
90Day	Negative regulators of DDX58/IFIH1 signaling	0.85486	0.39885	0.63684	tbk1;pin1	3003.045	3003.045	1058.39	2750.15748	2467.79178	2643.93156	CONFLICT	0.5	0.5	
7Day	Post-translational protein phosphorylation	0.75206	0.35185	0.6369	apoa5;apob;hsp90b1;nucb1;igfbp5;f5;c sf1;c4b;serpinc1;apoe;ahsg;afp;qsox1	2429.02581	1999.21	85.9375	2022.85744	2176.0983	2216.29449	DOWN	0.230769231	0.769230769	
28Day	ERK/MAPK targets	0.25858	1	0.63713											
28Day	Unblocking of NMDA receptors, glutamate binding and activation	0.25858	1	0.63713											
28Day	Oxygen-dependent proline hydroxylation of Hypoxia-inducible Factor Alpha	0.25858	1	0.63713											
28Day	Signaling by NOTCH3	0.25858	1	0.63713											
28Day	Regulation of FZD by ubiquitination	0.25858	1	0.63713											
28Day	NOTCH3 Activation and Transmission of Signal to the Nucleus	0.25858	1	0.63713											
28Day	Post NMDA receptor activation events	0.25858	1	0.63713											
90Day	Metabolism of vitamins and cofactors	0.73926	0.33982	0.63779	mccc2;pank1;nmnat3;slc52a3;pccb;pds s1;slc23a2;apob;ttr;pdck;sdca4;rbp1;pcx mut;mfthfd2;rdh11;hsp90aa1;apoe;ap oc3;aox1;hlcs;pcca;aldh1l1	2609.66878	2679.72	175.96	1884.21897	2916.31643	1749.4064	DOWN	0.347826087	0.652173913	
28Day	Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by uncoupling proteins.	0.76649	0.38594	0.63835	ndufab1;ndufaf1;ndufc2;atp5g2;etfdh; atp5j2	3654.68167	3868.245	1023.12	2215.21614	3642.68542	2294.18332	DOWN	0.333333333	0.666666667	
7Day	Metabolism of carbohydrates	0.33242	0.75078	0.6389	man2c1;dcxr;pfkp;hs3st3b1;hgsnat;gck r;uba52;sdca3;pgam1;man2b1;hyal1;gpi 1;ext1;calm3;calm2;bgn;arsb;pgd	3574.79881	3642.14	34.2395	1573.30178	3501.90606	1542.14129	DOWN	0.277777778	0.722222222	
7Day	G1/S Transition	0.74188	0.41754	0.64308	uba52;prim2;ppp2cb;cdkn1a;cdc25a;cc ne2	4281.55333	4302.165	2818.63	1050.99246	4140.65106	1002.74435	UP	1	0	
28Day	Receptor-type tyrosine-protein phosphatases	0.84574	0.40347	0.64426	ptprd;il1rap	3615.755	3615.755	3526	126.932738	3624.67675	126.304096	DOWN	0	1	
28Day	Na+/Cl- dependent neurotransmitter transporters	0.84574	0.40347	0.64426	slc22a1;slc6a13	916.396	916.396	151.142	1082.23259	892.041183	1081.68436	DOWN	0	1	
28Day	Endosomal/Vacuolar pathway	0.84574	0.40347	0.64426	h2-q7;h2-d1	4749.05	4749.05	3718.12	1457.95519	4309.40997	1318.73675	CONFLICT	0.5	0.5	
28Day	RHO GTPases activate PAKs	0.84574	0.40347	0.64426	cdc42;mylk	3872.595	3872.595	2463.49	1992.7754	3650.52709	1967.87334	UP	1	0	
28Day	VxPx cargo-targeting to cilium	0.84574	0.40347	0.64426	rab11a;exoc4	2316.245	2316.245	2192.92	174.407888	2290.29724	170.50378	UP	1	0	
7Day	Calnexin/calreticulin cycle	0.83789	0.41985	0.6462	uba52;sel1l	4493.74	4493.74	4225.92	378.754676	4638.58379	318.583834	UP	1	0	
7Day	Phosphorylation of CD3 and TCR zeta chains	0.83789	0.41985	0.6462	h2-ab1;h2-aa	2062.21	2062.21	1863.06	281.640631	2105.93651	274.767957	DOWN	0	1	
7Day	Activation of IRF3/IRF7 mediated by TBK1/IKK epsilon	0.83789	0.41985	0.6462	uba52;ptpn11	4195.615	4195.615	3629.67	800.367095	4234.65504	798.460542	UP	1	0	
7Day	Sema3A PAK dependent Axon repulsion	0.83789	0.41985	0.6462	pak2;hsp90aa1	1771.905	1771.905	1005.61	1083.70478	1287.67812	839.919468	UP	1	0	
7Day	Regulation of necroptotic cell death	0.83789	0.41985	0.6462	uba52;xia1	4817.795	4817.795	4761.56	79.5282997	4830.99188	77.3074074	CONFLICT	0.5	0.5	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
7Day	Metabolism	0.69987	0.33236	0.64802	mau1a;ugt1a;aba;pla1a;akr1c6;mas;mccl2;fads1;gstk1;dmgdh;man2c1;ugt2b1;amdhd1;kyat1;ndufaf1;elovl5;fitm1;ndufaf4;adipor2;ndufc2;bphl;nudt12;dcxr;coq10b;dgat2;qprt;ndufa13;lipt2;ndufa6;sdha;pccb;cris1;tnfaip8l1;bhmt2;dpy5;9130409i23rik;mocs1;txn2;vapb;fads2;pfkp;cyp3a25;ptges3;prodh2;cyp39a1;stard10;hs3st3b1;ndufa1;mtmr7;nudt5;acaa2;hgsnat;txnr1;ugt1a1;ugt1a9;i;di1;pdhx;gcdh;idh2;ecsit;ahcy;sptcl1;slc27a5;decr2;btd;naxe;uroc1;ugt2b35;apob;ces2c;blvrb;ugt2b36;gckr;osbpl2;ugt3a2;ugt2b5;ugdh;uba52;ttr;mtmr6;itpk1;aldh4a1;sdcs;smppd2;smppd1;slc25a17;slc22a1;slc10a2;slc10a1;sardh;pten;ptdss1;prkar2a;ppt1;pgam1;nqo2;nqo1;neu1;ndufa2;ncoa2;ncoa1;man2b1;i;dh3b;lrp1;phyh;itpr2;kpnb1;hyal1;hsp90aa1;hsd17b4;hsd17b2;hsd11b1;hmgcs2;hao1;h2-ke6;gstp1;gstp2;gstm4;gsta1;gss;gpi1;gnmt;gcl;cgc;ext1;ces3b;esd;ephx2;ebp;dlid;cyp3a11;cyp2e1;cyp2c37;cyp2c29;elovl3;cdo1;entpd5;calm3;calm2;bgn;bckdh;baat;atp5j;arsb;arnt;apoe;jacs	2811.83118	3128.375	34.2395	1721.84357	2825.66182	1617.98483	CONFLICT	0.422619048	0.577380952	
90Day	ZBP1(DAI) mediated induction of type I IFNs	0.82629	0.43979	0.65092	nfkbia;jikbk	3433.33	3433.33	3265.56	237.262609	3311.77597	163.5322	CONFLICT	0.5	0.5	
90Day	TRAF6 mediated NF-kB activation	0.82629	0.43979	0.65092	nfkbia;jikbk	3433.33	3433.33	3265.56	237.262609	3311.77597	163.5322	CONFLICT	0.5	0.5	
90Day	Trafficking of GluR2-containing AMPA receptors	0.82629	0.43979	0.65092	gria3;ap2m1	2040.685	2040.685	1097.82	1333.41247	1421.13725	1005.14177	UP	1	0	
90Day	Apoptotic cleavage of cell adhesion proteins	0.82629	0.43979	0.65092	dsg2;ctnnb1	4023.01	4023.01	3958.98	90.5520944	4010.29747	88.7494518	DOWN	0	1	
90Day	Signalling to RAS	0.82629	0.43979	0.65092	mapk14;sos1	5078.445	5078.445	4261.96	1154.68416	5603.32821	884.472008	DOWN	0	1	
90Day	Interleukin-15 signaling	0.82629	0.43979	0.65092	sos1;il15ra	4690.02	4690.02	3485.11	1704.00006	5116.83047	1593.51243	DOWN	0	1	
90Day	Complex I biogenesis	0.33942	0.81812	0.65165	ndufab1;ndufc2;ndufaf3;ndufb9	3371.749	3776.765	105.476	2395.08756	4696.0207	2048.29171	CONFLICT	0.5	0.5	
28Day	Nucleotide salvage	0.82865	0.42791	0.65213	hprt;adk	2990.7	2990.7	2420.29	806.681558	3160.53958	770.093613	CONFLICT	0.5	0.5	
28Day	Synaptic adhesion-like molecules	0.82865	0.42791	0.65213	gria3;ptpr	2789.285	2789.285	2052.57	1041.87234	2470.20021	939.078155	CONFLICT	0.5	0.5	
28Day	Synthesis of epoxy (EET) and dihydroxyeicosatrienoic acids (DHET)	0.82865	0.42791	0.65213	cyp2c37;cyp2c29	4152.97	4152.97	2751.06	1982.60014	3551.51531	1790.86789	CONFLICT	0.5	0.5	
28Day	PCNA-Dependent Long Patch Base Excision Repair	0.82865	0.42791	0.65213	pole3;polb	3329.279	3329.279	805.318	3569.41988	4286.22182	3302.91979	UP	1	0	
7Day	RNA Polymerase I Promoter Opening	0.71164	0.4521	0.65406	hist1h4h;hist1h2bc;hist2h2ac;mapk3;ubt;hist2h2aa1	3863.02833	3802.835	1976.31	1206.57215	4000.90003	1135.9748	CONFLICT	0.5	0.5	
7Day	Nonhomologous End-Joining (NHEJ)	0.71164	0.4521	0.65406	ube2n;ube2v2;rnf168;hist1h4h;bam1;hist1h2bc	3415.31167	3431.595	2423.08	578.797266	3318.19796	582.327022	UP	0.833333333	0.166666667	
7Day	Negative epigenetic regulation of rRNA expression	0.35082	0.80908	0.6546	hist1h4h;hist1h2bc;hist2h2ac;hist2h2aa1	4100.405	3802.835	3406.55	933.741438	4060.85571	1011.0164	CONFLICT	0.5	0.5	
90Day	Condensation of Prophase Chromosomes	0.3045	0.84174	0.65474	smc4;hist1h4h;hist1h4i;h2afx	3714.72	3979.26	2814.71	602.516084	3716.61964	599.320578	CONFLICT	0.5	0.5	
90Day	Apoptotic execution phase	0.3045	0.84174	0.65474	hmgb2;rock1;dsg2;ctnnb1	2668.968	3163.37	262.092	1785.01517	2087.46111	1493.84895	CONFLICT	0.5	0.5	
28Day	Transport to the Golgi and subsequent modification	0.71862	0.38442	0.65796	lman2;dync1l;ppp6r3;tubb4b;tubb2a;mgat2;sec22c;serpina1e;serpina1b;man1a;f5;capza2;bet1;gfb1	3585.64393	3488.25	185.394	1772.84744	3440.52945	1628.71841	CONFLICT	0.5	0.5	
7Day	mRNA decay by 3' to 5' exonuclease	0.81362	0.4532	0.65819	wdr61;hbs1l	4801.71	4801.71	3952.2	1201.38856	4349.57954	1017.09909	UP	1	0	
7Day	Metabolism of folate and pterines	0.81362	0.4532	0.65819	shmt2;aladh1l1	2129.5301	2129.5301	93.0602	2880.00335	2537.57278	2821.59913	DOWN	0	1	
7Day	Regulation of pyruvate dehydrogenase (PDH) complex	0.81362	0.4532	0.65819	pdhx;dld	4987.44	4987.44	4831.25	220.886016	4979.91771	220.629696	CONFLICT	0.5	0.5	
7Day	Hedgehog ligand biogenesis	0.81362	0.4532	0.65819	uba52;sel1l	4493.74	4493.74	4225.92	378.754676	4638.58379	318.583834	UP	1	0	
7Day	Organic cation/anion/zwitterion transport	0.81362	0.4532	0.65819	slc22a12;slc22a1	3715.525	3715.525	3194.01	737.533586	3488.48892	663.976675	CONFLICT	0.5	0.5	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
28Day	Metabolism of vitamins and cofactors	0.71156	0.39228	0.65934	akr1c6;nudt12;akr1c12;akr1c19;apob;c oq3;enpp1;pcx;lrp1;gpc4;apoe;acp5;cy b5a;akr1c14	3208.65343	3167.23	201.213	1768.46381	2676.66634	1701.17942	DOWN	0.214285714	0.785714286	
28Day	Cellular response to heat stress	0.32799	0.8236	0.65979	hikeshi;gm45902;mapkapk2;trp clasp2;pd55a;cenpk;tubb4b;uba52;tubb 2a;tuba4a;cdc27;ppp2cb;kif2a;xpo1	4640.02	4764.775	3638.67	883.900811	4474.97086	799.34375	CONFLICT	0.5	0.5	
7Day	Separation of Sister Chromatids	0.34119	0.76327	0.66025	clasp2;pd55a;cenpk;tubb4b;uba52;tubb 2a;tuba4a;cdc27;ppp2cb;kif2a;xpo1	3257.49964	3647.06	919.856	1227.93386	3222.5988	1220.34245	UP	0.909090909	0.090909091	
28Day	Sulfur amino acid metabolism	0.81106	0.4518	0.6606	ahcy;gm4737	2386.29	2386.29	2114.57	384.270109	2337.94463	378.13882	DOWN	0	1	
28Day	Mitochondrial biogenesis	0.81106	0.4518	0.6606	atp5g2;atp5j2	5554.105	5554.105	5480.89	103.541646	5551.28634	103.464887	CONFLICT	0.5	0.5	
7Day	Mitotic Anaphase	0.31208	0.78707	0.66188	clasp2;pd55a;cenpk;tubb4b;uba52;tubb 2a;tuba4a;cdc27;ppp2cb;kif2a;xpo1	3257.49964	3647.06	919.856	1227.93386	3222.5988	1220.34245	UP	0.909090909	0.090909091	
28Day	Integration of energy metabolism	0.30735	0.83765	0.6619	adipor2;gnb5;adcy9;acly	3048.6095	3510.095	953.648	1529.81693	2364.85446	1615.99454	DOWN	0.25	0.75	
90Day	KSRP (KHSRP) binds and destabilizes mRNA	0.79632	0.47914	0.66645	exosc9;ynthaz	1471.424	1471.424	137.958	1885.8057	1856.1388	1805.61685	UP	1	0	
90Day	p130Cas linkage to MAPK signaling for integrins	0.79632	0.47914	0.66645	tlm1;fn1	3294.495	3294.495	2110.06	1675.04404	3616.30164	1612.03397	DOWN	0	1	
90Day	SHC1 events in ERBB4 signaling	0.79632	0.47914	0.66645	nrg1;sos1	4903.635	4903.635	3912.34	1401.90283	5120.14662	1368.05592	CONFLICT	0.5	0.5	
90Day	GRB2 events in ERBB2 signaling	0.79632	0.47914	0.66645	nrg1;sos1	4903.635	4903.635	3912.34	1401.90283	5120.14662	1368.05592	CONFLICT	0.5	0.5	
90Day	Cell-extracellular matrix interactions	0.79632	0.47914	0.66645	arhgef6;actn1	5633.74	5633.74	5314.58	451.360401	5440.61636	359.350429	DOWN	0	1	
90Day	Methylation	0.79632	0.47914	0.66645	ahcy;gm4737	1523.115	1523.115	1418.37	148.1318	1471.13381	128.603818	DOWN	0	1	
90Day	FGFR4 ligand binding and activation	0.79632	0.47914	0.66645	klb;fgf1	2046.3595	2046.3595	242.429	2551.14298	3002.17622	2163.59869	DOWN	0	1	
28Day	MyD88-independent TLR4 cascade	0.75369	0.38892	0.667	ube2n;map2k4;mapkapk2;ly96;ikbk;g pp;birc2	4818.41571	5266.71	2616.5	1073.14504	4865.34093	1108.40121	CONFLICT	0.571428571	0.428571429	
28Day	TRIF (TICAM1)-mediated TLR4 signaling	0.75369	0.38892	0.667	ube2n;map2k4;mapkapk2;ly96;ikbk;g pp;birc2	4818.41571	5266.71	2616.5	1073.14504	4865.34093	1108.40121	CONFLICT	0.571428571	0.428571429	
28Day	Signaling by ROBO receptors	0.79303	0.47512	0.66955	pfn1;dag1	5248.835	5248.835	4831.18	590.653365	5394.18337	553.731975	CONFLICT	0.5	0.5	
28Day	Generation of second messenger molecules	0.79303	0.47512	0.66955	h2-ab1;h2-aa	3461.14	3461.14	3245.73	304.635743	3292.13505	188.885132	DOWN	0	1	
28Day	SMAD2/SMAD3:SMAD4 heterotrimer regulates transcription	0.79303	0.47512	0.66955	tfdp1;ccnk	5399.625	5399.625	5090.85	436.673793	5395.60681	436.636817	CONFLICT	0.5	0.5	
28Day	Triglyceride metabolism	0.79303	0.47512	0.66955	dgat2;agmo	1526.6865	1526.6865	163.973	1927.16791	2004.73883	1804.69059	DOWN	0	1	
28Day	Transcriptional Regulation by E2F6	0.79303	0.47512	0.66955	tfdp1;bmi1	4813.43	4813.43	3918.46	1265.67871	5237.63724	1114.46805	UP	1	0	
7Day	Regulation of TLR by endogenous ligand	0.78849	0.48543	0.67107	apob;lpb	3620.015	3620.015	1999.21	2292.16441	4179.97575	2151.02432	DOWN	0	1	
7Day	ABC transporters in lipid homeostasis	0.78849	0.48543	0.67107	abcg8;abca3	3065.465	3065.465	2076.62	1398.43801	3487.61295	1264.59918	DOWN	0	1	
7Day	G0 and Early G1	0.78849	0.48543	0.67107	tfdp1;ccne2	2652.727	2652.727	707.264	2751.30016	3693.00674	2324.92767	UP	1	0	
7Day	RIPK1-mediated regulated necrosis	0.78849	0.48543	0.67107	uba52;xiap	4817.795	4817.795	4761.56	79.5282997	4830.99188	77.3074074	CONFLICT	0.5	0.5	
7Day	Regulated Necrosis	0.78849	0.48543	0.67107	uba52;xiap	4817.795	4817.795	4761.56	79.5282997	4830.99188	77.3074074	CONFLICT	0.5	0.5	
7Day	L1CAM interactions	0.71955	0.43053	0.6728	ranbp9;sdcbb;mapk3;tubb4b;tubb2a;tu ba4a;csnk2b	2354.63657	2094.04	778.73	1408.22263	2352.67584	1511.15062	UP	0.857142857	0.142857143	
7Day	Signaling by FGFR2	0.70542	0.4464	0.67706	mapk3;polr2h;uba52;ptpn11;ppp2cb;kr as;fgf1	3941.36857	3964.6	2647.76	744.707179	3839.81356	761.564281	UP	0.714285714	0.285714286	
90Day	Hedgehog 'off' state	0.36704	0.78498	0.67737	tubb6;ift52;tubb4b;tubb2a;tuba1b	1277.8726	1722.38	154.682	776.85001	1233.28221	659.90165	UP	0.6	0.4	
90Day	Signaling by the B Cell Receptor (BCR)	0.34989	0.7977	0.67768	vav1;sos1;nfbk1a;ikbk;btcr	4415.068	4161.05	3265.56	1093.44984	4642.96983	1139.53614	DOWN	0.2	0.8	
90Day	Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3	0.33323	0.80983	0.67865	hist1h4h;hist1h4i;hist1h3c;h2afx;ar	2970.9958	3951.81	811.859	1490.29352	2257.59641	1663.47463	DOWN	0.4	0.6	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
7Day	Innate Immune System	0.68012	0.36282	0.67884	ube2n;rbsn;faf2;cotl1;ist1;fuca1;tmem30a;c8g;arl8a;ndufc2;npc2;ilf2;pycard;c1rb;psmd6;9130409i23rik;golga7;iqgap2;sdcbp;tax1bp1;hgsnat;c1s1;nckap1;cfhr1;ecsit;mapk3;map2k3;apob;mga m;tubb4b;yes1;pak2;uba52;ttr;hsp90b1;cdc34;nhlrc3;dsg1c;rab6a;rab18;rab10;ptpn11;psmc2;ppp2cb;pa2g4;pgam1;neu1;myh9;mme;man2b1;lbp;lamp1;kras;kpnb1;igf2r;hsp90aa1;h2-t23;h2-q10;gstp1;gstp2;gpi1;ftl1;f2;dhx9;ddx3x;ctsb;csnk2b;chil1;cfh;cdc42;cct2;ctnnb1;casp9;capza2;calm3;calm2;cab39;c4b;c2;c1qb;btrc;atp6v1e1;arsb;ahsg;aga;abl1;dsp;mlec;atad3a;qsox1;brk1	3259.52373	3422.8	34.2395	1464.93655	3154.0664	1455.3492	CONFLICT	0.505494505	0.494505495	
28Day	G beta:gamma signalling through PI3Kgamma	0.77463	0.49782	0.67888	pdpk1;gnb5	573.318	573.318	192.988	537.867844	867.34192	341.176914	CONFLICT	0.5	0.5	
28Day	Resolution of AP sites via the multiple-nucleotide patch replacement pathway	0.77463	0.49782	0.67888	pole3;polb	3329.279	3329.279	805.318	3569.41988	4286.22182	3302.91979	UP	1	0	
90Day	G2/M Transition	0.32932	0.76671	0.68018	haus7;tubb6;dcn3;gtse1;cntrl;tubb4b;cep76;tubb2a;tuba1b;hsp90aa1;cdkn1a;cdk7;btrc	2700.50008	2128.94	426.32	1618.52744	2593.60842	1735.8006	UP	0.846153846	0.153846154	
90Day	G2/M DNA damage checkpoint	0.31709	0.82137	0.68025	hist1h4h;babam1;hist1h4i;ywahz;h2afx	3596.4296	4006.71	137.958	2082.71447	3673.49502	1960.51471	UP	0.6	0.4	
90Day	TCR signaling	0.31709	0.82137	0.68025	cdc34;nfbkbia;ikbkq;h2-aa;btrc	3117.9204	3265.56	569.072	1651.20008	3314.96494	1742.89169	DOWN	0.4	0.6	
7Day	trans-Golgi Network Vesicle Budding	0.3715	0.78051	0.68037	picalm;jigf2r;ftl1;ap3b1;gbf1	2834.5032	3321.9	720.546	1253.27309	2750.64336	1195.02649	UP	0.8	0.2	
7Day	Clastrin derived vesicle budding	0.3715	0.78051	0.68037	picalm;jigf2r;ftl1;ap3b1;gbf1	2834.5032	3321.9	720.546	1253.27309	2750.64336	1195.02649	UP	0.8	0.2	
7Day	Cell junction organization	0.32948	0.81154	0.68199	vasp;flna;prkci;dst;ctnnb1	2974.30464	3409.24	54.5232	1777.63271	2180.24458	1910.18083	DOWN	0.4	0.6	
7Day	Transcriptional regulation by small RNAs	0.32948	0.81154	0.68199	hist1h4h;hist1h2bc;hist2h2ac;polr2h;hist2h2aa1	4073.244	3964.6	3406.55	810.921331	4033.48029	829.513011	UP	0.6	0.4	
90Day	Transcriptional regulation by RUNX2	0.7653	0.51675	0.68292	cbfb;ar	3034.77	3034.77	1998.95	1464.87069	3300.56119	1415.82352	CONFLICT	0.5	0.5	
90Day	Sema4D in semaphorin signaling	0.7653	0.51675	0.68292	rock2;rock1	2068.101	2068.101	262.092	2554.08242	1087.57877	2144.87514	UP	1	0	
90Day	Nucleobase biosynthesis	0.7653	0.51675	0.68292	gmpp;atic	3841.07	3841.07	2515.37	1874.82292	3607.96146	1845.6115	UP	1	0	
90Day	Activation of IRF3/IRF7 mediated by TBK1/IKK epsilon	0.7653	0.51675	0.68292	tbk1;irf7	3374.045	3374.045	1058.39	3274.83071	2689.26313	3128.36439	CONFLICT	0.5	0.5	
90Day	Regulation of innate immune responses to cytosolic DNA	0.7653	0.51675	0.68292	tmem173;tbk1	2558.24	2558.24	1058.39	2121.10821	2553.28861	2121.09665	DOWN	0	1	
90Day	Phospholipase C-mediated cascade; FGFR4	0.7653	0.51675	0.68292	klb;fgf1	2046.3595	2046.3595	242.429	2551.14298	3002.17622	2163.59869	DOWN	0	1	
7Day	Tie2 Signaling	0.76269	0.51644	0.68456	ptpn11;kras	3894.19	3894.19	3629.67	374.087772	3880.93363	373.617716	UP	1	0	
7Day	Metabolism of porphyrins	0.76269	0.51644	0.68456	ugt1a1;blvrb	2545.203	2545.203	178.786	3346.61902	2903.10937	3308.12105	CONFLICT	0.5	0.5	
7Day	Nicotinamide salvaging	0.76269	0.51644	0.68456	nudt12;naxe	2595.9995	2595.9995	820.079	2511.53086	3261.55578	2328.48812	CONFLICT	0.5	0.5	
7Day	DARPP-32 events	0.76269	0.51644	0.68456	prkar2a;ppp2cb	3846.8	3846.8	3627.04	310.787572	3752.6326	280.809393	CONFLICT	0.5	0.5	
7Day	Ephrin signaling	0.76269	0.51644	0.68456	sdcbp;pak2	2891.23	2891.23	2538.2	499.259814	2954.69377	491.126318	UP	1	0	
7Day	Gastrin-CREB signalling pathway via PKC and MAPK	0.76269	0.51644	0.68456	mapk3;kras	4479.475	4479.475	4158.71	453.630213	4552.01512	441.878074	CONFLICT	0.5	0.5	
7Day	PI-3K cascade:FGFR3	0.76269	0.51644	0.68456	ptpn11;fgf1	3138.715	3138.715	2647.76	694.31522	2984.26892	659.064823	CONFLICT	0.5	0.5	
7Day	SHC-mediated cascade:FGFR3	0.76269	0.51644	0.68456	kras;fgf1	3403.235	3403.235	2647.76	1068.40299	3131.99117	997.165244	CONFLICT	0.5	0.5	
28Day	Metabolism of carbohydrates	0.36447	0.73532	0.68518	slc25a10;hs2st1;pfkl;pcx;pck1;man2b2;man2b1;khk;hya1;gpi1;gpc4;gaa;bpgm	3350.90485	3361.03	240.253	1194.36178	3002.02789	1341.42233	DOWN	0.153846154	0.846153846	
28Day	G2/M Checkpoints	0.32717	0.81194	0.68608	ube2n;ube2v2;hist1h4i;cdc6;brca1	5182.904	5643.31	3288.55	1086.18586	5095.75689	1243.24827	UP	0.6	0.4	
28Day	Oxidative Stress Induced Senescence	0.31759	0.81883	0.68711	hist1h4i;map2k4;mdm2;mapkapk2;bm1i	4004.996	3918.46	2266.61	1599.41252	3457.62774	1668.23985	UP	0.6	0.4	
28Day	Carboxyterminal post-translational modifications of tubulin	0.75594	0.51989	0.68848	tubb4b;tubb2a	2631.245	2631.245	2359.45	384.376175	2702.45657	370.948608	UP	1	0	
28Day	CDK-mediated phosphorylation and removal of Cdc6	0.75594	0.51989	0.68848	cdc6;cdc27	5824.15	5824.15	5780.76	61.3627265	5829.67647	60.862965	UP	1	0	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
28Day	Processing of Capped Intronless Pre-mRNA	0.75594	0.51989	0.68848	cpsf2;papola	3117.8765	3117.8765	983.533	3018.41752	4045.49974	2718.43238	DOWN	0	1
28Day	Processing of Capped Intron-Containing Pre-mRNA	0.69114	0.40476	0.69144	phf5a;ccar1;rnpc3;sf3b6;cpsf2;prpf19;hnnpul1;prpf38a;u2af2;snrpd1;polr2a;prpf8;papola;srsf1;tptr;thoc5;bc005561	3965.02082	4603.26	131.831	1550.97798	3978.39031	1689.41416	UP	0.705882353	0.294117647
7Day	DNA Damage/Telomere Stress Induced Senescence	0.71416	0.42642	0.69292	ep400;hist1h4h;hist1h2bc;hist2h2ac;tef2;hist2h2aa1;cdkn1a;ccne2	3995.4025	3802.835	2818.63	877.134081	4069.18686	898.941015	UP	0.625	0.375
7Day	Fc epsilon receptor (FCER1) signaling	0.71416	0.42642	0.69292	alm2;btrc	3512.01125	3801.75	1018.89	1299.28996	3712.1249	884.606401	UP	0.875	0.125
28Day	Regulation of TP53 Degradation	0.73701	0.5413	0.69829	mdm2;ccng1	1695.93	1695.93	1125.25	807.063396	1814.89328	789.333136	UP	1	0
28Day	Regulation of TP53 Expression and Degradation	0.73701	0.5413	0.69829	mdm2;ccng1	1695.93	1695.93	1125.25	807.063396	1814.89328	789.333136	UP	1	0
28Day	Integrin alpha1b beta3 signaling	0.73701	0.5413	0.69829	pdgk1;fn1	1674.494	1674.494	192.988	2095.16588	2432.121	1800.47847	DOWN	0	1
28Day	Integrin signaling	0.73701	0.5413	0.69829	pdgk1;fn1	1674.494	1674.494	192.988	2095.16588	2432.121	1800.47847	DOWN	0	1
28Day	Trafficking of AMPA receptors	0.73701	0.5413	0.69829	gria3;mdm2	2159.59	2159.59	2052.57	151.349135	2164.79104	151.170299	UP	1	0
28Day	Glutamate binding, activation of AMPA receptors and synaptic plasticity	0.73701	0.5413	0.69829	gria3;mdm2	2159.59	2159.59	2052.57	151.349135	2164.79104	151.170299	UP	1	0
28Day	The role of GTSE1 in G2/M progression after G2 checkpoint	0.73701	0.5413	0.69829	tubb4b;tubb2a	2631.245	2631.245	2359.45	384.376175	2702.45657	370.948608	UP	1	0
7Day	ERK/MAPK targets	0.7364	0.54619	0.69844	mapk3;ppp2cb	4213.64	4213.64	3627.04	829.577676	4084.83206	809.330679	CONFLICT	0.5	0.5
7Day	Regulation of signaling by CBL	0.7364	0.54619	0.69844	yes1;uba52	4391.255	4391.255	4020.95	523.690353	4358.19543	521.59919	UP	1	0
7Day	Unblocking of NMDA receptors, glutamate binding and activation	0.7364	0.54619	0.69844	calm3;calm2	3983.44	3983.44	3050.32	1319.63096	3556.9103	1173.69957	CONFLICT	0.5	0.5
7Day	Activation of NF-kappaB in B cells	0.7364	0.54619	0.69844	uba52;btrc	4484.31	4484.31	4207.06	392.09071	4446.04923	388.339223	UP	1	0
7Day	Other interleukin signaling	0.7364	0.54619	0.69844	csf1r;csf1	2192.5255	2192.5255	729.901	2068.4634	1592.81686	1886.5948	CONFLICT	0.5	0.5
7Day	Regulation of FZD by ubiquitination	0.7364	0.54619	0.69844	uba52;lrp5	4760.865	4760.865	4760.17	0.98287843	4760.7558	0.97066913	CONFLICT	0.5	0.5
90Day	Processing of SMDT1	0.73353	0.5525	0.69992	afg3l2;micu2	3526.375	3526.375	1479.94	2894.09613	2753.64746	2679.8464	UP	1	0
90Day	Metabolism of Angiotensinogen to Angiotensins	0.73353	0.5525	0.69992	mme;ctsd	3821.095	3821.095	3756.53	91.3086987	3803.24857	87.7512875	CONFLICT	0.5	0.5
90Day	Metabolism of folate and pterines	0.73353	0.5525	0.69992	methfd2;aldh1l1	2812.785	2812.785	2673.17	197.445427	2817.17769	197.347675	CONFLICT	0.5	0.5
90Day	PI3K events in ERBB2 signaling	0.73353	0.5525	0.69992	nrg1;gab1	2019.384	2019.384	126.428	2677.04405	2617.01628	2540.12522	CONFLICT	0.5	0.5
90Day	Metabolism of cofactors	0.73353	0.5525	0.69992	pdss1;hsp90aa1	3059.05	3059.05	426.32	3723.24247	3544.99278	3659.26956	UP	1	0
90Day	p53-Dependent G1 DNA Damage Response	0.73353	0.5525	0.69992	mdm2;cdkn1a	2224.395	2224.395	913.71	1853.5885	2056.00777	1838.2279	UP	1	0
90Day	p53-Dependent G1/S DNA damage checkpoint	0.73353	0.5525	0.69992	mdm2;cdkn1a	2224.395	2224.395	913.71	1853.5885	2056.00777	1838.2279	UP	1	0
90Day	Norepinephrine Neurotransmitter Release Cycle	0.73353	0.5525	0.69992	unc13b;slc22a1	2810.74	2810.74	1050.57	2489.25629	3149.81569	2442.63223	CONFLICT	0.5	0.5
90Day	Signaling by NTRKs	0.327	0.80465	0.7008	irs2;mapk14;sos1;pcsk5;ntrk2;ap2m1	3453.50722	3752.895	74.8133	1919.8951	3207.75314	2451.07586	DOWN	0.166666667	0.833333333
7Day	Arachidonic acid metabolism	0.34856	0.78745	0.70184	akr1c6;ptges3;ephx2;cyp2c37;cyp2c29;akr1c14	2827.84362	2990.63	93.6517	1568.23608	2653.56942	1284.27005	UP	0.666666667	0.333333333
7Day	DNA Replication Pre-Initiation	0.34856	0.78745	0.70184	psmd5;psmd6;psmc4;uba52;psmc2;pri m2	3502.21	3625.07	2309.23	909.674091	3376.05087	1015.17591	UP	1	0
28Day	Toll Like Receptor 4 (TLR4) Cascade	0.68699	0.45459	0.70228	ube2n;map2k4;mapkapk2;ly96;lbp;ikbk g;app;birc2	4941.99375	5320.855	2616.5	1053.22955	4922.34751	1090.07569	CONFLICT	0.5	0.5
28Day	Nucleotide Excision Repair	0.68699	0.45459	0.70228	ube2n;usp45;ube2v2;pole3;prpf19;ino8 0c;polr2a;lfg3	3831.411	4295.465	805.318	1777.30939	4077.8285	1518.49647	CONFLICT	0.5	0.5
7Day	RNA Polymerase I Chain Elongation	0.32317	0.80656	0.70406	hist1h4h;hist1h2bc;hist2h2ac;polr2h;u btf;hist2h2aa1	3723.755	3691.5	1976.31	1122.02054	3843.70217	1012.37228	UP	0.666666667	0.333333333
28Day	Mitotic Prophase	0.37212	0.76792	0.7046	nek6;arpp19;set;cnepr1r;hist1h4i;tp rtrappc8;rab9;rab11a;dennd1a;rab18;tb c1d10a	4163.56667	3849.715	2388.34	1415.17198	4048.58649	1299.74126	UP	0.833333333	0.166666667
28Day	Rab regulation of trafficking	0.35299	0.78278	0.70516	c1d10a	3353.03333	2992.42	2192.92	1155.84614	3498.40632	1290.04174	DOWN	0.333333333	0.666666667
7Day	Positive epigenetic regulation of rRNA expression	0.73465	0.39474	0.70567	sf3b1;hist1h4h;hist1h2bc;gsk3b;ddx21; hist2h2ac;polr2h;mybbp1a;hist2h2aa1	3817.88444	3439.85	2845.95	780.915516	3713.87572	783.361635	UP	0.777777778	0.222222222
7Day	B-WICH complex positively regulates rRNA expression	0.73465	0.39474	0.70567	sf3b1;hist1h4h;hist1h2bc;gsk3b;ddx21; hist2h2ac;polr2h;mybbp1a;hist2h2aa1	3817.88444	3439.85	2845.95	780.915516	3713.87572	783.361635	UP	0.777777778	0.222222222
28Day	Insulin receptor recycling	0.71791	0.56203	0.70822	atp6v0e2;atp6v1e1	3839.965	3839.965	2385.58	2056.81099	2967.18762	1645.29352	CONFLICT	0.5	0.5

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
28Day	Deadenylation of mRNA	0.71791	0.56203	0.70822	cnot1;paip1	3500.885	3500.885	3132.16	521.455896	3494.40951	521.375476	UP	1	0	
90Day	SHC1 events in ERBB2 signaling	0.41366	0.86922	0.71236	nrg1	3912.34	3912.34	3912.34		3912.34		UP	1	0	
90Day	Regulation of TLR by endogenous ligand	0.41366	0.86922	0.71236	apob	175.96	175.96	175.96		175.96		DOWN	0	1	
90Day	G beta:gamma signalling through BTK	0.41366	0.86922	0.71236	gng11	4854.24	4854.24	4854.24		4854.24		UP	1	0	
90Day	Synthesis of glycosylphosphatidylinositol (GPI)	0.41366	0.86922	0.71236	pigp	3011.39	3011.39	3011.39		3011.39		UP	1	0	
90Day	Interferon gamma signaling	0.41366	0.86922	0.71236	ifngr2	4021.95	4021.95	4021.95		4021.95		DOWN	0	1	
90Day	Serotonin Neurotransmitter Release Cycle	0.41366	0.86922	0.71236	unc13b	4570.91	4570.91	4570.91		4570.91		UP	1	0	
90Day	GABA synthesis, release, reuptake and degradation	0.41366	0.86922	0.71236	slc6a12	3445.15	3445.15	3445.15		3445.15		DOWN	0	1	
90Day	RIPK1-mediated regulated necrosis	0.41366	0.86922	0.71236	tnfrsf10b	3826.99	3826.99	3826.99		3826.99		UP	1	0	
90Day	Regulated Necrosis	0.41366	0.86922	0.71236	tnfrsf10b	3826.99	3826.99	3826.99		3826.99		UP	1	0	
7Day	RUNX1 regulates transcription of genes involved in differentiation of HSCs	0.70978	0.57463	0.7125	uba52;abl1	4064.805	4064.805	3368.05	985.360371	4326.32968	913.315248	CONFLICT	0.5	0.5	
7Day	TGF-beta receptor signaling activates SMADs	0.70978	0.57463	0.7125	uba52;tgfb1	5206.805	5206.805	4761.56	629.671518	5273.58539	622.548776	UP	1	0	
7Day	Interleukin-12 family signaling	0.70978	0.57463	0.7125	stat1;jak1	3735.595	3735.595	3554.32	256.361564	3703.94	252.422609	UP	1	0	
7Day	Regulation of lipid metabolism by Peroxisome proliferator-activated receptor alpha (PPARalpha)	0.70978	0.57463	0.7125	ncoa2;ncoa1	1694.1743	1694.1743	86.7986	2273.17251	2801.46736	1647.76134	UP	1	0	
7Day	APC/C:Cdc20 mediated degradation of Securin	0.70978	0.57463	0.7125	uba52;cdc27	4316.07	4316.07	3870.58	630.018	4393.04009	620.543222	UP	1	0	
7Day	HS-GAG degradation	0.70978	0.57463	0.7125	hgsnat;sd3c	3460.675	3460.675	3118.3	484.191368	3385.715	472.443943	DOWN	0	1	
7Day	Endosomal/Vacuolar pathway	0.70978	0.57463	0.7125	h2-t23;h2-q10	3617.055	3617.055	2584.12	1460.79069	2959.99285	1127.14155	DOWN	0	1	
7Day	Signal transduction by L1	0.70978	0.57463	0.7125	mapk3;csnk2b	3814.955	3814.955	2829.67	1393.40341	4062.18886	1348.82315	CONFLICT	0.5	0.5	
7Day	PI-3K cascade:FGFR4	0.70978	0.57463	0.7125	ptpn11;fgf1	3138.715	3138.715	2647.76	694.31522	2984.26892	659.064823	CONFLICT	0.5	0.5	
7Day	SHC-mediated cascade:FGFR4	0.70978	0.57463	0.7125	kras;fgf1	3403.235	3403.235	2647.76	1068.40299	3131.99117	997.165244	CONFLICT	0.5	0.5	
28Day	HDR through Homologous Recombination (HRR) or Single Strand Annealing (SSA)	0.70907	0.42191	0.7127	ube2n;rm11;ube2v2;pole3;hist1h4i;rad51d;rad51;brca1;blm	3641.84933	3769.36	692.086	1890.0939	3817.81985	1459.82142	UP	0.777777778	0.222222222	
90Day	Negative regulation of MET activity	0.38176	0.88399	0.71287	sh3gl3	5266.23	5266.23	5266.23		5266.23		UP	1	0	
90Day	Phospholipase C-mediated cascade; FGFR2	0.38176	0.88399	0.71287	fgf1	242.429	242.429	242.429		242.429		DOWN	0	1	
90Day	Prostacyclin signalling through prostacyclin receptor	0.38176	0.88399	0.71287	gng11	4854.24	4854.24	4854.24		4854.24		UP	1	0	
90Day	Beta-catenin phosphorylation cascade	0.38176	0.88399	0.71287	ctnnb1	4087.04	4087.04	4087.04		4087.04		DOWN	0	1	
90Day	Metabolism of porphyrins	0.38176	0.88399	0.71287	blvrb	3840.4	3840.4	3840.4		3840.4		UP	1	0	
90Day	Deposition of new CENPA-containing nucleosomes at the centromere	0.38176	0.88399	0.71287	cenpu	5744.84	5744.84	5744.84		5744.84		UP	1	0	
90Day	Nucleosome assembly	0.38176	0.88399	0.71287	cenpu	5744.84	5744.84	5744.84		5744.84		UP	1	0	
90Day	Gastrin-CREB signalling pathway via PKC and MAPK	0.38176	0.88399	0.71287	sos1	5894.93	5894.93	5894.93		5894.93		DOWN	0	1	
90Day	Processing of Intronless Pre-mRNAs	0.38176	0.88399	0.71287	cstf2t	5843.41	5843.41	5843.41		5843.41		DOWN	0	1	
90Day	FOXO-mediated transcription	0.35178	0.89708	0.71525	ywhaz	137.958	137.958	137.958		137.958		UP	1	0	
90Day	ERK/MAPK targets	0.35178	0.89708	0.71525	mapk14	4261.96	4261.96	4261.96		4261.96		DOWN	0	1	
90Day	G beta:gamma signalling through PLC beta	0.35178	0.89708	0.71525	gng11	4854.24	4854.24	4854.24		4854.24		UP	1	0	
90Day	Regulation of signaling by CBL	0.35178	0.89708	0.71525	vav1	4161.05	4161.05	4161.05		4161.05		DOWN	0	1	
90Day	FGFR2 ligand binding and activation	0.35178	0.89708	0.71525	fgf1	242.429	242.429	242.429		242.429		DOWN	0	1	
90Day	Caspase activation via extrinsic apoptotic signalling pathway	0.35178	0.89708	0.71525	tnfrsf10b	3826.99	3826.99	3826.99		3826.99		UP	1	0	
90Day	Conversion from APC/C:Cdc20 to APC/C:Cdh1 in late anaphase	0.35178	0.89708	0.71525	anapc10	4390.47	4390.47	4390.47		4390.47		UP	1	0	
90Day	Regulation of FZD by ubiquitination	0.35178	0.89708	0.71525	lgr4	5316.37	5316.37	5316.37		5316.37		UP	1	0	
90Day	Signaling by Hippo	0.35178	0.89708	0.71525	wwc1	5949.63	5949.63	5949.63		5949.63		DOWN	0	1	
90Day	Post NMDA receptor activation events	0.35178	0.89708	0.71525	camkk2	98.0082	98.0082	98.0082		98.0082		DOWN	0	1	
7Day	Nucleotide salvage	0.39825	0.87515	0.71527	adk	124.762	124.762	124.762		124.762		DOWN	0	1	
7Day	Acyl chain remodelling of PS	0.39825	0.87515	0.71527	pla1a	3489.79	3489.79	3489.79		3489.79		DOWN	0	1	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.														
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
7Day	ADP signalling through P2Y purinoceptor 12	0.39825	0.87515	0.71527	gnai3	794.2	794.2	794.2		794.2		UP	1	0
7Day	Metal ion SLC transporters	0.39825	0.87515	0.71527	slc39a2	5557.48	5557.48	5557.48		5557.48		UP	1	0
7Day	Telomere C-strand (Lagging Strand) Synthesis	0.37246	0.88694	0.71631	prim2	4006.14	4006.14	4006.14		4006.14		UP	1	0
7Day	Cellular hexose transport	0.37246	0.88694	0.71631	slc2a8	3236.88	3236.88	3236.88		3236.88		DOWN	0	1
28Day	TNFR1-induced NfkbapB signaling pathway	0.6987	0.58209	0.71821	ikbkg;birc2	5639.965	5639.965	5417.68	314.358462	5681.7264	308.760771	UP	1	0
7Day	Glutamate Neurotransmitter Release Cycle	0.34799	0.89762	0.71857	slc1a2	1710.87	1710.87	1710.87		1710.87		DOWN	0	1
7Day	Triglyceride metabolism	0.34799	0.89762	0.71857	dgat2	623.511	623.511	623.511		623.511		DOWN	0	1
7Day	S Phase	0.35263	0.77603	0.71906	pds5a;uba52;cdc27;prim2;cdkn1a;cdc25a;cne2	4225.70286	4006.14	2818.63	969.895529	4116.90686	941.177518	UP	1	0
28Day	VEGFR2 mediated vascular permeability	0.39854	0.87326	0.71911	pdpk1	192.988	192.988	192.988		192.988		DOWN	0	1
28Day	Energy dependent regulation of mTOR by LKB1-AMPK	0.39854	0.87326	0.71911	stradb	5007.07	5007.07	5007.07		5007.07		DOWN	0	1
28Day	DAG and IP3 signaling	0.39854	0.87326	0.71911	adc9	4220.6	4220.6	4220.6		4220.6		DOWN	0	1
28Day	Negative regulation of FGFR1 signaling	0.39854	0.87326	0.71911	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1
28Day	Ovarian tumor domain proteases	0.39854	0.87326	0.71911	ikbkg	5417.68	5417.68	5417.68		5417.68		UP	1	0
28Day	Signaling by ERBB4	0.39854	0.87326	0.71911	hbegf	919.738	919.738	919.738		919.738		UP	1	0
28Day	Recognition of DNA damage by PCNA-containing replication complex	0.39854	0.87326	0.71911	pole3	805.318	805.318	805.318		805.318		UP	1	0
28Day	Nicotinate metabolism	0.39854	0.87326	0.71911	nudt12	5115.96	5115.96	5115.96		5115.96		DOWN	0	1
28Day	mRNA Capping	0.39854	0.87326	0.71911	polr2a	5040.67	5040.67	5040.67		5040.67		UP	1	0
28Day	RNA Polymerase I Promoter Escape	0.39854	0.87326	0.71911	polr1a	5863.06	5863.06	5863.06		5863.06		DOWN	0	1
90Day	Chondroitin sulfate biosynthesis	0.32371	0.9087	0.71926	bgn	4533.35	4533.35	4533.35		4533.35		DOWN	0	1
90Day	Presynaptic function of Kainate receptors	0.32371	0.9087	0.71926	gng11	4854.24	4854.24	4854.24		4854.24		UP	1	0
90Day	TGF-beta receptor signaling activates SMADs	0.32371	0.9087	0.71926	ube2m	678.11	678.11	678.11		678.11		UP	1	0
90Day	Interleukin-12 family signaling	0.32371	0.9087	0.71926	crf1	3200.93	3200.93	3200.93		3200.93		UP	1	0
90Day	Regulation of lipid metabolism by Peroxisome proliferator-activated receptor alpha (PPARalpha)	0.32371	0.9087	0.71926	hdac3	5394.1	5394.1	5394.1		5394.1		DOWN	0	1
90Day	Inhibition of the proteolytic activity of APC/C required for the onset of anaphase by mitotic spindle checkpoint components	0.32371	0.9087	0.71926	anapc10	4390.47	4390.47	4390.47		4390.47		UP	1	0
90Day	Inactivation of APC/C via direct inhibition of the APC/C complex	0.32371	0.9087	0.71926	anapc10	4390.47	4390.47	4390.47		4390.47		UP	1	0
90Day	APC/C:Cdc20 mediated degradation of Securin	0.32371	0.9087	0.71926	anapc10	4390.47	4390.47	4390.47		4390.47		UP	1	0
90Day	HS-GAG degradation	0.32371	0.9087	0.71926	sdc4	630.216	630.216	630.216		630.216		DOWN	0	1
90Day	Signal transduction by L1	0.32371	0.9087	0.71926	itga9	4436.62	4436.62	4436.62		4436.62		DOWN	0	1
90Day	RHO GTPases activate PAKs	0.32371	0.9087	0.71926	cdc42	156.487	156.487	156.487		156.487		UP	1	0
90Day	VxPx cargo-targeting to cilium	0.32371	0.9087	0.71926	exoc4	2113.16	2113.16	2113.16		2113.16		UP	1	0
28Day	Regulation of TP53 Activity through Acetylation	0.37985	0.88198	0.7197	meaf6	2859.88	2859.88	2859.88		2859.88		DOWN	0	1
28Day	Inactivation, recovery and regulation of the phototransduction cascade	0.37985	0.88198	0.7197	gnb5	953.648	953.648	953.648		953.648		UP	1	0
28Day	FCER1 mediated Ca+2 mobilization	0.37985	0.88198	0.7197	ppp3cb	4095.87	4095.87	4095.87		4095.87		UP	1	0
28Day	MET activates PTK2 signaling	0.37985	0.88198	0.7197	fn1	3156	3156	3156		3156		DOWN	0	1
28Day	EPH-ephrin mediated repulsion of cells	0.37985	0.88198	0.7197	epha7	5831.01	5831.01	5831.01		5831.01		UP	1	0
28Day	Downstream signaling of activated FGFR2	0.37985	0.88198	0.7197	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1
28Day	Termination of translesion DNA synthesis	0.37985	0.88198	0.7197	pole3	805.318	805.318	805.318		805.318		UP	1	0

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
28Day	RNA Polymerase I Transcription Termination	0.37985	0.88198	0.7197	polr1a	5863.06	5863.06	5863.06		5863.06		DOWN	0	1	
28Day	Ca-dependent events	0.37985	0.88198	0.7197	adcy9	4220.6	4220.6	4220.6		4220.6		DOWN	0	1	
28Day	Activation of kainate receptors upon glutamate binding	0.36185	0.89011	0.72094	gnb5	953.648	953.648	953.648		953.648		UP	1	0	
28Day	The phototransduction cascade	0.36185	0.89011	0.72094	gnb5	953.648	953.648	953.648		953.648		UP	1	0	
28Day	Neurexins and neuroligins	0.36185	0.89011	0.72094	epb41l3	5896.01	5896.01	5896.01		5896.01		DOWN	0	1	
28Day	Signal amplification	0.36185	0.89011	0.72094	gnb5	953.648	953.648	953.648		953.648		UP	1	0	
28Day	Downstream signaling of activated FGFR1	0.36185	0.89011	0.72094	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1	
28Day	Negative regulation of FGFR2 signaling	0.36185	0.89011	0.72094	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1	
28Day	G alpha (12/13) signalling events	0.36185	0.89011	0.72094	gnb5	953.648	953.648	953.648		953.648		UP	1	0	
28Day	Glucagon signaling in metabolic regulation	0.36185	0.89011	0.72094	adcy9	4220.6	4220.6	4220.6		4220.6		DOWN	0	1	
28Day	Formation of the Early Elongation Complex	0.36185	0.89011	0.72094	polr2a	5040.67	5040.67	5040.67		5040.67		UP	1	0	
28Day	DNA Replication	0.38497	0.74891	0.72143	psmd6;pole3;psmd8;cdc6;psmf1;cdc27	3773.95114	4413.43	805.318	2013.49365	4057.3808	1993.62148	CONFLICT	0.571428571	0.428571429	
7Day	Synthesis of PC	0.32482	0.90729	0.72192	stard10	4547.5	4547.5	4547.5		4547.5		UP	1	0	
7Day	Surfactant metabolism	0.32482	0.90729	0.72192	abca3	2076.62	2076.62	2076.62		2076.62		DOWN	0	1	
7Day	Antigen activates B Cell Receptor (BCR) leading to generation of second messengers	0.32482	0.90729	0.72192	itpr2	4098.21	4098.21	4098.21		4098.21		DOWN	0	1	
7Day	Telomere Maintenance	0.32482	0.90729	0.72192	prim2	4006.14	4006.14	4006.14		4006.14		UP	1	0	
7Day	Extension of Telomeres	0.32482	0.90729	0.72192	prim2	4006.14	4006.14	4006.14		4006.14		UP	1	0	
7Day	DNA strand elongation	0.32482	0.90729	0.72192	prim2	4006.14	4006.14	4006.14		4006.14		UP	1	0	
7Day	Scavenging of heme from plasma	0.32482	0.90729	0.72192	lrp1	1316.54	1316.54	1316.54		1316.54		DOWN	0	1	
7Day	FGFR2 alternative splicing	0.32482	0.90729	0.72192	polr2h	3964.6	3964.6	3964.6		3964.6		UP	1	0	
7Day	Orc1 removal from chromatin	0.32482	0.90729	0.72192	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0	
7Day	Cytochrome P450 - arranged by substrate type	0.71882	0.40566	0.7226	cyp3a25;cyp39a1;ncoa2;ncoa1;cyp3a11;cyp2e1;cyp2c37;cyp2c29;arnt;cyp3a41b	2995.27016	3207.45	86.7986	1706.55759	3069.02013	1300.90994	DOWN	0.4	0.6	
28Day	Glucagon-type ligand receptors	0.34452	0.89768	0.72278	gnb5	953.648	953.648	953.648		953.648		UP	1	0	
28Day	Regulation of APC/C activators between G1/S and early anaphase	0.34452	0.89768	0.72278	cdc27	5780.76	5780.76	5780.76		5780.76		UP	1	0	
28Day	RAF activation	0.34452	0.89768	0.72278	map3k11	4123.28	4123.28	4123.28		4123.28		DOWN	0	1	
7Day	N-glycan antennae elongation in the medial/trans-Golgi	0.30291	0.91605	0.72623	fuca1	2644.02	2644.02	2644.02		2644.02		DOWN	0	1	
7Day	Effects of PIP2 hydrolysis	0.30291	0.91605	0.72623	itpr2	4098.21	4098.21	4098.21		4098.21		DOWN	0	1	
7Day	COPI-mediated anterograde transport	0.69526	0.43188	0.72632	cog6;copz1;cog5;tubb4b;tubb2a;tuba4a;arcn1;rab1a;capza2;gbf1	2848.0736	3070.085	919.856	994.927228	2795.54103	958.513638	UP	0.9	0.1	
28Day	Metalloprotease DUBs	0.31186	0.91129	0.72803	brca1	5643.31	5643.31	5643.31		5643.31		UP	1	0	
28Day	Fanconi Anemia Pathway	0.31186	0.91129	0.72803	cenpx	5532.9	5532.9	5532.9		5532.9		DOWN	0	1	
28Day	Cytosolic sensors of pathogen-associated DNA	0.31186	0.91129	0.72803	ikbkg	5417.68	5417.68	5417.68		5417.68		UP	1	0	
28Day	Glucagon-like Peptide-1 (GLP1) regulates insulin secretion	0.31186	0.91129	0.72803	gnb5	953.648	953.648	953.648		953.648		UP	1	0	
7Day	G2/M Checkpoints	0.68329	0.44496	0.72855	ube2n;ube2v2;rnf168;hist1h4h;babam1;hist1h2bc;gtse1;ywhaz;uba52;cdc25a	3819.2	3506.09	2423.08	1013.09681	3600.20171	917.409884	UP	0.9	0.1	
90Day	Keratan sulfate/keratin metabolism	0.76935	0.45823	0.73129	omd;st3gal3;lum	4411.32667	4358.58	3651.14	787.885329	4239.33949	529.843763	UP	0.666666667	0.333333333	
90Day	Synthesis of very long-chain fatty acyl-CoAs	0.76935	0.45823	0.73129	acsl4;acsl1;elovl3	4415.75	4450.55	3817.19	581.940912	4378.99247	653.984583	UP	0.666666667	0.333333333	
90Day	FRS-mediated FGFR4 signaling	0.76935	0.45823	0.73129	klib;sos1;fgf1	3329.21633	3850.29	242.429	2862.05	4571.98571	2172.73633	DOWN	0	1	
7Day	Regulation of TP53 Degradation	0.77454	0.44912	0.73137	uba52;ppp2cb;ccng1	3207.74333	3627.04	1234.63	1800.46274	2951.96869	1731.17243	UP	1	0	
7Day	Regulation of TP53 Expression and Degradation	0.77454	0.44912	0.73137	uba52;ppp2cb;ccng1	3207.74333	3627.04	1234.63	1800.46274	2951.96869	1731.17243	UP	1	0	
28Day	Antigen Presentation: Folding, assembly and peptide loading of class I MHC	0.76813	0.4533	0.7351	tap1;h2-q7;h2-d1	3562.11333	3718.12	1188.24	2299.84187	3462.70475	1959.38094	DOWN	0.333333333	0.666666667	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
28Day	Platelet Aggregation (Plug Formation)	0.76813	0.4533	0.7351	pdpk1;fn1;f2	1563.246	1340.75	192.988	1493.98406	1721.26663	1119.56706	DOWN	0	1	
90Day	Fatty acid metabolism	0.67012	0.41346	0.73519	acac10;ndufab1;cyp4f16;pcpcb;gpx4;hacl1;acaa2;acsl4;cyp2c54;cyp4a12a;pon3;slc27a2;slc25a17;scd1;mut;acsl1;ephx2;cyp4a12b;cyp2c38;cyp2c37;cyp1a2;elovl3;pcca;cyp2c69	2894.76238	3148.415	105.476	1486.54079	3095.7356	1281.543	CONFLICT	0.458333333	0.541666667	
7Day	RNA Polymerase III Transcription Initiation From Type 1 Promoter	0.75348	0.47444	0.73723	brf1;gtf3c6;polr2h	2841.95	2665.35	1895.9	1045.59581	3394.41506	909.790933	UP	0.666666667	0.333333333	
7Day	RNA Polymerase III Transcription Initiation From Type 2 Promoter	0.75348	0.47444	0.73723	brf1;gtf3c6;polr2h	2841.95	2665.35	1895.9	1045.59581	3394.41506	909.790933	UP	0.666666667	0.333333333	
7Day	Interleukin-6 family signaling	0.75348	0.47444	0.73723	stat1;ptpn11;jak1	3700.28667	3629.67	3554.32	191.312992	3689.86935	200.012264	UP	1	0	
7Day	Downstream signaling of activated FGFR4	0.75348	0.47444	0.73723	ptpn11;kras;fgf1	3478.71333	3629.67	2647.76	766.702949	3262.18888	788.939216	UP	0.666666667	0.333333333	
7Day	Platelet calcium homeostasis	0.75348	0.47444	0.73723	itpr2;calm3;calm2	4021.69667	4098.21	3050.32	935.469749	3605.92075	987.837442	DOWN	0.333333333	0.666666667	
90Day	Branched-chain amino acid catabolism	0.74372	0.48852	0.73888	mccc2;ivd;aldh6a1	2901.54	2782.05	2413.93	557.051067	2905.96425	437.440481	DOWN	0	1	
28Day	Base Excision Repair	0.75295	0.4715	0.7392	pole3;polb;lig3	4016.65933	5391.42	805.318	2790.67273	4750.69575	2278.10973	UP	0.666666667	0.333333333	
28Day	Resolution of Abasic Sites (AP sites)	0.75295	0.4715	0.7392	pole3;polb;lig3	4016.65933	5391.42	805.318	2790.67273	4750.69575	2278.10973	UP	0.666666667	0.333333333	
28Day	Toll-like Receptor Cascades	0.69115	0.42871	0.7413	ube2n;map2k4;apob;eeaa1;mapkapk2;ly96;lbpi;ikbk;ctss;app;birc2	4705.72409	5375	939.205	1555.50389	4457.55552	1860.88208	DOWN	0.363636364	0.636363636	
7Day	Mitotic Prophase	0.67062	0.45252	0.74228	gm49336;hist1h4h;hist1h2bc;gmt5a;nek6;arpp19;hist2h2ac;mapk3;rab1a;hist2h2aa1;tpor	3464.91164	3489.14	770.098	1336.66819	3385.40368	1262.79732	UP	0.727272727	0.272727273	
90Day	VEGFA-VEGFR2 Pathway	0.37426	0.7464	0.74297	hsp90aa1;cdc42;ctnnb1	2740.53767	3874.11	156.487	2016.69226	2197.99008	2124.70017	CONFLICT	0.555555556	0.444444444	
28Day	Metabolism of polyamines	0.73755	0.48941	0.74362	otc;odc1;ass1	1555.824	1071.29	726.832	1150.51108	2152.64352	1141.9296	DOWN	0	1	
28Day	Fatty acids	0.73755	0.48941	0.74362	cyp4a12b;cyp2a5;cyp2a4	3719.93667	4062.67	2330.57	1253.64413	3560.79952	1366.51391	UP	1	0	
7Day	CYP2E1 reactions	0.73202	0.49922	0.7437	cyp2e1;cyp2c37;cyp2c29	2168.54433	2593.25	529.743	1473.10438	2359.55856	1350.29483	DOWN	0.333333333	0.666666667	
7Day	Endosomal Sorting Complex Required For Transport (ESCRT)	0.73202	0.49922	0.7437	chmp5;ubap1;uba52	4748.63667	4761.56	4143.71	598.596941	4466.39253	497.911596	UP	0.666666667	0.333333333	
7Day	Calmodulin induced events	0.73202	0.49922	0.7437	prkar2a;calm3;calm2	4011.14667	4066.56	3050.32	934.353205	3661.3101	940.743026	DOWN	0.333333333	0.666666667	
7Day	CaM pathway	0.73202	0.49922	0.7437	prkar2a;calm3;calm2	4011.14667	4066.56	3050.32	934.353205	3661.3101	940.743026	DOWN	0.333333333	0.666666667	
7Day	Estrogen-dependent gene expression	0.38074	0.74008	0.74512	hist1h4h;hist1h2bc;ptges3;hist2h2ac;polr2h;ncoa2;ncoa1;hsp90aa1;hist2h2aa1	3099.84762	3406.55	86.7986	1615.33069	3333.02753	1366.62708	UP	0.777777778	0.222222222	
28Day	Cargo trafficking to the periciliary membrane	0.72198	0.50703	0.74833	rab11a;bbs9;exoc4	3191.45667	2439.57	2192.92	1520.91927	2895.01352	1368.7554	UP	0.666666667	0.333333333	
7Day	DAG and IP3 signaling	0.71024	0.52339	0.75067	prkar2a;calm3;calm2	4011.14667	4066.56	3050.32	934.353205	3661.3101	940.743026	DOWN	0.333333333	0.666666667	
7Day	Signaling by ERBB4	0.71024	0.52339	0.75067	uba52;kras;wvwp1	3915.25667	4158.71	2825.5	990.724091	3677.90484	1055.68644	UP	1	0	
7Day	Nicotinate metabolism	0.71024	0.52339	0.75067	nudt12;qprt;naxe	1773.19433	820.079	127.584	2277.04164	1305.01876	2232.32789	DOWN	0.333333333	0.666666667	
7Day	HS-GAG biosynthesis	0.71024	0.52339	0.75067	hs3st3b1;sdcs;ext1	4352.01	3803.05	3370.58	1342.88039	4460.9593	1397.14798	DOWN	0.333333333	0.666666667	
7Day	Interferon alpha/beta signaling	0.71024	0.52339	0.75067	stat1;ptpn11;jak1	3700.28667	3629.67	3554.32	191.312992	3689.86935	200.012264	UP	1	0	
28Day	TNF signaling	0.70627	0.52433	0.75329	tax1bp1;ikbk;birc2	5416.20667	5417.68	4968.69	446.781822	5309.28907	473.741883	UP	0.666666667	0.333333333	
90Day	Downstream signaling of activated FGFR3	0.69103	0.54646	0.75626	sos1;gab1;fgf1	2087.929	242.429	126.428	3297.46971	3907.43024	3338.39856	DOWN	0	1	
7Day	Regulation of TNFR1 signaling	0.68823	0.5469	0.75805	tax1bp1;uba52;xiap	4305.42	4761.56	3280.67	889.239449	4538.5068	745.308274	UP	0.666666667	0.333333333	
7Day	Downstream signaling of activated FGFR2	0.68823	0.5469	0.75805	ptpn11;kras;fgf1	3478.71333	3629.67	2647.76	766.702949	3262.18888	788.939216	UP	0.666666667	0.333333333	
7Day	Ca-dependent events	0.68823	0.5469	0.75805	prkar2a;calm3;calm2	4011.14667	4066.56	3050.32	934.353205	3661.3101	940.743026	DOWN	0.333333333	0.666666667	
28Day	E3 ubiquitin ligases ubiquitinate target proteins	0.69044	0.54128	0.75846	ube2n;ube2v2;wdr61	4687.35	5266.71	3288.55	1217.32932	4527.85068	1325.9576	DOWN	0.333333333	0.666666667	
28Day	Formation of Incision Complex in GG-NER	0.69044	0.54128	0.75846	ube2n;usp45;ube2v2	3466.03	3288.55	1842.83	1718.82603	3280.75322	1178.82295	DOWN	0.333333333	0.666666667	
28Day	Vasopressin regulates renal water homeostasis via Aquaporins	0.69044	0.54128	0.75846	rab11a;gnb5;adcy9	2455.72267	2192.92	953.648	1649.25522	1742.1359	1240.36097	UP	0.666666667	0.333333333	
28Day	Signaling by Nuclear Receptors	0.37449	0.73889	0.75896	akr1c6;ppid;akr1c12;akr1c19;hist1h4a;dh4a;dh8a1;rdh16f2;polr2a;akr1c14	4222.7323	5014.36	912.843	1695.66273	3921.62892	1559.28116	DOWN	0.4	0.6	
7Day	Factors involved in megakaryocyte development and platelet production	0.67047	0.44262	0.7613	rbsn;mfn1;tubb4b;yps45;tubb2a;tuba4a;itpk1;prkar2a;kif2a;kif1c;cdc42;cbx5;capza2	3141.45738	3597.94	919.856	1608.01789	2958.75896	1521.1747	UP	0.615384615	0.384615385	
90Day	Regulation of TP53 Degradation	0.42605	0.80823	0.76178	mdm2;cng1	2199.502	2199.502	863.924	1888.79252	3071.06832	1431.18185	UP	1	0	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
90Day	Regulation of TP53 Expression and Degradation	0.42605	0.80823	0.76178	mdm2;ccng1	2199.502	2199.502	863.924	1888.79252	3071.06832	1431.18185	UP	1	0
90Day	TAK1 activates NFkB by phosphorylation and activation of IKKs complex	0.42605	0.80823	0.76178	nfkbia;ikbkg	3433.33	3433.33	3265.56	237.262609	3311.77597	163.5322	CONFLICT	0.5	0.5
90Day	SUMOylation of intracellular receptors	0.42605	0.80823	0.76178	nr5a2;ar	1086.5995	1086.5995	174.249	1290.25845	1071.30871	1290.07723	DOWN	0	1
90Day	A tetrasaccharide linker sequence is required for GAG synthesis	0.42605	0.80823	0.76178	sdc4;bgm	2581.783	2581.783	630.216	2759.93252	3403.41741	2503.40993	DOWN	0	1
90Day	Interleukin-6 family signaling	0.39963	0.82486	0.7622	ilfr;cnlf1	3403.375	3403.375	3200.93	286.300465	3314.11858	256.971864	CONFLICT	0.5	0.5
90Day	G-protein activation	0.39963	0.82486	0.7622	gng11;gna13	5378.655	5378.655	4854.24	741.634805	5266.80756	724.570551	UP	1	0
90Day	Synthesis of active ubiquitin: roles of E1 and E2 enzymes	0.37431	0.84018	0.76367	ube2k;cdc34	2429.116	2429.116	569.072	2630.49945	1344.2356	2136.72563	UP	1	0
90Day	Synthesis of bile acids and bile salts via 7alpha-hydroxycholesterol	0.37431	0.84018	0.76367	slc27a2;amacr	3510.085	3510.085	3419.78	127.710556	3490.24552	124.590434	DOWN	0	1
90Day	Negative regulation of FGFR4 signaling	0.37431	0.84018	0.76367	kib;fgf1	2046.3595	2046.3595	242.429	2551.14298	3002.17622	2163.59869	DOWN	0	1
28Day	Antigen processing-Cross presentation	0.67454	0.55788	0.76382	tap1;h2-q7;h2-d1	3562.11333	3718.12	1188.24	2299.84187	3462.70475	1959.38094	DOWN	0.333333333	0.666666667
28Day	Metabolism of steroid hormones	0.67454	0.55788	0.76382	hsd17b3;hsd11b1;fdxr	3448.4054	5126.12	67.9262	2927.60766	3847.46522	2710.49219	DOWN	0.333333333	0.666666667
7Day	Activation of kainate receptors upon glutamate binding	0.43028	0.80396	0.7642	calm3;calm2	3983.44	3983.44	3050.32	1319.63096	3556.9103	1173.69957	CONFLICT	0.5	0.5
7Day	Thrombin signalling through proteinase activated receptors (PARs)	0.43028	0.80396	0.7642	mapk3;f2	2478.4335	2478.4335	156.627	3283.53024	2159.69073	3252.44169	DOWN	0	1
7Day	Intrinsic Pathway for Apoptosis	0.38684	0.83132	0.76518	ywhaz;xiap	3800.505	3800.505	2726.98	1518.19361	4303.76091	1341.03648	CONFLICT	0.5	0.5
7Day	TBC/RABGAPs	0.38684	0.83132	0.76518	rab11a;rab6a	4298.915	4298.915	4055.48	344.269079	4355.93759	334.690971	UP	1	0
7Day	RHO GTPases Activate Formins	0.3822	0.72879	0.76558	clasp2;cenpk;tubb4b;tubb2a;tuba4a;ppp2cb;pfn2;pfn1;kif2a;cdc42;xpo1	3175.61509	3627.04	919.856	1191.81016	3128.68157	1280.33364	UP	0.909090909	0.090909091
90Day	Downstream signal transduction	0.35011	0.85427	0.76611	rasa1;sos1	4014.285	4014.285	2133.64	2659.63367	5271.62423	1977.83907	CONFLICT	0.5	0.5
90Day	Signaling by ERBB4	0.35011	0.85427	0.76611	nrg1;sos1	4903.635	4903.635	3912.34	1401.90283	5120.14662	1368.05592	CONFLICT	0.5	0.5
90Day	ER-Phagosome pathway	0.35011	0.85427	0.76611	tap2;snap23	2434.48	2434.48	544.33	2673.07576	3329.02624	2354.76285	CONFLICT	0.5	0.5
90Day	Interleukin-7 signaling	0.35011	0.85427	0.76611	irs2;hist1h3c	443.33615	443.33615	74.8133	521.170013	516.773173	510.717328	CONFLICT	0.5	0.5
7Day	Gamma carboxylation, hypusine formation and arylsulfatase activation	0.36626	0.84367	0.76673	f2;arsb	95.43325	95.43325	34.2395	86.5410312	126.416077	74.6289419	DOWN	0	1
28Day	Intra-Golgi traffic	0.42588	0.80479	0.76729	man1a;cux1	2205.787	2205.787	185.394	2857.26718	3712.11899	1904.18057	DOWN	0	1
28Day	PI3K Cascade	0.42588	0.80479	0.76729	pdpk1;fgf1	830.279	830.279	192.988	901.265575	1273.10558	648.142632	DOWN	0	1
28Day	Switching of origins to a post-replicative state	0.42588	0.80479	0.76729	cdc6;cdc27	5824.15	5824.15	5780.76	61.3627265	5829.67647	60.862965	UP	1	0
28Day	Formation of the ternary complex, and subsequently, the 43S complex	0.41002	0.81502	0.76741	eif3m;eif1ax	2737.81	2737.81	1517.45	1725.84966	2423.68091	1667.69388	CONFLICT	0.5	0.5
28Day	Ca2+ pathway	0.41002	0.81502	0.76741	ppp3cb;gmb5	2524.759	2524.759	953.648	2221.88648	2301.60545	2199.36003	UP	1	0
28Day	IRS-mediated signalling	0.41002	0.81502	0.76741	pdpk1;fgf1	830.279	830.279	192.988	901.265575	1273.10558	648.142632	DOWN	0	1
28Day	Retrograde transport at the Trans-Golgi-Network	0.41002	0.81502	0.76741	rab9;tmf1	3666.6	3666.6	2900.88	1082.89161	3862.31598	1046.92156	CONFLICT	0.5	0.5
28Day	Chondroitin sulfate/dermatan sulfate metabolism	0.37947	0.83405	0.76875	hyal1;gpc4	2868.94	2868.94	2376.85	695.920352	2635.93564	612.962541	DOWN	0	1
90Day	Regulation of TP53 Activity through Acetylation	0.75535	0.44236	0.76941	pin1;gata2b;pml;hdac2	2973.7305	3372.53	202.162	2000.2498	2520.57141	2294.44974	UP	0.75	0.25
90Day	Metabolism of water-soluble vitamins and cofactors	0.64977	0.46152	0.77049	mccc2;pank1;nmnat3;slc52a3;pcgb;slc23a2;pdck;pcx;mut;mtthfd2;aox1;hlcs;ppcca;aldh1l1	2376.61114	2730.885	338.932	1542.82357	2731.93797	1506.15671	DOWN	0.214285714	0.785714286
28Day	IRS-related events triggered by IGF1R	0.3505	0.8513	0.77146	pdpk1;fgf1	830.279	830.279	192.988	901.265575	1273.10558	648.142632	DOWN	0	1
7Day	Fatty acyl-CoA biosynthesis	0.7518	0.44424	0.77166	elovl5;ppt1;h2-ke6;elovl3	2943.36225	3453.59	212.399	1928.833	2974.02822	1575.38039	CONFLICT	0.5	0.5
28Day	IGF1R signaling cascade	0.33662	0.8593	0.77328	pdpk1;fgf1	830.279	830.279	192.988	901.265575	1273.10558	648.142632	DOWN	0	1
90Day	G alpha (12/13) signalling events	0.73309	0.46835	0.77349	gng11;rock2;rock1;adra1b	2858.7705	3159.375	262.092	1993.91208	2150.48638	1967.48202	UP	0.75	0.25
7Day	Binding and Uptake of Ligands by Scavenger Receptors	0.73334	0.46576	0.77494	apob;hsp90b1;lrp1;apoe	1320.5015	1584.74	113.316	856.630708	1503.0686	778.63729	DOWN	0.25	0.75
7Day	EPHB-mediated forward signaling	0.73334	0.46576	0.77494	kalrn;yes1;rasa1;cdc42	4449.69	4308.425	3395.83	1016.81766	4753.88739	995.095429	CONFLICT	0.5	0.5
7Day	Regulation of mRNA stability by proteins that bind AU-rich elements	0.73334	0.46576	0.77494	dcp2;ywhaz;uba52;xpo1	3417.9825	3109.105	2692.16	968.653438	3487.09233	1071.329	UP	1	0
28Day	Apoptotic execution phase	0.72908	0.46766	0.77773	dnm1l;pkp1;kpna1;birc2	5033.44	5531.66	3208.19	1232.6146	4608.97876	1444.68139	UP	1	0
28Day	ECM proteoglycans	0.72908	0.46766	0.77773	vtn;fn1;dag1;app	3475.1805	3893.235	447.762	2265.95602	4422.97912	1870.22533	DOWN	0	1

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
28Day	Pyruvate metabolism and Citric Acid (TCA) cycle	0.72908	0.46766	0.77773	suc1g2;me1;ldha;gstz1	4807.215	5341.16	2701.34	1426.60759	5227.92689	1161.60616	DOWN	0	1	
90Day	Downstream TCR signaling	0.7104	0.49389	0.77823	cdc34;nfbkbia;jkbkg;btrc	3147.108	3433.33	569.072	1905.15166	3410.68987	2043.61215	CONFLICT	0.5	0.5	
90Day	FCERI mediated NF-kB activation	0.7104	0.49389	0.77823	cdc34;nfbkbia;jkbkg;btrc	3147.108	3433.33	569.072	1905.15166	3410.68987	2043.61215	CONFLICT	0.5	0.5	
					hadha;pla1a;akr1c6;fads1;elovl5;fitm1;dgat2;pccb;cris1;tnfaip8l1;9130409i23rik;vapb;fads2;cyp3a25;ptges3;cyp39a1;stard10;mtmr7;acaa2;idi1;sptlc1;slc27a5;decr2;osbp12;mtmr6;smpd2;smpd1;slc25a17;slc10a2;slc10a1;pten;ptds1;ppt1;neu1;ncoa2;ncoa1;phyh;kpnb1;hsd17b4;hsd17b2;hsd11b1;hmgcs2;h2-ke6;gstm4;gc;ephx2;ebp;cyp3a11;cyp2e1;cyp2c37;cyp2c29;elovl3;baat;arsb;p										
7Day	Metabolism of lipids	0.38976	0.66291	0.78122	ecr;acat2;akr1c14;hsd3b7;cyp3a41b	2746.25929	3174.68	34.2395	1719.82553	2844.91315	1560.56945	CONFLICT	0.457627119	0.542372881	
7Day	mTOR signalling	0.69561	0.50785	0.78285	rps6kb1;rraga;eif4ebp1;cab39	3640.5775	3624.525	3116.98	548.193968	3866.9375	468.42227	UP	0.75	0.25	
7Day	Formation of Fibrin Clot (Clotting Cascade)	0.69561	0.50785	0.78285	f12,f5,f2;serpin1	698.358875	200.354	85.9375	1074.23654	310.699694	558.93663	DOWN	0	1	
28Day	Iron uptake and transport	0.70197	0.49802	0.78314	atp6v0e2;trf;ftl1;atp6v1e1	2823.62425	2736.09	527.967	1969.39643	2135.74969	1654.17081	CONFLICT	0.5	0.5	
90Day	TP53 Regulates Transcription of Cell Cycle Genes	0.68739	0.51889	0.78356	plk2;cdkn1a;btg2;bax	2194.0025	1943.11	913.71	1285.83436	1710.06551	1075.88404	UP	1	0	
					ube2n;atp6v0e2;arhgap45;c8g;ndufc2;npc2;cmtm6;ormdl3;psmd6;serpinb1a;golga7;dynl11;hebp2;methig1;iqgap2;tax1bp1;map2k4;apob;clec12a;tubb4b;vtm;ube2m;tnfrsf1b;eeaa1;serpina1e;serpina1b;s100a11;rab18;ppp3cb;pnp;pa2g4;pkp1;pfkl;pdpk1;mme;mapkapk2;man2b1;ly96;ita4h;lbp;anpep;jkbkg;h2-q7;h2-d1;gstp1;gstp2;gpi1;gaa;ftl1;f2;ctss;clu;cdc42;capza2;c4b;c3;c2;bcl2l1;atp6v1e1;app;birc2;atad3a;acly;qsox1;brk1;dnajc3										
28Day	Innate Immune System	0.64699	0.40447	0.78438	ajc3	3190.72403	3171.82	160.43	1921.18708	3116.35917	1948.69713	DOWN	0.318181818	0.681818182	
28Day	Respiratory electron transport	0.68825	0.51292	0.78616	ndufab1;ndufaf1;ndufc2;etfdh	2704.97	1988.385	1023.12	2137.1137	2428.10357	2123.03848	DOWN	0.25	0.75	
7Day	Glycosphingolipid metabolism	0.67644	0.52833	0.78738	smpd2;smpd1;neu1;arsb	3517.87488	4120.7	34.2395	2487.75667	4054.00508	2446.20526	DOWN	0	1	
7Day	TNF signaling	0.67644	0.52833	0.78738	tax1bp1;uba52;smpd2;xiap	4678.03	4817.795	3280.67	1040.44095	4863.61056	877.60986	CONFLICT	0.5	0.5	
7Day	Gap junction trafficking	0.67644	0.52833	0.78738	tubb4b;tubb2a;tuba4a;gja1	2276.434	1954.85	919.856	1424.18025	1763.60227	985.706882	UP	0.75	0.25	
7Day	Signaling by SCF-KIT	0.67644	0.52833	0.78738	yes1;stat1;ptpn11;kras	3931.55	3968.91	3629.67	224.307128	3931.63954	198.580589	UP	1	0	
28Day	Formation of RNA Pol II elongation complex	0.67444	0.52762	0.78937	iws1;wdr61;polr2a;ccnk	4124.69025	5065.76	860.451	2186.16416	4389.08607	2021.74453	CONFLICT	0.5	0.5	
28Day	RNA Polymerase II Transcription Elongation	0.67444	0.52762	0.78937	iws1;wdr61;polr2a;ccnk	4124.69025	5065.76	860.451	2186.16416	4389.08607	2021.74453	CONFLICT	0.5	0.5	
7Day	Signaling by NOTCH	0.65715	0.54838	0.79223	ywhaz;uba52;prkci;mdk	3820.895	3897.52	2726.98	925.576967	4101.75459	806.418941	UP	0.75	0.25	
90Day	Antigen Presentation: Folding, assembly and peptide loading of class I MHC	0.4099	0.78792	0.79254	erap1;tap2;sec13	3293.66667	2797.47	2758.9	893.048687	3139.69012	789.484091	DOWN	0.333333333	0.666666667	
90Day	SUMOylation of chromatin organization proteins	0.4099	0.78792	0.79254	hist1h4h;hist1h4i;hdac2	2720.22733	3951.81	202.162	2180.88131	1950.71221	2307.88021	DOWN	0.333333333	0.666666667	
90Day	Platelet Aggregation (Plug Formation)	0.4099	0.78792	0.79254	tlm1;sos1;fn1	4161.30667	4478.93	2110.06	1912.32154	4694.64696	1722.82421	DOWN	0	1	
28Day	Deadenylation-dependent mRNA decay	0.66058	0.5421	0.79274	exosc3;wdr61;cnot1;paip1	3828.5875	3500.885	2805.79	1204.04491	4227.20544	1273.09992	UP	0.75	0.25	
90Day	Signaling by FGFR3	0.38758	0.80341	0.7936	sos1;gab1;fgf1	2087.929	242.429	126.428	3297.46971	3907.43024	3338.39856	DOWN	0	1	
7Day	Regulation of PTEN gene transcription	0.43202	0.77063	0.79423	rraga;suz12;bmi1	3785.18667	3225.73	3193.23	997.285596	3681.52085	944.533221	UP	1	0	
7Day	Switching of origins to a post-replicative state	0.41291	0.78439	0.7945	uba52;cdc27;ccne2	4410.11	4598.19	3870.58	474.333116	4498.87719	394.432252	UP	1	0	
					usp16;tomm20;psmd5;psmd6;hist2h2ac;taf10;psmc4;vdac3;vdac2;uba52;tfgbr1;pten;psmc2;hist2h2aa1;cdc25a										
7Day	Ub-specific processing proteases	0.39179	0.70614	0.79473	brl1;pten;psmc2;hist2h2aa1;cdc25a	3744.69	3548.46	1811.97	1242.38365	3552.48514	1367.78801	UP	0.933333333	0.066666667	
7Day	Ca2+ pathway	0.39429	0.79747	0.79525	ctnnb1;calm3;calm2	2673.80107	3050.32	54.5232	2452.7893	2387.26243	2186.51911	DOWN	0.333333333	0.666666667	

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
90Day	Presynaptic phase of homologous DNA pairing and strand exchange	0.36604	0.81793	0.79532	rad51;brca2;rad51c	3127.57067	4249.95	513.022	2271.80208	3130.56464	2280.41	UP	1	0
28Day	Nonhomologous End-Joining (NHEJ)	0.64667	0.55634	0.79627	ube2n;ube2v2;hist1h4i;brca1	5011.745	5455.01	3288.55	1173.78176	4729.48604	1369.44158	CONFLICT	0.5	0.5
7Day	Nuclear Envelope Breakdown	0.3762	0.80987	0.79646	gm49336;nek6;tptr	2646.08933	2535	770.098	1933.93044	2710.863	1721.80663	UP	1	0
28Day	Synthesis of substrates in N-glycan biosynthesis	0.4159	0.78041	0.7971	nanp;gne;gfpt1	5085.35667	5755.83	3647.63	1246.04778	5180.06702	1205.69221	DOWN	0.333333333	0.666666667
28Day	Signaling by TGF-beta Receptor Complex	0.4159	0.78041	0.7971	ube2m;tfdp1;ccnk	4577.73667	5090.85	2933.96	1456.65483	4832.41634	1309.22256	UP	0.666666667	0.333333333
28Day	Dual incision in TC-NER	0.36352	0.81681	0.80021	pole3;prpf19;polr2a	3132.08267	3550.26	805.318	2148.41938	3348.7397	1703.23431	UP	1	0
28Day	C-type lectin receptors (CLRs)	0.71318	0.46404	0.80304	ube2n;ube2m;ppp3cb;pdpk1;ikbk	3581.4416	4095.87	192.988	2143.44278	3918.11922	1510.6886	UP	0.6	0.4
28Day	HATs acetylate histones	0.71318	0.46404	0.80304	msl1;meaf6;hist1h4i;kat7;hcfc1	4539.96	5043.8	2859.88	1234.05187	4409.47817	1273.01653	DOWN	0.4	0.6
28Day	Assembly of the pre-replicative complex	0.71318	0.46404	0.80304	psmd6;psmd8;cdc6;psmf1;psmb8	3966.316	4413.43	1415.14	1680.76279	4053.96174	1828.75774	DOWN	0.4	0.6
28Day	Platelet activation, signaling and aggregation	0.64418	0.44965	0.80465	spp2;cdc37l1;ola1;abcc4;a2m;trf;serpina1e;serpina1b;pdpk1;itih4;gnb5;fn1;f5;f2;clu;cdc42;app;anxa5;qsox1	2518.72995	2463.49	192.988	1720.69751	2423.18308	1716.29855	DOWN	0.263157895	0.736842105
28Day	Interleukin-1 family signaling	0.70103	0.47757	0.80473	ube2n;sgstm1;il1rap;ikbk;app	4940.87	5266.71	3705.51	791.86401	5097.48088	859.756978	DOWN	0.4	0.6
28Day	Toll Like Receptor 3 (TLR3) Cascade	0.68878	0.49099	0.8066	ube2n;map2k4;mapkapk2;ikbk;app	4661.272	5266.71	2616.5	1186.39761	4522.68638	1287.59598	DOWN	0.4	0.6
7Day	Fatty acid metabolism	0.65828	0.43334	0.80668	hadha;akr1c6;fads1;elovl5;pccbf;fads2;ptges3;acaa2;decr2;slc25a17;ppt1;phyh;hsl17b4;h2-ke6;ephx2;cyp2c37;cyp2c29;elovl3;pcr;akr1c14	2020.81211	2641.18	55.2305	1724.8506	2170.46283	1464.92174	DOWN	0.4	0.6
28Day	trans-Golgi Network Vesicle Budding	0.67644	0.50428	0.80864	picalm;hgs;ftl1;app;gbf1	3282.2154	3903.31	527.967	1620.92556	2497.62022	1908.50446	UP	0.8	0.2
28Day	Clathrin derived vesicle budding	0.67644	0.50428	0.80864	picalm;hgs;ftl1;app;gbf1	3282.2154	3903.31	527.967	1620.92556	2497.62022	1908.50446	UP	0.8	0.2
7Day	Condensation of Prophase Chromosomes	0.65206	0.53239	0.81154	hist1h4h;hist1h2bc;kmt5a;hist2h2ac;hist2h2aa1	3978.152	3489.14	3406.55	853.600483	3909.52678	885.518779	UP	0.6	0.4
7Day	Heparan sulfate/heparin (HS-GAG) metabolism	0.65206	0.53239	0.81154	hs3st3b1;hgsnat;sd3;ext1;bgm	3828.584	3370.58	2968.59	1190.86868	4003.60067	1265.31843	DOWN	0.2	0.8
7Day	Pyruvate metabolism and Citric Acid (TCA) cycle	0.65206	0.53239	0.81154	sdha;pdh;dh2;dh3b;dld	3266.496	3538.1	114.56	2018.40912	3640.89587	1559.57539	DOWN	0.2	0.8
28Day	Toll Like Receptor 10 (TLR10) Cascade	0.65159	0.53043	0.81314	ube2n;map2k4;mapkapk2;ikbk;app	4661.272	5266.71	2616.5	1186.39761	4522.68638	1287.59598	DOWN	0.4	0.6
28Day	Toll Like Receptor 5 (TLR5) Cascade	0.65159	0.53043	0.81314	ube2n;map2k4;mapkapk2;ikbk;app	4661.272	5266.71	2616.5	1186.39761	4522.68638	1287.59598	DOWN	0.4	0.6
28Day	MyD88 cascade initiated on plasma membrane	0.65159	0.53043	0.81314	ube2n;map2k4;mapkapk2;ikbk;app	4661.272	5266.71	2616.5	1186.39761	4522.68638	1287.59598	DOWN	0.4	0.6
90Day	Signaling by ERBB2	0.43732	0.74632	0.81326	nrg1;sos1;hsp90aa1;gab1	2590.0045	2169.33	126.428	2794.15124	3580.82543	2756.86322	CONFLICT	0.5	0.5
90Day	TP53 Regulates Metabolic Genes	0.41661	0.76222	0.81359	txnrd1;ywhaz;txn1;gsr	2630.852	2620.955	137.958	2080.55574	3004.54948	2352.81113	UP	0.75	0.25
7Day	Cell Cycle Checkpoints	0.39779	0.69086	0.81501	ube2n;clasp2;ube2v2;rfn168;hist1h4h;babam1;hist1h2bc;cenpgtse1;cop1;ywhaz;uba52;cdc27;ppp2cb;kif2a;cdkn1a;cdc25a;cne2;xpo1	3780.57105	3627.71	2423.08	852.712829	3670.51007	817.173885	UP	0.894736842	0.105263158
7Day	Interleukin-17 signaling	0.63469	0.55017	0.81509	mapk3;map2k3;uba52;ppp2cb;btcr	4058.048	4207.06	2894.34	807.460042	3936.95988	797.852297	UP	0.6	0.4
7Day	Semaphorin interactions	0.63469	0.55017	0.81509	gsk3b;pak2;sema4d;sema4a;hsp90aa1	3869.84	4499.44	1005.61	2047.60939	3962.70312	2199.68011	UP	0.6	0.4
7Day	Iron uptake and transport	0.43239	0.74875	0.81512	abcg2;uba52;ftl1;atp6v1e1	3576.0815	4272.24	720.546	1978.48703	3616.39084	2146.03772	UP	0.75	0.25
28Day	MyD88-MAL(TIRAP) cascade initiated on plasma membrane	0.6391	0.54327	0.8156	ube2n;map2k4;mapkapk2;ikbk;app	4661.272	5266.71	2616.5	1186.39761	4522.68638	1287.59598	DOWN	0.4	0.6
28Day	Toll Like Receptor TLR1:TLR2 Cascade	0.6391	0.54327	0.8156	ube2n;map2k4;mapkapk2;ikbk;app	4661.272	5266.71	2616.5	1186.39761	4522.68638	1287.59598	DOWN	0.4	0.6
28Day	Toll Like Receptor TLR6:TLR2 Cascade	0.6391	0.54327	0.8156	ube2n;map2k4;mapkapk2;ikbk;app	4661.272	5266.71	2616.5	1186.39761	4522.68638	1287.59598	DOWN	0.4	0.6
28Day	Toll Like Receptor 2 (TLR2) Cascade	0.6391	0.54327	0.8156	ube2n;map2k4;mapkapk2;ikbk;app	4661.272	5266.71	2616.5	1186.39761	4522.68638	1287.59598	DOWN	0.4	0.6
90Day	Sphingolipid de novo biosynthesis	0.37683	0.79167	0.81574	ormdl2;ppm1l;jacer2;ptlc2	4089.2325	3669.21	3502.64	963.349978	3708.02376	627.838636	CONFLICT	0.5	0.5
7Day	NORC negatively regulates rRNA expression	0.39859	0.77446	0.81613	hist1h4h;hist1h2bc;hist2h2ac;hist2h2aa1	4100.405	3802.835	3406.55	933.741438	4060.85571	1011.0164	CONFLICT	0.5	0.5
7Day	Intraflagellar transport	0.39859	0.77446	0.81613	hspb11;tubb4b;tubb2a;tuba4a	2178.474	1954.85	919.856	1242.69347	2388.51606	1364.4516	UP	1	0
7Day	Signaling by PDGF	0.38226	0.78651	0.81713	rasa1;stat1;ptpn11;kras	4372.8325	4037.79	3629.67	966.662513	4569.74061	1058.51347	UP	0.75	0.25
28Day	Transcription-Coupled Nucleotide Excision Repair (TC-NER)	0.40711	0.76638	0.81809	pole3;prpf19;polr2a;lig3	3696.917	4295.465	805.318	2086.45358	3989.40693	1722.6516	UP	0.75	0.25
28Day	Signaling by Insulin receptor	0.40711	0.76638	0.81809	atp6v0e2;pdpk1;fgf1;atp6v1e1	2335.122	1926.575	192.988	2168.02221	2304.43263	1455.8728	DOWN	0.25	0.75
7Day	SIRT1 negatively regulates rRNA expression	0.36634	0.79805	0.81844	hist1h4h;hist1h2bc;hist2h2ac;hist2h2aa1	4100.405	3802.835	3406.55	933.741438	4060.85571	1011.0164	CONFLICT	0.5	0.5
7Day	Signaling by the B Cell Receptor (BCR)	0.69622	0.46922	0.82004	uba52;kras;itpr2;calm3;calm2;btcr	4198.73667	4182.885	3050.32	657.674434	3976.2843	788.611862	UP	0.666666667	0.333333333

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
28Day	RNA Polymerase II Pre-transcription Events	0.37193	0.79249	0.82026	lws1;wdr61;polr2a;ccnk	4124.69025	5065.76	860.451	2186.16416	4389.08607	2021.74453	CONFLICT	0.5	0.5
28Day	TRAF6 mediated induction of NFkB and MAP kinases upon TLR7/8 or 9 activation	0.69072	0.47296	0.82248	ube2n;map2k4;mapkapk2;ly96;ikbk;g;ap	4644.44333	4948.59	2616.5	1061.94664	4533.01649	1074.62366	CONFLICT	0.5	0.5
28Day	APC/C-mediated degradation of cell cycle proteins	0.69072	0.47296	0.82248	psmd6;psmd8;cdc14a;psmf1;cdc27;psmb8	3415.512	3894.855	748.272	1975.49515	3457.19909	2020.42083	CONFLICT	0.5	0.5
28Day	Regulation of mitotic cell cycle	0.69072	0.47296	0.82248	psmd6;psmd8;cdc14a;psmf1;cdc27;psmb8	3415.512	3894.855	748.272	1975.49515	3457.19909	2020.42083	CONFLICT	0.5	0.5
90Day	Metabolism of amino acids and derivatives	0.63212	0.45352	0.82316	mccc2;dmgdh;amdhd1;ndufab1;hoga1;asrgl1;serinc1;ivd;txnrd1;ahcy;tst;slc25a21;suox;sardh;oat;hpd;gstz1;glul;slc6a12;cdol;arg2;gm4737;agxt;aldh6a1	2656.47342	2998.6	105.476	1333.22225	2688.41813	1392.52728	DOWN	0.208333333	0.791666667
28Day	Toll Like Receptor 7/8 (TLR7/8) Cascade	0.67949	0.48515	0.82379	ube2n;map2k4;mapkapk2;ly96;ikbk;g;ap	4644.44333	4948.59	2616.5	1061.94664	4533.01649	1074.62366	CONFLICT	0.5	0.5
28Day	MyD88 dependent cascade initiated on endosome	0.67949	0.48515	0.82379	ube2n;map2k4;mapkapk2;ly96;ikbk;g;ap	4644.44333	4948.59	2616.5	1061.94664	4533.01649	1074.62366	CONFLICT	0.5	0.5
28Day	DNA Replication Pre-Initiation	0.67949	0.48515	0.82379	psmd6;pole3;psmd8;cdc6;psmf1;psmb8	3439.483	3894.855	805.318	1981.23419	3717.90337	2013.21092	CONFLICT	0.5	0.5
7Day	Autodegradation of Cdh1 by Cdh1:APC/C	0.66493	0.50298	0.82404	psmd5;psmd6;psmc4;uba52;cdc27;psmc2	3479.61667	3598.515	2309.23	896.239144	3408.72083	977.398512	UP	1	0
7Day	EPH-Ephrin signaling	0.63323	0.53594	0.82899	kairn;sdcbp;yes1;pak2;rasa1;cdc42	3930.20333	3708.39	2538.2	1147.99056	4503.50691	1119.22462	UP	0.666666667	0.333333333
7Day	Cleavage of Growing Transcript in the Termination Region	0.63323	0.53594	0.82899	fip1l1;cpsf2;lsml0;srsf1;ctsf2;thoc5	3791.17333	3366.41	2905.24	1041.714	3506.15051	699.668867	UP	1	0
7Day	RNA Polymerase II Transcription Termination	0.63323	0.53594	0.82899	fip1l1;cpsf2;lsml0;srsf1;ctsf2;thoc5	3791.17333	3366.41	2905.24	1041.714	3506.15051	699.668867	UP	1	0
90Day	NRAGE signals death through JNK	0.4403	0.72787	0.82899	arhgef6;fgd4;vav1;tiam1;sos1	5279.148	5800.32	4161.05	841.81329	5353.08411	810.835565	DOWN	0.2	0.8
90Day	Respiratory electron transport	0.42133	0.7431	0.82929	ndufab1;ndufc2;etfdh;ndufaf3;ndufb9	3326.1292	3477.1	105.476	2076.71355	4597.15369	1965.30097	DOWN	0.4	0.6
90Day	Kinesins	0.42133	0.7431	0.82929	tubb6;tubb4b;tubb2a;tuba1b;kifc1	1389.634	1722.38	713.489	593.401723	1135.0221	585.08693	UP	0.8	0.2
90Day	G1/S Transition	0.40278	0.75769	0.82998	pole4;cables1;orc6;dbf4;cdk1a	3595.292	4071.91	913.71	1819.33413	2719.27209	1739.06073	UP	0.6	0.4
90Day	Intraflagellar transport	0.40278	0.75769	0.82998	tubb6;ifft52;tubb4b;tubb2a;tuba1b	1277.8726	1722.38	154.682	776.85001	1233.28221	659.90165	UP	0.6	0.4
28Day	Processing of DNA double-strand break ends	0.63401	0.53295	0.83032	ube2n;rm1;ube2v2;hist1h4i;brca1;blm	4031.196	4357.41	692.086	1973.26334	4212.5832	1623.69045	UP	0.666666667	0.333333333
7Day	PKMTs methylate histone lysines	0.43206	0.73322	0.83073	hist1h4h;km15a;suz12;setd2;km15b	3441.166	3406.55	3159.12	320.71106	3391.94842	276.159994	UP	0.6	0.4
7Day	HATs acetylate histones	0.41647	0.74569	0.83109	hist1h4h;hist1h2bc;kat7;ncoa2;ncoa1	2713.08172	3352.11	86.7986	1468.87603	3226.13378	748.206477	UP	0.8	0.2
7Day	Assembly of the pre-replicative complex	0.41647	0.74569	0.83109	psmd5;psmd6;psmc4;uba52;psmc2	3401.424	3326.45	2309.23	978.876936	3327.35463	1056.01708	UP	1	0
7Day	PRC2 methylates histones and DNA	0.40117	0.75773	0.8317	hist1h4h;hist1h2bc;suz12;hist2h2ac;hist2h2aa1	3918.97	3418.4	3193.23	904.708849	3846.64569	946.911026	UP	0.6	0.4
7Day	Protein-protein interactions at synapses	0.38618	0.76934	0.83257	gria3;ptprf;ptprd;il1rap;flot2	2550.5868	2247.36	131.024	2161.76821	2088.5953	1959.99374	DOWN	0.2	0.8
7Day	Asparagine N-linked glycosylation	0.40069	0.67929	0.83345	trappc6b;fuca1;cog6;O610009b22rik;ngly1;copz1;gnpna1;ppp6r1;cog5;tubb4b;uba52;tubb2a;tuba4a;arcn1;sel1;sec22b;rab1a;neu1;gfpt1;f5;capza2;asgr1;g	3351.56737	3410.995	244.081	1310.67174	3049.41852	1353.91995	UP	0.708333333	0.291666667
7Day	Toll Like Receptor 10 (TLR10) Cascade	0.66214	0.49341	0.83656	ube2n;ecsit;mapk3;map2k3;uba52;ppp2cb;btrc	3993.80429	4207.06	2894.34	704.971717	3855.96351	691.922621	CONFLICT	0.571428571	0.428571429
7Day	Toll Like Receptor 5 (TLR5) Cascade	0.66214	0.49341	0.83656	ube2n;ecsit;mapk3;map2k3;uba52;ppp2cb;btrc	3993.80429	4207.06	2894.34	704.971717	3855.96351	691.922621	CONFLICT	0.571428571	0.428571429
7Day	MyD88 cascade initiated on plasma membrane	0.66214	0.49341	0.83656	ube2n;ecsit;mapk3;map2k3;uba52;ppp2cb;btrc	3993.80429	4207.06	2894.34	704.971717	3855.96351	691.922621	CONFLICT	0.571428571	0.428571429
7Day	MyD88-MAL(TIRAP) cascade initiated on plasma membrane	0.64749	0.50882	0.8383	ube2n;ecsit;mapk3;map2k3;uba52;ppp2cb;btrc	3993.80429	4207.06	2894.34	704.971717	3855.96351	691.922621	CONFLICT	0.571428571	0.428571429
7Day	Toll Like Receptor TLR1:TLR2 Cascade	0.64749	0.50882	0.8383	ube2n;ecsit;mapk3;map2k3;uba52;ppp2cb;btrc	3993.80429	4207.06	2894.34	704.971717	3855.96351	691.922621	CONFLICT	0.571428571	0.428571429
7Day	Toll Like Receptor TLR6:TLR2 Cascade	0.64749	0.50882	0.8383	ube2n;ecsit;mapk3;map2k3;uba52;ppp2cb;btrc	3993.80429	4207.06	2894.34	704.971717	3855.96351	691.922621	CONFLICT	0.571428571	0.428571429
7Day	Toll Like Receptor 2 (TLR2) Cascade	0.64749	0.50882	0.8383	ube2n;ecsit;mapk3;map2k3;uba52;ppp2cb;btrc	3993.80429	4207.06	2894.34	704.971717	3855.96351	691.922621	CONFLICT	0.571428571	0.428571429

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
90Day	Regulation of actin dynamics for phagocytic cup formation	0.619	0.53966	0.84112	wasf2;vav1;myo9b;myo10;hsp90aa1;fgr2b;cdc42	2644.57429	3055.31	100.823	2388.05593	3312.00806	2193.71301	DOWN	0.285714286	0.714285714
90Day	EPH-Ephrin signaling	0.44242	0.71364	0.8413	tiam1;rasa1;rock2;rock1;mmp2;cdc42	2737.16317	3003.875	156.487	2236.40759	2441.83028	2378.23325	UP	0.666666667	0.333333333
7Day	RHO GTPase Effectors	0.59957	0.47881	0.84152	clasp2;myh14;hist1h4h;hist1h2bc;cenp k;iqgap2;nckap1;hist2h2ac;mapk3;tubb4b;ywahz;pak2;tubb2a;tuba4a;flna;ppp2cb;pfn2;pfn1;ncoa2;myh9;kif2a;hist2h2aa1;cdc42;ctnnb1;calm3;calm2;abl1;xpo1;brk1	3174.79406	3406.55	54.5232	1375.89626	3213.28147	1370.13031	UP	0.620689655	0.379310345
7Day	COPII-mediated vesicle transport	0.44599	0.70939	0.8428	trappc6b;O610009b22rik;ppp6r1;sec22b;rab1a;f5	3049.9035	3385.155	244.081	1691.22153	2500.88926	1631.85364	UP	0.666666667	0.333333333
7Day	Signaling by MET	0.43133	0.72163	0.84296	ranbp10;ranbp9;hgfac;uba52;ptpn11;kras	2747.02567	3298.26	186.634	1860.55789	2417.40203	1865.94033	UP	0.666666667	0.333333333
90Day	Peroxisomal protein import	0.39066	0.75578	0.84305	gstk1;hacl1;slc27a2;amacr;ephx2;agxt	3428.52667	3398.155	2157.32	816.22512	3062.66676	947.203112	DOWN	0	1
90Day	L1CAM interactions	0.67586	0.47009	0.84422	tubb6;ranbp9;tubb4b;tubb2a;tuba1b;msnap2m1;itga9	2660.11012	2467.28	779.791	1310.19834	1803.37656	1184.81498	UP	0.625	0.375
7Day	RHO GTPases activate PKNs	0.38877	0.75616	0.84467	hist1h4h;hist1h2bc;hist2h2ac;ywahz;ncoa2;hist2h2aa1	3202.56643	3412.475	86.7986	1776.19071	3725.32417	1328.83106	UP	0.666666667	0.333333333
7Day	Platelet homeostasis	0.38877	0.75616	0.84467	apob;ptpn11;ppp2cb;itpr2;calm3;calm2	3553.50167	3628.355	1999.21	983.347249	3501.98056	773.659418	CONFLICT	0.5	0.5
28Day	Metabolism of RNA	0.62327	0.45133	0.8461	las1a1cf;phf5a;ccar1;rnpc3;exosc3;wdr61;pno1;sf3b6;set;cpsf2;prpf19;cnot1;hnmpul1;prpf38a;smg5;u2af2;paip1;wdr18;dhx37;snrpd1;smn1;polr2a;prpf8;papola;fbl;bop1;srsf1;tptr;thoc5;bc005561	3604.15581	3919.15	131.831	1610.53153	3719.0459	1653.32351	UP	0.64516129	0.35483871
7Day	Mitotic G1-G1/S phases	0.63295	0.51386	0.84959	uba52;tfp1;prim2;ppp2cb;cdkn1a;cdc25a;ccne2;abl1	3720.57925	3816.59	707.264	1540.65955	3868.29641	1301.93724	UP	0.875	0.125
7Day	Fcgamma receptor (FCGR) dependent phagocytosis	0.63295	0.51386	0.84959	nckap1;mapk3;yes1;myh9;hsp90aa1;cdc42;abl1;brk1	3254.56125	3418.395	1005.61	1281.94634	3162.32786	1406.29011	UP	0.625	0.375
7Day	Cellular response to heat stress	0.63295	0.51386	0.84959	hspb8;gm49336;hsbp1;ptges3;dnajb6;hsp90aa1;hsp11;tptr	2879.9385	3330.73	589.118	1422.66123	2634.35759	1461.94836	UP	0.875	0.125
7Day	Processing of DNA double-strand break ends	0.44405	0.70102	0.85268	ube2n;ube2v2;rnf168;hist1h4h;babam1;hist1h2bc;uba52	3607.63286	3444.79	2423.08	733.542077	3447.91192	706.296567	UP	0.857142857	0.142857143
7Day	Mitochondrial translation elongation	0.44405	0.70102	0.85268	mrpl16;mrpl1;mrpl47;mrps17;mrps36;mrps31;mrpl2	4077.59429	3969.79	3223.73	605.190521	4004.64794	651.515278	UP	1	0
90Day	COPII-mediated vesicle transport	0.39536	0.74285	0.85281	trappc6b;lman1;stx17;tga;serpina1e;areg;sec13	3432.10557	3798.74	959.779	1610.18273	3119.79648	1439.58855	UP	0.714285714	0.285714286
7Day	Sphingolipid metabolism	0.41687	0.724	0.85325	g130409i23rik;vapb;sptlc1;smpd2;smpd1;neu1;arsb	3669.80564	3876.31	34.2395	1772.38512	3960.10113	1691.87893	DOWN	0.285714286	0.714285714
7Day	MyD88-independent TLR4 cascade	0.41687	0.724	0.85325	ube2n;mapk3;map2k3;uba52;ptpn11;ppp2cb;btrc	3909.24286	3629.67	2894.34	708.585348	3806.22655	683.032185	UP	0.714285714	0.285714286
7Day	TRIF(TICAM1)-mediated TLR4 signaling	0.41687	0.724	0.85325	ube2n;mapk3;map2k3;uba52;ptpn11;ppp2cb;btrc	3909.24286	3629.67	2894.34	708.585348	3806.22655	683.032185	UP	0.714285714	0.285714286
7Day	Mitochondrial translation termination	0.41687	0.724	0.85325	mrpl16;mrpl1;mrpl47;mrps17;mrps36;mrps31;mrpl2	4077.59429	3969.79	3223.73	605.190521	4004.64794	651.515278	UP	1	0
7Day	Mitochondrial translation	0.40358	0.73503	0.85378	mrpl16;mrpl1;mrpl47;mrps17;mrps36;mrps31;mrpl2	4077.59429	3969.79	3223.73	605.190521	4004.64794	651.515278	UP	1	0
28Day	Glycerophospholipid biosynthesis	0.45251	0.69221	0.85444	dgat2;pnpla8;phospho1;pla2g4c;etnk2;ptdss1;abhd4	3801.69429	3854.48	2889.4	718.035407	3698.35911	647.344505	CONFLICT	0.428571429	0.571428571
7Day	Cellular responses to external stimuli	0.60364	0.465	0.86009	hspb8;ep400;gm49336;cul2;hist1h4h;rraga;hsbp1;hist1h2bc;txn2;ptges3;suz12;txnd1;hist2h2ac;mapk3;map2k3;atg4c;dnajb6;tubb4b;uba52;tubb2a;tuba4a;terf2;cdc27;prdx2;tip1;sod1;hsp90aa1;hsp11;hist2h2aa1;gstp1;gstp2;cdkn1a;ccne2;capza2;bmi1;arnt;egl1;tptr	3243.93466	3392.01	589.118	1327.40568	3113.54853	1326.53415	UP	0.736842105	0.263157895
7Day	Oxidative Stress Induced Senescence	0.40399	0.727	0.86201	hist1h4h;hist1h2bc;suz12;hist2h2ac;map2k3;uba52;hist2h2aa1;bmi1	4023.41875	3802.835	2894.34	924.438937	3897.23919	961.420058	UP	0.625	0.375

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
28Day	Degradation of the extracellular matrix	0.45106	0.68523	0.8625	phylkpl;tmprss6;a2m;fn1;ctss;col8a1;capn5;bmp1	3632.22238	4286.025	182.399	2059.39605	3939.4751	1801.13642	UP	0.625	0.375
7Day	Epigenetic regulation of gene expression	0.6468	0.48397	0.86343	sf3b1;hist1h4h;hist1h2bc;gsk3b;ddx21;suz12;hist2h2ac;polr2h;mybbp1a;hist2h2aa1	3755.419	3429.125	2845.95	762.292318	3660.16077	755.922136	UP	0.8	0.2
90Day	Recruitment of NuMA to mitotic centrosomes	0.44602	0.68517	0.86659	haus7;tubb6;dcn3;cntrl;tubb4b;cep76;tubb2a;tuba1b;hsp90aa1	2642.33233	1951.01	426.32	1646.5088	2407.21003	1637.1364	UP	0.888888889	0.111111111
7Day	Toll Like Receptor 4 (TLR4) Cascade	0.44025	0.68916	0.8679	ube2n;ecsit;mapk3;map2k3;uba52;ptpn11;ppp2cb;lbpb;btcr	4091.90222	4207.06	2894.34	756.880427	3950.90744	747.335692	CONFLICT	0.555555556	0.444444444
7Day	ESR-mediated signaling	0.46202	0.66377	0.87377	hist1h4h;hist1h2bc;ppid;ptges3;hist2h2ac;polr2h;ncoa2;ncoa1;hsp90aa1;hist2h2aa1	2897.57586	3354.05	86.7986	1651.82033	3175.19169	1443.43193	UP	0.8	0.2
7Day	Metabolism of water-soluble vitamins and cofactors	0.43841	0.68486	0.87394	mccc2;nudt12;qprt;pccb;mocs1;btcd;nahe;cyb5a;shmt2;aldh1l1	1945.66428	1772.3595	77.8976	1848.22599	2127.08921	1776.81271	DOWN	0.2	0.8
28Day	Ub-specific processing proteases	0.43866	0.67829	0.88054	tom20;psmd6;psmd8;psmf1;usp12;polb;mdm2;psmb8;ikbk;hgs;birc2	3729.44755	3654.44	784.943	1731.84434	3412.99335	1936.53099	UP	0.727272727	0.272727273
7Day	Platelet degranulation	0.59477	0.52152	0.88291	tmx3;cdc37l1;abcc4;tuba4a;sod1;flna;l gals3bp;f5;ecm1;calm3;calm2;ahsg;qs ox1	3320.20592	3190.96	244.081	1797.47619	2990.51446	1857.71969	DOWN	0.384615385	0.615384615
7Day	Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)	0.59477	0.52152	0.88291	apoa5;apob;hsp90b1;nucb1;igfbp5;f5;c sf1;c4b;serpinc1;apoe;ahsg;afp;qsox1	2429.02581	1999.21	85.9375	2022.85744	2176.0983	2216.29449	DOWN	0.230769231	0.769230769
7Day	Mitotic G2-G2/M phases	0.46744	0.64879	0.88362	gts1;tubb4b;uba52;tubb2a;tuba4a;ppp2cb;nedd1;hsp90aa1;cdkn1a;cdc25a;btrc;xpo1	3102.3255	2946.665	919.856	1524.03417	2964.09012	1451.34659	UP	1	0
90Day	Post-translational protein phosphorylation	0.61197	0.50087	0.88489	notum;spp2;apob;trf;tnc;serpina1e;itih2;igfbp4;fn1;csf1;c3;apoe;ahsg;golm1	2072.66716	1808.155	82.4742	1716.50033	2402.55112	1823.09973	DOWN	0.142857143	0.857142857
7Day	ER to Golgi Anterograde Transport	0.6212	0.48655	0.88908	trapppc6b;cog6;0610009b22rik;cop21;ppp6r1;cog5;tubb4b;tubb2a;tuba4a;arcn1;sec22b;rab1a;f5;capza2;gbf1	2881.76513	3113.17	244.081	1280.05518	2587.34367	1266.21649	UP	0.8	0.2
7Day	Cellular Senescence	0.42144	0.68282	0.89208	ep400;hist1h4h;hist1h2bc;suz12;hist2h2ac;mapk3;map2k3;uba52;terf2;cdc27;hist2h2aa1;cdkn1a;ccne2;bmi1	4029.98357	4028.925	2818.63	848.565347	4022.93412	881.356636	UP	0.642857143	0.357142857
7Day	Signaling by Nuclear Receptors	0.459	0.64527	0.89479	akr1c6;hist1h4h;hist1h2bc;ppid;ptges3;hist2h2ac;pdhx;polr2h;rdh16f2;ncoa2;ncoa1;hsp90aa1;hist2h2aa1;dld;akr1c14	3258.57057	3406.55	86.7986	1603.45202	3238.65029	1384.02731	UP	0.733333333	0.266666667
7Day	Transport to the Golgi and subsequent modification	0.42807	0.67068	0.89832	trapppc6b;fuca1;cog6;0610009b22rik;cop21;ppp6r1;cog5;tubb4b;tubb2a;tuba4a;arcn1;sec22b;rab1a;f5;capza2;gbf1	2866.90606	3070.085	244.081	1238.07829	2588.85654	1246.45916	UP	0.75	0.25
28Day	Deubiquitination	0.46061	0.63976	0.89888	asxl2;tom20;psmd6;psmd8;uchl3;psmf1;ino80c;usp12;polb;mdm2;psmb8;ikbk;hgs;hcf1;brca1;birc2	3853.0265	4041.425	572.861	1803.26965	3618.32643	1970.31024	UP	0.6875	0.3125
7Day	Signaling by WNT	0.42646	0.66946	0.90116	tmcd5;gsk3b;vps29;klhl12;ywhaz;uba52;sox6;ppp2cb;pfn1;lrp5;csnk2b;ctnnb1;calm3;calm2;btcr;xiap;xpo1	3368.88013	3627.04	54.5232	1460.48609	3362.34156	1535.85026	UP	0.705882353	0.294117647
28Day	Asparagine N-linked glycosylation	0.57907	0.51673	0.90366	nanp;lmann2;ngly1;dynl1;ppp6r3;gne;tubb4b;tubb2a;mgat2;sec22c;serpina1e;serpina1b;man1a;gfp1t1;f5;capza2;bet1;asgr1;gbf1	4033.60763	3903.31	185.394	1747.19849	3926.40047	1680.86707	CONFLICT	0.473684211	0.526315789
7Day	Response to elevated platelet cytosolic Ca2+	0.53999	0.57586	1	tmx3;cdc37l1;abcc4;tuba4a;sod1;flna;l gals3bp;f5;ecm1;calm3;calm2;ahsg;qs ox1	3320.20592	3190.96	244.081	1797.47619	2990.51446	1857.71969	DOWN	0.384615385	0.615384615
7Day	Purine salvage	0.72196	0.66353	1	adk	124.762	124.762	124.762		124.762		DOWN	0	1
7Day	Activation of BAD and translocation to mitochondria	0.68564	0.69527	1	ywhaz	2726.98	2726.98	2726.98		2726.98		UP	1	0
7Day	Activation of BH3-only proteins	0.45381	0.84775	1	ywhaz	2726.98	2726.98	2726.98		2726.98		UP	1	0
7Day	Signaling by ERBB2	0.59904	0.60571	1	yes1;uba52;kras;hsp90aa1	3486.7075	4089.83	1005.61	1685.04165	3246.78653	1805.94232	UP	1	0
7Day	CD28 co-stimulation	0.4531	0.78885	1	pak2;cdc42	3567.05	3567.05	2538.2	1455.01362	4188.77837	1159.29819	UP	1	0

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.														
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
7Day	TP53 Regulates Metabolic Genes	0.57974	0.6238	1	rraga;txnr1;ywhaz;prdx2	3021.79	2976.355	2303.89	657.772449	3146.44726	649.412862	UP	0.75	0.25
7Day	Downregulation of ERBB2 signaling	0.6029	0.67518	1	uba52;hsp90aa1	2883.585	2883.585	1005.61	2655.85771	2564.36068	2617.20688	UP	1	0
7Day	Transcriptional regulation by RUNX2	0.58015	0.77365	1	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	FOXO-mediated transcription	0.45381	0.84775	1	ywhaz	2726.98	2726.98	2726.98		2726.98		UP	1	0
7Day	G2/M Transition	0.4896	0.62828	1	gts1;tubb4b;uba52;tubb2a;tuba4a;ppp2cb;nedd1;hsp90aa1;cdkn1a;cdc25a;btrc;xpo1	3102.3255	2946.665	919.856	1524.03417	2964.09012	1451.34659	UP	1	0
7Day	Energy dependent regulation of mTOR by LKB1-AMPK	0.47661	0.77272	1	rraga;cab39	3711.005	3711.005	3225.73	686.282486	3826.89474	666.425379	UP	1	0
7Day	Antigen Presentation: Folding, assembly and peptide loading of class I MHC	0.55576	0.67258	1	tap2;h2-t23;h2-q10	3822.20667	4232.51	2584.12	1092.34442	3453.18156	1077.07007	DOWN	0	1
7Day	Prostanoid ligand receptors	0.41021	1	1										
7Day	Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3	0.51381	0.66427	1	hist1h4h;hist1h2bc;hist2h2ac;ncoa2;hist2h2aa1	3297.68372	3418.4	86.7986	1968.68283	3851.16831	1376.36603	UP	0.6	0.4
7Day	UCH proteinases	0.48168	0.65952	1	psmd5;psmd6;hist2h2ac;psmc4;ino80c;uba52;psmc2;hist2h2aa1	3875.85375	4055.48	2309.23	1045.086	3896.76234	1200.81492	UP	0.875	0.125
7Day	Chondroitin sulfate/dermatan sulfate metabolism	0.56056	0.64136	1	sdcc3;hyal1;bgn;arsb	2973.70488	3385.82	34.2395	2144.95655	3428.03796	1961.6416	DOWN	0	1
7Day	Chondroitin sulfate biosynthesis	0.42537	0.86213	1	bgn	2968.59	2968.59	2968.59		2968.59		DOWN	0	1
7Day	Toll Like Receptor 9 (TLR9) Cascade	0.59137	0.55595	1	ube2n;rbsn;ecsit;mapk3;map2k3;uba52;ppp2cb;btrc	4237.3375	4214.33	2894.34	948.922894	3958.31477	823.420852	CONFLICT	0.5	0.5
7Day	Toll Like Receptor 3 (TLR3) Cascade	0.5536	0.61382	1	ube2n;mapk3;map2k3;uba52;ppp2cb;btrc	3955.83833	3917.05	2894.34	764.378356	3822.84942	721.933719	UP	0.666666667	0.333333333
7Day	Toll Like Receptor 7/8 (TLR7/8) Cascade	0.50046	0.65144	1	ube2n;ecsit;mapk3;map2k3;uba52;ppp2cb;btrc	3993.80429	4207.06	2894.34	704.971717	3855.96351	691.922621	CONFLICT	0.571428571	0.428571429
7Day	Toll-like Receptor Cascades	0.47509	0.63751	1	ube2n;rbsn;ecsit;mapk3;map2k3;apob;uba52;hsp90b1;ptpn11;ppp2cb;lbp;cts	3884.85385	3881.76	1852.94	1186.21385	3883.96422	915.388264	CONFLICT	0.538461538	0.461538462
7Day	Nuclear Events (kinase and transcription factor activation)	0.65616	0.62754	1	mapk3;ppp2cb	4213.64	4213.64	3627.04	829.577676	4084.83206	809.330679	CONFLICT	0.5	0.5
7Day	MAPK targets/ Nuclear events mediated by MAP kinases	0.50078	0.75552	1	mapk3;ppp2cb	4213.64	4213.64	3627.04	829.577676	4084.83206	809.330679	CONFLICT	0.5	0.5
7Day	TRAF6 mediated induction of NFkB and MAP kinases upon TLR7/8 or 9 activation	0.51491	0.63831	1	ube2n;ecsit;mapk3;map2k3;uba52;ppp2cb;btrc	3993.80429	4207.06	2894.34	704.971717	3855.96351	691.922621	CONFLICT	0.571428571	0.428571429
7Day	MyD88 dependent cascade initiated on endosome	0.50046	0.65144	1	ube2n;ecsit;mapk3;map2k3;uba52;ppp2cb;btrc	3993.80429	4207.06	2894.34	704.971717	3855.96351	691.922621	CONFLICT	0.571428571	0.428571429
7Day	Intracellular oxygen transport	0.7431	1	1										
7Day	Axon guidance	0.53171	0.5529	1	ranbp9;gsk3b;kalrn;sdcbp;mapk3;tubb4b;yes1;pak2;vasp;uba52;tubb2a;tuba4a;rasa1;sema4d;sema4a;reln;ptpn11;pf12;pf11;kras;hsp90aa1;gfra1;csnk2b;c	3515.54904	3629.67	778.73	1414.19868	3659.18086	1592.19662	UP	0.64	0.36
7Day	Glucose metabolism	0.48569	0.70607	1	pfkfb3;gckr;pgam1;gpi1	3402.63	3741.1	1853.98	1103.76765	3416.45976	1054.46301	DOWN	0.25	0.75
7Day	snRNP Assembly	0.58015	0.77365	1	snrpd2	5726.15	5726.15	5726.15		5726.15		UP	1	0
7Day	Metabolism of non-coding RNA	0.58015	0.77365	1	snrpd2	5726.15	5726.15	5726.15		5726.15		UP	1	0
7Day	Beta-oxidation of very long chain fatty acids	0.68564	0.69527	1	decr2	3510.23	3510.23	3510.23		3510.23		UP	1	0
7Day	Mitochondrial calcium ion transport	0.51457	0.81436	1	slc8b1	2876.78	2876.78	2876.78		2876.78		DOWN	0	1
7Day	Trafficking and processing of endosomal TLR	0.62942	0.65201	1	hsp90b1;ctsb	2867.35	2867.35	1852.94	1434.59238	3470.67949	1153.27462	UP	1	0
7Day	Intra-Golgi traffic	0.6184	0.58709	1	cog6;cog5;yps45;cyth1	3305.2525	3897.525	1099.15	1502.79538	2991.04604	1609.07416	CONFLICT	0.5	0.5
7Day	RNA Polymerase III Transcription	0.57754	0.65355	1	brf1;gtf3c6;polr2h	2841.95	2665.35	1895.9	1045.59581	3394.41506	909.790933	UP	0.666666667	0.333333333
7Day	RNA Polymerase III Transcription Initiation	0.57754	0.65355	1	brf1;gtf3c6;polr2h	2841.95	2665.35	1895.9	1045.59581	3394.41506	909.790933	UP	0.666666667	0.333333333
7Day	Metabolism of Angiotensinogen to Angiotensins	0.5468	0.79501	1	mme	2165.57	2165.57	2165.57		2165.57		DOWN	0	1

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
7Day	Formation of Incision Complex in GG-NER	0.45162	0.75615	1	ube2n;ube2v2;uba52	3543.14333	3444.79	2423.08	1172.33835	3265.85323	1041.89728	UP	1	0
7Day	G-protein mediated events	0.6184	0.58709	1	prkar2a;gnai3;calm3;calm2	3206.91	3558.44	794.2	1780.22388	2668.09864	1730.81535	CONFLICT	0.5	0.5
7Day	PLC beta mediated events	0.63779	0.56798	1	prkar2a;gnai3;calm3;calm2	3206.91	3558.44	794.2	1780.22388	2668.09864	1730.81535	CONFLICT	0.5	0.5
7Day	Inositol phosphate metabolism	0.52268	0.67483	1	itpk1;pten;calm3;calm2	3684.875	3386.31	3050.32	853.925176	3438.70794	788.233521	CONFLICT	0.5	0.5
7Day	Hedgehog 'off' state	0.5479	0.63366	1	tubb4b;uba52;tubb2a;tuba4a;prkar2a	2731.5352	2094.04	919.856	1614.82979	2575.30579	1620.66012	UP	0.8	0.2
7Day	Pentose phosphate pathway	0.5468	0.79501	1	pgd	4459.38	4459.38	4459.38		4459.38		UP	1	0
7Day	SUMOylation of transcription cofactors	0.57754	0.65355	1	ncoa1;bmi1;uhrf2	4116.22333	4110.52	3301.55	817.539921	4021.24749	882.151957	UP	1	0
7Day	ZBP1(DAI) mediated induction of type I IFNs	0.64974	0.72402	1	dhx9	3100.35	3100.35	3100.35		3100.35		UP	1	0
7Day	DDX58/IFIH1-mediated induction of interferon-alpha/beta	0.50078	0.75552	1	tax1bp1;uba52	4021.115	4021.115	3280.67	1047.14736	4201.81454	1015.48656	UP	1	0
7Day	RIP-mediated NfκB activation via ZBP1	0.68564	0.69527	1	dhx9	3100.35	3100.35	3100.35		3100.35		UP	1	0
7Day	Cytosolic sensors of pathogen-associated DNA	0.59953	0.63374	1	uba52;dhx9;ctnnb1	2638.81107	3100.35	54.5232	2387.21857	2223.71515	2513.95685	UP	0.666666667	0.333333333
7Day	TAK1 activates NfκB by phosphorylation and activation of IKKs complex	0.55088	0.71775	1	ube2n;uba52	4103.175	4103.175	3444.79	931.096996	3863.51066	867.216021	UP	1	0
7Day	Interleukin-1 signaling	0.50406	0.69073	1	ube2n;uba52;il1rap;bttrc	3136.1085	3825.925	131.024	2074.83709	2895.88682	2054.23699	UP	0.75	0.25
7Day	GPVI-mediated activation cascade	0.59953	0.63374	1	clec1b;ptpn11;cdc42	4148.05667	4218.6	3629.67	486.962396	4208.40007	528.675569	UP	0.666666667	0.333333333
7Day	NOD1/2 Signaling Pathway	0.66608	0.56972	1	ube2n;uba52;casp9	3951.67333	3648.67	3444.79	708.751771	3792.89388	627.63501	UP	0.666666667	0.333333333
7Day	Nucleotide-binding domain, leucine rich repeat containing receptor (NLR) signaling pathways	0.56056	0.64136	1	ube2n;pycard;uba52;casp9	4145.8625	4188.55	3444.79	696.938863	3907.68166	657.882053	CONFLICT	0.5	0.5
7Day	The canonical retinoid cycle in rods (twilight vision)	0.6029	0.67518	1	ttr;rdh16f2	3935.075	3935.075	2168.85	2497.81935	3201.02358	2271.87996	DOWN	0	1
7Day	Activation of NMDA receptors and postsynaptic events	0.57754	0.65355	1	prkar2a;calm3;calm2	4011.14667	4066.56	3050.32	934.353205	3661.3101	940.743026	DOWN	0.333333333	0.666666667
7Day	Deadenylation-dependent mRNA decay	0.56513	0.61774	1	dcp2;wdr61;hbs1;cnot1;eif4a2	3863.62	3491.23	2781.97	1082.84387	3360.85733	718.959455	UP	1	0
7Day	Butyrate Response Factor 1 (BRF1) binds and destabilizes mRNA	0.5468	0.79501	1	dcp2	3491.23	3491.23	3491.23		3491.23		UP	1	0
7Day	Interconversion of nucleotide di- and triphosphates	0.55088	0.71775	1	txnrd1;ak1	4121.665	4121.665	2303.89	2570.72206	4649.3665	2460.01507	UP	1	0
7Day	Digestion of dietary carbohydrate	0.61452	0.75006	1	mgam	132.859	132.859	132.859		132.859		DOWN	0	1
7Day	SUMOylation of chromatin organization proteins	0.55576	0.67258	1	hist1h4h;suz12;bmi1	3845.46	3406.55	3193.23	950.95543	3682.31274	838.77756	UP	0.666666667	0.333333333
7Day	Sema4D in semaphorin signaling	0.58015	0.77365	1	sema4d	5514.77	5514.77	5514.77		5514.77		DOWN	0	1
7Day	TP53 Regulates Transcription of Cell Cycle Genes	0.62166	0.61316	1	cnot1;cdkn1a;ccne2	3399.59667	2818.63	2781.97	1038.17411	3426.27872	1052.18962	UP	1	0
7Day	Apoptosis induced DNA fragmentation	0.68564	0.69527	1	kpnb1	4222.13	4222.13	4222.13		4222.13		UP	1	0
7Day	Activation of DNA fragmentation factor	0.68564	0.69527	1	kpnb1	4222.13	4222.13	4222.13		4222.13		UP	1	0
7Day	Formation of Senescence-Associated Heterochromatin Foci (SAHF)	0.51457	0.81436	1	ep400	3377.47	3377.47	3377.47		3377.47		DOWN	0	1
7Day	Apoptotic execution phase	0.46761	0.72085	1	dsg1c;kpnb1;ctnnb1;dsp	1885.67405	1633.0215	54.5232	2067.00433	1763.10246	1971.21268	DOWN	0.25	0.75
7Day	FCERI mediated MAPK activation	0.57669	0.69709	1	pak2;kras	3348.455	3348.455	2538.2	1145.87361	3692.75181	1037.27805	UP	1	0
7Day	FCERI mediated Ca ²⁺ mobilization	0.4531	0.78885	1	calm3;calm2	3983.44	3983.44	3050.32	1319.63096	3556.9103	1173.69957	CONFLICT	0.5	0.5
7Day	Antigen processing-Cross presentation	0.63779	0.56798	1	tap2;sec22b;h2-t23;h2-q10	3670.8125	3724.57	2584.12	941.890827	3414.68027	934.619277	DOWN	0.25	0.75
7Day	Signaling by EGFR	0.6184	0.58709	1	uba52;ptpn11;kras;cdc42	4286.46	4377.305	3629.67	506.34846	4337.45426	495.668123	UP	1	0
7Day	GRB2 events in EGFR signaling	0.64974	0.72402	1	kras	4158.71	4158.71	4158.71		4158.71		UP	1	0
7Day	GAB1 signalosome	0.51457	0.81436	1	ptpn11	3629.67	3629.67	3629.67		3629.67		UP	1	0
7Day	SHC1 events in EGFR signaling	0.61452	0.75006	1	kras	4158.71	4158.71	4158.71		4158.71		UP	1	0
7Day	EGFR downregulation	0.50078	0.75552	1	uba52;cdc42	4678.73	4678.73	4595.9	117.139309	4668.27085	116.201678	UP	1	0
7Day	Signaling by TGF-beta Receptor Complex	0.51381	0.66427	1	uba52;tgfbr1;tfdp1;prkcz;ccnk	3804.8848	4761.56	707.264	2279.30374	4710.02856	1911.5824	UP	0.8	0.2
7Day	Fibronectin matrix formation	0.55214	1	1										
7Day	MAP2K and MAPK activation	0.47167	0.74095	1	mapk3;pepb1;kras	4436.69333	4351.13	4158.71	329.212695	4476.19461	324.644236	UP	0.666666667	0.333333333
7Day	EPHA-mediated growth cone collapse	0.45381	0.84775	1	yes1	4020.95	4020.95	4020.95		4020.95		UP	1	0

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
7Day	Ion homeostasis	0.44983	0.73508	1	htr2;dmpr;calm3;calm2	3890.9575	3798.475	3050.32	807.324813	3574.7767	786.454883	DOWN	0.25	0.75
7Day	Negative regulation of MET activity	0.48356	0.83188	1	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	Signaling by FGFR	0.51491	0.63831	1	mapk3;polr2h;uba52;ptpn11;ppp2cb;kras;fgf1	3941.36857	3964.6	2647.76	744.707179	3839.81356	761.564281	UP	0.714285714	0.285714286
7Day	FGFR2 ligand binding and activation	0.45381	0.84775	1	fgf1	2647.76	2647.76	2647.76		2647.76		DOWN	0	1
7Day	FGFR1 ligand binding and activation	0.58015	0.77365	1	fgf1	2647.76	2647.76	2647.76		2647.76		DOWN	0	1
7Day	Phospholipase C-mediated cascade: FGFR1	0.5468	0.79501	1	fgf1	2647.76	2647.76	2647.76		2647.76		DOWN	0	1
7Day	Phospholipase C-mediated cascade: FGFR2	0.48356	0.83188	1	fgf1	2647.76	2647.76	2647.76		2647.76		DOWN	0	1
7Day	Downstream signaling of activated FGFR1	0.66608	0.56972	1	ptpn11;kras;fgf1	3478.71333	3629.67	2647.76	766.702949	3262.18888	788.939216	UP	0.666666667	0.333333333
7Day	SHC-mediated cascade:FGFR1	0.68298	0.60175	1	kras;fgf1	3403.235	3403.235	2647.76	1068.40299	3131.99117	997.165244	CONFLICT	0.5	0.5
7Day	PI-3K cascade:FGFR1	0.68298	0.60175	1	ptpn11;fgf1	3138.715	3138.715	2647.76	694.31522	2984.26892	659.064823	CONFLICT	0.5	0.5
7Day	PI-3K cascade:FGFR2	0.62942	0.65201	1	ptpn11;fgf1	3138.715	3138.715	2647.76	694.31522	2984.26892	659.064823	CONFLICT	0.5	0.5
7Day	SHC-mediated cascade:FGFR2	0.62942	0.65201	1	kras;fgf1	3403.235	3403.235	2647.76	1068.40299	3131.99117	997.165244	CONFLICT	0.5	0.5
7Day	mRNA 3'-end processing	0.58246	0.60141	1	flp1l1;cpsf2;srsf1;cstf2;thoc5	3968.36	3485.7	3207.13	1058.77133	3686.98511	697.626174	UP	1	0
7Day	Synthesis of very long-chain fatty acyl-CoAs	0.65616	0.62754	1	elovl5;elovl3	1653.9245	1653.9245	212.399	2038.62491	2396.21501	1747.57007	CONFLICT	0.5	0.5
7Day	p75NTR regulates axonogenesis	0.75842	0.62848	1	lingo1	3247.44	3247.44	3247.44		3247.44		UP	1	0
7Day	Sema4D induced cell migration and growth-cone collapse	0.72196	0.66353	1	sema4d	5514.77	5514.77	5514.77		5514.77		DOWN	0	1
7Day	RHO GTPases activate CIT	0.45292	1	1										
7Day	RHO GTPases activate KTN1	0.72196	0.66353	1	cdc42	4595.9	4595.9	4595.9		4595.9		UP	1	0
7Day	RHO GTPases Activate ROCKs	0.60961	1	1										
7Day	Ovarian tumor domain proteases	0.47661	0.77272	1	uba52;pten	3968.12	3968.12	3174.68	1122.09361	3805.44643	1098.25711	UP	1	0
7Day	Activation of the AP-1 family of transcription factors	0.75842	0.62848	1	mapk3	4800.24	4800.24	4800.24		4800.24		DOWN	0	1
7Day	IL-6-type cytokine receptor ligand interactions	0.42537	0.86213	1	jak1	3554.32	3554.32	3554.32		3554.32		UP	1	0
7Day	Adenylate cyclase inhibitory pathway	0.61452	0.75006	1	gnai3	794.2	794.2	794.2		794.2		UP	1	0
7Day	Inhibition of adenylate cyclase pathway	0.61452	0.75006	1	gnai3	794.2	794.2	794.2		794.2		UP	1	0
7Day	GRB7 events in ERBB2 signaling	0.60961	1	1										
7Day	Inflammasomes	0.58015	0.77365	1	pycard	4728.43	4728.43	4728.43		4728.43		DOWN	0	1
7Day	Kinesins	0.59985	0.58469	1	tubb4b;tubb2a;tuba4a;kif2a;kif1c	2136.1572	1815.66	919.856	1552.81607	2213.42063	1590.85728	UP	0.8	0.2
7Day	SUMO is proteolytically processed	0.55214	1	1										
7Day	Processing and activation of SUMO	0.75842	0.62848	1	uba2	2542.64	2542.64	2542.64		2542.64		UP	1	0
7Day	Tryptophan catabolism	0.72196	0.66353	1	kyat1	4788.28	4788.28	4788.28		4788.28		DOWN	0	1
7Day	Androgen biosynthesis	0.41021	1	1										
7Day	Senescence-Associated Secretory Phenotype (SASP)	0.49512	0.64737	1	hist1h4h;hist1h2bc;hist2h2ac;mapk3;uba52;cdc27;hist2h2aa1;cdkn1a	4081.57875	4028.925	2818.63	864.824131	4038.51343	934.807892	UP	0.625	0.375
7Day	Oncogene Induced Senescence	0.64974	0.72402	1	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	Type I hemidesmosome assembly	0.72196	0.66353	1	dst	2982.34	2982.34	2982.34		2982.34		UP	1	0
7Day	Gap junction trafficking and regulation	0.63779	0.56798	1	tubb4b;tubb2a;tuba4a;gja1	2276.434	1954.85	919.856	1424.18025	1763.60227	985.706882	UP	0.75	0.25
7Day	RUNX1 interacts with co-factors whose precise effect on RUNX1 targets is not known	0.57754	0.65355	1	pcgf5;csnk2b;bmi1	4052.24667	4390.47	2829.67	1093.42799	4167.82963	1022.92134	UP	1	0
7Day	Translesion synthesis by REV1	0.61452	0.75006	1	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	Translesion Synthesis by POLH	0.51457	0.81436	1	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	Polymerase switching on the C-strand of the telomere	0.61452	0.75006	1	prim2	4006.14	4006.14	4006.14		4006.14		UP	1	0
7Day	Translesion synthesis by POLK	0.58015	0.77365	1	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	Translesion synthesis by POLI	0.58015	0.77365	1	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	Gap-filling DNA repair synthesis and ligation in GG-NER	0.42537	0.86213	1	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	Polymerase switching	0.61452	0.75006	1	prim2	4006.14	4006.14	4006.14		4006.14		UP	1	0
7Day	Leading Strand Synthesis	0.61452	0.75006	1	prim2	4006.14	4006.14	4006.14		4006.14		UP	1	0
7Day	Lagging Strand Synthesis	0.42537	0.86213	1	prim2	4006.14	4006.14	4006.14		4006.14		UP	1	0

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
7Day	TP53 regulates transcription of additional cell cycle genes whose exact role in the p53 pathway remain uncertain	0.51457	0.81436	1	cnot1	2781.97	2781.97	2781.97		2781.97		UP	1	0
7Day	Transcriptional activity of SMAD2/SMAD3:SMAD4 heterotrimer	0.51302	0.7083	1	uba52;tfdp1;ccnk	2524.87467	2105.8	707.264	2059.38017	3053.07053	2186.83839	UP	1	0
7Day	Extrinsic Pathway of Fibrin Clot Formation	0.60961	1	1										
7Day	Gamma-carboxylation of protein precursors	0.72196	0.66353	1	f2	156.627	156.627	156.627		156.627		DOWN	0	1
7Day	Transport of gamma-carboxylated protein precursors from the endoplasmic reticulum to the Golgi apparatus	0.72196	0.66353	1	f2	156.627	156.627	156.627		156.627		DOWN	0	1
7Day	Removal of aminoterminal propeptides from gamma-carboxylated proteins	0.68564	0.69527	1	f2	156.627	156.627	156.627		156.627		DOWN	0	1
7Day	Gamma-carboxylation, transport, and amino-terminal cleavage of proteins	0.64974	0.72402	1	f2	156.627	156.627	156.627		156.627		DOWN	0	1
7Day	Zinc transporters	0.68564	0.69527	1	slc39a2	5557.48	5557.48	5557.48		5557.48		UP	1	0
7Day	Miscellaneous substrates	0.57754	0.65355	1	cyp3a25;cyp3a11;cyp3a41b	4490.5	5106.56	2813.51	1469.25114	4069.13875	1571.9222	DOWN	0.333333333	0.666666667
7Day	Synthesis of (16-20)-hydroxyelicosatetraenoic acids (HETE)	0.65616	0.62754	1	cyp2c37;cyp2c29	2987.945	2987.945	2593.25	558.183022	2960.06961	556.789198	CONFLICT	0.5	0.5
7Day	SHC1 events in ERBB4 signaling	0.61452	0.75006	1	kras	4158.71	4158.71	4158.71		4158.71		UP	1	0
7Day	GRB2 events in ERBB2 signaling	0.61452	0.75006	1	kras	4158.71	4158.71	4158.71		4158.71		UP	1	0
7Day	G beta:gamma signalling through CDC42	0.45381	0.84775	1	cdc42	4595.9	4595.9	4595.9		4595.9		UP	1	0
7Day	Purine ribonucleoside monophosphate biosynthesis	0.68564	0.69527	1	atic	3859.67	3859.67	3859.67		3859.67		UP	1	0
7Day	Nucleobase biosynthesis	0.58015	0.77365	1	atic	3859.67	3859.67	3859.67		3859.67		UP	1	0
7Day	HDL assembly	0.50008	1	1										
7Day	HDL clearance	0.60961	1	1										
7Day	HDL remodeling	0.75842	0.62848	1	apoe	113.316	113.316	113.316		113.316		DOWN	0	1
7Day	Deadenylation of mRNA	0.52556	0.73721	1	cnot1;eif4a2	3111.725	3111.725	2781.97	466.343993	3093.7181	465.648175	UP	1	0
7Day	AUF1 (hnRNP D0) binds and destabilizes mRNA	0.75842	0.62848	1	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	Electron transport from NADPH to Ferredoxin	0.7431	1	1										
7Day	Signaling by NOTCH1	0.48356	0.83188	1	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0
7Day	Sulfide oxidation to sulfate	0.67306	1	1										
7Day	Interleukin-12 signaling	0.75842	0.62848	1	jak1	3554.32	3554.32	3554.32		3554.32		UP	1	0
7Day	Synthesis of glycosylphosphatidylinositol (GPI)	0.51457	0.81436	1	pigw	4464.3	4464.3	4464.3		4464.3		UP	1	0
7Day	Acyl chain remodelling of PG	0.5468	0.79501	1	cris1	4148.47	4148.47	4148.47		4148.47		UP	1	0
7Day	Interleukin-2 signaling	0.68564	0.69527	1	jak1	3554.32	3554.32	3554.32		3554.32		UP	1	0
7Day	Nucleobase catabolism	0.55576	0.67258	1	dpys;nudt5;entpd5	1032.25	821.082	395.538	764.491527	1229.95011	711.717804	UP	0.666666667	0.333333333
7Day	Ethanol oxidation	0.68564	0.69527	1	aldh2	303.779	303.779	303.779		303.779		DOWN	0	1
7Day	Trafficking of GluR2-containing AMPA receptors	0.64974	0.72402	1	gria3	3853.21	3853.21	3853.21		3853.21		UP	1	0
7Day	Recycling pathway of L1	0.59953	0.63374	1	tubb4b;tubb2a;tuba4a	1609.852	1815.66	919.856	613.550908	1582.39232	663.092821	UP	1	0
7Day	TNFR1-induced NFkappaB signaling pathway	0.50078	0.75552	1	uba52;xiap	4817.795	4817.795	4761.56	79.5282997	4830.99188	77.3074074	CONFLICT	0.5	0.5
7Day	Synthesis of pyrophosphates in the cytosol	0.75842	0.62848	1	itpk1	3597.94	3597.94	3597.94		3597.94		DOWN	0	1
7Day	Adrenoceptors	0.41021	1	1										
7Day	Alternative complement activation	0.67306	1	1										
7Day	Post-transcriptional silencing by small RNAs	0.50008	1	1										
7Day	MET activates STAT3	0.7431	1	1										
7Day	Na+/Cl- dependent neurotransmitter transporters	0.42537	0.86213	1	slc22a1	4237.04	4237.04	4237.04		4237.04		DOWN	0	1

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.																
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down		
7Day	Apoptotic cleavage of cellular proteins	0.49215	0.725	1	dsg1c;ctnnb1;dsp	1106.8554	240.593	54.5232	1664.15427	1209.2455	1689.05741	DOWN	0	1		
7Day	Golgi Associated Vesicle Biogenesis	0.44983	0.73508	1	picalm;igf2r;ftl1;ap3b1	2855.5565	3390.82	720.546	1446.1338	2750.71883	1359.65521	UP	0.75	0.25		
7Day	Downregulation of SMAD2/3-SMAD4 transcriptional activity	0.42537	0.86213	1	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0		
7Day	Transcriptional regulation by RUNX3	0.55576	0.67258	1	uba52;kras;ctnnb1	2991.59773	4158.71	54.5232	2561.37895	2455.7853	2724.14338	UP	0.666666667	0.333333333		
7Day	Mitochondrial biogenesis	0.65616	0.62754	1	idh2;atp5j	3837.36	3837.36	2704.94	1601.48372	4362.13372	1419.14594	CONFLICT	0.5	0		
7Day	Formation of ATP by chemiosmotic coupling	0.61452	0.75006	1	atp5j	4969.78	4969.78	4969.78		4969.78		UP	1	0		
7Day	Cristae formation	0.61452	0.75006	1	atp5j	4969.78	4969.78	4969.78		4969.78		UP	1	0		
7Day	Regulation of KIT signaling	0.61452	0.75006	1	yes1	4020.95	4020.95	4020.95		4020.95		UP	1	0		
7Day	Caspase activation via extrinsic apoptotic signalling pathway	0.45381	0.84775	1	cas9	3648.67	3648.67	3648.67		3648.67		DOWN	0	1		
7Day	IKK complex recruitment mediated by RIP1	0.68298	0.60175	1	ube2n;uba52	4103.175	4103.175	3444.79	931.096996	3863.51066	867.216021	UP	1	0		
7Day	TRAF6-mediated induction of TAK1 complex within TLR4 complex	0.61452	0.75006	1	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0		
7Day	IRAK2 mediated activation of TAK1 complex upon TLR7/8 or 9 stimulation	0.64974	0.72402	1	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0		
7Day	ChREBP activates metabolic gene expression	0.50008	1	1												
7Day	Inhibition of the proteolytic activity of APC/C required for the onset of anaphase by mitotic spindle checkpoint components	0.42537	0.86213	1	cdc27	3870.58	3870.58	3870.58		3870.58		UP	1	0		
7Day	Inactivation of APC/C via direct inhibition of the APC/C complex	0.42537	0.86213	1	cdc27	3870.58	3870.58	3870.58		3870.58		UP	1	0		
7Day	APC/C:Cdc20 mediated degradation of Cyclin B	0.68298	0.60175	1	uba52;cdc27	4316.07	4316.07	3870.58	630.018	4393.04009	620.543222	UP	1	0		
7Day	APC/C-mediated degradation of cell cycle proteins	0.51491	0.63831	1	psmd5;psmd6;psmc4;uba52;cdc27;psmc2;btrc	3583.53714	3870.58	2309.23	863.11457	3583.52534	923.347336	UP	1	0		
7Day	APC/C:Cdh1 mediated degradation of Cdc20 and other APC/C:Cdh1 targeted proteins in late mitosis/early G1	0.57669	0.69709	1	uba52;cdc27	4316.07	4316.07	3870.58	630.018	4393.04009	620.543222	UP	1	0		
7Day	Cdc20:Phospho-APC/C mediated degradation of Cyclin A	0.57669	0.69709	1	uba52;cdc27	4316.07	4316.07	3870.58	630.018	4393.04009	620.543222	UP	1	0		
7Day	Conversion from APC/C:Cdc20 to APC/C:Cdh1 in late anaphase	0.45381	0.84775	1	cdc27	3870.58	3870.58	3870.58		3870.58		UP	1	0		
7Day	Regulation of APC/C activators between G1/S and early anaphase	0.64386	0.59181	1	uba52;cdc27;btrc	4279.73333	4207.06	3870.58	449.91377	4311.88815	418.982594	UP	1	0		
7Day	APC/C:Cdc20 mediated degradation of mitotic proteins	0.50078	0.75552	1	uba52;cdc27	4316.07	4316.07	3870.58	630.018	4393.04009	620.543222	UP	1	0		
7Day	Phosphorylation of the APC/C	0.5468	0.79501	1	cdc27	3870.58	3870.58	3870.58		3870.58		UP	1	0		
7Day	Activation of APC/C and APC/C:Cdc20 mediated degradation of mitotic proteins	0.50078	0.75552	1	uba52;cdc27	4316.07	4316.07	3870.58	630.018	4393.04009	620.543222	UP	1	0		
7Day	APC-Cdc20 mediated degradation of Nek2A	0.62942	0.65201	1	uba52;cdc27	4316.07	4316.07	3870.58	630.018	4393.04009	620.543222	UP	1	0		
7Day	APC-Cdc20 mediated degradation of cell cycle proteins prior to satisfaction of the cell cycle checkpoint	0.55088	0.71775	1	uba52;cdc27	4316.07	4316.07	3870.58	630.018	4393.04009	620.543222	UP	1	0		
7Day	Regulation of mitotic cell cycle	0.51491	0.63831	1	psmd5;psmd6;psmc4;uba52;cdc27;psmc2;btrc	3583.53714	3870.58	2309.23	863.11457	3583.52534	923.347336	UP	1	0		
7Day	Dissolution of Fibrin Clot	0.51457	0.81436	1	serpinb8	2712.82	2712.82	2712.82		2712.82		DOWN	0	1		
7Day	Phenylalanine and tyrosine catabolism	0.68564	0.69527	1	kyat1	4788.28	4788.28	4788.28		4788.28		DOWN	0	1		
7Day	Gap junction degradation	0.72196	0.66353	1	gja1	4276.18	4276.18	4276.18		4276.18		DOWN	0	1		
7Day	Formation of annular gap junctions	0.75842	0.62848	1	gja1	4276.18	4276.18	4276.18		4276.18		DOWN	0	1		
7Day	RNA Polymerase I Promoter Escape	0.47661	0.77272	1	polr2h;ubtf	2970.455	2970.455	1976.31	1405.93334	3441.15761	1238.35644	UP	1	0		
7Day	RNA Polymerase I Transcription Termination	0.4531	0.78885	1	polr2h;ubtf	2970.455	2970.455	1976.31	1405.93334	3441.15761	1238.35644	UP	1	0		
7Day	Pyruvate metabolism	0.50078	0.75552	1	pdhx;dld	4987.44	4987.44	4831.25	220.880616	4979.91771	220.629696	CONFLICT	0.5	0.5		
7Day	Hyaluronan uptake and degradation	0.50008	1	1												

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.																
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down		
7Day	A tetrasaccharide linker sequence is required for GAG synthesis	0.55088	0.71775	1	sdcbgn	3385.82	3385.82	2968.59	590.052325	3628.87151	479.597402	DOWN	0	1		
7Day	Serine biosynthesis	0.41021	1	1												
7Day	Regulation of innate immune responses to cytosolic DNA	0.58015	0.77365	1	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0		
7Day	The NLRP3 inflammasome	0.75842	0.62848	1	pycard	4728.43	4728.43	4728.43		4728.43		DOWN	0			
7Day	Deposition of new CENPA-containing nucleosomes at the centromere	0.48356	0.83188	1	cenpk	3911.13	3911.13	3911.13		3911.13		UP	1	0		
7Day	Nucleosome assembly	0.48356	0.83188	1	cenpk	3911.13	3911.13	3911.13		3911.13		UP	1	0		
7Day	Triglyceride biosynthesis	0.68564	0.69527	1	dgat2	623.511	623.511	623.511		623.511		DOWN	0	1		
7Day	Miscellaneous transport and binding events	0.62942	0.65201	1	nipa2;azgp1	1792.7206	1792.7206	73.2912	2431.64038	2195.51779	2363.97626	CONFLICT	0.5	0.5		
7Day	Establishment of Sister Chromatid Cohesion	0.72196	0.66353	1	pds5a	3647.06	3647.06	3647.06		3647.06		UP	1	0		
7Day	CDT1 association with the CDC6/ORC/origin complex	0.56513	0.61774	1	psmd5;psmd6;psmc4;uba52;psmc2	3401.424	3326.45	2309.23	978.876936	3327.35463	1056.01708	UP	1	0		
7Day	DCC mediated attractive signaling	0.72196	0.66353	1	cdc42	4595.9	4595.9	4595.9		4595.9		UP	1	0		
7Day	Asymmetric localization of PCP proteins	0.58015	0.77365	1	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0		
7Day	mRNA decay by 5' to 3' exoribonuclease	0.64974	0.72402	1	dcp2	3491.23	3491.23	3491.23		3491.23		UP	1	0		
7Day	FCGR activation	0.61452	0.75006	1	yes1	4020.95	4020.95	4020.95		4020.95		UP	1	0		
7Day	CD22 mediated BCR regulation	0.55214	1	1												
7Day	Interleukin-23 signaling	0.45292	1	1												
7Day	Mitochondrial Fatty Acid Beta-Oxidation	0.49215	0.725	1	hadha;pccb;acaa2	144.187867	157.61	77.8976	60.7025232	152.608919	42.1833052	DOWN	0	1		
7Day	Purine catabolism	0.45381	0.84775	1	nudt5	1880.13	1880.13	1880.13		1880.13		UP	1	0		
7Day	Signaling by Retinoic Acid	0.59985	0.58469	1	akr1c6;pdhx;rdh16f2;dld;akr1c14	3980.56	4831.25	2168.85	1371.92456	3373.89278	1403.06273	UP	0.6	0.4		
7Day	RA biosynthesis pathway	0.62166	0.61316	1	akr1c6;rdh16f2;akr1c14	3309.30667	2842.81	2168.85	1431.87981	2672.74701	975.286841	UP	0.666666667	0.333333333		
7Day	Signaling by NOTCH3	0.45381	0.84775	1	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0		
7Day	NF-kB is activated and signals survival	0.72196	0.66353	1	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0		
7Day	MicroRNA (miRNA) biogenesis	0.50008	1	1												
7Day	Small interfering RNA (siRNA) biogenesis	0.41021	1	1												
7Day	Interleukin-37 signaling	0.82042	1	1												
7Day	Cohesin Loading onto Chromatin	0.75842	0.62848	1	pds5a	3647.06	3647.06	3647.06		3647.06		UP	1	0		
7Day	Mitotic Telophase/Cytokinesis	0.61452	0.75006	1	pds5a	3647.06	3647.06	3647.06		3647.06		UP	1	0		
7Day	Dermatan sulfate biosynthesis	0.72196	0.66353	1	bgn	2968.59	2968.59	2968.59		2968.59		DOWN	0	1		
7Day	Smooth Muscle Contraction	0.66608	0.56972	1	pak2;calm3;calm2	3501.69333	3050.32	2538.2	1251.77973	3460.1468	1033.85516	UP	0.666666667	0.333333333		
7Day	CD209 (DC-SIGN) signaling	0.65616	0.62754	1	pak2;kras	3348.455	3348.455	2538.2	1145.87361	3692.75181	1037.27805	UP	1			
7Day	Beta oxidation of lauroyl-CoA to decanoyl-CoA-CoA	0.7431	1	1												
7Day	Prolonged ERK activation events	0.75842	0.62848	1	mapk3	4800.24	4800.24	4800.24		4800.24		DOWN	0	1		
7Day	Signalling to ERKs	0.62942	0.65201	1	mapk3;kras	4479.475	4479.475	4158.71	453.630213	4552.01512	441.878074	CONFLICT	0.5	0.5		
7Day	VxPx cargo-targeting to cilium	0.42537	0.86213	1	rab11a	4542.35	4542.35	4542.35		4542.35		UP	1	0		
7Day	Rap1 signalling	0.61452	0.75006	1	ywhaz	2726.98	2726.98	2726.98		2726.98		UP	1	0		
7Day	Synthesis of dolichyl-phosphate-glucose	0.82042	1	1												
7Day	NOTCH3 Activation and Transmission of Signal to the Nucleus	0.45381	0.84775	1	uba52	4761.56	4761.56	4761.56		4761.56		UP	1	0		
7Day	CRMPs in Sema3A signaling	0.5468	0.79501	1	gsk3b	4499.44	4499.44	4499.44		4499.44		UP	1	0		
7Day	SUMOylation of SUMOylation proteins	0.55214	1	1												
7Day	Signalling to RAS	0.64974	0.72402	1	kras	4158.71	4158.71	4158.71		4158.71		UP	1	0		
7Day	Nuclear Pore Complex (NPC) Disassembly	0.64386	0.59181	1	gm49336;nek6;tptr	2646.08933	2535	770.098	1933.93044	2710.863	1721.80663	UP	1	0		
7Day	SUMOylation of DNA replication proteins	0.45162	0.75615	1	gm49336;top2b;tptr	3332.64	2829.75	2535	1135.89309	3116.87225	994.282581	UP	1	0		
7Day	Breakdown of the nuclear lamina	0.7431	1	1												
7Day	Release of Hh-Np from the secreting cell	0.55214	1	1												

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
7Day	PDE3B signalling	0.90577	1	1										
7Day	Signaling by Leptin	0.82042	1	1										
7Day	PKA-mediated phosphorylation of key metabolic factors	0.90577	1	1										
28Day	CDO in myogenesis	0.48011	0.83141	1	cdc42	2463.49	2463.49	2463.49		2463.49		UP	1	0
28Day	Myogenesis	0.48011	0.83141	1	cdc42	2463.49	2463.49	2463.49		2463.49		UP	1	0
28Day	Activation of BH3-only proteins	0.62145	0.74142	1	dynll1	5791.54	5791.54	5791.54		5791.54		UP	1	0
28Day	Costimulation by the CD28 family	0.57711	0.6238	1	pdpk1,h2-ab1,h2-aa;cdc42	2394.6895	2854.61	192.988	1551.3069	2791.05227	959.057983	DOWN	0.25	0.75
28Day	CD28 co-stimulation	0.66015	0.62015	1	pdpk1;cdc42	1328.239	1328.239	192.988	1605.48736	2052.23855	1236.62402	CONFLICT	0.5	0.5
28Day	CD28 dependent PI3K/Akt signaling	0.5482	0.7912	1	pdpk1	192.988	192.988	192.988		192.988		DOWN	0	1
28Day	Downregulation of ERBB2 signaling	0.50218	0.81895	1	hbegf	919.738	919.738	919.738		919.738		UP	1	0
28Day	Sphingolipid de novo biosynthesis	0.59484	0.63522	1	ormdl2;ormdl3;aldh3a2	3690.26	3444.81	2456.59	1372.94999	3564.34119	1439.47386	UP	0.666666667	0.333333333
28Day	Formation of a pool of free 40S subunits	0.45872	0.78282	1	eif3m;eif1ax	2737.81	2737.81	1517.45	1725.84966	2423.68091	1667.69388	CONFLICT	0.5	0.5
28Day	Lysosome Vesicle Biogenesis	0.62174	0.65548	1	hgs;app	3925.595	3925.595	3220.72	996.843785	3872.79325	994.042998	CONFLICT	0.5	0.5
28Day	N-glycan antennae elongation in the medial/trans-Golgi	0.48011	0.83141	1	mgat2	3478.56	3478.56	3478.56		3478.56		UP	1	0
28Day	MHC class II antigen presentation	0.5482	0.59626	1	dynll1;tubb4b;tubb2a;cd74;h2-ab1;h2-aa;ctss;capza2	4356.4125	4556.49	2359.45	1451.31924	4308.08647	1498.46386	DOWN	0.375	0.625
28Day	Eicosanoid ligand-binding receptors	0.7508	0.63077	1	cysltr1	4610.42	4610.42	4610.42		4610.42		UP	1	0
28Day	Formation of the beta-catenin:TCF transactivating complex	0.4587	0.84301	1	pygo2	3936.43	3936.43	3936.43		3936.43		DOWN	0	1
28Day	Nuclear Events (kinase and transcription factor activation)	0.5482	0.7912	1	mapkapk2	5375	5375	5375		5375		DOWN	0	1
28Day	ERKs are inactivated	0.39648	1	1										
28Day	Interleukin-17 signaling	0.51707	0.70261	1	map2k4;mapkapk2;ikbk	4469.72667	5375	2616.5	1605.08324	4378.98863	1647.6138	UP	0.666666667	0.333333333
28Day	MAPK targets/ Nuclear events mediated by MAP kinases	0.41791	0.86388	1	mapkapk2	5375	5375	5375		5375		DOWN	0	1
28Day	MAP kinase activation	0.62665	0.60545	1	map2k4;mapkapk2;ikbk	4469.72667	5375	2616.5	1605.08324	4378.98863	1647.6138	UP	0.666666667	0.333333333
28Day	DNA Double-Strand Break Repair	0.53551	0.59406	1	ube2n;mi1;ube2v2;pole3;hist1h4i;rad51d;rad51;lig3;brca1;blm	3816.8064	3892.075	692.086	1865.9087	4049.79857	1462.97446	UP	0.7	0.3
28Day	Recruitment and ATM-mediated phosphorylation of repair and signaling proteins at DNA double strand breaks	0.56331	0.63648	1	ube2n;ube2v2;hist1h4i;brca1	5011.745	5455.01	3288.55	1173.78176	4729.48604	1369.44158	CONFLICT	0.5	0.5
28Day	DNA Double Strand Break Response	0.54959	0.64888	1	ube2n;ube2v2;hist1h4i;brca1	5011.745	5455.01	3288.55	1173.78176	4729.48604	1369.44158	CONFLICT	0.5	0.5
28Day	G2/M DNA damage checkpoint	0.60486	0.5976	1	ube2n;ube2v2;hist1h4i;brca1	5011.745	5455.01	3288.55	1173.78176	4729.48604	1369.44158	CONFLICT	0.5	0.5
28Day	RHO GTPases Activate WASPs and WAVES	0.56515	0.70349	1	cdc42;brk1	3960.63	3960.63	2463.49	2117.27569	4417.2828	2016.38111	CONFLICT	0.5	0.5
28Day	RUNX1 regulates transcription of genes involved in differentiation of HSCs	0.59653	0.75921	1	tal1	1424.03	1424.03	1424.03		1424.03		DOWN	0	1
28Day	Mitochondrial calcium ion transport	0.6725	0.70182	1	micu2	5256.23	5256.23	5256.23		5256.23		DOWN	0	1
28Day	Processing of SMDT1	0.69847	0.6798	1	micu2	5256.23	5256.23	5256.23		5256.23		DOWN	0	1
28Day	Trafficking and processing of endosomal TLR	0.52488	0.80557	1	ctss	5780.39	5780.39	5780.39		5780.39		DOWN	0	1
28Day	Complex I biogenesis	0.56334	0.66338	1	ndufab1;ndufaf1;ndufc2	2854.76	1721.17	1023.12	2591.57484	2475.6788	2540.36649	DOWN	0.333333333	0.666666667
28Day	COPI-mediated anterograde transport	0.49757	0.66308	1	dynll1;tubb4b;tubb2a;capza2;bet1;gbf	3921.455	3519.135	2359.45	1406.29296	3960.61037	1431.19614	UP	0.833333333	0.166666667
28Day	Global Genome Nucleotide Excision Repair (GG-NER)	0.53932	0.63939	1	ube2n;usp45;ube2v2;pole3;ino80c	3333.7876	3288.55	805.318	2055.39985	3663.82139	1926.19448	DOWN	0.4	0.6
28Day	G beta:gamma signalling through PLC beta	0.62145	0.74142	1	gnb5	953.648	953.648	953.648		953.648		UP	1	0
28Day	Presynaptic function of Kainate receptors	0.59653	0.75921	1	gnb5	953.648	953.648	953.648		953.648		UP	1	0
28Day	Synthesis of PC	0.50218	0.81895	1	phospho1	4698.14	4698.14	4698.14		4698.14		DOWN	0	1
28Day	Hedgehog 'off' state	0.44366	0.76008	1	tubb4b;tubb2a;adc9	3161.03	2903.04	2359.45	957.020878	2870.18918	656.933577	UP	0.666666667	0.333333333
28Day	Elastic fibre formation	0.47567	0.77104	1	vtn;fn1	1801.881	1801.881	447.762	1915.01345	2418.97549	1704.60122	DOWN	0	1
28Day	Molecules associated with elastic fibres	0.51059	0.74579	1	vtn;fn1	1801.881	1801.881	447.762	1915.01345	2418.97549	1704.60122	DOWN	0	1
28Day	Surfactant metabolism	0.50218	0.81895	1	abca3	2494.49	2494.49	2494.49		2494.49		DOWN	0	1

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
28Day	Regulation of HSF1-mediated heat shock response	0.56331	0.63648	1	hikeshi;gm45902;mapkapk2;tptr	4640.02	4764.775	3638.67	883.900811	4474.97086	799.34375	CONFLICT	0.5	0.5
28Day	N-glycan trimming in the ER and Calnexin/Calreticulin cycle	0.5482	0.7912	1	ngly1	5615.31	5615.31	5615.31		5615.31		DOWN	0	1
28Day	ER Quality Control Compartment (ERQC)	0.42575	1	1										
28Day	GPVI-mediated activation cascade	0.58383	0.68814	1	pdpk1;cdc42	1328.239	1328.239	192.988	1605.48736	2052.23855	1236.62402	CONFLICT	0.5	0.5
28Day	Netrin-1 signaling	0.4587	0.84301	1	cdc42	2463.49	2463.49	2463.49		2463.49		UP	1	0
28Day	Protein-protein interactions at synapses	0.50901	0.68439	1	gria3;ptprd;il1rap;epb4113	3795.0225	3615.755	2052.57	1584.36894	3120.2557	1402.73545	DOWN	0.25	0.75
28Day	The canonical retinoid cycle in rods (twilight vision)	0.50218	0.81895	1	rdh16f2	2673.93	2673.93	2673.93		2673.93		DOWN	0	1
28Day	ROS, RNS production in phagocytes	0.66015	0.62015	1	atp6v0e2;atp6v1e1	3839.965	3839.965	2385.58	2056.81099	2967.18762	1645.29352	CONFLICT	0.5	0.5
28Day	TBC/RABGAPs	0.60271	0.67214	1	rab11a;tbc1d10a	3249.27	3249.27	2192.92	1493.9045	2704.58757	1279.99717	CONFLICT	0.5	0.5
28Day	RAB geranylgeranylation	0.59096	0.61083	1	rab9;rab11a;rab29;rab18	3519.6475	3352.36	2192.92	1288.89752	3601.15039	1504.38651	CONFLICT	0.5	0.5
28Day	Butyrate Response Factor 1 (BRF1) binds and destabilizes mRNA	0.69847	0.6798	1	exosc3	2805.79	2805.79	2805.79		2805.79		UP	1	0
28Day	Regulation of mRNA stability by proteins that bind AU-rich elements	0.5285	0.7323	1	exosc3;set	3433.275	3433.275	2805.79	887.397797	3679.80909	816.037216	UP	1	0
28Day	KSRP (KHSRP) binds and destabilizes mRNA	0.7508	0.63077	1	exosc3	2805.79	2805.79	2805.79		2805.79		UP	1	0
28Day	Major pathway of rRNA processing in the nucleolus and cytosol	0.48288	0.66555	1	las1l;exosc3;pno1;wdr18;dhx37;fbl;bop1	3014.84343	3919.15	185.964	1717.0495	3391.14106	1585.91685	CONFLICT	0.571428571	0.428571429
28Day	rRNA processing	0.48288	0.66555	1	las1l;exosc3;pno1;wdr18;dhx37;fbl;bop1	3014.84343	3919.15	185.964	1717.0495	3391.14106	1585.91685	CONFLICT	0.571428571	0.428571429
28Day	rRNA processing in the nucleus and cytosol	0.48288	0.66555	1	las1l;exosc3;pno1;wdr18;dhx37;fbl;bop1	3014.84343	3919.15	185.964	1717.0495	3391.14106	1585.91685	CONFLICT	0.571428571	0.428571429
28Day	Nucleotide-like (purinergic) receptors	0.69847	0.6798	1	adora1	907.506	907.506	907.506		907.506		UP	1	0
28Day	ADP signalling through P2Y purinoceptor 1	0.50218	0.81895	1	gnb5	953.648	953.648	953.648		953.648		UP	1	0
28Day	Signaling by Activin	0.39648	1	1										
28Day	Antagonism of Activin by Follistatin	0.75238	1	1										
28Day	SUMOylation of chromatin organization proteins	0.5467	0.7182	1	hist1h4i;bmi1	4883.435	4883.435	3918.46	1364.68073	5169.0195	1303.54765	CONFLICT	0.5	0.5
28Day	Recycling of bile acids and salts	0.62145	0.74142	1	slc10a1	2878.3	2878.3	2878.3		2878.3		DOWN	0	1
28Day	TNFR2 non-canonical NF-kB pathway	0.51707	0.70261	1	ube2m;tnfrsf1b;birc2	3321.17667	2933.96	1167.32	2371.29595	2952.86511	2468.02167	UP	0.666666667	0.333333333
28Day	TNF receptor superfamily (TNFSF) members mediating non-canonical NF-kB pathway	0.6725	0.70182	1	birc2	5862.25	5862.25	5862.25		5862.25		UP	1	0
28Day	TP53 Regulates Transcription of Cell Cycle Genes	0.60271	0.67214	1	e2f7;cnot1	3791.975	3791.975	3132.16	933.119322	3822.04232	932.149978	UP	1	0
28Day	Histidine catabolism	0.56601	1	1										
28Day	Fc epsilon receptor (FCER1) signaling	0.57652	0.60482	1	ube2n;map2k4;ppp3cb;pdpk1;ikbkg	3517.9496	4095.87	192.988	2171.92953	3919.16084	1585.36842	UP	0.6	0.4
28Day	FCER1 mediated MAPK activation	0.48011	0.83141	1	map2k4	2616.5	2616.5	2616.5		2616.5		UP	1	0
28Day	Sialic acid metabolism	0.6409	0.63815	1	nanp;gne	4701.73	4701.73	3647.63	1490.72252	4718.87066	1490.52542	DOWN	0	1
28Day	Transport of vitamins, nucleosides, and related molecules	0.44212	0.79406	1	slc35d2;slco2b1	3128.045	3128.045	2439.34	973.975951	3030.48208	964.153571	CONFLICT	0.5	0.5
28Day	SHC1 events in ERBB2 signaling	0.6725	0.70182	1	hbegf	919.738	919.738	919.738		919.738		UP	1	0
28Day	Multifunctional anion exchangers	0.56601	1	1										
28Day	Nuclear Receptor transcription pathway	0.53234	0.68993	1	nr1d2;rorc;nrbp1	4105.93333	3736.79	3688.98	681.199256	3809.92148	421.24327	UP	0.666666667	0.333333333
28Day	Signaling by EGFR	0.65859	0.57412	1	hgs;hbegf;cdc42	2201.316	2463.49	919.738	1172.68109	2028.69886	1124.36761	UP	1	0
28Day	GAB1 signalosome	0.6725	0.70182	1	hbegf	919.738	919.738	919.738		919.738		UP	1	0
28Day	SHC1 events in EGFR signaling	0.7508	0.63077	1	hbegf	919.738	919.738	919.738		919.738		UP	1	0
28Day	RNA polymerase II transcribes snRNA genes	0.60153	0.58077	1	ints14;ell3;rpap2;polr2a;ccnk	4003.346	3559.08	2852.38	1007.63001	3883.3938	943.742673	UP	0.6	0.4
28Day	TGF-beta receptor signaling activates SMADs	0.59653	0.75921	1	ube2m	2933.96	2933.96	2933.96		2933.96		UP	1	0
28Day	Non-integrin membrane-ECM interactions	0.51059	0.74579	1	vtn;fn1	1801.881	1801.881	447.762	1915.01345	2418.97549	1704.60122	DOWN	0	1

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.														
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
28Day	GRB2:SOS provides linkage to MAPK signaling for Integrins	0.7508	0.63077	1	fn1	3156	3156	3156		3156		DOWN	0	1
28Day	p130Cas linkage to MAPK signaling for integrins	0.7508	0.63077	1	fn1	3156	3156	3156		3156		DOWN	0	1
28Day	EPHA-mediated growth cone collapse	0.62145	0.74142	1	epha7	5831.01	5831.01	5831.01		5831.01		UP	1	0
28Day	Branched-chain amino acid catabolism	0.52488	0.80557	1	aldh6a1	2600.38	2600.38	2600.38		2600.38		DOWN	0	1
28Day	Peptide hormone biosynthesis	0.45717	1	1										
28Day	Negative regulation of MET activity	0.6468	0.72232	1	hgs	3220.72	3220.72	3220.72		3220.72		UP	1	0
28Day	FGFR2 ligand binding and activation	0.62145	0.74142	1	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1
28Day	FGFR1 ligand binding and activation	0.72461	0.65616	1	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1
28Day	Phospholipase C-mediated cascade: FGFR1	0.69847	0.6798	1	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1
28Day	Phospholipase C-mediated cascade: FGFR2	0.6468	0.72232	1	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1
28Day	SHC-mediated cascade:FGFR1	0.57209	0.77577	1	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1
28Day	PI-3K cascade:FGFR1	0.57209	0.77577	1	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1
28Day	FRS-mediated FGFR1 signaling	0.52488	0.80557	1	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1
28Day	PI-3K cascade:FGFR2	0.52488	0.80557	1	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1
28Day	SHC-mediated cascade:FGFR2	0.52488	0.80557	1	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1
28Day	FRS-mediated FGFR2 signaling	0.48011	0.83141	1	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1
28Day	FGFR1 modulation of FGFR1 signaling	0.39648	1	1										
28Day	Transport of Mature mRNA derived from an Intron-Containing Transcript	0.58901	0.59289	1	u2af2;srsf1;tptr;thoc5;bc005561	4059.426	3638.67	3469.84	668.012629	4008.58851	597.208978	UP	0.8	0.2
28Day	Transport of Mature Transcript to Cytoplasm	0.58901	0.59289	1	u2af2;srsf1;tptr;thoc5;bc005561	4059.426	3638.67	3469.84	668.012629	4008.58851	597.208978	UP	0.8	0.2
28Day	ERBB2 Regulates Cell Motility	0.72461	0.65616	1	hbegf	919.738	919.738	919.738		919.738		UP	1	0
28Day	SUMOylation of DNA damage response and repair proteins	0.54959	0.64888	1	rad21;brca1;blm;tptr	3527.834	3887.97	692.086	2073.67647	4059.64798	1691.6082	UP	1	0
28Day	Downstream signaling events of B Cell Receptor (BCR)	0.60271	0.67214	1	ppp3cb;ikbkkg	4756.775	4756.775	4095.87	934.660814	4545.37184	885.555333	UP	1	0
28Day	Activation of NF-kappaB in B cells	0.62145	0.74142	1	ikbkkg	5417.68	5417.68	5417.68		5417.68		UP	1	0
28Day	Nuclear Envelope Breakdown	0.62665	0.60545	1	nek6;cnep1r1;tptr	4227.96333	3638.67	3203.61	1414.28815	3739.88139	1152.28749	UP	1	0
28Day	Interleukin-12 family signaling	0.59653	0.75921	1	p4hb	5730.92	5730.92	5730.92		5730.92		DOWN	0	1
28Day	Interleukin-6 family signaling	0.43797	0.85382	1	lifr	727.581	727.581	727.581		727.581		DOWN	0	1
28Day	IL-6-type cytokine receptor ligand interactions	0.59653	0.75921	1	lifr	727.581	727.581	727.581		727.581		DOWN	0	1
28Day	Interleukin-35 Signalling	0.42575	1	1										
28Day	Interleukin-27 signaling	0.45717	1	1										
28Day	Adenylate cyclase inhibitory pathway	0.7508	0.63077	1	adcy9	4220.6	4220.6	4220.6		4220.6		DOWN	0	1
28Day	G-protein activation	0.43797	0.85382	1	gnb5	953.648	953.648	953.648		953.648		UP	1	0
28Day	Chaperonin-mediated protein folding	0.5285	0.7323	1	gnb5;cct4	3395.259	3395.259	953.648	3452.95939	3138.05293	3433.74702	UP	1	0
28Day	Protein folding	0.5285	0.7323	1	gnb5;cct4	3395.259	3395.259	953.648	3452.95939	3138.05293	3433.74702	UP	1	0
28Day	ADP signalling through P2Y purinoceptor 12	0.57209	0.77577	1	gnb5	953.648	953.648	953.648		953.648		UP	1	0
28Day	Cooperation of PDCL (PhLP1) and TRiC/CCT in G-protein beta folding	0.5467	0.7182	1	gnb5;cct4	3395.259	3395.259	953.648	3452.95939	3138.05293	3433.74702	UP	1	0
28Day	Inhibition of adenylate cyclase pathway	0.7508	0.63077	1	adcy9	4220.6	4220.6	4220.6		4220.6		DOWN	0	1
28Day	PI3K events in ERBB2 signaling	0.69847	0.6798	1	hbegf	919.738	919.738	919.738		919.738		UP	1	0
28Day	Inflammasomes	0.72461	0.65616	1	bcl2l1	2151.36	2151.36	2151.36		2151.36		UP	1	0
28Day	SUMO is proteolytically processed	0.65259	1	1										
28Day	Processing and activation of SUMO	0.4909	1	1										
28Day	Aquaporin-mediated transport	0.57904	0.6495	1	rab11a;gnb5;adcy9	2455.72267	2192.92	953.648	1649.25522	1742.1359	1240.36097	UP	0.666666667	0.333333333
28Day	Endogenous sterols	0.4587	0.84301	1	fdxr	5126.12	5126.12	5126.12		5126.12		DOWN	0	1
28Day	Gap junction trafficking and regulation	0.44212	0.79406	1	tubb4b;tubb2a	2631.245	2631.245	2359.45	384.376175	2702.45657	370.948608	UP	1	0
28Day	Gap junction trafficking	0.47567	0.77104	1	tubb4b;tubb2a	2631.245	2631.245	2359.45	384.376175	2702.45657	370.948608	UP	1	0
28Day	Gap junction assembly	0.66015	0.62015	1	tubb4b;tubb2a	2631.245	2631.245	2359.45	384.376175	2702.45657	370.948608	UP	1	0
28Day	Metabolism of cofactors	0.69847	0.6798	1	coq3	1252.61	1252.61	1252.61		1252.61		DOWN	0	1

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
28Day	Telomere Maintenance	0.50218	0.81895	1	pole3	805.318	805.318	805.318		805.318		UP	1	0	
28Day	Telomere C-strand (Lagging Strand) Synthesis	0.5482	0.7912	1	pole3	805.318	805.318	805.318		805.318		UP	1	0	
28Day	Extension of Telomeres	0.50218	0.81895	1	pole3	805.318	805.318	805.318		805.318		UP	1	0	
28Day	Gap-filling DNA repair synthesis and ligation in GG-NER	0.59653	0.75921	1	pole3	805.318	805.318	805.318		805.318		UP	1	0	
28Day	Gap-filling DNA repair synthesis and ligation in TC-NER	0.57711	0.6238	1	pole3;prpf19;polr2a;lig3	3696.917	4295.465	805.318	2086.45358	3989.40693	1722.6516	UP	0.75	0.25	
28Day	TNFs bind their physiological receptors	0.4587	0.84301	1	tnfrsf1b	1167.32	1167.32	1167.32		1167.32		DOWN	0	1	
28Day	TP53 regulates transcription of additional cell cycle genes whose exact role in the p53 pathway remain uncertain	0.6725	0.70182	1	cnot1	3132.16	3132.16	3132.16		3132.16		UP	1	0	
28Day	Transcriptional activity of SMAD2/SMAD3:SMAD4 heterotrimer	0.51059	0.74579	1	tfdp1;ccnk	5399.625	5399.625	5090.85	436.673793	5395.60681	436.636817	CONFLICT	0.5	0.5	
28Day	Zinc transporters	0.42575	1	1											
28Day	Eicosanoids	0.6468	0.72232	1	cyp4a12b	4766.57	4766.57	4766.57		4766.57		UP	1	0	
28Day	Intraflagellar transport	0.47238	0.73825	1	dynl1l;tubb4b;tubb2a	3684.67667	2903.04	2359.45	1844.72961	3931.15502	1868.40338	UP	1	0	
28Day	SHC1 events in ERBB4 signaling	0.7508	0.63077	1	hbegf	919.738	919.738	919.738		919.738		UP	1	0	
28Day	GRB2 events in ERBB2 signaling	0.7508	0.63077	1	hbegf	919.738	919.738	919.738		919.738		UP	1	0	
28Day	Prostacyclin signalling through prostacyclin receptor	0.6468	0.72232	1	gnb5	953.648	953.648	953.648		953.648		UP	1	0	
28Day	Adrenaline,noradrenaline inhibits insulin secretion	0.5482	0.7912	1	gnb5	953.648	953.648	953.648		953.648		UP	1	0	
28Day	G alpha (2) signalling events	0.62174	0.65548	1	gnb5;adcy9	2587.124	2587.124	953.648	2310.08391	1477.92173	1695.82674	CONFLICT	0.5	0.5	
28Day	Thromboxane signalling through TP receptor	0.5482	0.7912	1	gnb5	953.648	953.648	953.648		953.648		UP	1	0	
28Day	Thrombin signalling through proteinase activated receptors (PARs)	0.6409	0.63815	1	gnb5;f2	1147.199	1147.199	953.648	273.722449	1145.11067	273.706516	CONFLICT	0.5	0.5	
28Day	G beta:gamma signalling through BTK	0.6725	0.70182	1	gnb5	953.648	953.648	953.648		953.648		UP	1	0	
28Day	Nucleobase biosynthesis	0.72461	0.65616	1	adss	3213.44	3213.44	3213.44		3213.44		UP	1	0	
28Day	ATF6 (ATF6-alpha) activates chaperones	0.75238	1	1											
28Day	Activation of IRF3/IRF7 mediated by TBK1/IKK epsilon	0.72461	0.65616	1	ly96	4560.3	4560.3	4560.3		4560.3		UP	1	0	
28Day	Platelet Adhesion to exposed collagen	0.45717	1	1											
28Day	Scavenging of heme from plasma	0.50218	0.81895	1	lrp1	1882.51	1882.51	1882.51		1882.51		DOWN	0	1	
28Day	Tetrahydrobiopterin (BH4) synthesis, recycling, salvage and regulation	0.45717	1	1											
28Day	Signaling by NOTCH1	0.6468	0.72232	1	notch1	908.573	908.573	908.573		908.573		UP	1	0	
28Day	Amine-derived hormones	0.69847	0.6798	1	ddc	5580.16	5580.16	5580.16		5580.16		DOWN	0	1	
28Day	Recycling pathway of L1	0.58383	0.68814	1	tubb4b;tubb2a	2631.245	2631.245	2359.45	384.376175	2702.45657	370.948608	UP	1	0	
28Day	WNT5A-dependent internalization of FZD2, FZD5 and ROR2	0.42575	1	1											
28Day	Adrenoceptors	0.52712	1	1											
28Day	TP53 Regulates Transcription of DNA Repair Genes	0.44212	0.79406	1	polr2a;ccnk	5065.76	5065.76	5040.67	35.4826183	5074.14393	33.4430194	CONFLICT	0.5	0.5	
28Day	MET Receptor Activation	0.65259	1	1											
28Day	GABA A receptor activation	0.39648	1	1											
28Day	Apoptotic cleavage of cellular proteins	0.49297	0.7587	1	pkp1;birc2	4535.22	4535.22	3208.19	1876.70382	4209.41526	1819.26353	UP	1	0	
28Day	HS-GAG biosynthesis	0.67943	0.60146	1	hs2st1;gpc4	4234.355	4234.355	3361.03	1235.06806	4554.00819	1149.36364	DOWN	0	1	
28Day	Transcriptional regulation by RUNX3	0.5467	0.7182	1	notch1;mdm2	1587.5915	1587.5915	908.573	960.277172	1863.66593	877.32438	UP	1	0	
28Day	p53-Dependent G1 DNA Damage Response	0.69847	0.6798	1	mdm2	2266.61	2266.61	2266.61		2266.61		UP	1	0	
28Day	p53-Dependent G1/S DNA damage checkpoint	0.69847	0.6798	1	mdm2	2266.61	2266.61	2266.61		2266.61		UP	1	0	
28Day	G1/S DNA Damage Checkpoints	0.62145	0.74142	1	mdm2	2266.61	2266.61	2266.61		2266.61		UP	1	0	
28Day	Glutamate Neurotransmitter Release Cycle	0.52488	0.80557	1	slc1a2	1774.78	1774.78	1774.78		1774.78		DOWN	0	1	
28Day	Attachment of GPI anchor to uPAR	0.65259	1	1											

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
28Day	TRAF6-mediated induction of TAK1 complex within TLR4 complex	0.7508	0.63077	1	ly96	4560.3	4560.3	4560.3		4560.3		UP	1	0	
28Day	Inhibition of the proteolytic activity of APC/C required for the onset of anaphase by mitotic spindle checkpoint components	0.59653	0.75921	1	cdc27	5780.76	5780.76	5780.76		5780.76		UP	1	0	
	Inactivation of APC/C via direct inhibition of the APC/C complex	0.59653	0.75921	1	cdc27	5780.76	5780.76	5780.76		5780.76		UP	1	0	
28Day	APC/C:Cdc20 mediated degradation of Cyclin B	0.57209	0.77577	1	cdc27	5780.76	5780.76	5780.76		5780.76		UP	1	0	
28Day	APC/C:Cdc20 mediated degradation of Securin	0.59653	0.75921	1	cdc27	5780.76	5780.76	5780.76		5780.76		UP	1	0	
28Day	APC/C:Cdh1 mediated degradation of Cdc20 and other APC/C:Cdh1 targeted proteins in late mitosis/early G1	0.48011	0.83141	1	cdc27	5780.76	5780.76	5780.76		5780.76		UP	1	0	
28Day	Cdc20:Phospho-APC/C mediated degradation of Cyclin A	0.48011	0.83141	1	cdc27	5780.76	5780.76	5780.76		5780.76		UP	1	0	
28Day	APC/C:Cdc20 mediated degradation of mitotic proteins	0.41791	0.86388	1	cdc27	5780.76	5780.76	5780.76		5780.76		UP	1	0	
28Day	Phosphorylation of the APC/C	0.69847	0.6798	1	cdc27	5780.76	5780.76	5780.76		5780.76		UP	1	0	
28Day	Activation of APC/C and APC/C:Cdc20 mediated degradation of mitotic proteins	0.41791	0.86388	1	cdc27	5780.76	5780.76	5780.76		5780.76		UP	1	0	
	APC-Cdc20 mediated degradation of Nek2A	0.52488	0.80557	1	cdc27	5780.76	5780.76	5780.76		5780.76		UP	1	0	
28Day	APC:Cdc20 mediated degradation of cell cycle proteins prior to satisfaction of the cell cycle checkpoint	0.4587	0.84301	1	cdc27	5780.76	5780.76	5780.76		5780.76		UP	1	0	
28Day	HS-GAG degradation	0.59653	0.75921	1	gpc4	3361.03	3361.03	3361.03		3361.03		DOWN	0	1	
28Day	FRS-mediated FGFR3 signaling	0.59653	0.75921	1	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1	
28Day	Downstream signaling of activated FGFR3	0.48011	0.83141	1	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1	
28Day	FRS-mediated FGFR4 signaling	0.5482	0.7912	1	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1	
28Day	Downstream signaling of activated FGFR4	0.43797	0.85382	1	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1	
28Day	Nicotinamide salvaging	0.6468	0.72232	1	nudt12	5115.96	5115.96	5115.96		5115.96		DOWN	0	1	
28Day	Triglyceride catabolism	0.45717	1	1											
28Day	FGFR2 alternative splicing	0.50218	0.81895	1	polr2a	5040.67	5040.67	5040.67		5040.67		UP	1	0	
28Day	RNA Pol II CTD phosphorylation and interaction with CE	0.43797	0.85382	1	polr2a	5040.67	5040.67	5040.67		5040.67		UP	1	0	
28Day	Regulation of pyruvate dehydrogenase (PDH) complex	0.69847	0.6798	1	gstz1	5233.2	5233.2	5233.2		5233.2		DOWN	0	1	
28Day	Hyaluronan metabolism	0.45717	1	1											
28Day	Hyaluronan uptake and degradation	0.60776	1	1											
28Day	A tetrasaccharide linker sequence is required for GAG synthesis	0.4587	0.84301	1	gpc4	3361.03	3361.03	3361.03		3361.03		DOWN	0	1	
28Day	Transport of nucleosides and free purine and pyrimidine bases across the plasma membrane	0.56601	1	1											
	The NLRP3 inflammasome	0.4909	1	1											
28Day	G0 and Early G1	0.6725	0.70182	1	tfdp1	5708.4	5708.4	5708.4		5708.4		UP	1	0	
28Day	Glycoprotein hormones	0.52712	1	1											
28Day	Miscellaneous transport and binding events	0.52488	0.80557	1	azgp1	190.758	190.758	190.758		190.758		DOWN	0	1	
28Day	Orc1 removal from chromatin	0.50218	0.81895	1	cdc6	5867.54	5867.54	5867.54		5867.54		UP	1	0	
28Day	Activation of the pre-replicative complex	0.62174	0.65548	1	pole3;cdc6	3336.429	3336.429	805.318	3579.5315	4404.50906	3245.22045	UP	1	0	
28Day	Sodium/Calcium exchangers	0.42575	1	1											
28Day	Ionotropic activity of kainate receptors	0.42575	1	1											
28Day	Activation of Ca-permeable Kainate Receptor	0.42575	1	1											

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
28Day	Zinc influx into cells by the SLC39 gene family	0.56601	1	1										
28Day	Processive synthesis on the C-strand of the telomere	0.52712	1	1										
28Day	Removal of the Flap Intermediate from the C-strand	0.52712	1	1										
28Day	Organic cation/anion/zwitterion transport	0.69847	0.6798	1	slc22a1	1681.65	1681.65	1681.65		1681.65		DOWN	0	1
28Day	GABA synthesis, release, reuptake and degradation	0.6725	0.70182	1	slc6a13	151.142	151.142	151.142		151.142		DOWN	0	1
28Day	PI-3K cascade:FGFR3	0.6468	0.72232	1	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1
28Day	PI-3K cascade:FGFR4	0.59653	0.75921	1	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1
28Day	NRIF signals cell death from the nucleus	0.7508	0.63077	1	sqstm1	5683.98	5683.98	5683.98		5683.98		UP	1	0
28Day	CLEC7A/Inflammasome pathway	0.75238	1	1										
28Day	Glycerophospholipid catabolism	0.80786	1	1										
28Day	Propionyl-CoA catabolism	0.70071	1	1										
28Day	Protein repair	0.65259	1	1										
28Day	Beta oxidation of palmitoyl-CoA to myristoyl-CoA	0.93135	1	1										
28Day	Beta oxidation of butanoyl-CoA to acetyl-CoA	0.93135	1	1										
28Day	Transcriptional Regulation by MECP2	0.70071	1	1										
28Day	NGF processing	0.75238	1	1										
28Day	Expression and Processing of Neurotrophins	0.75238	1	1										
28Day	Regulation of IFNG signaling	0.45717	1	1										
28Day	Cam-PDE 1 activation	0.65259	1	1										
28Day	Long-term potentiation	0.75238	1	1										
28Day	Biosynthesis of protectins	0.86741	1	1										
28Day	Aromatic amines can be N-hydroxylated or N-dealkylated by CYP1A2	0.93135	1	1										
28Day	Synthesis of dolichyl-phosphate mannose	0.80786	1	1										
28Day	Regulation of MECP2 expression and activity	0.70071	1	1										
28Day	FGFR4 ligand binding and activation	0.7508	0.63077	1	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1
28Day	Phospholipase C-mediated cascade; FGFR4	0.72461	0.65616	1	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1
28Day	SHC-mediated cascade:FGFR3	0.6468	0.72232	1	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1
28Day	SHC-mediated cascade:FGFR4	0.59653	0.75921	1	fgf1	1467.57	1467.57	1467.57		1467.57		DOWN	0	1
28Day	Platelet sensitization by LDL	0.6725	0.70182	1	apob	939.205	939.205	939.205		939.205		DOWN	0	1
28Day	Assembly of the ORC complex at the origin of replication	0.65259	1	1										
28Day	SDK interactions	0.86741	1	1										
90Day	Purine salvage	0.64343	0.73175	1	adk	2663.49	2663.49	2663.49		2663.49		DOWN	0	1
90Day	Nucleotide salvage	0.5728	0.70251	1	tk1;adk	3584.32	3584.32	2663.49	1302.25027	4057.93025	1116.80009	DOWN	0	1
90Day	Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)	0.53277	0.57618	1	notum;spp2;apob;trf;tnc;serpina1e;mp2;itih2;igfbp4;fn1;csf1;c3;apoae;ahs;g;golm1	2295.16335	1866.49	82.4742	1865.07009	2483.87114	1863.40676	DOWN	0.133333333	0.866666667
90Day	Intrinsic Pathway for Apoptosis	0.48111	0.73533	1	ywhaz;bmf;bax	1193.33933	1597.1	137.958	922.350781	1275.32396	881.071038	UP	0.666666667	0.333333333
90Day	Activation of BAD and translocation to mitochondria	0.60115	0.76201	1	ywhaz	137.958	137.958	137.958		137.958		UP	1	0
90Day	Activation of BH3-only proteins	0.63654	0.64822	1	ywhaz;bmf	867.529	867.529	137.958	1031.7692	957.421294	1023.90744	CONFLICT	0.5	0.5
90Day	Downregulation of ERBB2:ERBB3 signaling	0.77469	0.61588	1	nrg1	3912.34	3912.34	3912.34		3912.34		UP	1	0
90Day	G-protein beta:gamma signalling	0.53165	0.69487	1	arhgef6;gng11;cdc42	3654.54233	4854.24	156.487	3078.80769	3619.71528	3169.47674	UP	0.666666667	0.333333333
90Day	VEGFR2 mediated vascular permeability	0.584	0.64989	1	vav1;hsp90aa1;ctnnb1	2891.47	4087.04	426.32	2135.20321	2629.79926	2233.41338	DOWN	0.333333333	0.666666667

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
90Day	Cyclin E associated events during G1/S transition	0.60445	0.67629	1	cables1;cdkn1a	2492.81	2492.81	913.71	2233.18464	1416.85383	1634.54894	CONFLICT	0.5	0.5
90Day	Cyclin A:Cdk2-associated events at S phase entry	0.5728	0.70251	1	cables1;cdkn1a	2492.81	2492.81	913.71	2233.18464	1416.85383	1634.54894	CONFLICT	0.5	0.5
90Day	Downregulation of ERBB2 signaling	0.48204	0.77071	1	nrg1;hsp90aa1	2169.33	2169.33	426.32	2464.98838	2502.38562	2419.56931	UP	1	0
90Day	Regulation of localization of FOXO transcription factors	0.73069	0.6592	1	ywhaz	137.958	137.958	137.958		137.958		UP	1	0
90Day	Peroxisomal lipid metabolism	0.61063	0.62569	1	hacl1;slc27a2;slc25a17	3683.26	3419.78	2910.82	932.527616	3761.45897	916.721686	DOWN	0.333333333	0.666666667
90Day	Nonsense-Mediated Decay (NMD)	0.56021	0.78886	1	smg5	2531.67	2531.67	2531.67		2531.67		UP	1	0
90Day	Nonsense Mediated Decay (NMD) enhanced by the Exon Junction Complex (EJC)	0.56021	0.78886	1	smg5	2531.67	2531.67	2531.67		2531.67		UP	1	0
90Day	Cargo concentration in the ER	0.59398	0.61242	1	lman1;tgfa;serpina1e;areg	3227.46225	3066.45	959.779	2124.07144	2615.34503	1585.21285	CONFLICT	0.5	0.5
90Day	Signaling by Nuclear Receptors	0.54559	0.55191	1	hist1h4h;ppid;rdh7;hist1h4i;hist1h3c;pd4;adh4;nr5a2;aldh1a7;aldh8a1;pd1;yy1;rxrg;rarg;rdh11;hsp90aa1;h2afx;ddx5;cbf1	3422.01516	3563.02	174.249	1587.20613	3203.98005	1657.68063	UP	0.631578947	0.368421053
90Day	Role of ABL in ROBO-SLIT signaling	0.61984	1	1										
90Day	RUNX1 regulates transcription of genes involved in differentiation of HSCs	0.60445	0.67629	1	cdk7;cbfb	3600.375	3600.375	3130.16	664.98443	3784.03771	612.160364	UP	1	0
90Day	Amino acid synthesis and interconversion (transamination)	0.50611	0.71566	1	serinc1;pat;glul	3429.27667	2970.16	1556.81	2139.29899	3287.57914	2457.41055	DOWN	0.333333333	0.666666667
90Day	Mitochondrial calcium ion transport	0.7013	0.58634	1	afg3l2;micu2	3526.375	3526.375	1479.94	2894.09613	2753.64746	2679.8464	UP	1	0
90Day	Complement cascade	0.51976	0.66058	1	cpn2;c5ar2;vtm;crp;c3	1958.91334	639.57	45.5307	2312.16663	1418.61854	1923.42509	DOWN	0.2	0.8
90Day	Regulation of Complement cascade	0.45854	0.72963	1	cpn2;c5ar2;vtm;c3	1482.31668	433.493	45.5307	2369.3579	696.504019	1435.23764	DOWN	0.25	0.75
90Day	Mitophagy	0.51148	0.74964	1	tomm20;tomm70a	3015.0435	3015.0435	786.107	3152.19223	2376.38885	3020.02588	UP	1	0
90Day	Pink/Parkin Mediated Mitophagy	0.63654	0.64822	1	tomm20;tomm70a	3015.0435	3015.0435	786.107	3152.19223	2376.38885	3020.02588	UP	1	0
90Day	Pentose phosphate pathway	0.4475	0.85258	1	rpe	54.2263	54.2263	54.2263		54.2263		DOWN	0	1
90Day	Resolution of D-Loop Structures	0.48111	0.73533	1	rad51;brca2;rad51c	3127.57067	4249.95	513.022	2271.80208	3130.56464	2280.41	UP	1	0
90Day	Resolution of D-loop Structures through Holliday Junction Intermediates	0.50611	0.71566	1	rad51;brca2;rad51c	3127.57067	4249.95	513.022	2271.80208	3130.56464	2280.41	UP	1	0
90Day	Regulation of ornithine decarboxylase (ODC)	0.48796	1	1										
90Day	Synthesis of PI	0.54997	1	1										
90Day	Lectin pathway of complement activation	0.69859	1	1										
90Day	Initial triggering of complement	0.66889	0.61824	1	crp;c3	2252.435	2252.435	639.57	2280.93556	1977.85009	2247.63726	DOWN	0	1
90Day	Creation of C4 and C2 activators	0.60115	0.76201	1	crp	3865.3	3865.3	3865.3		3865.3		DOWN	0	1
90Day	N-glycan trimming in the ER and Calnexin/Calreticulin cycle	0.54177	0.72694	1	ngly1;rnf5	4475.645	4475.645	3718.83	1070.29804	4617.15875	1051.42075	UP	1	0
90Day	ER Quality Control Compartment (ERQC)	0.60115	0.76201	1	rnf5	3718.83	3718.83	3718.83		3718.83		UP	1	0
90Day	Calnexin/calreticulin cycle	0.48325	0.83383	1	rnf5	3718.83	3718.83	3718.83		3718.83		UP	1	0
90Day	VEGFR2 mediated cell proliferation	0.56021	0.78886	1	rasa1	2133.64	2133.64	2133.64		2133.64		UP	1	0
90Day	PTK6 Regulates RHO GTPases, RAS GTPase and MAP kinases	0.52086	0.81269	1	rasa1	2133.64	2133.64	2133.64		2133.64		UP	1	0
90Day	Interleukin-1 family signaling	0.52991	0.62587	1	irak3;tbk1;nfbk1a;il1rap;ikbk;il18bp;bt	2734.35957	3115.46	262.957	1630.24673	2470.42611	1941.7124	DOWN	0.142857143	0.857142857
90Day	Interleukin-1 signaling	0.51976	0.66058	1	irak3;nfbk1a;il1rap;ikbk;bt	2993.3334	3265.56	262.957	1778.81827	2754.88632	2105.90813	DOWN	0.2	0.8
90Day	Antigen activates B Cell Receptor (BCR) leading to generation of second messengers	0.48204	0.77071	1	vav1;sos1	5027.99	5027.99	4161.05	1226.03831	5362.02772	1131.37418	DOWN	0	1
90Day	PI3K Cascade	0.45854	0.72963	1	klb;irs2;gab1;fgf1	1073.49008	184.4285	74.8133	1852.5264	1155.9193	1943.48751	DOWN	0	1
90Day	IRS-mediated signalling	0.62406	0.56268	1	klb;irs2;sos1;gab1;fgf1	2037.77806	242.429	74.8133	2687.59133	2592.91452	2898.02513	DOWN	0	1
90Day	PI3K/AKT activation	0.73069	0.6592	1	irs2	74.8133	74.8133	74.8133		74.8133		DOWN	0	1
90Day	Tie2 Signaling	0.66889	0.61824	1	tek;sos1	3169.313	3169.313	443.696	3854.60453	4968.4106	2895.59523	DOWN	0	1
90Day	Signaling by Type 1 Insulin-like Growth Factor 1 Receptor (IGF1R)	0.49942	0.67836	1	klb;irs2;sos1;gab1;fgf1	2037.77806	242.429	74.8133	2687.59133	2592.91452	2898.02513	DOWN	0	1
90Day	IGF1R signaling cascade	0.51976	0.66058	1	klb;irs2;sos1;gab1;fgf1	2037.77806	242.429	74.8133	2687.59133	2592.91452	2898.02513	DOWN	0	1

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
90Day	IRS-related events triggered by IGF1R	0.54033	0.64218	1	klb;irs2;sos1;gab1;fgf1	2037.77806	242.429	74.8133	2687.59133	2592.91452	2898.02513	DOWN	0	1
90Day	Insulin receptor signalling cascade	0.47938	0.6955	1	klb;irs2;sos1;gab1;fgf1	2037.77806	242.429	74.8133	2687.59133	2592.91452	2898.02513	DOWN	0	1
90Day	Netrin-1 signaling	0.66427	0.57395	1	mapk14;siah2;cdc42	1520.492	156.487	143.029	2374.19047	944.958876	1990.34255	DOWN	0.333333333	0.666666667
90Day	DS-CAM interactions	0.73069	0.6592	1	mapk14	4261.96	4261.96	4261.96		4261.96		DOWN	0	1
90Day	MET receptor recycling	0.68675	0.69764	1	gab1	126.428	126.428	126.428		126.428		DOWN	0	1
90Day	LGI-ADAM interactions	0.56021	0.78886	1	stx1b	328.2	328.2	328.2		328.2		DOWN	0	1
90Day	Synaptic adhesion-like molecules	0.5728	0.70251	1	gria3;ptprd	2252.495	2252.495	1097.82	1632.95705	2230.33073	1632.65618	CONFLICT	0.5	0.5
90Day	Apoptotic factor-mediated response	0.73069	0.6592	1	bax	1844.96	1844.96	1844.96		1844.96		UP	1	0
90Day	mRNA decay by 3' to 5' exonuclease	0.4475	0.85258	1	exosc9	2804.89	2804.89	2804.89		2804.89		UP	1	0
90Day	Butyrate Response Factor 1 (BRF1) binds and destabilizes mRNA	0.4475	0.85258	1	exosc9	2804.89	2804.89	2804.89		2804.89		UP	1	0
90Day	Digestion of dietary carbohydrate	0.52086	0.81269	1	mgam	2596.25	2596.25	2596.25		2596.25		DOWN	0	1
90Day	Signal amplification	0.53165	0.69487	1	gng11;mapk14;gna13	5006.42333	4854.24	4261.96	831.071798	4956.1591	771.687345	UP	0.666666667	0.333333333
90Day	Nucleotide-like (purinergic) receptors	0.4475	0.85258	1	adora1	1587.43	1587.43	1587.43		1587.43		DOWN	0	1
90Day	ADP signalling through P2Y purinoceptor 1	0.48204	0.77071	1	gng11;mapk14	4558.1	4558.1	4261.96	418.805204	4602.80994	414.004639	CONFLICT	0.5	0.5
90Day	Synthesis of PS	0.78732	1	1										
90Day	YAP1- and WWTR1 (TAZ)-stimulated gene expression	0.43294	1	1										
90Day	Recycling of bile acids and salts	0.63654	0.64822	1	slc27a5;slc10a1	3047.255	3047.255	2758.21	408.771359	2997.14048	402.580545	DOWN	0	1
90Day	CLEC7A (Dectin-1) signaling	0.58201	0.60356	1	ube2m;cdc34;nfkbia;ikbk;trc	2653.3084	3265.56	569.072	1985.29402	2657.76128	2167.87416	UP	0.6	0.4
90Day	Histidine, lysine, phenylalanine, tyrosine, proline and tryptophan catabolism	0.62406	0.56268	1	amdhd1;asrgl1;slc25a21;hpd;gstz1	2628.7694	3209.99	932.277	1194.08148	2495.47326	1167.59929	DOWN	0	1
90Day	Histidine catabolism	0.77469	0.61588	1	amdhd1	3887.79	3887.79	3887.79		3887.79		DOWN	0	1
90Day	Apoptosis induced DNA fragmentation	0.60115	0.76201	1	hmgb2	2367.76	2367.76	2367.76		2367.76		UP	1	0
90Day	Activation of DNA fragmentation factor	0.60115	0.76201	1	hmgb2	2367.76	2367.76	2367.76		2367.76		UP	1	0
90Day	FCER1 mediated MAPK activation	0.45354	0.79021	1	vav1;sos1	5027.99	5027.99	4161.05	1226.03831	5362.02772	1131.37418	DOWN	0	1
90Day	SEMA3A-Plexin repulsion signaling by inhibiting Integrin adhesion	0.68675	0.69764	1	tlm1	4478.93	4478.93	4478.93		4478.93		DOWN	0	1
90Day	Multifunctional anion exchangers	0.77469	0.61588	1	slc26a2	3962.48	3962.48	3962.48		3962.48		DOWN	0	1
90Day	Nuclear Receptor transcription pathway	0.47938	0.6955	1	nr5a2;esrrg;xrg;rarg;ar	1966.2334	1998.95	174.249	1868.5268	2021.14167	1818.34825	DOWN	0.2	0.8
90Day	Non-integrin membrane-ECM interactions	0.57072	0.63396	1	vtn;ttr;sd4;fn1	1730.32918	1370.138	45.5307	1823.72195	1054.70846	1572.60387	DOWN	0.25	0.75
90Day	ECM proteoglycans	0.47938	0.6955	1	vtn;tnc;fn1;bgn;itga9	3388.13014	4436.62	45.5307	2297.14105	3504.64194	2580.55043	DOWN	0.2	0.8
90Day	Integrin alpha1b beta3 signaling	0.66427	0.57395	1	tlm1;sos1;fn1	4161.30667	4478.93	2110.06	1912.32154	4694.64696	1722.82421	DOWN	0	1
90Day	Integrin signaling	0.66427	0.57395	1	tlm1;sos1;fn1	4161.30667	4478.93	2110.06	1912.32154	4694.64696	1722.82421	DOWN	0	1
90Day	Organic anion transporters	0.68675	0.69764	1	slc17a8	2572.47	2572.47	2572.47		2572.47		UP	1	0
90Day	Retrograde neurotrophin signalling	0.64343	0.73175	1	ap2m1	2983.55	2983.55	2983.55		2983.55		UP	1	0
90Day	Receptor-type tyrosine-protein phosphatases	0.60445	0.67629	1	ptprd;il1rap	3045.76	3045.76	2684.35	511.110924	3054.7998	510.951015	DOWN	0	1
90Day	Carnitine synthesis	0.61984	1	1										
90Day	Neurotransmitter release cycle	0.54033	0.64218	1	lin7c;unc13b;slc22a1;slc1a2;slc6a12	2723.9178	3445.15	777.189	1704.97764	3301.41504	1207.79029	DOWN	0.4	0.6
90Day	Acetylcholine Neurotransmitter Release Cycle	0.4475	0.85258	1	unc13b	4570.91	4570.91	4570.91		4570.91		UP	1	0
90Day	Peptide hormone biosynthesis	0.64343	0.73175	1	inhbc	2508.36	2508.36	2508.36		2508.36		DOWN	0	1
90Day	Pyrimidine salvage	0.68675	0.69764	1	tk1	4505.15	4505.15	4505.15		4505.15		DOWN	0	1
90Day	FGFR1 ligand binding and activation	0.48325	0.83383	1	fgf1	242.429	242.429	242.429		242.429		DOWN	0	1
90Day	FGFR2b ligand binding and activation	0.73069	0.6592	1	fgf1	242.429	242.429	242.429		242.429		DOWN	0	1
90Day	Phospholipase C-mediated cascade: FGFR1	0.4475	0.85258	1	fgf1	242.429	242.429	242.429		242.429		DOWN	0	1
90Day	Downstream signaling of activated FGFR1	0.53165	0.69487	1	sos1;gab1;fgf1	2087.929	242.429	126.428	3297.46971	3907.43024	3338.39856	DOWN	0	1
90Day	SHC-mediated cascade:FGFR1	0.5728	0.70251	1	sos1;fgf1	3068.6795	3068.6795	242.429	3996.92179	4960.29053	2969.67998	DOWN	0	1
90Day	PI-3K cascade:FGFR1	0.5728	0.70251	1	gab1;fgf1	184.4285	184.4285	126.428	82.0250937	169.646309	79.3163895	DOWN	0	1
90Day	FRS-mediated FGFR1 signaling	0.51148	0.74964	1	sos1;fgf1	3068.6795	3068.6795	242.429	3996.92179	4960.29053	2969.67998	DOWN	0	1
90Day	PI-3K cascade:FGFR2	0.51148	0.74964	1	gab1;fgf1	184.4285	184.4285	126.428	82.0250937	169.646309	79.3163895	DOWN	0	1

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
90Day	Downstream signaling of activated FGFR2	0.55764	0.67295	1	sos1;gab1;fgf1	2087.929	242.429	126.428	3297.46971	3907.43024	3338.39856	DOWN	0	1
90Day	SHC-mediated cascade:FGFR2	0.51148	0.74964	1	sos1;fgf1	3068.6795	3068.6795	242.429	3996.92179	4960.29053	2969.67998	DOWN	0	1
90Day	FRS-mediated FGFR2 signaling	0.45354	0.79021	1	sos1;fgf1	3068.6795	3068.6795	242.429	3996.92179	4960.29053	2969.67998	DOWN	0	1
90Day	Fatty acyl-CoA biosynthesis	0.61736	0.5901	1	acsl4;scd1;acsl1;elovl3	3458.811	4133.87	587.994	1971.97849	3579.47816	1867.87989	UP	0.75	0.25
90Day	RHO GTPases activate KTN1	0.64343	0.73175	1	cdc42	156.487	156.487	156.487		156.487		UP	1	0
90Day	ERBB2 Regulates Cell Motility	0.48325	0.83383	1	nrg1	3912.34	3912.34	3912.34		3912.34		UP	1	0
90Day	DNA Damage Recognition in GG-NER	0.61736	0.5901	1	mcrs1;yy1;ino80c;rad23a	3516.8375	3761.895	1252.26	1879.48684	3649.65772	1980.59354	CONFLICT	0.5	0.5
90Day	Sodium-coupled sulphate, di- and tri-carboxylate transporters	0.54997	1	1										
90Day	Activation of the AP-1 family of transcription factors	0.68675	0.69764	1	mapk14	4261.96	4261.96	4261.96		4261.96		DOWN	0	1
90Day	Lysosphingolipid and LPA receptors	0.52086	0.81269	1	lpar3	5175	5175	5175		5175		UP	1	0
90Day	Downstream signaling events of B Cell Receptor (BCR)	0.48111	0.73533	1	nfkbia;ikbk;btcr	4006.45333	3601.1	3265.56	1006.7561	4283.92049	1129.74967	DOWN	0.333333333	0.666666667
90Day	WNT5A-dependent internalization of FZD4	0.48325	0.83383	1	ap2m1	2983.55	2983.55	2983.55		2983.55		UP	1	0
90Day	IL-6-type cytokine receptor ligand interactions	0.60445	0.67629	1	lifr;cr1f1	3403.375	3403.375	3200.93	286.300465	3314.11858	256.971864	CONFLICT	0.5	0.5
90Day	Interleukin-27 signaling	0.64343	0.73175	1	cr1f1	3200.93	3200.93	3200.93		3200.93		UP	1	0
90Day	Adenylate cyclase inhibitory pathway	0.52086	0.81269	1	gnai3	5903.07	5903.07	5903.07		5903.07		UP	1	0
90Day	ADP signalling through P2Y purinoceptor 12	0.5728	0.70251	1	gng11;gnai3	5378.655	5378.655	4854.24	741.634805	5266.80756	724.570551	UP	1	0
90Day	Inhibition of adenylate cyclase pathway	0.52086	0.81269	1	gnai3	5903.07	5903.07	5903.07		5903.07		UP	1	0
90Day	ERBB2 Activates PTK6 Signaling	0.56021	0.78886	1	nrg1	3912.34	3912.34	3912.34		3912.34		UP	1	0
90Day	Inflammasomes	0.48325	0.83383	1	txn1	5143.54	5143.54	5143.54		5143.54		DOWN	0	1
90Day	The NLRP1 inflammasome	0.61984	1	1										
90Day	SUMO is proteolytically processed	0.48796	1	1										
90Day	Processing and activation of SUMO	0.68675	0.69764	1	sae1	3998.58	3998.58	3998.58		3998.58		UP	1	0
90Day	Molybdenum cofactor biosynthesis	0.48796	1	1										
90Day	POLB-Dependent Long Patch Base Excision Repair	0.43294	1	1										
90Day	Phosphorylation of CD3 and TCR zeta chains	0.48325	0.83383	1	h2-aa	3001.17	3001.17	3001.17		3001.17		DOWN	0	1
90Day	Oncogene Induced Senescence	0.56021	0.78886	1	mdm2	3535.08	3535.08	3535.08		3535.08		UP	1	0
90Day	RUNX1 interacts with co-factors whose precise effect on RUNX1 targets is not known	0.64078	0.56705	1	smarcd2;cbx6;smarcb1;cbfb	3636.44975	4020.575	744.949	2095.15915	3779.92877	2174.25311	UP	0.75	0.25
90Day	Translesion synthesis by POLK	0.48325	0.83383	1	polk	3652.71	3652.71	3652.71		3652.71		UP	1	0
90Day	Gap-filling DNA repair synthesis and ligation in GG-NER	0.60445	0.67629	1	pole4;polk	4753.255	4753.255	3652.71	1556.40567	3884.77714	955.97646	CONFLICT	0.5	0.5
90Day	TP53 regulates transcription of additional cell cycle genes whose exact role in the p53 pathway remain uncertain	0.7013	0.58634	1	plk2;btg2	3008.67	3008.67	2041.26	1368.12434	2563.00625	1214.30303	UP	1	0
90Day	Gamma-carboxylation of protein precursors	0.64343	0.73175	1	f7	3350.52	3350.52	3350.52		3350.52		DOWN	0	1
90Day	Transport of gamma-carboxylated protein precursors from the endoplasmic reticulum to the Golgi apparatus	0.64343	0.73175	1	f7	3350.52	3350.52	3350.52		3350.52		DOWN	0	1
90Day	Removal of aminoterminal propeptides from gamma-carboxylated proteins	0.60115	0.76201	1	f7	3350.52	3350.52	3350.52		3350.52		DOWN	0	1
90Day	Gamma-carboxylation, transport, and amino-terminal cleavage of proteins	0.56021	0.78886	1	f7	3350.52	3350.52	3350.52		3350.52		DOWN	0	1
90Day	Synthesis of Leukotrienes (LT) and Eoxins (EX)	0.63743	0.60037	1	cyp4f16;cyp4a12a;cyp4a12b	3624.98	3568.65	3465.22	194.153566	3583.99801	170.385902	UP	1	0
90Day	PI3K events in ERBB4 signaling	0.68675	0.69764	1	nrg1	3912.34	3912.34	3912.34		3912.34		UP	1	0
90Day	Unfolded Protein Response (UPR)	0.66889	0.61824	1	crebrf;mbtps2	3657.4	3657.4	3467.51	268.545013	3577.10508	243.355453	UP	1	0

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
90Day	Josephin domain DUBs	0.73069	0.6592	1	rad23a	2713.02	2713.02	2713.02		2713.02		DOWN	0	1
90Day	G2/M DNA replication checkpoint	0.61984	1	1										
90Day	alpha-linolenic (omega3) and linoleic (omega6) acid metabolism	0.73069	0.6592	1	acs1	4979.51	4979.51	4979.51		4979.51		DOWN	0	1
90Day	alpha-linolenic acid (ALA) metabolism	0.77469	0.61588	1	acs1	4979.51	4979.51	4979.51		4979.51		DOWN	0	1
90Day	Beta-oxidation of pristanoyl-CoA	0.43294	1	1										
90Day	HDL clearance	0.54997	1	1										
90Day	VLDLR internalisation and degradation	0.60115	0.76201	1	ap2m1	2983.55	2983.55	2983.55		2983.55		UP	1	0
90Day	Tetrahydrobiopterin (BH4) synthesis, recycling, salvage and regulation	0.64343	0.73175	1	hsp90aa1	426.32	426.32	426.32		426.32		UP	1	0
90Day	Attenuation phase	0.56021	0.78886	1	hsp90aa1	426.32	426.32	426.32		426.32		UP	1	0
90Day	Electron transport from NADPH to Ferredoxin	0.69859	1	1										
90Day	Interleukin-9 signaling	0.73069	0.6592	1	il9r	5362.87	5362.87	5362.87		5362.87		UP	1	0
90Day	WNT5A-dependent internalization of FZD2, FZD5 and ROR2	0.60115	0.76201	1	ap2m1	2983.55	2983.55	2983.55		2983.55		UP	1	0
90Day	Adrenoceptors	0.73069	0.6592	1	adra1b	2444.64	2444.64	2444.64		2444.64		DOWN	0	1
90Day	JNK (c-Jun kinases) phosphorylation and activation mediated by activated human TAK1	0.54997	1	1										
90Day	Post-transcriptional silencing by small RNAs	0.43294	1	1										
90Day	MET activates RAP1 and RAC1	0.68675	0.69764	1	gab1	126.428	126.428	126.428		126.428		DOWN	0	1
90Day	Na+/Cl- dependent neurotransmitter transporters	0.60445	0.67629	1	slc22a1;slc6a12	2247.86	2247.86	1050.57	1693.22376	3017.91745	1296.54531	DOWN	0	1
90Day	GABA A receptor activation	0.56021	0.78886	1	gabrb3	4201.91	4201.91	4201.91		4201.91		DOWN	0	1
90Day	Transcriptional regulation by RUNX3	0.61736	0.5901	1	mdm2;brd2;cbfb;ctnnb1	4263.645	4078.815	3535.08	775.750103	3966.25751	640.611894	UP	0.75	0.25
90Day	Formation of ATP by chemiosmotic coupling	0.52086	0.81269	1	atp5k	135.802	135.802	135.802		135.802		DOWN	0	1
90Day	Cristae formation	0.52086	0.81269	1	atp5k	135.802	135.802	135.802		135.802		DOWN	0	1
90Day	SCF(Skp2)-mediated degradation of p27/p21	0.4475	0.85258	1	cdkn1a	913.71	913.71	913.71		913.71		UP	1	0
90Day	TP53 Regulates Transcription of Genes Involved in G1 Cell Cycle Arrest	0.73069	0.6592	1	cdkn1a	913.71	913.71	913.71		913.71		UP	1	0
90Day	G1/S DNA Damage Checkpoints	0.63654	0.64822	1	mdm2;cdkn1a	2224.395	2224.395	913.71	1853.5885	2056.00777	1838.2279	UP	1	0
90Day	Lysine catabolism	0.60115	0.76201	1	slc25a21	3224.71	3224.71	3224.71		3224.71		DOWN	0	1
90Day	Glutamate Neurotransmitter Release Cycle	0.51148	0.74964	1	unc13b;slc1a2	2674.0495	2674.0495	777.189	2682.56585	3235.52021	2562.35454	CONFLICT	0.5	0.5
90Day	Regulation of KIT signaling	0.52086	0.81269	1	sos1	5894.93	5894.93	5894.93		5894.93		DOWN	0	1
90Day	Proline catabolism	0.69859	1	1										
90Day	Caspase activation via Death Receptors in the presence of ligand	0.48325	0.83383	1	tnfrsf10b	3826.99	3826.99	3826.99		3826.99		UP	1	0
90Day	ChREBP activates metabolic gene expression	0.43294	1	1										
90Day	Vitamin B5 (pantothenate) metabolism	0.56021	0.78886	1	pank1	2679.72	2679.72	2679.72		2679.72		DOWN	0	1
90Day	Phosphorylation of the APC/C	0.4475	0.85258	1	anapc10	4390.47	4390.47	4390.47		4390.47		UP	1	0
90Day	Dissolution of Fibrin Clot	0.7013	0.58634	1	plg;plaur	1145.545	1145.545	668.86	674.134392	1394.68147	574.734041	DOWN	0	1
90Day	TP53 Regulates Transcription of Genes Involved in Cytochrome C Release	0.48796	1	1										
90Day	Vitamin C (ascorbate) metabolism	0.77469	0.61588	1	slc23a2	338.932	338.932	338.932		338.932		DOWN	0	1
90Day	Stabilization of p53	0.77469	0.61588	1	mdm2	3535.08	3535.08	3535.08		3535.08		UP	1	0
90Day	Gap junction degradation	0.64343	0.73175	1	ap2m1	2983.55	2983.55	2983.55		2983.55		UP	1	0
90Day	Formation of annular gap junctions	0.68675	0.69764	1	ap2m1	2983.55	2983.55	2983.55		2983.55		UP	1	0
90Day	FRS-mediated FGFR3 signaling	0.60445	0.67629	1	sos1;fgf1	3068.6795	3068.6795	242.429	3996.92179	4960.29053	2969.67998	DOWN	0	1
90Day	Signaling by FGFR4	0.57072	0.63396	1	klb;sos1;gab1;fgf1	2528.51925	2046.3595	126.428	2832.90488	3890.50542	2640.67822	DOWN	0	1
90Day	Triglyceride metabolism	0.51148	0.74964	1	dgat2;agmo	3065.025	3065.025	2903.14	228.939963	3009.70495	215.157829	DOWN	0	1
90Day	Pyruvate metabolism	0.61063	0.62569	1	pdk4;pdk1;gstz1	4115.21	3345.98	3209.99	1451.70948	3914.67407	1357.04203	DOWN	0.333333333	0.666666667
90Day	Pyruvate metabolism and Citric Acid (TCA) cycle	0.47938	0.6955	1	sdha;pdk4;pdk1;suc1g2;gstz1	3556.456	3209.99	2609.96	1282.57086	3264.47055	1059.70182	DOWN	0.2	0.8

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.

Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
90Day	Transport of nucleosides and free purine and pyrimidine bases across the plasma membrane	0.77469	0.61588	1	slc29a1	1131.79	1131.79	1131.79		1131.79		DOWN	0	1
90Day	Serine biosynthesis	0.73069	0.6592	1	serinc1	2970.16	2970.16	2970.16		2970.16		UP	1	0
90Day	The NLRP3 inflammasome	0.68675	0.69764	1	txn1	5143.54	5143.54	5143.54		5143.54		DOWN	0	1
90Day	Termination of O-glycan biosynthesis	0.4475	0.85258	1	st3gal3	5224.26	5224.26	5224.26		5224.26		DOWN	0	1
90Day	Glycoprotein hormones	0.73069	0.6592	1	inhbc	2508.36	2508.36	2508.36		2508.36		DOWN	0	1
90Day	Establishment of Sister Chromatid Cohesion	0.64343	0.73175	1	esco2	3568.8	3568.8	3568.8		3568.8		UP	1	0
90Day	Activation of the pre-replicative complex	0.50611	0.71566	1	pole4;orc6;dbf4	4330.28	4168.34	2968.7	1449.35121	3793.77257	1067.30893	UP	0.666666667	0.333333333
90Day	Synthesis of PIPs at the Golgi membrane	0.52086	0.81269	1	pi4ka	3636.02	3636.02	3636.02		3636.02		DOWN	0	1
90Day	DCC mediated attractive signaling	0.64343	0.73175	1	cdc42	156.487	156.487	156.487		156.487		UP	1	0
90Day	Classical antibody-mediated complement activation	0.73069	0.6592	1	crp	3865.3	3865.3	3865.3		3865.3		DOWN	0	1
90Day	FCGR activation	0.52086	0.81269	1	fcgr2b	3055.31	3055.31	3055.31		3055.31		DOWN	0	1
90Day	Interleukin-10 signaling	0.48796	1	1										
90Day	Interferon alpha/beta signaling	0.584	0.64989	1	usp18;abce1;ifnar1	2450.37233	3026.26	250.557	1975.8511	2122.02408	2095.71228	UP	0.666666667	0.333333333
90Day	Regulation of IFNA signaling	0.48204	0.77071	1	usp18;ifnar1	2162.4285	2162.4285	250.557	2703.7946	1821.52235	2660.46448	CONFLICT	0.5	0.5
90Day	Glucuronidation	0.48204	0.77071	1	ugt2b35;ugdh	497.0045	497.0045	444.891	73.6996185	491.891363	73.344021	UP	1	0
90Day	Signaling by NOTCH3	0.63654	0.64822	1	psen2;dll1	2793.24	2793.24	2451.29	483.590328	2851.27329	476.575156	DOWN	0	1
90Day	SUMOylation of RNA binding proteins	0.48796	1	1										
90Day	Other interleukin signaling	0.63654	0.64822	1	stx3;csf1	4961.12	4961.12	4474.79	687.774482	4742.6821	614.49451	DOWN	0	1
90Day	p75NTR signals via NF-kB	0.52086	0.81269	1	nfkbia	3601.1	3601.1	3601.1		3601.1		DOWN	0	1
90Day	Regulated proteolysis of p75NTR	0.60115	0.76201	1	psen2	3135.19	3135.19	3135.19		3135.19		DOWN	0	1
90Day	NF-kB is activated and signals survival	0.64343	0.73175	1	nfkbia	3601.1	3601.1	3601.1		3601.1		DOWN	0	1
90Day	Citric acid cycle (TCA cycle)	0.60445	0.67629	1	sdha;succlg2	2718.325	2718.325	2609.96	153.251253	2737.61233	150.804323	DOWN	0	1
90Day	PI3P Regulates TP53 Acetylation	0.68675	0.69764	1	pin1	4947.7	4947.7	4947.7		4947.7		UP	1	0
90Day	Mitotic Telophase/Cytokinesis	0.52086	0.81269	1	nucd	3184.54	3184.54	3184.54		3184.54		UP	1	0
90Day	Dermatan sulfate biosynthesis	0.64343	0.73175	1	bgn	4533.35	4533.35	4533.35		4533.35		DOWN	0	1
90Day	COPI-independent Golgi-to-ER retrograde traffic	0.5611	0.62317	1	tubb6;dctn3;tubb4b;tubb2a;tuba1b	1992.6502	1781.5	779.791	1072.82446	1774.95351	1190.4266	UP	0.8	0.2
90Day	Dopamine Neurotransmitter Release Cycle	0.54177	0.72694	1	lin7c;unc13b	4173.34	4173.34	3775.77	562.248886	4004.12754	508.780988	UP	1	0
90Day	Sema3A PAK dependent Axon repulsion	0.48325	0.83383	1	hsp90aa1	426.32	426.32	426.32		426.32		UP	1	0
90Day	Hedgehog ligand biogenesis	0.4475	0.85258	1	notum	4035.02	4035.02	4035.02		4035.02		DOWN	0	1
90Day	Beta oxidation of lauroyl-CoA to decanoyl-CoA-CoA	0.69859	1	1										
90Day	Frs2-mediated activation	0.43294	1	1										
90Day	Signalling to ERKs	0.51148	0.74964	1	mapk14;sos1	5078.445	5078.445	4261.96	1154.68416	5603.32821	884.472008	DOWN	0	1
90Day	Insulin processing	0.48325	0.83383	1	exoc4	2113.16	2113.16	2113.16		2113.16		UP	1	0
90Day	IRAK1 recruits IKK complex	0.60115	0.76201	1	ikbkg	3265.56	3265.56	3265.56		3265.56		UP	1	0
90Day	TRAF6 mediated IRF7 activation in TLR7/8 or 9 signaling	0.60115	0.76201	1	irf7	5689.7	5689.7	5689.7		5689.7		UP	1	0
90Day	IRAK1 recruits IKK complex upon TLR7/8 or 9 stimulation	0.60115	0.76201	1	ikbkg	3265.56	3265.56	3265.56		3265.56		UP	1	0
90Day	The retinoid cycle in cones (daylight vision)	0.54997	1	1										
90Day	Opsins	0.77469	0.61588	1	opn3	5797.17	5797.17	5797.17		5797.17		UP	1	0
90Day	Resolution of D-loop Structures through Synthesis-Dependent Strand Annealing (SDSA)	0.66427	0.57395	1	rad51;brca2;rad51c	3127.57067	4249.95	513.022	2271.80208	3130.56464	2280.41	UP	1	0
90Day	Activation of RAS in B cells	0.54997	1	1										
90Day	Rap1 signalling	0.52086	0.81269	1	ywhaz	137.958	137.958	137.958		137.958		UP	1	0
90Day	Transport of organic anions	0.48325	0.83383	1	slco2b1	1935.84	1935.84	1935.84		1935.84		DOWN	0	1
90Day	Urea cycle	0.73069	0.6592	1	arg2	4132.01	4132.01	4132.01		4132.01		UP	1	0
90Day	Protein methylation	0.52086	0.81269	1	etfbkmt	3942.91	3942.91	3942.91		3942.91		UP	1	0
90Day	SCF-beta-TrCP mediated degradation of Emi1	0.77469	0.61588	1	btrc	5152.7	5152.7	5152.7		5152.7		DOWN	0	1

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.															
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down	
90Day	Regulation of expression of SLITs and ROBOs	0.48796	1	1											
90Day	NOTCH3 Activation and Transmission of Signal to the Nucleus	0.63654	0.64822	1	psen2;dll1	2793.24	2793.24	2451.29	483.590328	2851.27329	476.575156	DOWN	0	1	
90Day	TFAP2 (AP-2) family regulates transcription of cell cycle factors	0.69859	1	1											
90Day	p38MAPK events	0.77469	0.61588	1	mapk14	4261.96	4261.96	4261.96		4261.96		DOWN	0	1	
90Day	Metabolism of ingested SeMet, Sec, MeSec into H2Se	0.78732	1	1											
90Day	Creatine metabolism	0.68675	0.69764	1	slc6a12	3445.15	3445.15	3445.15		3445.15		DOWN	0	1	
90Day	Nuclear Pore Complex (NPC) Disassembly	0.50611	0.71566	1	nek6;nup153;sec13	3294.01	3442.78	2758.9	478.400366	3382.9906	363.640364	UP	1	0	
90Day	Coenzyme A biosynthesis	0.77469	0.61588	1	pank1	2679.72	2679.72	2679.72		2679.72		DOWN	0	1	
90Day	Anchoring fibril formation	0.48325	0.83383	1	bmp1	190.369	190.369	190.369		190.369		DOWN	0	1	
90Day	GP1b-IX-V activation signalling	0.60115	0.76201	1	ywhaz	137.958	137.958	137.958		137.958		UP	1	0	
90Day	PD-1 signaling	0.4475	0.85258	1	h2-aa	3001.17	3001.17	3001.17		3001.17		DOWN	0	1	
90Day	Metabolism of nitric oxide	0.4475	0.85258	1	hsp90aa1	426.32	426.32	426.32		426.32		UP	1	0	
90Day	eNOS activation	0.60115	0.76201	1	hsp90aa1	426.32	426.32	426.32		426.32		UP	1	0	
90Day	eNOS activation and regulation	0.4475	0.85258	1	hsp90aa1	426.32	426.32	426.32		426.32		UP	1	0	
90Day	Glyoxylate metabolism and glycine degradation	0.584	0.64989	1	ndufab1;hoga1;agxt	2143.492	3027.04	105.476	1770.16421	2350.01449	1669.89196	DOWN	0.333333333	0.666666667	
90Day	TNFR1-mediated ceramide production	0.48796	1	1											
90Day	Regulation of gene expression by Hypoxia-inducible Factor	0.43294	1	1											
90Day	Translocation of SLC2A4 (GLUT4) to the plasma membrane	0.73069	0.6592	1	ywhaz	137.958	137.958	137.958		137.958		UP	1	0	
90Day	TP53 regulates transcription of several additional cell death genes whose specific roles in p53-dependent apoptosis remain uncertain	0.69859	1	1											
90Day	Nuclear signaling by ERBB4	0.48796	1	1											
90Day	RUNX3 regulates YAP1-mediated transcription	0.61984	1	1											
90Day	Synthesis of bile acids and bile salts via 27-hydroxycholesterol	0.48796	1	1											
90Day	Mismatch repair (MMR) directed by MSH2:MSH3 (MutSbeta)	0.48796	1	1											
90Day	Aryl hydrocarbon receptor signalling	0.43294	1	1											
90Day	Phosphorylation of Emi1	0.54997	1	1											
90Day	AMPK inhibits chREBP transcriptional activation activity	0.48796	1	1											
90Day	RHO GTPases Activate NADPH Oxidases	0.63654	0.64822	1	mapk14;pin1	4604.83	4604.83	4261.96	484.891404	4787.23244	410.582968	CONFLICT	0.5	0.5	
90Day	Organic cation/anion/zwitterion transport	0.4475	0.85258	1	slc22a1	1050.57	1050.57	1050.57		1050.57		DOWN	0	1	
90Day	PI-3K cascade:FGFR3	0.66889	0.61824	1	gab1;fgf1	184.4285	184.4285	126.428	82.0250937	169.646309	79.3163895	DOWN	0	1	
90Day	NRIF signals cell death from the nucleus	0.52086	0.81269	1	psen2	3135.19	3135.19	3135.19		3135.19		DOWN	0	1	
90Day	Telomere Extension By Telomerase	0.78732	1	1											
90Day	Chk1/Chk2(Cds1) mediated inactivation of Cyclin B:Cdk1 complex	0.64343	0.73175	1	ywhaz	137.958	137.958	137.958		137.958		UP	1	0	
90Day	ARMS-mediated activation	0.54997	1	1											
90Day	CREB phosphorylation	0.43294	1	1											
90Day	Beta oxidation of butanoyl-CoA to acetyl-CoA	0.88732	1	1											
90Day	Elevation of cytosolic Ca2+ levels	0.56021	0.78886	1	p2rx4	185.907	185.907	185.907		185.907		DOWN	0	1	
90Day	Neurotransmitter clearance	0.43294	1	1											
90Day	Advanced glycosylation endproduct receptor signaling	0.61984	1	1											
90Day	PTK6 Regulates RTKs and Their Effectors AKT1 and DOK1	0.43294	1	1											

BMD analysis results for functional classification based on dose-responsive genes, using the Reactome database for gene sets in BMDExpress2.2 software.														
Study Day	Gene Set Name	Fisher's Exact Left P-Value	Fisher's Exact Right P-Value	Fisher's Exact Two Tail	Gene Symbols	BMD Mean	BMD Median	BMD Minimum	BMD Standard Deviation	BMD wMean	BMD wSD	Overall Direction	Percent Genes With Overall Direction Up	Percent Genes With Overall Direction Down
90Day	Neurofascin interactions	0.61984	1	1										
90Day	Regulation of IFNG signaling	0.64343	0.73175	1	ifngr2	4021.95	4021.95	4021.95		4021.95		DOWN	0	1
90Day	Synthesis of Ketone Bodies	0.43294	1	1										
90Day	Regulation by c-FLIP	0.68675	0.69764	1	tnfrsf10b	3826.99	3826.99	3826.99		3826.99		UP	1	0
90Day	CASP8 activity is inhibited	0.68675	0.69764	1	tnfrsf10b	3826.99	3826.99	3826.99		3826.99		UP	1	0
90Day	Regulation of necroptotic cell death	0.48325	0.83383	1	tnfrsf10b	3826.99	3826.99	3826.99		3826.99		UP	1	0
90Day	Dimerization of procaspase-8	0.68675	0.69764	1	tnfrsf10b	3826.99	3826.99	3826.99		3826.99		UP	1	0
90Day	Formation of apoptosome	0.78732	1	1										
90Day	Cytochrome c-mediated apoptotic response	0.78732	1	1										
90Day	Regulation of the apoptosome activity	0.78732	1	1										
90Day	Prolactin receptor signaling	0.73069	0.6592	1	btrc	5152.7	5152.7	5152.7		5152.7		DOWN	0	1
90Day	Cam-PDE 1 activation	0.48796	1	1										
90Day	Long-term potentiation	0.61984	1	1										
90Day	Caspase activation via Dependence Receptors in the absence of ligand	0.61984	1	1										
90Day	Organic cation transport	0.60115	0.76201	1	slc22a1	1050.57	1050.57	1050.57		1050.57		DOWN	0	1
90Day	Transfer of LPS from LBP carrier to CD14	0.78732	1	1										
90Day	Translocation of ZAP-70 to Immunological synapse	0.64343	0.73175	1	h2-aa	3001.17	3001.17	3001.17		3001.17		DOWN	0	1
90Day	Enzymatic degradation of dopamine by COMT	0.78732	1	1										
90Day	Dopamine clearance from the synaptic cleft	0.69859	1	1										
90Day	Ligand-receptor interactions	0.43294	1	1										
90Day	Synthesis of dolichyl-phosphate mannose	0.69859	1	1										
90Day	EGFR Transactivation by Gastrin	0.73069	0.6592	1	sos1	5894.93	5894.93	5894.93		5894.93		DOWN	0	1
90Day	Interconversion of 2-oxoglutarate and 2-hydroxyglutarate	0.69859	1	1										
90Day	Oxygen-dependent asparagine hydroxylation of Hypoxia-inducible Factor Alpha	0.69859	1	1										
90Day	FGFR3 ligand binding and activation	0.56021	0.78886	1	fgf1	242.429	242.429	242.429		242.429		DOWN	0	1
90Day	FGFR3c ligand binding and activation	0.56021	0.78886	1	fgf1	242.429	242.429	242.429		242.429		DOWN	0	1
90Day	FGFR1c ligand binding and activation	0.64343	0.73175	1	fgf1	242.429	242.429	242.429		242.429		DOWN	0	1
90Day	FGFR2c ligand binding and activation	0.56021	0.78886	1	fgf1	242.429	242.429	242.429		242.429		DOWN	0	1
90Day	Phospholipase C-mediated cascade; FGFR3	0.56021	0.78886	1	fgf1	242.429	242.429	242.429		242.429		DOWN	0	1
90Day	SHC-mediated cascade:FGFR3	0.66889	0.61824	1	sos1;fgf1	3068.6795	3068.6795	242.429	3996.92179	4960.29053	2969.67998	DOWN	0	1
90Day	Platelet sensitization by LDL	0.7013	0.58634	1	mapk14;apob	2218.96	2218.96	175.96	2889.23831	1673.63662	2784.41068	DOWN	0	1
90Day	Neurophilin interactions with VEGF and VEGFR	0.61984	1	1										
90Day	Formyl peptide receptors bind formyl peptides and many other ligands	0.77469	0.61588	1	hebp1	2191.05	2191.05	2191.05		2191.05		DOWN	0	1
90Day	Role of LAT2/NTAL/LAB on calcium mobilization	0.73069	0.6592	1	sos1	5894.93	5894.93	5894.93		5894.93		DOWN	0	1
90Day	Regulation of commissural axon pathfinding by SLIT and ROBO	0.69859	1	1										
90Day	Degradation of GABA	0.78732	1	1										
90Day	Beta oxidation of decanoyl-CoA to octanoyl-CoA-CoA	0.88732	1	1										
90Day	Telomere C-strand synthesis initiation	0.77469	0.61588	1	pole4	5853.8	5853.8	5853.8		5853.8		DOWN	0	1
90Day	DNA replication initiation	0.77469	0.61588	1	pole4	5853.8	5853.8	5853.8		5853.8		DOWN	0	1
90Day	Rhesus glycoproteins mediate ammonium transport.	0.69859	1	1										
90Day	Signaling by Leptin	0.78732	1	1										
90Day	PKA-mediated phosphorylation of key metabolic factors	0.88732	1	1										