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# Provisional Peer-Reviewed Toxicity Values for

# Diisopropyl Methylphosphonate
(CASRN 1445-75-6)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
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## COMMONLY USED ABBREVIATIONS

| | |
|---|---|
| BMC | benchmark concentration |
| BMCL | benchmark concentration lower bound 95% confidence interval |
| BMD | benchmark dose |
| BMDL | benchmark dose lower bound 95% confidence interval |
| HEC | human equivalent concentration |
| HED | human equivalent dose |
| IUR | inhalation unit risk |
| LOAEL | lowest-observed-adverse-effect level |
| $LOAEL_{ADJ}$ | LOAEL adjusted to continuous exposure duration |
| $LOAEL_{HEC}$ | LOAEL adjusted for dosimetric differences across species to a human |
| NOAEL | no-observed-adverse-effect level |
| $NOAEL_{ADJ}$ | NOAEL adjusted to continuous exposure duration |
| $NOAEL_{HEC}$ | NOAEL adjusted for dosimetric differences across species to a human |
| NOEL | no-observed-effect level |
| OSF | oral slope factor |
| p-IUR | provisional inhalation unit risk |
| POD | point of departure |
| p-OSF | provisional oral slope factor |
| p-RfC | provisional reference concentration (inhalation) |
| p-RfD | provisional reference dose (oral) |
| RfC | reference concentration (inhalation) |
| RfD | reference dose (oral) |
| UF | uncertainty factor |
| $UF_A$ | animal-to-human uncertainty factor |
| $UF_C$ | composite uncertainty factor |
| $UF_D$ | incomplete-to-complete database uncertainty factor |
| $UF_H$ | interhuman uncertainty factor |
| $UF_L$ | LOAEL-to-NOAEL uncertainty factor |
| $UF_S$ | subchronic-to-chronic uncertainty factor |
| WOE | weight of evidence |

# PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR DIISOPROPYL METHYLPHOSPHONATE (CASRN 1445-75-6)

## BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (www.epa.gov/iris), the respective PPRTVs are removed from the database.

## DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

## QUESTIONS REGARDING PPRTVS

Questions regarding the contents and appropriate use of this PPRTV assessment should be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

## INTRODUCTION

Diisopropyl methylphosphonate (DIMP), CAS No. 1445-75-6, is an organophosphorus compound (structure provided in Figure 1) that is a byproduct of the manufacture of the nerve agent sarin (ATSDR, 1998). DIMP constitutes 2−3% of the crude sarin product (ATSDR, 1998). It may also be used to simulate G-type chemical agents (HSDB, 2000). A table of the physicochemical properties is provided below (see Table 1).

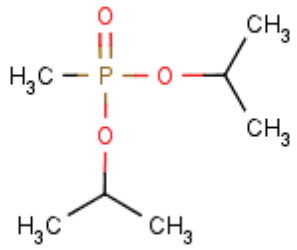


**Figure 1. DIMP Structure**

**Table 1. Physicochemical Properties of DIMP (CASRN 1445-75-6)[a]**

| Property (unit) | Value |
|---|---|
| Boiling point (ºC at 10 mm Hg) | 121.05 |
| Melting point (ºC) | No data |
| Density (g/mL at 25ºC) | 0.976 |
| Vapor pressure (mm Hg at 25ºC) | 0.28 |
| Solubility in water (g/1000 mL at 25ºC) | 160 |
| Relative vapor density (air = 1) | 0.976 |
| Molecular weight (g/mol) | 180.21 |

[a]Sources: HSDB, 2000; U.S. EPA, 1989.

A Reference Dose (RfD) of $8 \times 10^{-2}$ mg/kg-day for DIMP is included on IRIS (U.S. EPA, 1993), but a Reference Concentration (RfC) is not included. The Drinking Water Standards and Health Advisories List (U.S. EPA, 2009) lists various health advisory values, including an RfD of $8 \times 10^{-2}$ mg/kg-day for DIMP. No RfD or RfC values are reported in the Health Effects Assessment Summary Tables (HEAST) (U.S. EPA, 2011). The Chemical Assessments and Related Activities (CARA) list does not include a Health and Environmental Effects Profile (HEEP) that derived noncancer toxicity or potential carcinogenicity values for DIMP (U.S. EPA, 1994). The toxicity of DIMP has been reviewed by the Agency for Toxic Substances and Disease Registry (ATSDR, 1998). ATSDR recommends an intermediate-duration oral Minimum Risk Level (MRL) of 0.8 mg/kg-day based on the lack of

noticeable effects in dogs treated with DIMP for 90 days (Hart, 1980a). ATSDR also lists a chronic-duration oral MRL of 0.6 mg/kg-day based on the lack of noticeable effects in mink treated with DIMP for 13 months (Bucci et al., 2003). The toxicity of DIMP has not been reviewed by the World Health Organization (WHO, 2011). The California Environmental Protection Agency (CalEPA, 2008, 2009) has not derived toxicity values for exposure to DIMP. No occupational exposure limits for DIMP have been derived or recommended by the American Conference of Governmental Industrial Hygienists (ACGIH, 2011), the National Institute of Occupational Safety and Health (NIOSH, 2011), or the Occupational Safety and Health Administration (OSHA, 2011).

IRIS (U.S. EPA, 1993) reports a cancer weight-of-evidence (WOE) classification of Group D ("*Not Classifiable as a Human Carcinogen*") due to the lack of epidemiological studies or animal bioassays for DIMP. The HEAST (U.S. EPA, 2011) does not report a cancer WOE classification or an oral slope factor. The International Agency for Research on Cancer (IARC, 2011) has not reviewed the carcinogenic potential of DIMP. DIMP is not included in the *12th Report on Carcinogens* (NTP, 2011). CalEPA (2008) has not derived a quantitative estimate of carcinogenic potential for DIMP.

Literature searches were conducted on sources published from 1900 through January 2012 for studies relevant to the derivation of provisional toxicity values for DIMP, CAS No. 1445-75-6. Searches were conducted using EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications [NSCEP] and National Environmental Publications Internet Site [NEPIS] database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI, and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others); World Health Organization; and Worldwide Science. The following databases outside of HERO were searched for relevant health information: ACGIH, ATSDR, CalEPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, U.S. EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

## REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 2 provides an overview of the relevant database for DIMP and includes all potentially relevant repeated short-term-, subchronic-, and chronic-duration studies. Principal studies are identified. The phrase "statistical significance," used throughout the document, indicates a $p$-value of $<0.05$. Finally, studies that are not published in peer-refereed journals are reported as unpublished studies in the text and Table 2.

**Table 2. Summary of Potentially Relevant Data for DIMP (CASRN 1445-75-6)**

| Category | Number of Male/Female, Strain, Species, Study Type, Study Duration | Dosimetry[a] | Critical effects | NOAEL[a] | BMDL/ BMCL[a] | LOAEL[a] | Reference (Comments) | Notes[b] |
|---|---|---|---|---|---|---|---|---|
| **Human** | | | | | | | | |
| **1. Oral (mg/kg-d)[a]** | | | | | | | | |
| Subchronic | ND | | | | | | | |
| Chronic | ND | | | | | | | |
| Developmental | ND | | | | | | | |
| Reproductive | ND | | | | | | | |
| Carcinogenicity | ND | | | | | | | |
| **2. Inhalation ($mg/m^3$)[a]** | | | | | | | | |
| Subchronic | ND | | | | | | | |
| Chronic | ND | | | | | | | |
| Developmental | ND | | | | | | | |
| Reproductive | ND | | | | | | | |
| Carcinogenicity | ND | | | | | | | |
| **Animal** | | | | | | | | |
| **1. Oral (mg/kg-d)[a]** | | | | | | | | |
| Subchronic | 32/32 per dose, S-D, rat, diet, 7 d/wk, 90 d | Males: 0, 24.74, 74.58, 229.17; Females: 0, 27.98, 92.31, 257.58 (Adjusted) | No adverse effects | 257.58 | NDr | NDr | Hart (1976a) | NPR |

**Table 2. Summary of Potentially Relevant Data for DIMP (CASRN 1445-75-6)**

| Category | Number of Male/Female, Strain, Species, Study Type, Study Duration | Dosimetry[a] | Critical effects | NOAEL[a] | BMDL/ BMCL[a] | LOAEL[a] | Reference (Comments) | Notes[b] |
|---|---|---|---|---|---|---|---|---|
| Subchronic | 30 (29 at high dose)/30 per dose, ICR Swiss Albino, mouse, diet, 7 d/wk, 90 d | Males: 0, 37.94, 108.18, 337.27; Females: 0, 42.00, 142.59, 460.38 (Adjusted) | No adverse effects | 460.38 | NDr | NDr | Hart (1976b) | NPR |
| | 4/4 per dose, Beagle, dog, diet, 7 d/wk, 90 d | Males: 0, 5.30, 40.43, 85.32; Females: 0, 4.55, 46.97, 92.78 (Adjusted) | No adverse effects | 92.78 | NDr | NDr | U.S. DOD (1980); Hart (1980a) | IRIS, NPR |
| | **10/10 per dose, Ranch Wild, brown mink, diet, 90 d** | **Males: 0, 6.8, 63.4, 344.7, 747.1, 1008.6; Females: 0, 9.0, 82.3, 455.2, 907.7, 1263.5 (Adjusted)** | **Increased Heinz bodies** | **344.7** | **NDr** | **747.1** | **Bucci et al. (1994)** | **PS, PR** |
| Chronic | ND/ND, S-D, rat, drinking water, 7 d/wk, 26 wk | 0.8[c] (Adjusted) | No adverse effects | 0.8 | NDr | NDr | U.S. DOD (1978) as reported by U.S. EPA (1993) | PR |
| Developmental | 0/20 per dose, CRL:COBS CD (SD) BR rat, diet, GDs 6−15 | 0, 7.4, 21.6, 232.5 | No adverse effects | 232.5 | NDr | NDr | Hart (1980b) | NPR |

**Table 2. Summary of Potentially Relevant Data for DIMP (CASRN 1445-75-6)**

| Category | Number of Male/Female, Strain, Species, Study Type, Study Duration | Dosimetry[a] | Critical effects | NOAEL[a] | BMDL/ BMCL[a] | LOAEL[a] | Reference (Comments) | Notes[b] |
|---|---|---|---|---|---|---|---|---|
| Reproductive | 10/20 per dose, S-D, CD rat, diet, 3-generation reproductive study dosed through the end of lactation, 13-wk exposure for males and 19 wk exposure for females | 135[d] (Adjusted) | No adverse effects | 135 | NDr | NDr | U.S. DOD (1980); Hart (1980c) | NPR |
| | 6/24 per dose, dark mink, diet, 1-generation reproductive study, 12 mo | 0, 11, 37, 95 (Adjusted) | Mortality seen in low-, mid-, and high-dose groups; significance is questionable since no other effects were seen and the mortality rate of first-year mink in commercial fur ranch operations is approximately 6% annually; however, no mortality observed in the controls | NDr | NDr | NDr | U.S. DOD (1979); Aulerich et al. (1979) | PR |
| | 9/35 per dose, Ranch Wild, brown mink, diet, 2-generation reproductive study | F0 males: 0, 14.94, 47.36, 284.79; F0 females: 0, 25.61, 84.81, 460.72 (Adjusted)<br><br>F1 males: 0, 15.67, 45.00, 261.73; F1 females: 0, 19.74, 56.50, 329.47 (Adjusted) | Hematological changes seen at the highest dose in F0 females and F1 males and females | 56.5 | NDr | 329.5 | Bucci et al. (2003); Concerns regarding the methodology and data interpretation of the data have been raised (Calabrese, 2003a,b, 2005; Colagiovanni , 2006; Calonge, 2006). | PR |

**Table 2. Summary of Potentially Relevant Data for DIMP (CASRN 1445-75-6)**

| Category | Number of Male/Female, Strain, Species, Study Type, Study Duration | Dosimetry[a] | Critical effects | NOAEL[a] | BMDL/ BMCL[a] | LOAEL[a] | Reference (Comments) | Notes[b] |
|---|---|---|---|---|---|---|---|---|
| Carcinogenicity | ND | | | | | | | |
| **2. Inhalation (mg/m$^3$)[a]** | | | | | | | | |
| Subchronic | ND | | | | | | | |
| Chronic | ND | | | | | | | |
| Developmental | ND | | | | | | | |
| Reproductive | ND | | | | | | | |
| Carcinogenicity | ND | | | | | | | |

[a]Dosimetry: NOAEL, BMDL/BMCL, and LOAEL values are converted to an adjusted daily dose (ADD in mg/kg-d) for oral noncancer effects. All long-term exposure values (4 wk and longer) are converted from a discontinuous to a continuous (weekly) exposure. Values from animal developmental studies are not adjusted to a continuous exposure.
[b]Notes: IRIS = Utilized by IRIS, date of last update; PS = principal study, PR = peer reviewed, NPR = not peer reviewed.
[c]U.S. EPA (1993) reported doses of 0, 0.0000044, 0.000044, 0.0736, and 7.36 mg/L, but only provided the adjusted value for the highest dose.
[d]U.S. EPA (1993) reported doses of 0, 300, and 3000 ppm, but only provided the adjusted value for the highest dose.

NA = Not applicable, ND = No data, NDr = Not determined, NR = Not reported, S-D = Sprague-Dawley.

## HUMAN STUDIES

### Oral Exposures

No studies were identified on the oral exposure of DIMP to humans.

### Inhalation Exposures

No studies were identified on the inhalation exposure of DIMP to humans.

## ANIMAL STUDIES

### Oral Exposures

The effects of oral exposure to DIMP in animals have been evaluated in four subchronic (Hart, 1976a,b, 1980a; Bucci et al., 1994), one chronic (U.S. Department of Defense [DOD], 1978, as reported by U.S. EPA, 1993), one developmental (Hart, 1980b), and three reproductive (U.S. DOD, 1979, as reported by U.S. EPA, 1993; Hart, 1980c, as reported by U.S. EPA, 1993; Bucci et al., 2003) studies.

#### *Subchronic Studies*

*Hart (1976a)*

Hart (1976a) administered DIMP (88−95% pure) at concentrations of 0, 300, 1000, or 3000 ppm in the diet for 90 days to male and female Sprague-Dawley rats (32/sex/treatment group). The data are available but are not published in a peer-refereed journal. Because this proprietary study is summarized by IRIS (U.S. EPA, 1993), the Hart (1976a) study is considered to be sufficiently peer-reviewed for use in this assessment. In the study, average daily doses are estimated to be 0, 24.74, 74.58, or 229.17 mg/kg-day for males and 0, 27.98, 92.31, or 257.58 mg/kg-day for females based on the average body weights and food consumption reported. Animals were obtained from ARS/Sprague Dawley (Madison, WI). Water was provided ad libitum. Body weight and food consumption were measured weekly throughout the study. Weekly examinations for overall appearance, behavior, and signs of toxicity were performed. Hematocytology, blood biochemistry, acetylcholinesterase, and urinalysis measurements were taken from 5 animals/sex/treatment group at 4 and 13 weeks. The following endpoints were measured: erythrocyte count, packed cell volume, hemoglobin, leukocyte count, differential leukocyte count, glucose, blood urea nitrogen, serum glutamic-pyruvic transaminase, serum glutamic-oxaloacetic transaminase, serum alkaline phosphatase, sodium, potassium, chloride, acetylcholinesterase (red blood cell [RBC], plasma, and brain), color, specific gravity, pH, sugar, protein, ketones, and a microscopic examination of the sediment in the urine. The following organs were removed and weighed at necropsy: liver, brain, thyroid, kidneys, adrenal glands, heart, gonads, and spleen. Histopathological examinations were conducted on five animals/sex in the control and high-dose groups.

No treatment-related mortality, or alterations of body weight, or food consumption were seen during the course of the study (see Table B.1). Opacity of the eye lens was seen in 2−5 rats per dose group (data not provided). However, the study authors reported that this is considered normal and unrelated to DIMP exposure. There were sporadic, statistically significant changes in the hematology and blood biochemistry results, but these are not considered to be treatment-related by the authors, who stated that any statistically significant results were "of no toxicologic importance" (see Tables B.2 and B.3 for males and females, respectively). No significant findings were stated in the urinalysis report. An evaluation of the RBC, plasma, and brain cholinesterase levels indicates a decrease in plasma cholinesterase levels after 13 weeks of exposure in the low- and mid-dose groups and a statistically significant increase in plasma

cholinesterase levels in high-dose males; however, no treatment-related effects were seen in the RBC or brain cholinesterase levels (see Tables B.4 and B.5 for males and females, respectively). It should be noted that plasma cholinesterase is considered a biomarker of exposure (ATSDR, 1998) and is not considered an adverse effect when other indications of neurotoxicity or liver toxicity are lacking. Please see the section titled "Derivation of Oral Reference Doses" for a discussion of the use of cholinesterase inhibition as a POD. There were no treatment-related effects on organ weight; however, several pages of the document photocopy (the only obtainable copy) were of poor quality, and the organ-weight data were unreadable. Due to the lack of adverse effects, the NOAEL is considered to be 257.58 mg/kg-day; no LOAEL can be determined.

*Hart (1976b)*

Hart (1976b) conducted a subchronic (90-day) oral toxicity study of DIMP using ICR Swiss Albino mice. The data are available, but are not published in a peer-refereed journal. Each treatment group and control group contained 30 mice per sex, except the high-dose group of males that contained only 29 animals. DIMP was obtained from Richmond Organics (Richmond, VA) with a reported purity of between 88−95%. The animals were fed 0, 210, 700, or 2100 ppm DIMP in a diet of Purina Rodent Chow. Average daily doses are estimated to be 0, 37.94, 108.18, or 337.27 mg/kg-day for males and 0, 42.00, 142.59, or 460.38 mg/kg-day for females based on the average body weights and food consumption reported in the study. Animals were obtained from Flow Laboratories (Rockville, MD). Water was provided ad libitum, and mice were housed five to a cage. Body weight and food consumption were measured weekly throughout the course of the study. Weekly examinations for overall appearance, behavior, and signs of toxicity were performed. Twenty mice per sex per group were necropsied at 13 weeks. The remaining animals were maintained on the control diet for 2 or 4 weeks to evaluate possible recovery effects. The following organs were removed and weighed at necropsy: heart, liver, thyroid, kidneys, adrenal glands, spleen, and gonads. The following body parts were microscopically examined for abnormalities in five animals per sex in the control and high-dose group: brain, pituitary, thyroid, heart, liver, spleen, kidneys, adrenals, stomach, pancreas, small intestines, large intestines, mesenteric lymph node, testes or ovaries, uterus or prostate, bone marrow, and urinary bladder. The study authors did not provide any information on the statistical methods used.

No treatment-related mortality was seen. Two male mice in the control group and 3 male mice in the 210 mg/kg-day group escaped. One female mouse in the control was missexed. Therefore, these animals were not available for evaluation. No treatment-related effects were seen in body weight or food consumption (see Table B.6). The study authors did not report any significant changes in the relative organ weights compared with the control. Data tables for the organ weights could not be transcribed because several pages of the study photocopy were not readable. Microscopic examination revealed no treatment-related effects. The planned recovery experiments were deemed "noncontributory" because no toxic effects were seen during the dosing period. The study authors concluded that DIMP does not cause toxic effects in mice at the administered doses. Based on a lack of treatment-related effects, the NOAEL for this study is 460.38 mg/kg-day; no LOAEL can be determined.

*Hart (1980a)*

Hart (1980a) conducted a subchronic (90-day) oral toxicity study of DIMP using beagle dogs. The data are available but are not published in a peer-refereed journal. Each treatment group and control group contained 4 dogs per sex (5−6 months old). DIMP was obtained from Richmond Organics (Richmond, VA) with a reported purity of between 88−96%. Animals were fed 0-, 150-, 1500-, or 3000-ppm DIMP in the diet using PEG 400 as a vehicle. Average daily doses are estimated to be 0, 5.30, 40.43 or 85.32 mg/kg-day for males and 0, 4.55, 46.97, 92.78 mg/kg-day for females based on the average body weights and food consumption reported in the study. It should be noted that both IRIS and ATSDR reported 75 mg/kg-day for the high-dose group. IRIS used the assumption that the dogs consumed 2.5% of their body weight; the estimates for this assessment were based on the average food consumption reported by the study authors. Animals were obtained from Hazleton Research Animals, Inc. (Cumberland, VA). Water was provided ad libitum. All dogs were housed in individual cages with 12 hours of light and 12 hours of darkness per day. Standard immunizations were given by the supplier.

Body weight was measured weekly throughout the course of the study. Food consumption was determined twice per week. Daily examinations for each animal's overall condition, behavior, and fecal consistency were performed. Instances of *Giardia canis* and *Isospora canis* were reported, and all animals were treated with sulfamethazine and quinacrine hydrochloride for 12 days. Hematology and blood chemistry were measured at 0, 4, 8, and 13 weeks. The following endpoints were measured: erythrocyte count, leukocyte count, differential leukocyte count, hemoglobin, packed cell volume, clotting time, glucose, blood urea nitrogen, serum glutamic-pyruvic transaminase, serum glutamic-oxaloacetic transaminase, serum alkaline phosphatase, total protein, albumin/globulin ratio, creatinine, sodium, chloride, calcium, uric acid, bilirubin, cholesterol, lactic dehydrogenase, acetylcholinesterase (RBC and plasma), creatinine phosphokinase (CPK), total iron, triglycerides, carbon dioxide, phosphorus, albumin, and potassium. The following organs were removed and weighed at necropsy: liver, brain, thyroid, kidneys, adrenal glands, testes or ovaries, heart, and spleen. Statistical significance between the treatment and control groups was determined using the Dunnett's *t*-test ($p \leq 0.05$); calculations were performed by the American Statistical Association.

Body weight and food consumption remained normal throughout the course of the study (see Table B.7). The hematology and clinical chemistry results are summarized in Tables B.8 and B.9 for males and females, respectively. After 4 weeks of treatment, an increase in clotting time in males in the 39.08-mg/kg-day dose group was statistically different from the control, but clotting time was not statistically elevated in males receiving the highest dose. Following 8 weeks of treatment, a decrease in phosphorous was seen in all of the treated males, but levels were not statistically different by Week 13. No other changes in hematology or clinical chemistry data were seen throughout the course of the study. The authors noted that RBC cholinesterase measurements could not be used for comparisons due to technical difficulties with the samples. Absolute and relative organ weights are provided in Tables B.10 and B.11, respectively. The relative ovary weight was increased in all female treatment groups, but a level of statistical significance was only achieved in the mid-dose group. There were no other dose responses or histopathological results to indicate the adversity of this endpoint, nor were standard deviations or individual data provided to determine the variability within each group. No other relative or absolute organ weights were significantly different from the control group. Due to the lack of treatment-related effects seen at the highest dose, a NOAEL of 92.78 mg/kg-day is determined; no LOAEL can be determined.

*Bucci et al. (1994)*

**Bucci et al. (1994) is selected as the principal study for the derivation of the subchronic p-RfD.** Bucci et al. (1994) conducted a peer-reviewed, subchronic (90-day) oral toxicity study on exposure to DIMP in Ranch Wild brown mink (*Mustela vison*). The proprietary data (Bucci et al., 1992) were also available for review. Each dose group and the 3 control groups contained 10 mink per sex per group (12 months old). DIMP was obtained from Lancaster Synthesis Inc., Ltd. (Windham, NH) with a reported purity of 95%. The animals were fed 0-, 50-, 450-, 2700-, 5400-, or 8000-ppm DIMP in the diet. The study authors reported average daily doses of 0, 6.8, 63.4, 344.7, 747.1, or 1008.6 mg/kg-day for males and 0, 9.0, 82.3, 455.2, 907.7, or 1263.5 mg/kg-day for females. Water was provided ad libitum. The control groups consisted of one group that was fed ad libitum, one group that was fed to match the food intake of the second highest dose group, and one group that was fed to match the food intake of the highest dose group. The study authors reported that the study followed Good Laboratory Practice (GLP) Standards. All mink were housed individually with 12.5 hours of light and 11.5 hours of darkness. The temperature was maintained at 23 ± 5°C and 30−70% relative humidity. Body weight and food consumption were reported weekly. Clinical observations were recorded twice daily. Hematology and clinical chemistry were determined from blood samples taken on Weeks 0, 3, 7, and 13. The measured endpoints included the following: hematocrit, hemoglobin, and erythrocyte counts, mean cell volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocyte count, RBC morphology, Heinz bodies, total leukocyte count, differential leukocyte count, and platelet count; in addition, plasma and RBC cholinesterase, blood urea nitrogen, creatinine, glucose, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, sodium chloride, potassium, total osmolarity, total $CO_2$, anion gap, total calcium, and inorganic phosphorus levels were measured. Two male and two female mink from the 2700- and 8000-ppm groups were necropsied after a 4-week observation period. All other mink were necropsied at the end of the exposure period. At necropsy, tissues samples were taken from all organ systems for microscopic examination. The study authors reported that statistical significance was determined using the "repeated" option of PROC GLM of SAS 1987 to account for the repeated measurements of each endpoint. Additional details on the statistical methods of analysis were not provided.

The study authors reported a statistically significant reduction in the body weights of the males and females in the high-dose group when compared with the controls (see Table B.12). The study authors concluded that these reductions in body weight were caused by decreased food consumption due to taste aversion. This was supported by a similar decrease in body weight seen in the control group with matched food consumption. The study authors noted that matching the food consumption of the control group was only partially successful because the mink in the control group tended to overcompensate when their food was available ad libitum. Tables B.13 and B.14 show the reported changes in hematocrit, hemoglobin, erythrocyte count, reticulocytes, Heinz bodies, and plasma cholinesterase levels recorded in females and males, respectively. The study authors reported statistically significant decreases in hematocrit, hemoglobin, erythrocyte, and plasma cholinesterase levels. There were also significant increases in reticulocytes, and Heinz bodies, that started at Week 3 in females receiving 1263.5 mg/kg-day. In females receiving 907.7 mg/kg-day, statistically significant reductions were seen in hematocrit, hemoglobin, and plasma cholinesterase levels starting at Week 3. Statistically significant increases were seen in the reticulocyte count at Week 3 and the number of Heinz bodies starting at Week 7.

In males, statistically significant decreases (hematocrit and erythrocytes) and increases (reticulocytes) were seen in animals receiving 1008.6 mg/kg-day starting at Week 13 for hematocrit, starting at Week 7 for erythrocytes and reticulocytes, and statistically significant decreases (hemoglobin and plasma cholinesterase) and increases (Heinz bodies) starting at Week 3 for hemoglobin, Heinz bodies, and plasma cholinesterase levels. In males receiving 747.1 mg/kg-day, statistically significant increases were seen at Week 3 for reticulocytes, starting at Week 7 for Heinz bodies, and decreases starting at Week 3 for plasma cholinesterase levels. In animals receiving 344.7 mg/kg-day, statistically significant reductions were found in plasma cholinesterase levels starting at Week 7. As previously discussed, the plasma cholinesterase level is considered a biomarker of exposure and is not considered an adverse effect. The RBC acetylcholinesterase level was not affected by treatment with DIMP. Erythrocyte morphology indicated mild-to-moderate dose- and time-dependent changes in both male and female mink (data not reported). Platelet count and white blood cell (WBC) counts were not biologically or statistically different from the controls. During a 4-week untreated phase at the end of the study, animals in the mid- and high-dose groups showed no treatment-related effects to any of the erythrocyte-related endpoints (see Table B.15). Examination of the spleen revealed no statistically significant increase in the incidence or severity of hematopoiesis in high-dose males and females; no effects were seen following the 4-week recovery phase (see Table B.16). For this study, a NOAEL of 344.7 mg/kg-day and a LOAEL of 747.1 mg/kg-day are determined based on the observed increased Heinz bodies.

***Chronic Studies***

There is one chronic study (U.S. DOD, 1978) summarized by IRIS (U.S. EPA, 1993) where animals were administered adjusted daily doses of up to 0.8-mg/kg-day DIMP (purity not reported) in the diet for 26 weeks; however, no adverse effects were reported. Therefore, the information is provided in Table 2, but is not summarized again here.

***Developmental Studies***

*Hart (1980b)*

Hart (1980b) examined the developmental effects of prenatal exposure to DIMP in CRL:COBS CD (SD) BR rats. The unpublished data are available but are not published in a peer-refereed journal. In the study, all rats were obtained from Charles River Breeding Laboratory (Portage, MI) and provided Purina laboratory chow and water ad libitum. The study authors did not report whether the study was conducted in compliance with GLP guidelines. DIMP (purity unspecified) was suspended in 100 mL of polyethylene glycol 400, blended with 10 kg of the basal diet, and incorporated into the diets of 20 pregnant rats per group at doses of 0, 100, 300, or 3000 ppm on Gestation Days (GDs) 6−15. Mean body weights (an average of the body weights recorded on Days 6 and 16) and mean daily food consumption (Days 6−16) during the treatment period were provided by the authors and used to estimate daily average doses of 0, 7.4, 21.6, and 232.5 mg/kg-day, respectively. The female rats were weighed on GDs 0, 6, 16, and 20. Food consumption was measured on GDs 0−6, 6−16, and 16−20. All animals were observed daily for changes in appearance, behavior, and condition. On GD 20, the adult females were sacrificed, and the visceral and thoracic organs were examined. The number of implantation sites and their placement in the uterine horns, live and dead fetuses, and resorption sites were also evaluated in each pregnant female. All fetuses were removed and evaluated for developmental abnormalities, including weight, crown-to-rump length, changes in the soft tissues of the head, thoracic, and visceral organs, and skeletal abnormalities. This study is

considered an acceptable developmental study because it uses an appropriate number of animals and evaluates the offspring for treatment-related visceral and skeletal abnormalities

No treatment-related mortality was reported. Treatment with DIMP did not have any effects on the mean body weight or food consumption (see Table B.17). Table B.18 summarizes the reproductive indices. A statistically significant decrease in the number of implantation sites was observed in the mid-dose group using a $\chi^2$ test of independence (with Yates' correction for continuity), but the number of implantation sites was normal in the high-dose group. The authors also noted that no significant difference was observed in the mid-dose group when the Wilcoxon rank sum test was used. No other treatment-related effects on reproduction were noted. Examination of the offspring indicated a slight, though significant, increase in the number of common skeletal abnormalities in animals that received the highest dose (see Table B.19). The authors noted that this increase, while statistically significant, was not a treatment-related effect for the following reasons: (1) while the increase was significant when using a $2 \times 2$ contingency table, the Wilcoxon rank sum test did not indicate a statistically significant effect; and (2) the observed changes did not suggest a specific area of involvement. No other treatment-related effects on development were noted. Therefore, a NOAEL of 232.5 mg/kg-day is determined; no LOAEL can be determined.

***Reproductive Studies***

Three reproductive studies have been conducted with DIMP. Studies by Bucci et al. (2003) and the U.S. DOD (1979)/Aulerich, et al. (1979) examined reproductive effects of DIMP in mink while the U.S. DOD (1980)/Hart (1980c) study examined reproductive effects in rats.

*Bucci et al. (2003)*

Bucci et al. (2003) conducted a peer-reviewed, continuous breeding, reproductive toxicity study on exposure to DIMP using Ranch Wild brown mink (*Mustela vison*). Each dose group and the 2 control groups contained 9 male and 35 female mink (9 months old). DIMP was obtained from Lancaster Synthesis Inc., Ltd. (Windham, NH) with a reported purity of between 97−99%. The animals were fed 0, 150, 450, or 2500 ppm in the diet. The study authors reported the average daily dose to be 0, 14.94, 47.36, and 284.79 mg/kg-day in F0 males and 0, 25.61, 84.81, and 460.72 mg/kg-day in F0 females. Exposure began when the mink were 9.5 months old. Harem mating occurred at 10.5 months of age, at which point, the F0 males were sacrificed. The F1 generation was born approximately 1.75 months later. The study authors reported the average daily doses as 0, 15.67, 45.00, and 261.73 mg/kg-day in F1 males and 0, 19.74, 56.50, and 329.47 mg/kg-day in F1 females. F0 female mink were sacrificed after weaning was completed (approximately 4 months). The F1 generation was administered feed that contained DIMP at the same doses as the F0 generation. The F1 males were sacrificed after mating (10.5 months of exposure, not including gestational exposure). F1 females were sacrificed after weaning (13.5 months of exposure, not including gestational exposure). The F2 generation males and females were sacrificed at the end of weaning. The study authors state that the study was designed to follow the *Health Effects Test Guidelines for Reproductive and Fertility Effects*, as published by the EPA's Office of Prevention, Pesticides, and Toxic Substances. The study authors also report that the study was GLP compliant. All mink were obtained from the North Branch Fur Farm (North Branch, MN). The study authors stated that realistic photoperiods were maintained because they are critical for mink breeding patterns. Mink in both the F0 and F1 generations were vaccinated at 11 weeks of age for "common mink diseases." Body weight and food consumption were measured weekly until mating and then on the day of whelping, 28 days

after whelping, and on the day of sacrifice. The number of kits per litter, live kits per litter, litter weights at birth, litter weights at 28 days after birth, and the sex ratios were measured in both the F0 and F1 generations. Gross necropsy and microscopic examinations were conducted on all parents and kits. The microscopic examination was limited to the reproductive organs of the males and any lesions found in the kits. A total of 10 females per group had cholinesterase levels measured in the brain. Male sperm count, motility, and morphology were measured using IVOS Automated Semen Analyzers (Beverly, MA). The Krustal-Wallis nonparametric ANOVA test using SAS was used to determine the statistical significance of the sperm count, motility, and morphology data. The LABCAT system was used for statistical comparisons of the body weight, food consumption, and hematological data.

The study authors reported that 3.4% (6/175) of the female mink in the F0 generation died, but the causes of death were unrelated to DIMP exposure. The authors noted that mink are susceptible to physical changes due to increased stress that can lead to death. Approximately 10−15% of nursing dams are susceptible to "nursing disease," in which they are not able to maintain the energy required to nurse their offspring. The authors reported that 4.6% (8/175) of the F1 female mink died early, but, again, DIMP exposure was not determined as the cause of death. Six out of eight of these deaths, which were distributed across the dose and control groups, were associated with the stress of anesthetic administration. No significant differences were seen in the body weights or food consumptions of the dose groups in comparison with the control in either the F0 or F1 male and female mink (see Table B.20). No adverse clinical observations were attributed to DIMP exposure. The authors reported no significant effects to semen, litter size, percent live births, kit weight, or sex distribution (see Tables B.21 and B.22 for female and male reproductive indices, respectively). The study report only provided the hematological results of the high-dose females from the F0 and F1 generations. The authors noted that treatment-related hematological effects were not seen in the females in the other dose groups; however, these data were not reported. The authors noted that data on the hematological effects in males were limited to the effects observed in the high-dose group, as discussed below. F0 females showed significant decreases in the RBC count and increases in reticulocytes, mean corpuscular volume (MCV), and Heinz bodies when compared with the control at the time of necropsy. F1 females showed significant increases in Heinz bodies at 7.5 months of age and at the time of necropsy. The high-dose males in the F2 generation showed significantly decreased RBC counts (4.06 million/µL compared with 4.51 million/µL in the control). No other hematological effects were seen in the F2 generation males or females. Plasma cholinesterase levels were decreased in F1 males (14% decrease compared with control) at 4.5 months of age, and whole blood cholinesterase was decreased in F1 males at 7.5 months of age (6% decrease compared with control) (data not provided). F0 females showed significant decreases in plasma, whole blood cell, and RBC cholinesterase levels at necropsy (see Table B.23). F1 females showed significant decreases in plasma and whole blood cell cholinesterase levels at 4.5, 7.5, and 13.5 months of age, and decreases in RBC cholinesterase levels at 4.5 months of age (see Table B.24). Brain cholinesterase was not found to be affected in any of the animals at terminal sacrifice (see Tables B.23 and B.24; data in males not reported). For this study, a NOAEL of 56.5 mg/kg-day and a LOAEL of 329.5 mg/kg-day are determined based on the hematological changes that were observed in the high-dose F1 females.

It should be noted that a number of concerns regarding the methodology and data interpretation of the Bucci et al. (2003) study have been raised (Calabrese, 2003a,b, 2005; Colagiovanni, 2006; Calonge, 2006). These include the use of medical intervention to increase

the survival odds of many animals, expunging the data on 19 animals, and a number of protocol and procedure deviations that question the study's compliance with GLP guidelines (Calabrese, 2005). Calabrese (2003a,b) evaluated the data on the animals that received intervention. Following an accidental overdose of anesthesia, Bucci et al. (2003) provided medical intervention for 24 F1 generation females (11 control and 13 treated animals). Despite intervention, 5 of the 24 animals died (2 control and 3 treated animals). Comparison between the surviving treated animals and the control animals that received intervention show that more of the treated animals had abnormal physiological or clinical values (33% of controls [3/9] vs. 90% of treated animals [9/10]) (see Table B.25) (Calabrese, 2003a). Among the animals that did not survive, RBC damage was seen in three of the four treated animals but not in either of the control animals. Calabrese (2003a) concluded that the intervention was more beneficial for the DIMP-treated animals and possibly reduced the number of treatment-related effects that were observed.

*U.S. DOD (1979) and Aulerich et al. (1979)*

The U.S. DOD commissioned a 1-generation reproductive toxicity study in mink given DIMP in the diet (U.S. DOD, 1979) that is also cited as Aulerich et al. (1979) in the literature. Four groups of immature dark variety mink (6 males; 24 females) were administered 0 (control), 50, 150, or 450 ppm (corresponding to 0, 11, 37, and 95 mg/kg-day as calculated by study authors) daily in the diet for one 12 month reproductive cycle. Mortality and signs of intoxication were recorded throughout the study. Body weights were measured every two weeks. Food consumption was measured at two week intervals. Hematology measurements included hematocrit, hemoglobin, and differential leukocyte counts. Following mating, newborn kits were sexed and weighed on the day of welping and again at one month of age. Length of gestation, litter size, sex ratio, kit mortality, weight gain of kits during lactation, and weight changes of the dams were recorded. At study termination, blood samples were taken and the mink were weighed and necropsied. Gross morphological changes were recorded and the following organs were weighed and histologically examined: brain, liver, kidneys, spleen, gonads, lungs, heart, adrenal glands as well as portions of the intestine, stomach, skeletal muscle, adipose tissue, and integument. All parameters were analyzed by the study authors for statistical significance using analysis of variance and Dunnett's t-test.

Mortality was elevated in female and male parent mink in all treatment groups but the male sample size was too small to reach statistical significance. There were no statistically significant differences compared to control values in body weight, percent change in body weight, or feed consumption. Hematocrit was elevated in males at the two highest doses (37 and 95 mg/kg-day) but there were no changes in hemoglobin or in differential leukocyte counts.

There were no statistically significant differences in kit mortality. Kit weight at four weeks and body weight of lactating females was unchanged with the exception of a 15% elevation in kit weight seen only at the low dose (11 mg/kg-day). Reproductive success was unaffected by treatment with DIMP. The study authors found no adverse effects on the following parameters: welping rates, gestation length, fecundity, and kit weight at birth. Additionally, gross and histopathological examination revealed no consistent pathological changes and organ weights were not significantly changed from control values. The study authors concluded that chronic treatment with DIMP in the diet failed to alter the reproductive capacity of mink. The significance of the observed mortality in this study is questionable since no other treatment-related effects were seen and there is about a 6% mortality rate in first-year

mink within commercial fur ranch operations. Additionally, no mortality was observed at higher administered oral doses in other mink studies (Bucci et al. 1994; 2003). Thus, neither a NOAEL nor a LOAEL were identified due to the inherent uncertainty associated with this study.

*U.S. DOD (1980) and Hart (1980c)*

The U.S. DOD commissioned a 3-generation reproductive toxicity study in rats exposed orally to DIMP (U.S. DOD, 1980) that is also cited as Hart (1980c) in the literature. Sprague-Dawley CD rats (10 males and 20 females/dose group) were given daily doses of DIMP (0, 13.5, or 135 mg/kg-day) in food. Two litters (designated a and b) were produced by each succeeding generation. The first generation parents (F0) were weighed and food consumption estimated in weeks 4, 9, 11 and 20. These animals were observed daily for mortality, weekly for general appearance, and for anatomic observations at necropsy. Dosing began after weaning in each generation. Observations of rat pups within each generation included the following: number of live and dead pups at birth; sex and body weight; number and sex of surviving pups at postnatal day (PND) 4; number, sex and body weights at PND 21; daily appearance observations and anatomic observations at necropsy. Observations of the second generation were conducted on a similar schedule. Observations of the third generation were as follows: newborn viability ratios (live pups/total pups); pup viability ratios (pups at PND 4/pups at PND 0); lactation indices (pups at PND 21/pups at PND 4) and gestation indices (females giving birth/females pregnant). Treatment groups were compared with controls using 2 x 2 contingency tables with Chi-squared correction for continuity. Treatment and control means for parent body weights, parent food consumption, and pup weights were compared using Dunnett's t-test.

The authors reported no dose-related, statistically significant results that could be attributed to daily treatment with DIMP over three successive generations of rats with two matings per generation. There were a number of observations that differed statistically from the untreated controls but the effects were not consistent between litters or generations. For example, statistically significant pup loss was reported from PND 4 through PND 21 in the treatment groups of the first mating within the third generation, but pup loss was not observed in the second mating. In another example, food consumption and body weight were statistically equivalent to controls in all groups except the F2b high-dose females that had significantly lower values. Litter observations of the first breeding rats from the three generations were not significantly different and the necropsy observations were "unremarkable and free of any dose-dependent relationship." A NOAEL of 135 mg/kg-day was identified for this study. A LOAEL was not identified.

***Carcinogenicity Studies***

No studies were identified on the carcinogenicity of DIMP to animals.

**Inhalation Exposures**

No studies were identified on the inhalation exposure of DIMP to animals.

**OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)**

**Tests Evaluating Carcinogenicity, Genotoxicity, and/or Mutagenicity**

The majority of the genotoxicity and mutagenicity studies were negative or equivocal (see Table 3A). DIMP was negative for mutagenicity in bacteria and yeast (Hart, 1980d,e). In the L5178Y TK+/- mouse lymphoma assay, equivocal results were obtained without metabolic activation while negative results were reported in the presence of metabolic activation

(U.S. DOD, 1991a). Assays using Chinese hamster ovary cells reported a significant increase in chromosomal aberrations both with or without S9 metabolic activation, but neither SCEs nor DNA damage were induced with or without S9 (U.S. DOD, 1991b,c,d). Increased SCEs were seen in human lymphocytes obtained from 4 healthy donors (2 male and 2 female) following incubation with ≥40-ppm DIMP (Li et al., 1998). Equivocal and negative results were reported in micronucleus induction assays conducted in male $B6C3F_1$ mice and male F344 rats, respectively (U.S. DOD, 1991e,f). The assay was conducted twice in mice, and a small, though significant, increase was reported the first time; however, negative results were reported the second time. In addition, the maximum increase was noted as within the laboratory's historical control limits. No increase in DNA damage was observed in male $B6C3F_1$ mice following oral exposure to 1000-mg/kg DIMP (U.S. DOD, 1991g). DNA damage was seen in the leukocytes, but not the liver parenchymal cells, that were obtained from F344 rats that were orally treated with DIMP (U.S. DOD, 1991h).

**Other Toxicity Studies (Exposures Other Than Oral or Inhalation)**

Ahlin et al. (1975) evaluated the effects of DIMP on the reproductive development of male and female rats following subcutaneous exposure to DIMP (see Table 3B). No effect on nipple formation was seen in either the male or female offspring. However, a number of abnormalities were seen in the male offspring that indicate that DIMP may cause antiandrogenic effects. These included the presence of female sex organs, undescended testicles, absence of ventral prostatic glands, and decreased weight and alteration of the seminal vesicles.

**Metabolic/Toxicokinetic Studies**

Following the oral administration of DIMP to mice, rats, dogs, and mink (Bucci et al., 1992; Hart, 1976c, 1980f) and subcutaneous injection to swine (Snodgrass and Metker, 1992), DIMP was reported to be rapidly absorbed, metabolized to isopropyl methyl phosphonic acid (IMPA), and excreted in the urine (see Table 3B). However, following dermal exposure to swine (Snodgrass and Metker, 1992), DIMP is poorly absorbed (i.e., approximately 7%), but is rapidly excreted. None of the studies found accumulation of DIMP in any of the organs.

**Mode-of-Action/Mechanistic Studies**

There is no suitable information to provide in this regard.

**Immunotoxicity**

The immunotoxicity of DIMP was evaluated in an in vitro study that used mouse splenocytes and human peripheral blood lymphocytes (Li et al., 2000) (see Table 3B). Following exposure to DIMP, both dose- and time-dependent decreases in lymphocytes were observed, indicating that exposure to DIMP may result in a decrease in lymphocytic functions.

**Neurotoxicity**

The ability of DIMP to cause organophosphate-induced delayed neurotoxicity (OPIDN), from acute exposure, was evaluated in adult, white Leghorn hens (Hart, 1980g). The data are available but are not published in a peer-refereed journal. Although important details were not reported, it is inferred that 20 hens/dose were pretreated with atropine and then received a single dose of either 0-, 500-, 1000-, or 1500-mg DIMP/kg by oral gavage or with the positive, neurotoxic control, tri-ortho cresyl phosphate. After a 21-day recovery period, the hens were euthanized, and the left sciatic nerve was dissected and examined microscopically. Hens in the low and middle dose groups received a second dose of DIMP followed by a second 21-day

recovery period and examination of the sciatic nerve. Increased mortality was observed in mid- and high-dose animals, and unsteady gait was observed to occur in a dose-dependent fashion. However, microscopic examination indicated no DIMP-related effects on nerve fiber degeneration. Hart (1980g) inexplicably discounted the unsteady gait of the hens as unrelated to the neurotoxicity endpoint, sciatic nerve degeneration. The unsteady gait, at all doses of DIMP, suggests that 500 mg/kg-day is a LOAEL for neurotoxicity.

**Table 3A. Summary of DIMP Genotoxicity Studies**

| Endpoint | Test System | Dose Concentration[a] | Results[b] | | Comments | References |
|---|---|---|---|---|---|---|
| | | | Without Activation | With Activation | | |
| **Genotoxicity studies in prokaryotic organisms** | | | | | | |
| Reverse mutation | Ames assay; *Salmonella typhimurium* strains TA 98, 100, 1535, 1537, and/or 1538 in the presence or absence of S9 | 5.0 µL/plate | – | – | Study was conducted in duplicate with the same results reached in each study | Hart (1980d) |
| SOS repair induction | ND | ND | ND | ND | ND | NA |
| **Genotoxicity studies in nonmammalian eukaryotic organisms** | | | | | | |
| Mutation | *Saccharomyces cerevisiae* strain D4 in the presence or absence of S9 | 5.0 µL/plate | – | – | Study was conducted in duplicate with the same results reached in each study | Hart (1980e) |
| Recombination induction | ND | ND | ND | ND | ND | NA |
| Chromosomal aberration | ND | ND | ND | ND | ND | NA |
| Chromosomal malsegregation | ND | ND | ND | ND | ND | NA |
| Mitotic arrest | ND | ND | ND | ND | ND | NA |
| **Genotoxicity studies in mammalian cells—in vitro** | | | | | | |
| Mutation | L5178Y TK +/- mouse lymphoma mutagenesis assay | NR | ± | – | No comments | U.S. DOD (1991a)[c] |
| Chromosomal aberrations | Chinese hamster ovary cells evaluated for clastogenic damage | 5 or 15 µL/mL | + | + | Increased chromosomal aberrations were seen at 5 µL/mL without activation and at 15 µL/mL with S9 activation | U.S. DOD (1991b)[c] |

**Table 3A. Summary of DIMP Genotoxicity Studies**

| Endpoint | Test System | Dose Concentration[a] | Results[b] | | Comments | References |
|---|---|---|---|---|---|---|
| | | | Without Activation | With Activation | | |
| Sister chromatid exchange (SCE) | Chinese hamster ovary cells | NR | – | – | No comments | U.S. DOD (1991c)[c] |
| Sister chromatid exchange (SCE) | Human lymphocytes were obtained from 4 healthy donors (2 males and 2 females, 24−33 yr old) and evaluated for SCE following incubation with DIMP | 40 ppm | + | ND | No comments | Li et al. (1998) |
| DNA damage | Chinese hamster ovary cells | NR | – | – | No comments | U.S. DOD (1991d)[c] |
| DNA adducts | ND | ND | ND | ND | ND | NA |
| **Genotoxicity studies in mammals—in vivo** | | | | | | |
| Chromosomal aberrations | ND | ND | ND | ND | ND | NA |
| Micronucleus Induction | Bone marrow from male $B6C3F_1$ mice were evaluated for micronuclei | 1000 mg/kg | ± | ND | The assay was conducted twice; a small but significant increase was noted the first time; however, the maximum response was noted to be within the laboratory's historical control limits; the assay was repeated with no observed increase in micronuclei | U.S. DOD (1991e)[c] |
| Micronucleus Induction | Bone marrow from male F344 rat evaluated for micronuclei | 800 mg/kg | – | ND | No comments | U.S. DOD (1991f)[c] |
| Sister chromatid exchange (SCE) | ND | ND | ND | ND | ND | NA |

**Table 3A. Summary of DIMP Genotoxicity Studies**

| Endpoint | Test System | Dose Concentration[a] | Results[b] | | Comments | References |
|---|---|---|---|---|---|---|
| | | | Without Activation | With Activation | | |
| DNA damage | Male B6C3$F_1$ mice treated with DIMP; liver parenchymal cells and leukocytes evaluated for DNA damage | 1000 mg/kg | – | ND | No comments | U.S. DOD (1991g)[c] |
| DNA damage | F344 rats (sex unspecified) treated with DIMP; liver parenchymal cells evaluated for DNA damage | NR | – | ND | Results are questionable because no increase in DNA damage was seen in the positive controls | U.S. DOD (1991h)[c] |
| DNA damage | F344 rats (sex unspecified) treated with DIMP; leukocytes evaluated for DNA damage | NR | + | ND | No comments | U.S. DOD (1991h)[c] |
| DNA adducts | ND | ND | ND | ND | ND | NA |
| Mouse biochemical or visible specific locus test | ND | ND | ND | ND | ND | NA |
| Dominant lethal | ND | ND | ND | ND | ND | NA |
| **Genotoxicity studies in subcellular systems** | | | | | | |
| DNA binding | ND | ND | ND | ND | ND | NA |

[a]Lowest effective dose for positive results, highest dose tested for negative results.
[b]+ = Positive, ± = Equivocal or weakly positive, – = Negative, T = Cytotoxicity, NA = Not applicable, ND = No data, NDr = Not determined, NR = Not reported, NR/Dr = Not reported by the study author, but determined from data.
[c]Information was obtained from ATSDR (1998). The original data are not available.

**Table 3B. Other Studies**

| Test | Materials and Methods | Results | Conclusions | References |
|---|---|---|---|---|
| Carcinogenicity other than oral/inhalation | ND | ND | ND | NA |
| Other toxicity studies (exposures other than oral or inhalation) | In a 1-generation reproductive study, a total of 11 female rats (9 albino [strain unknown] and 2 piebald) were administered 50−60 mg/day DIMP via subcutaneous injection on GDs 14−20; offspring were sacrificed at birth or on PNDs 10−91 and examined for abnormalities of the genital organs (males only) and nipples | DIMP was well tolerated by the maternal rats; in the male offspring, abnormalities of the male genital organs were noted and included the presence of female sex organs, undescended testicles, absence of the ventral prostatic glands, and decreased weight and alteration of the seminal vesicles; no effect on nipple formation was seen in the male or female offspring | At high concentrations, subcutaneous injections of DIMP may cause antiandrogenic effects in male offspring | Ahlin et al. (1975) |
| Metabolism/ toxicokinetic | Radiolabeled $^{14}$C-DIMP (97% pure) was diluted with DIMP and administered to rats (66 or 660 mg/kg) and mink (27 or 270 mg/kg) by gavage; blood was collected through the first 24 hr following administration; urine and feces were collected at 4, 8, 12, and 24 hr following administration and once daily thereafter for 5 d; collections were analyzed for radioactivity and DIMP metabolites | DIMP was rapidly absorbed and removed from the blood of the rats and mink, as indicated by peak radioactivity blood levels in rats (2−3 hr) and mink (2 hr), except for high-dose male mink where the peak was seen at 4 hr; no significant accumulation was seen in any organ; in both rats and mink, the majority of the radioactivity was recovered in the urine and was largely (>97%) associated with the metabolite IMPA | Following oral administration to rats and mink, DIMP is rapidly absorbed, metabolized to IMPA, and excreted in the urine | Bucci et al. (1992) |

**Table 3B. Other Studies**

| Test | Materials and Methods | Results | Conclusions | References |
|---|---|---|---|---|
| Metabolism/ toxicokinetic | Radiolabeled $^{14}$C-DIMP (≥99% pure) was combined with DIMP (>97% pure) in 95% ethyl alcohol resulting in DIMP concentrations of 0.4, 4, or 40 mg/mL; each solution contained 10 μCi/mL of radiocarbon content; Yorkshire Cross male swine (3/dose group) were percutaneously treated with DIMP; an additional 3 animals were treated with 40 mg/mL $^{14}$C-DIMP by subcutaneous injection; urine and feces were collected 24 hr after treatment and daily thereafter through the 7-d study; animals were sacrificed at the end of study and the brain, heart, kidneys, liver, lungs, spleen, adrenal glands, thyroid gland, bladder, skin, bone, bone marrow, fat, skeletal muscle, and blood were collected and analyzed for residual $^{14}$C | Percutaneous administration of $^{14}$C-DIMP in swine resulted in less than 7% of the dose being absorbed through the 7-d study; the majority of the absorbed dose (>80%) was eliminated in the urine within 24 hr of treatment; no significant accumulation was seen in any organ<br><br>Following subcutaneous injection, DIMP was rapidly eliminated in the urine (91% within 24 hr); by Day 7, 99% of the dose had been excreted in the urine; DIMP accumulation was not seen in any organ | In swine, DIMP is poorly absorbed following dermal application; following dermal treatment or subcutaneous injection, DIMP does not bioaccumulate significantly and is rapidly excreted | Snodgrass and Metker (1992) |
| Metabolism/ toxicokinetic | A single oral dose (225 mg/kg) of radiolabeled $^{14}$C-DIMP (≥99% pure) was administered to S-D rats, Swiss Webster mice, and purebred beagle dogs; blood, urine, feces, and expired carbon dioxide were collected intermittently for the first 72 hr following the initial administration of $^{14}$C-DIMP and 14 d later and examined for $^{14}$C; the major organs were also obtained at these times and examined for residual $^{14}$C | Peak plasma levels occurred within 15 min following exposure in mice and 2 hr following exposure in rats and dogs; plasma radioactivity quickly decreased in all animals with high levels of radioactivity seen in all of the examined tissues; in mice (15 min after administration) and rats (2 hr after administration), the highest levels were measured in the bladder, lungs, liver, and kidneys; in dogs, the highest tissue levels of radioactivity were recorded at 4 hr after the administration of $^{14}$C-DIMP and were found in the lungs, bone marrow, cecum, and bladder; radioactivity levels rapidly decreased in all tissues; urinary excretion was the major route of elimination with over 90% of $^{14}$C radioactivity recovered in all animals within 24 hr of administration | DIMP is rapidly absorbed in rats, dogs, and mice with absorption occurring more rapidly in mice; DIMP is rapidly eliminated through the urine | Hart (1976c) |

**Table 3B. Other Studies**

| Test | Materials and Methods | Results | Conclusions | References |
|---|---|---|---|---|
| Metabolic/ toxicokinetic | Urine collected in rats, mice, and dogs over 24 hr was analyzed for radioactivity and DIMP metabolites | Over 90% of the radioactivity of $^{14}$C-DIMP administered to rats, mice, and dogs was recovered in the urine; most of the recovered radioactivity (93.2% in rat, 95.6% in mouse, 99.6% in dog) was associated with the metabolite IMPA | In rat, mouse, and dog, DIMP is transformed to the metabolite IMPA | Hart (1980f) |
| Mode of action/ mechanistic | ND | ND | ND | NA |
| Immunotoxicity | Splenic lymphocytes were harvested from 6-wk-old male CBA/N mice; cytotoxic T lymphocytes (CTL) were induced from the mouse splenocytes; human peripheral blood lymphocytes (PBL) were obtained from 10 healthy donors (5 males and 5 females); lymphocytes were treated with 0, 500, 1000, or 2000 ppm for 1 hr; using a separate assay, lymphocytes were treated with DIMP for 3−5 hr as follows: mouse splenocytes were treated with 0, 62.5, 125, 250, 500, 1000, or 2000 ppm; mouse CTL were treated with 0, 250, 500, 1000, or 2000 ppm; human PBL were treated with 0, 125, 250, or 500 ppm; cell suspensions were use to determine the effect of DIMP on natural killer (NK) and CTL (mouse only) activities | Dose- and time-dependent decreases in mouse- and human-derived lymphocytes were observed | Exposure to DIMP may result in decreased lymphocyte function | Li et al. (2000) |

**Table 3B. Other Studies**

| Test | Materials and Methods | Results | Conclusions | References |
|---|---|---|---|---|
| Neurotoxicity | White Leghorn hens (20/group) received 2 oral doses of 0, 500, or 1000 mg/kg DIMP 3 wk apart; an additional group of 20 hens received a single dose of 1500 mg/kg DIMP; animals were sacrificed 24 d (21 d in high-dose group) following the last dose<br><br>For positive controls, 20 animals were exposed to 500 mg/kg Tri-o-cresyl phosphate (TOCP) | Increased mortality was seen in animals that received the mid- and high-doses; a total of 5 animals in the low-dose group developed signs of unsteady gait, but these signs were determined to be unrelated to effects observed in the positive control; in the mid-dose group, 2 animals developed an unsteady gait following the administration of DIMP, but returned to normal by the end of the initial observation period; in the highest dose group, some animals became prostrate following treatment with DIMP, but most recovered; most high-dose animals developed an unsteady gait within 1−3 d after treatment but recovered; the authors noted that the unsteady gait was dissimilar to the effects seen in the positive control animals and unrelated to nerve fiber degeneration; no effect on nerve fiber degeneration was seen during the histopathological examination | Treatment with DIMP did not cause nerve fiber degeneration in white Leghorn hens; however, unsteady gait was noted | Hart (1980g) |

NA = Not applicable; ND = No data.

## DERIVATION OF PROVISIONAL VALUES

Tables 4 and 5 present a summary of the noncancer reference and cancer values, respectively. IRIS data are indicated in the table, if available.

**Table 4. Summary of Noncancer Reference Values for DIMP (CASRN 1445-75-6)**

| Toxicity Type (Units) | Species/ Sex | Critical Effect | p-Reference Value | POD Method | POD | $UF_C$ | Principal Study |
|---|---|---|---|---|---|---|---|
| Subchronic p-RfD (mg/kg-day) | Mink/M | Increased Heinz bodies | $1 \times 10^{0}$ | NOAEL | 344.7 | 300 | Bucci et al. (1994) |
| Chronic RfD (mg/kg-day) IRIS (U.S. EPA, 1993) | Dog/M+F | No treatment-related effects | $8 \times 10^{-2}$ (IRIS) | NOAEL | 75[a] | 1000 | Hart (1980a) |
| Subchronic p-RfC ($mg/m^3$) | NDr | NDr | NDr | NDr | NDr | NDr | NDr |
| Chronic p-RfC ($mg/m^3$) | NDr | NDr | NDr | NDr | NDr | NDr | NDr |

[a]The NOAEL reported by IRIS does not match the NOAEL reported for this study in Table 2 due to differences in dose conversion calculations applied to the administered dose (3000 ppm).

NDr = Not determined.

**Table 5. Summary of Cancer Values for DIMP (CASRN 1445-75-6)**

| Toxicity Type | Species/Sex | Tumor Type | Cancer Value | Principal Study |
|---|---|---|---|---|
| p-OSF | NDr | NDr | NDr | NDr |
| p-IUR | NDr | NDr | NDr | NDr |

NDr = Not determined

## DERIVATION OF ORAL REFERENCE DOSES

### Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

The study by Bucci et al. (1994) is selected as the principal study for the derivation of the subchronic p-RfD. The critical effect is increased Heinz bodies in male mink given DIMP for 90 days with an associated NOAEL of 344.7 mg/kg-day. The details of this study are provided in the "Review of Potentially Relevant Data" section. This study is published in a peer-reviewed journal and was performed according to GLP guidelines. Benchmark dose (BMD) analysis is not possible with these data because the number of blood samples available for each endpoint was not reported. Consequently, the NOAEL/LOAEL approach is used. From the available database of studies (see Table 2), Bucci et al. (1994; 2003) are the only studies that examined animals that were administered doses sufficient to cause observable toxic effects. An increase in Heinz bodies was reported in both sexes and represented the most sensitive effect. Heinz bodies are inclusions seen in erythrocytes that are indicative of oxidative damage to hemoglobin. Their occurrence can result in anemia. In addition, decreased hematocrit, hemoglobin, and erythrocyte counts, and the increased reticulocyte count, indicate damage to RBC, providing further supporting evidence of treatment-related effects (see Tables B.13 and B.14). Bucci et al. (2003) was considered as a potential principal study, but serious questions about the methodology and accusations of scientific misconduct (Calabrese, 2003 a,b; Colagiovanni, 2006; Calonge, 2006) precluded further consideration of the study.

A decrease in plasma cholinesterase levels was observed in subchronic studies in rats (see Tables B.4 and B.5; Hart, 1976a), dogs (see Tables B.8 and B.9; Hart, 1980a), and mink (see Tables B.13 and B.14; Bucci et al., 1994). However, measures of brain cholinesterase, in test animals, are the most direct evidence of a potential human health hazard. RBC cholinesterase also provides a good estimate of potential hazards and is preferred over plasma cholinesterase. Plasma cholinesterase is best used as part of a weight-of-evidence approach when RBC and brain cholinesterase levels are not available (U.S. EPA, 2000). In this case, Hart (1976a) found that the brain cholinesterase level was decreased in male and female rats administered ≥74.58 mg/kg-day or ≥27.98 mg/kg-day, respectively, by 16−37% (see Tables B.4 and B.5); however, these results are not dose-dependent or statistically significant and were only measured in 5 rats per sex per treatment group (Hart, 1976a). In addition, brain cholinesterase levels were not decreased in the mink (Bucci et al., 2003) (see Tables B.23 and B.24). There were no clinical signs of neurotoxicity observed in any of these studies. A study performed on chickens indicates that DIMP has a dose-dependent effect on gait when administered at doses that cause mortality, but these doses did not result in the degeneration of the nerve fibers (Hart, 1980g).

Red blood cell cholinesterase was not changed in mink (Bucci et al., 1994) at the two highest dose levels (907.7 and 1263.5 mg/kg-day) and was increased in mink by no more than 8% in a second study (Bucci et al. 2003). And while plasma cholinesterase was statistically significantly decreased at lower doses than other endpoints, there was no dose response, with male rats having an increase (rather than a decrease) in plasma cholinesterase at the highest dose, and the results were highly variable at the different time points measured (Hart, 1980a). For the reasons stated above, the observation of Heinz bodies in RBCs (Bucci et al., 1994) represented the best choice of critical effect, and the NOAEL of 344.7 mg/kg-day was selected as the POD.

IRIS (U.S. EPA, 2011) used the Hart (1980a) subchronic study in beagle dogs to derive a chronic RfD based on a NOAEL at the highest level tested. The Bucci et al. (1994) study, selected here as the principal study, was not available to IRIS at the time (02/01/93 date of last

revision). Nonetheless, there are several reasons it is superior to the Hart (1980a) study as the choice of principal study. The Bucci et al. (1994) study employed more animals (10/sex/dose vs. 4/sex/dose) than the Hart (1980a) study; more doses were tested (5 doses vs. 3 doses); a greater dose range was employed (6.8 to 1263.5 mg/kg-day vs. 4.6 to 92.8 mg/kg-day); a LOAEL and NOAEL (versus a NOAEL only) were clearly identified; and it was published in a peer-refereed journal.

No dosimetric adjustments are made as the study authors provided estimates of daily consumption, presumably using the ppm in the diet, individual food consumption, and body weight measurements.

The subchronic p-RfD for DIMP, based on the $NOAEL_{ADJ}$ of 344.7 mg/kg-day (Bucci et al., 1994), is derived as follows:

$$\begin{aligned} \textbf{Subchronic p-RfD} &= \textbf{NOAEL}_{\textbf{ADJ}} \div \textbf{UF} \\ &= 344.7 \div 300 \\ &= \textbf{1} \times \textbf{10}^{\textbf{0}}\ \textbf{mg/kg-day} \end{aligned}$$

Table 6 summarizes the uncertainty factors for the subchronic p-RfD for DIMP.

**Table 6. Uncertainty Factors for Subchronic p-RfD of DIMP**

| UF | Value | Justification | Notes |
|---|---|---|---|
| $UF_A$ | 10 | A $UF_A$ of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between animal models and humans. | No notes |
| $UF_D$ | 3 | A $UF_D$ of 3 is applied because the database includes an acceptable oral three-generation reproductive study in rats (Hart, 1980c) and an acceptable oral developmental study in rats (Hart, 1980b). However, there is clear indication of the need for a repeated dose, subchronic- or chronic-duration neurotoxicity study. | Uneven gaits were observed in chickens; possible decrease in brain cholinesterase levels in rats, but not in mink; no clinical signs of toxicity in rats, mice, or dogs, but doses were not high enough in rats, dogs, or mice to observe adverse effects |
| $UF_H$ | 10 | A $UF_H$ of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response to humans. | No notes |
| $UF_L$ | 1 | A $UF_L$ of 1 is applied because the POD was developed using a NOAEL. | No notes |
| $UF_S$ | 1 | A $UF_S$ of 1 is applied because a subchronic-duration study was utilized. | No notes |
| $UF_C$ ≤3000 | 300 | A $UF_c$ of 300 is applied for derivation of the subchronic p-RfD. | No notes |

$UF_A$ for interspecies animal-to-human extrapolation.
$UF_D$ for deficiencies in the database.
$UF_H$ for sensitive human subgroups.
$UF_L$ for extrapolation from a LOAEL to a NOAEL.
$UF_S$ for extrapolation from subchronic to chronic duration.
$UF_C$ is the composite uncertainty factor.

The confidence of the subchronic p-RfD for DIMP is medium, as explained in Table 7 below.

**Table 7. Confidence Descriptors for Subchronic p-RfD for DIMP**

| Confidence Categories | Designation[a] | Discussion |
|---|---|---|
| Confidence in study | H | Confidence in the key study is high. Bucci et al. (1994) was adequate in design for a 90-d study in mink. The study was peer-reviewed and followed GLP guidelines. The study included multiple effect levels, and both a NOAEL and LOAEL are identified. |
| Confidence in database | M | The database includes subchronic toxicity studies on rat, mouse, dog, and mink, (Hart, 1976a,b, 1980a; Bucci et al., 1994), a developmental toxicity study on the rat (Hart, 1980b), and one 3-generation reproductive study on the rat (Hart, 1980c). Of the four available subchronic studies, only the study performed in mink was performed at a dose level sufficient to cause observable toxic effects. The available evidence indicates the need for a neurological study. |
| Confidence in subchronic p-RfD[b] | M | The overall confidence in the subchronic p-RfD is medium. |

[a]L = Low, M = Medium, H = High.
[b]The overall confidence cannot be greater than lowest entry in table.

**Derivation of Chronic Provisional RfD (Chronic p-RfD)**

A chronic RfD of $8 \times 10^{-2}$ mg/kg-day is available on IRIS (U.S. EPA, 1993) based on the 90-day feeding study in dogs (Hart 1980a, referenced as U.S. DOD, 1980 in IRIS). The IRIS database should be checked to determine if any significant changes have been made.

## DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

No subchronic or chronic p-RfC can be derived because no inhalation studies on exposure of humans or animals to DIMP were identified.

## CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

Table 8 identifies the cancer WOE descriptor for DIMP.

**Table 8. Cancer WOE Descriptor for DIMP**

| Possible WOE Descriptor | Designation | Route of Entry (Oral, Inhalation, or Both) | Comments |
|---|---|---|---|
| *"Carcinogenic to Humans"* | NS | NA | No human carcinogenicity studies were identified. |
| *"Likely to Be Carcinogenic to Humans"* | NS | NA | No animal carcinogenicity studies were identified. |
| *"Suggestive Evidence of Carcinogenic Potential"* | NS | NA | No animal carcinogenicity studies were identified. |
| ***"Inadequate Information to Assess Carcinogenic Potential"*** | **Selected** | **Both** | **This is selected due to the lack of any data on carcinogenicity.** |
| *"Not Likely to Be Carcinogenic to Humans"* | NS | NA | Although the genotoxicity studies were negative or equivocal, there are no data to indicate that DIMP is not carcinogenic to humans or animals. |

NS = Not selected; NA = Not applicable.

## DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

The lack of data on the carcinogenicity of DIMP precludes the derivation of quantitative estimates for either oral (p-OSF) or inhalation (p-IUR) exposure.

## APPENDIX A. PROVISIONAL SCREENING VALUES

There are no screening values for DIMP.

## APPENDIX B. DATA TABLES

**Table B.1. Average Body Weights and Food Consumption of Male and Female Rats Exposed to DIMP for 90 Days[a]**

| Parameter | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | | |
|---|---|---|---|---|
| | **0** | **300 (24.74)** | **1000 (74.58)** | **3000 (229.17)** |
| **Male** | | | | |
| Mean body weight (kg) | 0.296 | 0.291 | 0.295 | 0.288 |
| Food consumption (kg/d) | 0.022 | 0.024 | 0.022 | 0.022 |
| **Parameter** | **Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b]** | | | |
| | **0** | **300 (27.98)** | **1000 (92.31)** | **3000 (257.58)** |
| **Female** | | | | |
| Body weight (kg) | 0.195 | 0.193 | 0.195 | 0.198 |
| Food consumption (kg/d) | 0.019 | 0.018 | 0.018 | 0.017 |

[a]Source: Hart (1976a).
[b]Calculated from average body weights and food consumption provided in study using the following equation $Dose_{ADJ} = Dose_{ppm} \times$ Food Consumption per Day $\times$ (1 $\div$ Body Weight) $\times$ (Days Dosed $\div$ Total Days).

**Table B.2. Selected Mean Hematology and Blood Chemistry Levels of Male Rats Exposed to DIMP for 90 Days[a]**

| Parameter | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | | |
|---|---|---|---|---|
| | **0** | **300 (24.74)** | **1000 (74.58)** | **3000 (229.17)** |
| *N* | 5 | 5 | 5 | 5 |
| **Wk 4** | | | | |
| PCV (%) | 48.0 ± 1.4[c] | 50.0 ± 0.75 (104) | 50.5 ± 0.24 (105) | 48.0 ± 1.2 (100) |
| Hemoglobin (gm %) | 15.6 ± 0.86 | 16.6 ± 0.43 (106) | 16.4 ± 0.41 (105) | 15.6 ± 0.56 (100) |
| RBC ($mm^3 \times 10^6$) | 6.19 ± 0.32 | 6.85 ± 0.21 (111) | 6.76 ± 0.16 (109) | 6.06 ± 0.28 (98) |
| WBC ($mm^3 \times 10^3$) | 11.5 ± 0.93 | 13.1 ± 0.58 (114) | 12.1 ± 1.0 (105) | 10.8 ± 1.3 (94) |
| BUN (mg %) | 18 ± 1.2 | 19 ± 0.73 (106) | 20 ± 0.80 (111) | 18 ± 0.51 (100) |
| Glucose (mg %) | 79 ± 5.4 | 73 ± 6.8 (92) | 79 ± 6.5 (100) | 72 ± 3.0 (91) |
| Alkaline phosphatase (i.u.) | 168 ± 12 | 163 ± 6.5 (97) | 177 ± 22 (105) | 140 ± 11 (83) |
| SGPT (i.u.) | 16 ± 1.2 | 18 ± 0.85 (113) | 15 ± 0.63 (94) | 16 ± 0.92 (100) |
| **Wk 13** | | | | |
| PCV (%) | 50.5 ± 1.0 | 52.5 ± 0.93 (104) | 50.0 ± 0.72 (99) | 52.0 ± 2.3 (103) |
| Hemoglobin (gm %) | 16.8 ± 0.33 | 16.9 ± 0.64 (101) | 16.8 ± 0.21 (100) | 17.2 ± 0.68 (102) |
| RBC ($mm^3 \times 10^6$) | 7.62 ± 0.31 | 7.76 ± 0.39 (102) | 7.53 ± 0.24 (99) | 7.52 ± 0.24 (99) |
| WBC ($mm^3 \times 10^3$) | 12.1 ± 1.8 | 12.3 ± 2.3 (102) | 11.3 ± 0.92 (93) | 12.9 ± 1.7 (107) |
| BUN (mg %) | 18 ± 0.87 | 23 ± 3.9 (128) | 21 ± 3.0 (117) | 19 ± 1.5 (106) |
| Glucose (mg %) | 99 ± 6.2 | 97 ± 3.6 (98) | 103 ± 10 (104) | 102 ± 6.4 (103) |
| Alkaline phosphatase (i.u.) | 109 ± 14 | 239 ± 12 (219)[d] | 116 ± 2.7 (106) | 130 ± 26 (119) |
| SGOT (i.u.) | 261 ± 19 | 239 ± 20 (92) | 263 ± 28 (101) | 245 ± 7.2 (94) |
| SGPT (i.u.) | 26 ± 2.2 | 30 ± 3.3 (115) | 30 ± 4.8 (115) | 24 ± 1.2 (92) |
| Potassium (mEq/L) | 8.9 ± 0.86 | 8.1 ± 0.28 (91) | 8.3 ± 0.56 (93) | 10.5 ± 1.4 (118) |
| Sodium (mEq/L) | 194 ± 7.8 | 192 ± 5.8 (99) | 194 ± 5.3 (100) | 196 ± 7.4 (101) |

[a]Source: Hart (1976a).
[b]Calculated from average body weights and food consumption provided in study using the following equation $Dose_{ADJ} = Dose_{ppm} \times$ Food Consumption per Day × (1 ÷ Body Weight) × (Days Dosed ÷ Total Days).
[c]Mean ± S.E.(% of control).
[d]$p \leq 0.01$ by independent Student's *t*-test; not calculated by study authors.

PCV = Packed cell volume, BUN = Blood urea nitrogen, SGOT = Serum glutamic oxaloacetic transaminase, SGPT = Serum glutamic pyruvic transaminase.

**Table B.3. Mean Hematology and Blood Chemistry Results of Female Rats Exposed to DIMP for 90 Days[a]**

| Parameter | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | | |
|---|---|---|---|---|
| | 0 | 300 (27.98) | 1000 (92.31) | 3000 (257.58) |
| *N* | 5 | 5 | 5 | 5 |
| **Wk 4** | | | | |
| PCV (%) | 46.5 ± 1.8 | 48.5 ± 1.1 (104)[c] | 47.5 ± 1.0 (102) | 46.0 ± 1.4 (99) |
| Hemoglobin (gm %) | 14.7 ± 0.58 | 16.7 ± 0.43 (114)[d] | 16.1 ± 0.47 (110) | 15.5 ± 0.44 (105) |
| RBC ($mm^3 \times 10^6$) | 5.72 ± 0.46 | 6.92 ± 0.18 (121)[d] | 6.43 ± 0.20 (112) | 6.42 ± 0.14 (112) |
| WBC ($mm^3 \times 10^3$) | 8.3 ± 1.3 | 8.9 ± 1.5 (107) | 6.8 ± 0.59 (82) | 7.7 ± 0.71 (93) |
| BUN (mg %) | 19 ± 0.87 | 20 ± 0.86 (105) | 21 ± 2.3 (111)[d] | 20 ± 1.5 (105) |
| Glucose (mg %) | 83 ± 2.8 | 84 ± 8.0 (101) | 90 ± 7.7 (108) | 86 ± 5.5 (104) |
| Alkaline phosphatase (i.u.) | 97 ± 5.3 | 86 ± 5.3 (89) | 95 ± 11 (98) | 87 ± 14.0 (90) |
| SGPT (i.u.) | 15 ± 0.73 | 15 ± 1.4 (100) | 13 ± 0.81 (87) | 12 ± 0.68 (80)[d] |
| **Wk 13** | | | | |
| PCV (%) | 47.0 ± 0.54 | 48.5 ± 0.85 (103) | 50.5 ± 1.4 (107)[d] | 50.5 ± 0.88 (107)[e] |
| Hemoglobin (gm %) | 15.7 ± 0.22 | 16.3 ± 0.27 (104) | 16.8 ± 0.40 (107)[d] | 16.6 ± 0.18 (106)[d] |
| RBC ($mm^3 \times 10^6$) | 7.04 ± 0.18 | 7.15 ± 0.27 (102) | 7.12 ± 0.35 (101) | 6.92 ± 0.20 (98) |
| WBC ($mm^3 \times 10^3$) | 9.1 ± 1.1 | 8.6 ± 1.5 (95) | 7.9 ± 0.59 (87) | 8.6 ± 1.2 (95) |
| BUN (mg %) | 22 ± 1.2 | 21 ± 0.71 (95) | 18 ± 0.51 (82) | 21 ± 1.1 (95) |
| Glucose (mg %) | 112 ± 6.6 | 110 ± 11 (98) | 93 ± 12 (83) | 107 ± 8.1 (96) |
| Alkaline phosphatase (i.u.) | 108 ± 13 | 80 ± 6.0 (74)[d] | 78 ± 4.6 (72) | 68 ± 12 (63) |
| SGOT (i.u.) | 226 ± 11 | 236 ± 24 (104) | 228 ± 26 (101) | 229 ± 8.1 (101) |
| SGPT (i.u.) | 18 ± 0.45 | 17 ± 0.89 (94) | 20 ± 3.0 (111) | 20 ± 0.68 (111)[d] |
| Potassium (mEq/L) | 7.8 ± 0.67 | 7.7 ± 0.36 (99) | 7.4 ± 0.27 (95) | 8.8 ± 0.19 (113) |
| Sodium (mEq/L) | 187 ± 8.3 | 186 ± 9.1 (99) | 180 ± 10 (96) | 194 ± 8.0 (104) |

[a]Source: Hart (1976a).
[b]Calculated from average body weights and food consumption provided in study using the following equation $Dose_{ADJ} = Dose_{ppm} \times$ Food Consumption per Day × (1 ÷ Body Weight) × (Days Dosed ÷ Total Days).
[c]Mean ± S.E. (% of control).
[d]$p \leq 0.05$ by independent Student's *t*-test; not calculated by study authors.
[e]$p \leq 0.01$ by independent Student's *t*-test; not calculated by study authors.

**Table B.4. Cholinesterase Levels in Male Rats Exposed to DIMP for 90 Days[a]**

| Parameter | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | | |
|---|---|---|---|---|
| | **0** | **150 (24.74)** | **1500 (74.58)** | **3000 (229.17)** |
| **Wk 4** | | | | |
| RBC (µU/mL) | 207 ± 23 | 211 ± 31 (102) | 240 ± 35 (116) | 155 ± 21 (75) |
| *N* | 3 | 4 | 4 | 4 |
| Plasma (µU/mL) | 673 ± 211 | 523 ± 39 (78) | 782 ± 245 (116) | 795 ± 198 (118) |
| *N* | 3 | 4 | 4 | 4 |
| **Wk 13** | | | | |
| RBC (µU/mL) | 189 ± 19 | 285 ± 56 (151) | 460 ± 19 (243)[c] | 222 ± 72 (117) |
| *N* | 3 | 4 | 5 | 4 |
| Plasma (µU/mL) | 925 ± 34 | 469 ± 31 (51)[c] | 564 ± 27 (61)[c] | 1229 ± 64 (133)[c] |
| *N* | 4 | 4 | 5 | 4 |
| Brain (µU/mg tissue) | 14.73 ± 4.7 | 16.69 ± 6.2 (113) | 13.16 ± 4.1 (89) | 11.59 ± 2.8 (79) |
| *N* | 5 | 5 | 5 | 5 |

[a]Source: Hart (1976a).
[b]Calculated from average body weight and food consumption provided in study using the following equation $Dose_{ADJ} = Dose_{ppm} \times$ Food Consumption per Day × (1 ÷ Body Weight) × (Days Dosed ÷ Total Days).
[c]$p \leq 0.01$ by independent Student's *t*-test; not calculated by study authors.

U = amount of enzyme necessary to catalyze the conversion of 1µM of substrate per minute.

**Table B.5. Cholinesterase Levels in Female Rats Exposed to DIMP for 90 Days[a]**

| Parameter | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | | |
|---|---|---|---|---|
| | **0** | **150 (27.98)** | **1500 (92.31)** | **3000 (257.58)** |
| **Wk 4** | | | | |
| RBC (µU/mL) | 165 ± 32 | 141 ± 34 (85) | 132 ± 41 (80) | 169 ± 13 (102) |
| *N* | 4 | 4 | 4 | 3 |
| Plasma (µU/mL) | 937 ± 207 | 1447 ± 353 (154) | 1466 ± 319 (156) | 1401 ± 137 (150) |
| *N* | 4 | 4 | 4 | 3 |
| **Wk 13** | | | | |
| RBC (µU/mL) | 143 ± 10 | 252 ± 86 (176) | 134 ± 40 (94) | 114 ± 40 (80) |
| *N* | 3 | 4 | 4 | 3 |
| Plasma (µU/mL) | 2361 ± 29 | 2062 ± 147 (87) | 1977 ± 301 (84) | 912 ± 40 (34)[c] |
| *N* | 3 | 5 | 4 | 3 |
| Brain (µU/mg tissue) | 11.17 ± 1.4 | 7.29 ± 1.3 (65) | 7.00 ± 1.2 (63) | 9.36 ± 2.4 (84) |
| *N* | 5 | 5 | 5 | 5 |

[a]Source: Hart (1976a).
[b]Calculated from average body weight and food consumption provided in study using the following equation $Dose_{ADJ} = Dose_{ppm} \times$ Food Consumption per Day × (1 ÷ Body Weight) × (Days Dosed ÷ Total Days).
[c]$p \leq 0.01$ by independent Student's *t*-test; not calculated by study authors.

**Table B.6. Body Weights and Food Consumption of Male and Female Mice Exposed to DIMP for 90 Days[a]**

| Parameter | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | | |
|---|---|---|---|---|
| | **0** | **150 (37.94)** | **1500 (108.18)** | **3000 (337.27)** |
| **Male** | | | | |
| *N* | 4 | 4 | 4 | 4 |
| Mean body weight (kg)[c] | 0.032 | 0.031 | 0.033 | 0.032 |
| Food consumption (kg/d)[c] | 0.0056 | 0.0056 | 0.0051 | 0.0053 |
| **Parameter** | **Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b]** | | | |
| | **0** | **150 (42.00)** | **1500 (142.59)** | **3000 (460.38)** |
| **Female** | | | | |
| *N* | 4 | 4 | 4 | 4 |
| Mean body weight (kg)[c] | 0.027 | 0.027 | 0.027 | 0.026 |
| Food consumption (kg/d)[c] | 0.0056 | 0.0054 | 0.0055 | 0.0057 |

[a]Source: Hart (1976b).
[b]Calculated from average body weight and food consumption provided in study using the following equation $Dose_{ADJ} = Dose_{ppm} \times$ Food Consumption per Day $\times (1 \div$ Body Weight$) \times$ (Days Dosed $\div$ Total Days).
[c]Data calculated from individual weekly animal data. If data were missing, the previously reported value was used for that week.

**Table B.7. Mean Body Weights and Average Food Consumption of Male and Female Dogs Exposed to DIMP for 90 Days[a]**

| Parameter | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | | |
|---|---|---|---|---|
| | **0** | **150 (5.30)** | **1500 (40.43)** | **3000 (85.32)** |
| **Male** | | | | |
| *N* | 4 | 4 | 4 | 4 |
| Mean body weight (kg)[c] | 10.9 | 11.6 | 11.5 | 10.9 |
| Food consumption (kg/d)[c] | 0.37 | 0.41 | 0.31 | 0.31 |
| **Parameter** | **Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b]** | | | |
| | **0** | **150 (4.55)** | **1500 (46.97)** | **3000 (92.78)** |
| **Female** | | | | |
| *N* | 4 | 4 | 4 | 4 |
| Mean body weight (kg)[c] | 9.7 | 9.9 | 9.9 | 9.7 |
| Food consumption (kg/d)[c] | 0.30 | 0.30 | 0.31 | 0.30 |

[a]Source: Hart (1980a).
[b]Calculated from average body weights and food consumption provided in study using the following equation $Dose_{ADJ} = Dose_{ppm} \times$ Food Consumption per Day $\times (1 \div$ Body Weight$) \times$ (Days Dosed $\div$ Total Days).
[c]Data calculated from individual weekly animal data. If data were missing, the previously reported value was used for that week.

**Table B.8. Mean Hematology and Clinical Chemistry Levels of Male Dogs Exposed to DIMP for 90 Days[a]**

| Parameter | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | | |
|---|---|---|---|---|
| | **0** | **150 (5.30)** | **1500 (40.43)** | **3000 (85.32)** |
| *N* | 4 | 4 | 4 | 4 |
| **Wk 0** | | | | |
| PCV (%) | 48 | 44 (92)[c] | 42[d] (88) | 44 (92) |
| HGB (g %) | 15.7 | 14.8 (94) | 14.2 (90) | 15.0 (96) |
| RBC ($mm^3 \times 10^6$) | 7.54 | 6.57 (87) | 6.49 (86) | 6.63 (88) |
| WBC ($mm^3 \times 10^3$) | 7.7 | 7.9 (103) | 6.5 (84) | 7.6 (99) |
| Clotting time (sec) | 353 | 375 (106) | 465 (132) | 435 (123) |
| Glucose (mg/dL) | 99 | 120 (121) | 94 (95) | 111 (112) |
| BUN (mg/dL) | 12 | 10 (83) | 14 (117) | 10 (83) |
| SGOT (miu/mL) | 40 | 40 (100) | 36 (90) | 31 (78) |
| SGPT (miu/mL) | 32 | 37 (116) | 29 (91) | 32 (100) |
| Alkaline phosphatase (miu/mL) | 152 | 112 (74) | 113 (74) | 106 (70) |
| LDH (miu/mL) | 225 | 238 (106) | 213 (95) | 158 (70) |
| Calcium (mg/dL) | 11.9 | 11.6 (97) | 11.8 (99) | 11.4 (96) |
| Phosphorus (mg/dL) | 6.8 | 6.0 (88) | 6.3 (93) | 6.4 (94) |
| Total protein (g/dL) | 6.3 | 5.8 (92) | 6.0 (95) | 5.8 (92) |
| Albumin (g/dL) | 3.5 | 3.2 (91) | 2.9 (83) | 2.9 (83) |
| Bilirubin (mg/dL) | 0.2 | 0.3 (150) | 0.3 (150) | 0.3 (150) |
| Uric acid (mg/dL) | 0.4 | 0.3 (75) | 0.2 (50) | 0.3 (75) |
| Cholesterol (mg/dL) | 182 | 163 (90) | 167 (92) | 169 (93) |
| Plasma cholinesterase (mu/mL) | 2359 | 2062 (87) | 1775 (75) | 2087 (88) |
| RBC cholinesterase (mu/mL) | 685 | 798 (116) | 815 (119) | 523 (76) |
| **Wk 4** | | | | |
| PCV (%) | 48 | 50 (104) | 48 (100) | 46 (96) |
| HGB (g %) | 16.9 | 17.2 (102) | 17.1 (101) | 15.9 (94) |
| RBC ($mm^3 \times 10^6$) | 6.91 | 7.00 (101) | 6.95 (101) | 6.82 (99) |
| WBC ($mm^3 \times 10^3$) | 9.1 | 10.3 (113) | 10.9 (120) | 9.9 (109) |
| Clotting time (sec) | 405 | 555 (137) | 675[d] (167) | 578 (143) |
| Glucose (mg/dL) | 97 | 109 (112) | 109 (112) | 106 (109) |
| BUN (mg/dL) | 15 | 14 (93) | 14 (93) | 12 (80) |
| SGOT (miu/mL) | 37 | 41 (111) | 37 (100) | 32 (86) |
| SGPT (miu/mL) | 41 | 36 (88) | 35 (85) | 42 (102) |

**Table B.8. Mean Hematology and Clinical Chemistry Levels of Male Dogs Exposed to DIMP for 90 Days[a]**

| Parameter | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | | |
|---|---|---|---|---|
| | **0** | **150 (5.30)** | **1500 (40.43)** | **3000 (85.32)** |
| Alkaline phosphatase (miu/mL) | 127 | 87 (69) | 84 (66) | 72 (57) |
| LDH (miu/mL) | 87 | 98 (113) | 83 (95) | 53 (61) |
| Calcium (mg/dL) | 11.3 | 11.4 (101) | 11.4 (101) | 11.3 (100) |
| Phosphorus (mg/dL) | 4.9 | 4.6 (94) | 4.5 (92) | 4.4 (90) |
| Total protein (g/dL) | 6.3 | 5.9 (94) | 6.1 (97) | 6.0 (95) |
| Albumin (g/dL) | 3.5 | 3.5 (100) | 3.7 (106) | 3.5 (100) |
| Bilirubin (mg/dL) | 0.1 | 0.1 (100) | 0.1 (100) | 0.1 (100) |
| Uric acid (mg/dL) | 0.4 | 0.8 (200) | 0.3 (75) | 0.3 (75) |
| Cholesterol (mg/dL) | 164 | 141 (86) | 167 (102) | 153 (93) |
| Plasma cholinesterase (mu/mL) | NR | 1862 | 1571 | 1750 |
| RBC cholinesterase (mu/mL) | NR | 2667 | 4804 | 4889 |
| **Wk 8** | | | | |
| PCV (%) | 48 | 48 (100) | 48 (100) | 48 (100) |
| HGB (g %) | 16.9 | 16.9 (100) | 17.1 (101) | 17.6 (104) |
| RBC ($mm^3 \times 10^6$) | 8.46 | 8.07 (95) | 7.88 (93) | 7.71 (91) |
| WBC ($mm^3 \times 10^3$) | 12.3 | 14.5 (118) | 13.5 (110) | 11.2 (91) |
| Clotting time (sec) | 488 | 488 (100) | 533 (109) | 488 (100) |
| Glucose (mg/dL) | 88 | 93 (106) | 93 (106) | 101 (115) |
| BUN (mg/dL) | 18 | 15 (83) | 14 (78) | 13 (72) |
| SGOT (miu/mL) | 35 | 46 (131) | 45 (129) | 40 (114) |
| SGPT (miu/mL) | 38 | 35 (92) | 36 (95) | 42 (111) |
| Alkaline phosphatase (miu/mL) | 124 | 77 (62) | 74 (60) | 71 (57) |
| LDH (miu/mL) | 183 | 287 (157) | 269 (147) | 201 (110) |
| Calcium (mg/dL) | 10.8 | 10.8 (100) | 10.6 (98) | 10.5 (97) |
| Phosphorus (mg/dL) | 5.4 | 4.8[d] (89) | 4.7[d] (87) | 4.7[d] (87) |
| Total protein (g/dL) | 6.9 | 6.6 (96) | 6.6 (96) | 6.5 (94) |
| Albumin (g/dL) | 3.2 | 3.1 (97) | 3.1 (97) | 3.1 (97) |
| Bilirubin (mg/dL) | 0.4 | 0.4 (100) | 0.1 (25) | 0.1 (25) |
| Uric acid (mg/dL) | 0.4 | 0.6 (150) | 0.5 (125) | 0.5 (125) |
| Cholesterol (mg/dL) | 176 | 152 (86) | 166 (94) | 152 (86) |
| Plasma cholinesterase (mu/mL) | NR | 2176 | 1692 | 1798 |
| RBC cholinesterase (mu/mL) | NR | 2688 | 3181 | 2709 |

**Table B.8. Mean Hematology and Clinical Chemistry Levels of Male Dogs Exposed to DIMP for 90 Days[a]**

| Parameter | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | | |
|---|---|---|---|---|
| | 0 | 150 (5.30) | 1500 (40.43) | 3000 (85.32) |
| **Wk 13** | | | | |
| PCV (%) | 49 | 47 (96) [c] | 47 (96) | 49 (100) |
| HGB (g %) | 16.6 | 15.8 (95) | 15.6 (94) | 16.4 (99) |
| RBC ($mm^3 \times 10^6$) | 7.21 | 7.11 (99) | 7.23 (100) | 7.60 (105) |
| WBC ($mm^3 \times 10^3$) | 11.0 | 10.6 (96) | 10.7 (97) | 9.4 (85) |
| Clotting time (sec) | 458 | 570 (124) | 518 (113) | 480 (105) |
| Glucose (mg/dL) | 89 | 99 (111) | 104 (117) | 105 (118) |
| BUN (mg/dL) | 14 | 14 (100) | 14 (100) | 13 (93) |
| SGOT (miu/mL) | 45 | 52 (116) | 50 (111) | 49 (109) |
| SGPT (miu/mL) | 44 | 44 (100) | 36 (82) | 44 (100) |
| Alkaline phosphatase (miu/mL) | 82 | 53 (65) | 51 (62) | 48 (59) |
| LDH (miu/mL) | 231 | 518 (224) | 499 (216) | 332 (144) |
| Calcium (mg/dL) | 11.2 | 10.9 (97) | 11.2 (100) | 11.0 (98) |
| Phosphorus (mg/dL) | 5.1 | 4.5 (88) | 4.6 (90) | 4.6 (90) |
| Total protein (g/dL) | 6.6 | 6.3 (95) | 6.6 (100) | 6.4 (97) |
| Albumin (g/dL) | 3.3 | 3.3 (100) | 3.4 (103) | 3.3 (100) |
| Bilirubin (mg/dL) | 0.1 | 0.1 (100) | 0.4 (400) | 0.2 (200) |
| Uric acid (mg/dL) | 0.6 | 1.1 (183) | 0.9 (150) | 0.6 (100) |
| Cholesterol (mg/dL) | 156 | 145 (93) | 170 (109) | 142 (91) |
| Plasma cholinesterase (mu/mL) | 2704 | 1888 (70) | 1687 (62) | 1839 (68) |
| RBC cholinesterase (mu/mL) | 2688 | 2302 (86) | 1982 (74) | 3392 (126) |

[a]Source: Hart (1980a).
[b]Calculated from average body weight and food consumption provided in study using the following equation $Dose_{ADJ} = Dose_{ppm} \times$ Food Consumption per Day $\times$ (1 ÷ Body Weight) $\times$ (Days Dosed ÷ Total Days).
[c]Mean (% of control).
[d]$p \leq 0.05$ by Dunnett's *t*-test, conducted by the study author.

NR = Not reported.

**Table B.9. Mean Hematology and Clinical Chemistry Levels of Female Dogs Exposed to DIMP for 90 Days[a]**

| Parameter | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | | |
|---|---|---|---|---|
| | **0** | **150 (4.55)** | **1500 (46.97)** | **3000 (92.78)** |
| *N* | 4 | 4 | 4 | 4 |
| **Wk 0** | | | | |
| PCV (%) | 45 | 46 (102)[c] | 48 (107) | 45 (100) |
| HGB (g %) | 15.2 | 15.1 (99) | 16.4 (108) | 15.1 (99) |
| RBC ($mm^3 \times 10^6$) | 6.84 | 6.58 (96) | 7.09 (104) | 6.84 (100) |
| WBC ($mm^3 \times 10^3$) | 5.7 | 6.4 (112) | 6.7 (118) | 7.6 (133) |
| Clotting time (sec) | 338 | 443 (131) | 443 (131) | 465 (138) |
| Glucose (mg/dL) | 108 | 109 (101) | 113 (105) | 122 (113) |
| BUN (mg/dL) | 11 | 11 (100) | 12 (109) | 13 (118) |
| SGOT (miu/mL) | 36 | 32 (89) | 30 (83) | 33 (92) |
| SGPT (miu/mL) | 27 | 32 (119) | 33 (122) | 37 (137) |
| Alkaline phosphatase (miu/mL) | 110 | 107 (97) | 99 (90) | 103 (94) |
| LDH (miu/mL) | 269 | 160 (59) | 156 (58) | 182 (68) |
| Calcium (mg/dL) | 11.9 | 11.8 (99) | 11.8 (99) | 11.6 (97) |
| Phosphorus (mg/dL) | 6.2 | 6.5 (105) | 6.1 (98) | 6.2 (100) |
| Total Protein (g/dL) | 6.1 | 5.8 (95) | 6.0 (98) | 5.8 (95) |
| Albumin (g/dL) | 3.4 | 3.1 (91) | 3.1 (91) | 2.9 (85) |
| Bilirubin (mg/dL) | 0.4 | 0.3 (75) | 0.2 (50) | 0.2 (50) |
| Uric acid (mg/dL) | 0.3 | 0.2 (67) | 0.3 (100) | 0.2 (67) |
| Cholesterol (mg/dL) | 188 | 177 (94) | 176 (94) | 174 (93) |
| Plasma cholinesterase (mu/mL) | 2324 | 1820 (78) | 2296 (99) | 2016 (87) |
| RBC cholinesterase (mu/mL) | 1075 | 865 (80) | 1018 (95) | 735 (68) |
| **Wk 4** | | | | |
| PCV (%) | 49 | 48 (98)[c] | 50 (102) | 49 (100) |
| HGB (g %) | 17.2 | 16.9 (98) | 17.3 (101) | 17.3 (101) |
| RBC ($mm^3 \times 10^6$) | 7.04 | 6.84 (97) | 6.90 (98) | 7.07 (100) |
| WBC ($mm^3 \times 10^3$) | 9.8 | 9.8 (100) | 9.5 (97) | 7.7 (79) |
| Clotting time (sec) | 465 | 555 (119) | 668 (144) | 600 (129) |
| Glucose (mg/dL) | 109 | 105 (96) | 118 | 112 |
| BUN (mg/dL) | 13 | 14 (108) | 15 (115) | 14 (108) |
| SGOT(miu/mL) | 37 | 37 (100) | 39 (105) | 30 (81) |
| SGPT (miu/mL) | 31 | 38 (123) | 37 (119) | 38 (123) |

**Table B.9. Mean Hematology and Clinical Chemistry Levels of Female Dogs Exposed to DIMP for 90 Days[a]**

| Parameter | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | | |
|---|---|---|---|---|
| | **0** | **150 (4.55)** | **1500 (46.97)** | **3000 (92.78)** |
| Alkaline phosphatase (miu/mL) | 95 | 92 (97) | 81 (85) | 73 (77) |
| LDH (miu/mL) | 83 | 105 (127) | 54 (65) | 46 (55) |
| Calcium (mg/dL) | 11.4 | 11.5 (101) | 11.7 (103) | 11.3 (99) |
| Phosphorus (mg/dL) | 4.3 | 4.5 (105) | 4.7 (109) | 4.5 (105) |
| Total Protein (g/dL) | 6.2 | 6.1 (98) | 6.0 (97) | 5.7 (92) |
| Albumin (g/dL) | 3.7 | 3.7 (100) | 3.7 (100) | 3.5 (95) |
| Bilirubin (mg/dL) | 0.1 | 0.1 (100) | 0.1 (100) | 0.1 (100) |
| Uric acid (mg/dL) | 0.5 | 0.5 (100) | 0.7 (140) | 0.3 (60) |
| Cholesterol (mg/dL) | 165 | 180 (109) | 162 (98) | 151 (92) |
| Plasma cholinesterase (mu/mL) | NR | 1739 | 2003 | 1603 |
| RBC cholinesterase (mu/mL) | NR | 3772 | 4576 | 4016 |
| **Wk 8** | | | | |
| PCV (%) | 49 | 48 (98)[c] | 50 (102) | 49 (100) |
| HGB (g %) | 17.8 | 17.0 (96) | 17.7 (99) | 17.7 (99) |
| RBC ($mm^3 \times 10^6$) | 8.14 | 7.87 (97) | 8.05 (99) | 8.10 (100) |
| WBC ($mm^3 \times 10^3$) | 11.7 | 12.4 (106) | 10.8 (92) | 14.1 (121) |
| Clotting time (sec) | 413 | 495 (120) | 570 (138) | 480 (116) |
| Glucose (mg/dL) | 92 | 91 (99) | 103 (112) | 102 (111) |
| BUN (mg/dL) | 15 | 15 (100) | 16 (107) | 15 (100) |
| SGOT (miu/mL) | 39 | 34 (87) | 42 (108) | 44 (113) |
| SGPT (miu/mL) | 34 | 41 (121) | 40 (118) | 46 (135) |
| Alk phos (miu/mL) | 96 | 96 (100) | 74 (77) | 76 (79) |
| LDH (miu/mL) | 175 | 175 (100) | 234 (134) | 256 (146) |
| Calcium (mg/dL) | 11.0 | 10.8 (98) | 11.1 (101) | 10.6 (96) |
| Phosphorus (mg/dL) | 4.6 | 4.8 (104) | 4.5 (98) | 4.5 (98) |
| Total protein (g/dL) | 6.7 | 6.4 (96) | 6.8 (101) | 6.6 (99) |
| Albumin (g/dL) | 3.3 | 3.2 (97) | 3.3 (100) | 3.2 (97) |
| Bilirubin (mg/dL) | 0.4 | 0.4 (100) | 0.1 (25) | 0.1 (25) |
| Uric acid (mg/dL) | 1.2 | 0.5 (42) | 0.4 (33) | 0.4 (33) |
| Cholesterol (mg/dL) | 175 | 191 (109) | 173 (99) | 166 (95) |
| Plasma cholinesterase (mu/mL) | NR | 1890 | 2257 | 1846 |
| RBC cholinesterase (mu/mL) | NR | 2919 | 2478 | 2281 |

**Table B.9. Mean Hematology and Clinical Chemistry Levels of Female Dogs Exposed to DIMP for 90 Days[a]**

| Parameter | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | | |
|---|---|---|---|---|
| | 0 | 150 (4.55) | 1500 (46.97) | 3000 (92.78) |
| **Wk 13** | | | | |
| PCV (%) | 50 | 46 (92)[c] | 49 (98) | 48 (96) |
| HGB (g %) | 16.9 | 15.5 (92) | 16.6 (98) | 16.5 (98) |
| RBC ($mm^3 \times 10^6$) | 7.38 | 7.02 (95) | 7.43 (101) | 7.32 (99) |
| WBC ($mm^3 \times 10^3$) | 9.8 | 10.2 (104) | 11.3 (115) | 9.8 (100) |
| Clotting time (sec) | 458 | 638 (139) | 540 (118) | 600 (131) |
| Glucose (mg/dL) | 88 | 101 (115) | 103 (117) | 104 (118) |
| BUN (mg/dl) | 13 | 14 (108) | 15 (115) | 15 (115) |
| SGOT (miu/mL) | 42 | 54 (129) | 51 (121) | 46 (110) |
| SGPT (miu/mL) | 35 | 38 (109) | 41 (117) | 43 (123) |
| Alkaline phosphatase (miu/mL) | 63 | 69 (110) | 60 (95) | 50 (79) |
| LDH (miu/mL) | 232 | 620 (267) | 422 (182) | 362 (156) |
| Calcium (mg/dL) | 11.1 | 11.1 (100) | 11.4 (103) | 10.9 (98) |
| Phosphorus (mg/dL) | 4.4 | 4.5 (102) | 4.5 (102) | 4.6 (105) |
| Total protein (g/dL) | 6.4 | 6.3 (98) | 6.5 (102) | 6.4 (100) |
| Albumin (g/dL) | 3.4 | 3.4 (100) | 3.1 (91) | 3.3 (97) |
| Bilirubin (mg/dL) | 0.1 | 0.1 (100) | 0.3 (300) | 0.2 (200) |
| Uric acid (mg/dL) | 0.5 | 0.8 (160) | 0.6 (120) | 0.5 (100) |
| Cholesterol (mg/dL) | 158 | 215 (136) | 186 (118) | 173 (109) |
| Plasma cholinesterase (mu/mL) | 1779[d] | 1919 (108) | 2284 (128) | 1779 (100) |
| RBC cholinesterase (mu/mL) | 2431[d] | 2302 (95) | 2045 (84) | 2045 (84) |

[a]Source: Hart (1980a).
[b]Calculated from average body weight and food consumption provided in study using the following equation $Dose_{ADJ} = Dose_{ppm} \times$ Food Consumption per Day × (1 ÷ Body Weight) × (Days Dosed ÷ Total Days).
[c]Mean (% of control).
[d]$n = 2$.

**Table B.10. Absolute Organ Weights of Male and Female Dogs Exposed to DIMP for 90 Days[a]**

| Parameter | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | | |
|---|---|---|---|---|
| | **0** | **150 (5.30)** | **1500 (40.43)** | **3000 (85.32)** |
| **Male** | | | | |
| *N* | 4 | 4 | 4 | 4 |
| Brain (g) | 75.45 | 78.87 (105)[c] | 80.40 (107) | 79.65 (106) |
| Heart (g) | 90.44 | 88.10 (97) | 86.79 (96) | 85.77 (95) |
| Liver (g) | 296.2 | 314.6 (106) | 314.6 (106) | 296.4 (100) |
| Spleen (g) | 61.89 | 63.54 (103) | 63.49 (103) | 56.38 (91) |
| Kidney (g) | 57.49 | 59.18 (103) | 60.05 (104) | 62.04 (108) |
| Thyroids (g) | 0.878 | 0.95 (108) | 1.00 (114) | 0.86 (98) |
| Adrenals (g) | 0.93 | 0.96 (103) | 1.05 (113) | 0.97 (104) |
| Testes (g) | 22.09 | 23.78 (108) | 22.59 (102) | 18.40 (83) |
| **Parameter** | **Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b]** | | | |
| | **0** | **150 (4.55)** | **1500 (46.97)** | **3000 (92.78)** |
| **Female** | | | | |
| *N* | 4 | 4 | 4 | 4 |
| Brain (g) | 73.32 | 75.19 (103) | 70.43 (96) | 73.58 (100) |
| Heart (g) | 81.58 | 74.88 (92) | 78.85 (97) | 74.69 (92) |
| Liver (g) | 262.4 | 283.8 (108) | 283.2 (108) | 276.0 (105) |
| Spleen (g) | 58.06 | 50.06 (86) | 55.76 (96) | 69.12 (119) |
| Kidney (g) | 50.14 | 50.39 (100) | 46.13 (92) | 45.29 (90) |
| Thyroids (g) | 0.84 | 0.89 (106) | 0.77 (92) | 0.83 (99) |
| Adrenals (g) | 0.97 | 1.03 (106) | 1.10 (113) | 0.88 (91) |
| Ovaries (g) | 0.73 | 1.04 (142) | 1.96 (268) | 1.46 (200) |

[a]Source: Hart (1980a).
[b]Values are calculated from average body weight and food consumption provided in study using the following equation $Dose_{ADJ} = Dose_{ppm} \times$ Food Consumption per Day $\times$ (1 $\div$ Body Weight) $\times$ (Days Dosed $\div$ Total Days).
[c]Mean (% of control).

**Table B.11. Relative Organ Weights of Male and Female Dogs Exposed to DIMP for 90 Days[a]**

| Parameter | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | | |
|---|---|---|---|---|
| | **0** | **150 (5.30)** | **1500 (40.43)** | **3000 (85.32)** |
| **Male[c]** | | | | |
| *N* | 4 | 4 | 4 | 4 |
| Brain | 0.657 | 0.643 (98)[d] | 0.679 (103) | 0.733 (112) |
| Heart | 0.783 | 0.713 (91) | 0.731 (93) | 0.785 (100) |
| Liver | 2.575 | 2.560 (99) | 2.661 (103) | 2.721 (106) |
| Spleen | 0.549 | 0.511 (93) | 0.536 (98) | 0.517 (94) |
| Kidney | 0.492 | 0.480 (98) | 0.509 (103) | 0.570 (116) |
| Thyroids | 7.77 | 7.71 (99) | 8.48 (109) | 8.06 (104) |
| Adrenals | 8.18 | 7.80 (95) | 8.83 (108) | 8.79 (107) |
| Testes | 0.192 | 0.193 (101) | 0.191 (99) | 0.168 (88) |
| **Parameter** | **Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b]** | | | |
| | **0** | **150 (4.55)** | **1500 (46.97)** | **3000 (92.78)** |
| **Female[c]** | | | | |
| *N* | 4 | 4 | 4 | 4 |
| Brain | 0.713 | 0.752 (105) | 0.674 (95) | 0.744 (104) |
| Heart | 0.786 | 0.743 (95) | 0.751 (96) | 0.746 (95) |
| Liver | 2.514 | 2.829 (113) | 2.689 (107) | 2.776 (110) |
| Spleen | 0.549 | 0.496 (90) | 0.527 (96) | 0.692 (126) |
| Kidney | 0.485 | 0.505 (104) | 0.439 (91) | 0.449 (93) |
| Thyroids | 8.08 | 8.75 (108) | 7.27 (90) | 8.34 (103) |
| Adrenals | 9.36 | 10.24 (109) | 10.38 (111) | 8.85 (95) |
| Ovaries | 7.12 | 9.96 (140) | 18.27[e] (257) | 14.58 (205) |

[a]Source: Hart (1980a).
[b]Values are calculated from average body weight and food consumption provided in study using the following equation: $Dose_{ADJ} = Dose_{ppm} \times$ Food Consumption per Day $\times$ (1 ÷ Body Weight) $\times$ (Days Dosed ÷ Total Days).
[c]g or mg/100 g body weight; authors do not differentiate which units go with which organs.
[d]Mean (% of control).
[e]$p \leq 0.05$ by Dunnet's *t*-test; conducted by the study authors.

**Table B.12. Body Weights and Food Consumption of Male and Female Ranch Wild Mink Exposed to DIMP for 90 Days[a]**

| Parameter | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | | | | |
|---|---|---|---|---|---|---|
| | **0** | **50 (6.8)** | **450 (63.4)** | **2700 (344.7)** | **5400 (747.1)** | **8000 (1008.6)** |
| **Male** | | | | | | |
| *N* | 10 | 10 | 10 | 10 | 10 | 10 |
| Feed consumed (g/mink/d) | 238.2 | 252.2 (106)[c] | 246.1 (103) | 235.6 (99) | 240.2 (101) | 190.4 (80) |
| DIMP consumed (mg/mink/d) | 0 | 14.4 | 129.9 | 690.3 | 1483.0 | 1711.7 |
| Mean body weight (g) | 2084.1 | 2127.3 (102) | 2047.5 (98) | 2002.8 (96) | 1985.1 (95) | 1697.1 (81) |
| | **Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b]** | | | | | |
| **Parameter** | **0** | **50 (9.0)** | **450 (82.3)** | **2700 (455.2)** | **5400 (907.7)** | **8000 (1263.5)** |
| **Female** | | | | | | |
| *N* | 10 | 10 | 10 | 10 | 10 | 10 |
| Feed consumed (g/mink/d) | 169.1 | 167.6 (99) | 173.5 (103) | 170.3 (101) | 149.1 (88) | 128.0 (76) |
| DIMP consumed (mg/mink/d) | 0 | 9.6 | 91.6 | 499.0 | 920.9 | 1150.7 |
| Mean body weight (g) | 1113.0 | 1062.5 (95) | 1112.8 (100) | 1096.3 (98) | 1014.1 (91) | 910.7 (82) |

[a]Source: Bucci et al. (1994).
[b]Doses converted by authors.
[c]Mean (% of control).

**Table B.13. Hematology of Male Ranch Wild Mink Exposed to DIMP for 90 Days[a]**

| Parameter | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | | | | |
|---|---|---|---|---|---|---|
| | **0** | **50 (6.8)** | **450 (63.4)** | **2700 (344.7)** | **5400 (747.1)** | **8000 (1008.6)** |
| *N* | 10 | 10 | 10 | 10 | 10 | 10 |
| **Wk 0** | | | | | | |
| Hematocrit (%) | 45.31 ± 2.86 | 46.76 ± 3.94 (103)[c] | 45.43 ± 2.89 (100) | 45.48 ± 2.92 (100) | 46.71 ± 3.60 (103) | 45.56 ± 2.28 (101) |
| Hemoglobin (g/dL) | 15.52 ± 1.00 | 15.91 ± 1.42 (103) | 15.43 ± 1.03 (99) | 15.52 ±1.08 (100) | 15.76 ± 1.14 (102) | 15.48 ± 0.81 (100) |
| Erythrocyte Count ($10^6$/µL) | 7.95 ± 0.75 | 8.35 ± 0.82 (105) | 8.00 ± 0.76 (101) | 7.96 ± 0.64 (100) | 8.25 ± 0.56 (104) | 8.02 ± 0.50 (101) |
| Reticulocytes (% × RBC) | 2.16 ± 1.28 | 2.43 ± 0.67 (113) | 2.22 ± 0.96 (103) | 2.00 ± 0.67 (93) | 2.14 ± 1.06 (99) | 1.81 ± 0.80 (84) |
| Heinz Bodies (% × RBC) | 0.00 ± 0 | 0.00 ± 0 (NA) | 0.00 ± 0 (NA) | 0.00 ± 0 (NA) | 0.00 ± 0 (NA) | 0.00 ± 0 (NA) |
| Plasma Cholinesterase (units/L) | 1519.67 ± 144.84 | 1545.22 ± 247.56 (102) | 1486.30 ± 297.67 (98) | 1522.70 ±1 87.59 (100) | 1595.40 ± 178.24 (105) | 1503.70 ± 131.40 (99) |
| **Wk 3** | | | | | | |
| Hematocrit (%) | 46.24 ± 1.49 | 47.53 ± 1.79 (103) | 48.63 ± 3.13 (105) | 48.14 ± 3.58 (104) | 46.40 ± 2.71 (100) | 45.23 ± 2.29 (98) |
| Hemoglobin (g/dL) | 15.36 ± 0.61 | 15.79 ± 0.58 (103) | 15.96 ± 1.08 (104) | 15.67 ± 1.13 (102) | 15.27 ± 0.93 (99) | 14.89 ± 0.78[d] (97) |
| Erythrocyte Count ($10^6$/µL) | 7.74 ± 0.50 | 8.15 ± 0.29 (105) | 8.24 ± 0.55 (106) | 7.99 ± 0.63 (103) | 7.76 ± 0.41 (100) | 7.60 ± 0.50 (98) |
| Reticulocytes (% × RBC) | 2.32 ± 0.75 | 2.15 ± 0.72 (93) | 2.46 ± 0.51 (106) | 2.67 ± 1.01 (115) | 3.61 ± 1.09[d] (156) | 2.75 ± 1.17 (119) |
| Heinz Bodies (% × RBC) | 0.07 ± 0.11 | 0.04 ± 0.07 (57) | 0.07 ± 0.08 (100) | 0.56 ± 0.86 (800) | 1.98 ± 2.42 (2829) | 4.85 ± 9.99[d] (6929) |
| Plasma Cholinesterase (units/L) | 1469.10 ± 172.27 | 1563.90 ± 263.22 (106) | 1393.70 ± 240.50 (95) | 1029.80 ± 123.99 (70) | 784.20 ± 120.96[d] (53) | 733.30 ± 85.18[d] (50) |
| **Wk 7** | | | | | | |
| Hematocrit (%) | 51.25 ± 2.11 | 52.37 ± 2.43 (102) | 52.69 ± 2.07 (103) | 52.45 ± 4.07 (102) | 49.41 ± 2.08 (96) | 45.40 ± 2.00 (89) |
| Hemoglobin (g/dL) | 16.31 ± 0.81 | 16.43 ± 0.60 (101) | 16.60 ± 0.69 (102) | 16.38 ± 1.36 (100) | 15.69 ± 0.51 (96) | 14.71 ± 0.58[d] (90) |
| Erythrocyte Count ($10^6$/µL) | 8.33 ± 0.64 | 8.65 ± 0.47 (104) | 8.61 ± 0.50 (103) | 8.41 ± 0.88 (101) | 7.98 ± 0.30 (96) | 7.40 ± 0.37[d] (89) |
| Reticulocytes (% × RBC) | 1.43 ± 0.63 | 1.60 ± 0.68 (112) | 2.24 ± 0.94 (157) | 2.60 ± 1.47 (182) | 2.23 ± 1.17 (156) | 3.42 ± 1.42[d] (239) |
| Heinz Bodies (% × RBC) | 0.13 ± 0.24 | 0.32 ± 0.53 (246) | 0.41 ± 0.96 (315) | 0.32 ± 0.69 (246) | 3.26 ± 2.12[d] (2508) | 13.78 ± 7.71[d] (10,600) |

**Table B.13. Hematology of Male Ranch Wild Mink Exposed to DIMP for 90 Days[a]**

| Parameter | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | | | | |
|---|---|---|---|---|---|---|
| | **0** | **50 (6.8)** | **450 (63.4)** | **2700 (344.7)** | **5400 (747.1)** | **8000 (1008.6)** |
| Plasma Cholinesterase (units/L) | 1542.10 ± 157.93 | 1563.00 ± 248.98 (101) | 1427.90 ± 273.63 (93) | 982.00 ± 144.22[d] (64) | 763.30 ± 115.51[d] (49) | 646.00 ± 73.66[d] (42) |
| **Wk 13** | | | | | | |
| Hematocrit (%) | 48.15 ± 2.11 | 48.29 ± 2.44 (100) | 48.58 ± 2.53 (101) | 48.14 ± 2.20 (100) | 48.33 ± 3.51 (100) | 44.01 ± 2.12[d] (91) |
| Hemoglobin (g/dL) | 15.80 ± 0.65 | 15.99 ± 0.65 (101) | 15.96 ± 0.77 (101) | 15.82 ± 1.04 (100) | 15.95 ± 1.28 (101) | 14.49 ± 0.59[d] (92) |
| Erythrocyte Count ($10^6$/µL) | 8.13 ± 0.57 | 8.39 ± 0.56 (103) | 8.33 ± 0.48 (102) | 8.05 ± 0.60 (99) | 8.22 ± 0.54 (101) | 7.44 ± 0.44[d] (92) |
| Reticulocytes (% × RBC) | 2.05 ± 0.66 | 2.23 ± 1.06 (109) | 2.14 ± 0.54 (104) | 2.22 ± 0.88 (108) | 2.96 ± 0.57 (144) | 4.48 ± 2.45[d] (219) |
| Heinz Bodies (% × RBC) | 0.00 ± 0.00 | 0.20 ± 0.31 (NA) | 0.03 ± 0.07 (NA) | 0.70 ± 0.73 (NA) | 4.88 ± 5.62[d] (NA) | 14.45 ± 8.48[d] (NA) |
| Plasma Cholinesterase (units/L) | 1446.70 ± 134.14 | 1460.70 ± 183.65 (101) | 1340.50 ± 227.17 (93) | 865.70 ± 87.24[d] (60) | 722.10 ± 118.39[d] (50) | 609.50 ± 117.00[d] (42) |

[a]Source: Bucci et al. (1994, 1992).
[b]Doses converted by authors.
[c]Mean ± standard deviation (% of control).
[d]$p \leq 0.05$ by repeated measures using an incomplete block design in SAS; conducted by the study authors.

NA = Not applicable.

**Table B.14. Hematology of Female Ranch Wild Mink Exposed to DIMP for 90 Days[a]**

| Parameter | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | | | | |
|---|---|---|---|---|---|---|
| | **0** | **50 (9.0)** | **450 (82.3)** | **2700 (455.2)** | **5400 (907.7)** | **8000 (1263.5)** |
| *N* | 10 | 10 | 10 | 10 | 10 | 10 |
| **Week 0** | | | | | | |
| Hematocrit (%) | 48.68 ±3.11 | 44.74 ± 2.90 (92)[c] | 47.60 ± 1.85 (98) | 48.64 ± 3.36 (100) | 48.18 ± 3.55 (99) | 47.15 ± 2.93 (97) |
| Hemoglobin (g/dL) | 15.86 ± 0.99 | 14.88 ± 0.59 (94) | 15.59 ± 0.69 (98) | 15.81 ± 1.13 (100) | 15.63 ± 1.09 (99) | 15.33 ± 0.91 (97) |
| Erythrocyte Count ($10^6$/µL) | 7.84 ± 0.31 | 7.35 ± 0.55 (94) | 7.78 ± 0.29 (99) | 7.85 ± 0.53 (100) | 7.94 ± 0.60 (101) | 7.68 ± 0.52 (98) |
| Reticulocytes (%× RBC) | 1.64 ± 0.78 | 1.41 ± 0.62 (86) | 1.71 ± 0.58 (104) | 2.03 ± 0.48 (124) | 1.44 ± 0.42 (88) | 1.32 ± 0.69 (80) |
| Heinz Bodies (% × RBC) | 0.01 ± 0.03 | 0.01 ± 0.03 (100) | 0.00 ± 0 (0) | 0.01 ± 0.03 (100) | 0.01 ± 0.03 (100) | 0.01 ± 0.03 (100) |
| Plasma Cholinesterase (units/L) | 1351.40 ± 130.25 | 1424.20 ± 202.24 (105) | 1331.11 ± 213.68 (98) | 1341.30 ± 165.79 (99) | 1410.60 ± 178.55 (104) | 1236.80 ± 111.33 (92) |
| **Week 3** | | | | | | |
| Hematocrit (%) | 47.29 ± 2.61 | 47.39 ± 2.59 (100) | 46.13 ± 1.41 (98) | 46.69 ± 2.99 (99) | 44.74 ± 2.92[d] (95) | 43.79 ± 2.62[d] (93) |
| Hemoglobin (g/dL) | 15.63 ± 0.76 | 15.44 ± 0.91 (99) | 15.25 ± 0.37 (98) | 15.33 ± 0.88 (98) | 14.77 ± 0.99[d] (94) | 14.52 ± 0.83[d] (93) |
| Erythrocyte Count ($10^6$/µL) | 7.75 ± 0.46 | 7.67 ± 0.50 (99) | 7.60 ± 0.24 (98) | 7.59 ± 0.42 (98) | 7.37 ± 0.61 (95) | 7.11 ± 0.44[d] (92) |
| Reticulocytes (% × RBC) | 1.80 ± 0.71 | 1.87 ± 0.71 (104) | 1.76 ± 0.63 (98) | 2.19 ± 0.59 (122) | 3.21 ± 1.32[d] (178) | 3.10 ± 1.58[d] (172) |
| Heinz Bodies (% × RBC) | 0.01 ± 0.03 | 0.08 ± 0.10 (800) | 0.05 ± 0.11 (500) | 0.12 ± 0.14 (1200) | 1.65 ± 1.65 (16,500) | 9.24 ± 12.93[d] (92,400) |
| Plasma Cholinesterase (units/L) | 1332.60 ± 104.66 | 1342.80 ± 194.97 (101) | 1276.40 ± 203.54 (96) | 872.40 ± 152.22[d] (65) | 722.50 ± 101.14[d] (54) | 620.40 ± 90.20[d] (47) |
| **Week 7** | | | | | | |
| Hematocrit (%) | 49.15 ± 4.51 | 49.20 ± 2.68 (100) | 49.86 ± 2.58 (101) | 50.63 ± 1.49 (103) | 46.33 ± 3.88[d] (94) | 45.71 ± 4.92[d] (93) |
| Hemoglobin (g/dL) | 16.01 ± 0.99 | 15.34 ± 0.87 (96) | 15.62 ± 0.76 (98) | 15.93 ± 0.59 (100) | 14.87 ± 1.27[d] (93) | 14.84 ± 1.45[d] (93) |
| Erythrocyte Count ($10^6$/µL) | 8.06 ± 0.78 | 7.76 ± 0.47 (96) | 8.00 ± 0.46 (99) | 8.01 ± 0.22 (99) | 7.52 ± 0.80 (93) | 7.29 ± 0.95[d] (90) |
| Reticulocytes (% × RBC) | 1.70 ± 0.68 | 1.52 ± 0.99 (89) | 2.12 ± 0.87 (125) | 2.09 ± 0.76 (123) | 2.17 ± 0.82 (128) | 5.16 ± 2.19[d] (304) |
| Heinz Bodies (% × RBC) | 0.19 ± 0.16 | 0.02 ± 0.04 (11) | 0.15 ± 0.25 (79) | 0.90 ± 0.92 (474) | 6.98 ± 6.03[d] (3674) | 20.56 ± 8.22[d] (10,821) |

**Table B.14. Hematology of Female Ranch Wild Mink Exposed to DIMP for 90 Days[a]**

| Parameter | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | | | | |
|---|---|---|---|---|---|---|
| | **0** | **50 (9.0)** | **450 (82.3)** | **2700 (455.2)** | **5400 (907.7)** | **8000 (1263.5)** |
| Plasma Cholinesterase (units/L) | 1467.00 ± 205.92 | 1460.10 ± 213.82 (100) | 1324.90 ± 123.12 (90) | 874.20 ± 130.47[d] (60) | 722.10 ± 118.17[d] (49) | 541.40 ± 90.84[d] (37) |
| **Week 13** | | | | | | |
| Hematocrit (%) | 47.41 ± 3.75 | 47.12 ± 2.12 (99) | 46.44 ± 2.84 (98) | 46.30 ± 3.87 (98) | 44.51 ± 2.26[d] (94) | 44.95 ± 2.39[d] (95) |
| Hemoglobin (g/dL) | 15.46 ± 1.03 | 15.29 ± 0.72 (99) | 15.00 ± 0.95 (97) | 15.25 ± 1.23 (99) | 14.72 ± 0.74[d] (95) | 14.92 ± 0.76[d] (97) |
| Erythrocyte Count ($10^6$/µL) | 7.90 ± 0.44 | 7.75 ± 0.45 (98) | 7.75 ± 0.50 (98) | 7.61 ± 0.61 (96) | 7.41 ± 0.32 (94) | 7.51 ± 0.61[d] (95) |
| Reticulocytes (% × RBC) | 1.98 ± 0.77 | 1.83 ±0.54 (92) | 2.13 ± 0.92 (108) | 2.33 ± 0.97 (118) | 3.27 ± 1.70 (165) | 4.95 ± 2.62[d] (250) |
| Heinz Bodies (% × RBC) | 0.02 ± 0.06 | 0.41 ± 0.89 (2050) | 0.17 ± 0.16 (850) | 1.70 ± 1.91 (8500) | 14.01 ± 9.22[d] (70,050) | 16.99 ± 6.65[d] (84,950) |
| Plasma Cholinesterase (units/L) | 1395.10 ± 236.96 | 1387.30 ± 224.75 (99) | 1252.10 ± 126.21[d] (90) | 771.30 ± 128.77[d] (55) | 646.60 ± 85.69[d] (46) | 479.60 ± 50.01[d] (34) |

[a]Source: Bucci et al. (1994, 1992).
[b]Doses converted by authors.
[c]Mean ± standard deviation (% of control).
[d]$p \leq 0.05$ by repeated measures using an incomplete block design in SAS; conducted by the study authors.

**Table B.15. Plasma and Red Blood Cell Cholinesterase (ChE) Levels in Mink Exposed to DIMP for 90 Days[a]**

| Parameter | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | |
|---|---|---|---|
| | **0** | **2700 (344.7)** | **8000 (1008.6)** |
| **Male** | | | |
| Sample size | 3 | 3 | 3 |
| HCT (decimal)[c] | 0.462 | 0.481 (104) | 0.441 (95) |
| Whole blood ChE (U/L)[d] | 2165 ± 175 | 1972 ± 260 (91) | 1729 ± 37 (80) |
| Plasma ChE (U/L)[d] | 1365 ± 37 | 563 ± 76 (41) | 512 ± 140 (38) |
| RBC AChE (U/L) [d, e] | 3097 ± 359 | 3492 ± 145 (113) | 3272 ± 130 (106) |
| **Parameter** | **Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b]** | | |
| | **0** | **2700 (455.2)** | **8000 (1263.5)** |
| **Female** | | | |
| Sample size | 3 | 3 | 3 |
| HCT (decimal)[c] | 0.450 | 0.451 (100) | 0.434 (96) |
| Whole blood ChE (U/L)[d] | 2216 ± 28 | 2057 ± 294 (93) | 1624 ± 436 (73) |
| Plasma ChE (U/L)[d] | 987 ± 58 | 495 ± 63 (50) | 322 ± 20 (33) |
| RBC AChE (U/L) [d, e] | 3718 ± 157 | 3958 ± 474 (106) | 3322 ± 1110 (89) |

[a]Source: Bucci et al. (1994).
[b]Doses converted by authors.
[c]Values expressed as mean (% of control)
[d]Values expressed as mean ± SD (% of control).
[e]Red blood cell acetylcholinesterase content (RBC AChe) was calculated using the formula: RBC AChE = Whole blood ChE − [Plasma ChE × (1 − HCT)] ÷ HCT.

**Table B.16. Hematopoiesis in the Spleens of Mink Exposed to DIMP for 90 Days[a]**

| Parameter | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | |
|---|---|---|---|
| | **0** | **8000 (1008.6)** | **8000 (1008.6) Recovery Group[c]** |
| **Male** | | | |
| Increased hematopoiesis[d] | 6/10 (1.0) | 7/8 (1.7) | 0/2 (NA) |
| **Parameter** | **Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b]** | | |
| | **0** | **8000 (1263.5)** | **8000 (1263.5) Recovery Group** |
| **Female** | | | |
| Increased hematopoiesis[d] | 4/10 (1.5) | 7/8 (1.6) | 0/2 (NA) |

[a]Source: Bucci et al. (1994).
[b]Doses converted by authors.
[c]Two animals from the high-dose group of each sex were observed for 1 additional month after the cessation of treatment.
[d]Values expressed as the number of animals affected/number examined (average severity grade; maximum = 4).

NA = Not applicable.

**Table B.17. Body Weight and Food Consumption in Female Sprague-Dawley Rats Exposed by Diet to DIMP on GDs 6−15[a]**

| Parameter | | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | | |
|---|---|---|---|---|---|
| | | 0 | 100 (7.4) | 300 (21.6) | 3000 (232.5) |
| **Mean Body Weight (g)** | | | | | |
| Day 0[c] | Mean | 214 ± 17 | 219 ± 17 (102) | 217 ± 19 (101) | 217 ± 15 (101) |
| | *N* | 13 | 14 | 11 | 15 |
| Day 6[c] | Mean | 240 ± 19 | 245 ± 16 (102) | 242 ± 19 (101) | 247 ± 13 (103) |
| | *N* | 13 | 14 | 11 | 15 |
| Day 16[c] | Mean | 281 ± 22 | 299 ± 27 (106) | 286 ± 25 (102) | 295 ± 19 (105) |
| | *N* | 13 | 14 | 11 | 15 |
| Day 20[c] | Mean | 337 ± 28 | 346 ± 40 (103) | 341 ± 34 (101) | 346 ± 29 (103) |
| | *N* | 13 | 14 | 11 | 15 |
| **Mean Daily Food Consumption (g)** | | | | | |
| Days 0−6[c] | Mean | 20 ± 7 | 22 ± 9 (110) | 18 ± 2 (90) | 19 ± 1 (95) |
| | *N* | 10 | 13 | 11 | 15 |
| Day 6−16[c] | Mean | 18 ± 1 | 20 ± 2 (111) | 19 ± 3 (106) | 21 ± 2 (117) |
| | *N* | 5 | 11 | 7 | 8 |
| Day 16−20[c] | Mean | 25 ± 5 | 23 ± 4 (92) | 25 ± 4 (100) | 26 ± 3 (104) |
| | *N* | 13 | 14 | 11 | 15 |

[a]Source: Hart (1980b).
[b]Doses are converted from ppm to mg/kg-day using the following equation: $Dose_{ADJ} = Dose_{ppm} \times$ Food Consumption per Day × (1 ÷ Body Weight) × (Days Dosed ÷ Total Days).
[c]Values expressed as mean ± SD (% of control).

**Table B.18. Reproductive Effects in Female Sprague-Dawley Rats Exposed to DIMP by Diet on GDs 6−15[a]**

| Parameter | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | | |
|---|---|---|---|---|
| | **0** | **100 (7.4)** | **300 (21.6)** | **3000 (232.5)** |
| Pregnancy ratio[c] | 14/20 | 14/20 | 11/20 | 15/20 |
| Implantation sites[d, e] | 86/67 | 78/90 | 50[f]/68[f] | 91/91 |
| Resorptions/live fetuses | 13/140 | 16/152 | 7/110 | 9/173 |
| Average fetal weight (g)[f] | 3.7 | 3.9 | 3.8 | 3.9 |
| Average fetal length (cm)[f] | 3.1 | 3.1 | 3.1 | 3.1 |
| Mean live litter size (pups) | 11 | 11 | 10 | 12 |

[a]Source: Hart (1980b).
[b]Doses are converted from ppm to mg/kg-day using the following equation: $Dose_{ADJ}$ = Dose × Food Consumption per Day × (1 ÷ Body Weight) × (Days Dosed ÷ Total Days).
[c]Number pregnant/ number mated.
[d]Based on average of litter means.
[e]Left horn/right horn.
[f]Significantly different from controls ($p \leq 0.05$) based on a 2 × 2 contingency table with the Yate's correction; not significant for $p > 0.05$ based on Wilcoxon rank sum test as reported by the study author.

**Table B.19. Skeletal Effects in Sprague-Dawley Rats Exposed to DIMP In Utero on GDs 6−15[a]**

| Parameter | Exposure Group, ppm (Adjusted Daily Dose, mg/kg-d)[b] | | | |
|---|---|---|---|---|
| | 0 | 100 (7.4) | 300 (21.6) | 3000 (232.5) |
| Number examined[c] | 100 | 102 | 75 | 114 |
| Number normal | 73 | 69 | 58 | 67 |
| Number with common skeletal variations[d] | 27 | 33 | 15 | 45[e] |
| Number with unusual changes[f] | 0 | 2 | 4 | 3 |

[a]Source: Hart (1980b).
[b]Doses are converted from ppm to mg/kg-day using the following equation: $Dose_{ADJ} = Dose_{ppm} \times$ Food Consumption per Day × (1 ÷ Body Weight) × (Days Dosed ÷ Total Days).
[c]The author examined two-thirds of the fetuses in each litter.
[d]The author note that these are changes that are frequently observed in 21-day-old rat fetuses of this strain and source in their laboratory and typically include unilateral and bilateral ribs; reduced ossification of interparietal, hyoid, and supraoccipital bones; and nonfused thoracic vertebral centra.
[e]Significantly different from control ($p \leq 0.05$) based on a 2 × 2 contingency table; not significant for $p > 0.05$ based on Wilcoxon rank sum test as reported by the study author.
[f]Unusual changes include malformed maxilla or mandible; reduced ossification of sternebrae, pubes, sacral vertebral arches, right ischium, parietal bone, or maxilla; wavy ribs; nonossified hyoid; and nonossified distal phalanges of the hind extremities.

**Table B.20. Mean Body Weights and Food Consumption of Ranch Wild Mink After Dietary Exposure to DIMP[a]**

| Parameter | Exposure Group, % (Adjusted Daily Dose, mg/kg-d)[b] | | | |
|---|---|---|---|---|
| | **0** | **150 (14.94)** | **450 (47.36)** | **2500 (284.79)** |
| **F0 Male** | | | | |
| Mean body weight (kg) | 2.274 | 2.199 (97)[c] | 2.244 (99) | 2.227 (98) |
| Food consumed (g/100g bw) | 9.8 | 9.2 (94) | 9.9 (101) | 10.5 (107) |
| **Parameter** | **Exposure Group, % (Adjusted Daily Dose, mg/kg-d)[b]** | | | |
| | **0** | **150 (15.67)** | **450 (45.00)** | **2500 (261.73)** |
| **F1 Male** | | | | |
| Mean body weight (kg) | 2.400 | 2.343 (98) | 2.425 (101) | 2.302 (96) |
| Food consumed (g/100g bw) | 9.4 | 9.3 (99) | 9.2 (98) | 9.4 (100) |
| **Parameter** | **Exposure Group, % (Adjusted Daily Dose, mg/kg-d)[b]** | | | |
| | **0** | **150 (25.61)** | **450 (84.81)** | **2500 (460.72)** |
| **F0 Female** | | | | |
| Mean body weight (kg) | 1.142 | 1.156 (101) | 1.137 (100) | 1.132 (99) |
| Food consumed (g/100g bw) | 18.6 | 15.8 (85) | 17.7 (95) | 16.9 (91) |
| **Parameter** | **Exposure Group, % (Adjusted Daily Dose, mg/kg-d)[b]** | | | |
| | **0** | **150 (19.74)** | **450 (56.50)** | **2500 (329.47)** |
| **F1 Female** | | | | |
| Mean body weight (kg) | 1.208 | 1.212 (100) | 1.210 (100) | 1.188 (98) |
| Food consumed (g/100g bw) | 11.5 | 11.7 (102) | 11.5 (100) | 11.9 (103) |

[a]Source: Bucci et al. (2003).
[b]Reported by study authors.
[c]Mean (% of control).

**Table B.21. Breeding Outcomes of F0 Female Ranch Wild Mink After Dietary Exposure to DIMP[a]**

| Parameter | Exposure Group, % (Adjusted Daily Dose, mg/kg-d)[b] | | | |
|---|---|---|---|---|
| | **0** | **150 (25.61)** | **450 (84.81)** | **2500 (460.72)** |
| **F0 Female** | | | | |
| Number of dams | 35 | 35 | 35 | 35 |
| Number of litters | 32 | 19 | 32 | 29 |
| Total kits | 226 | 134 | 232 | 217 |
| Mean kits per litter | 7.06 | 7.05 | 7.25 | 7.48 |
| Mean live kits per litter | 6.50 | 6.53 | 6.63 | 6.38 |
| Litter biomass (g) | 75.36 | 71.84 | 74.81 | 73.26 |
| Mean individual weight (g) | 10.97 | 10.13 | 10.59 | 10.46 |
| **Parameter** | **Exposure Group, % (Adjusted Daily Dose, mg/kg-d)[b]** | | | |
| | **0** | **150 (19.74)** | **450 (56.50)** | **2500 (329.47)** |
| **F1 Female** | | | | |
| Number of dams | 35 | 35 | 35 | 35 |
| Number of litters | 28 | 22 | 23 | 23 |
| Total kits | 188 | 147 | 144 | 144 |
| Mean kits per litter | 6.71 | 6.68 | 6.26 | 6.26 |
| Mean live kits per litter | 5.75 | 4.95 | 4.83 | 5.70 |
| Litter biomass (g) | 67.27 | 63.54 | 61.37 | 65.40 |
| Mean individual weight (g) | 10.37 | 9.54 | 9.54 | 10.43 |

[a]Source: Bucci et al. (2003).
[b]Reported by study authors.

**Table B.22. Sperm Evaluation of Male Ranch Wild Mink After Dietary Exposure to DIMP[a]**

| Parameter | Exposure Group, % (Adjusted Daily Dose, mg/kg-d)[b] | | | |
|---|---|---|---|---|
| | **0** | **150 (14.94)** | **450 (47.36)** | **2500 (284.79)** |
| Sperm count | 1244.9 ± 418.0[c] (*n* = 13) | 1417.2 ± 699.8 (*n* =13) | 1434.3 ± 657.4 (*n* = 12) | 1561.5 ± 1945.9 (*n* = 13) |
| Motility | 99.8 ± 0.6 (*n* = 10) | 100 ± 0 (*n* = 9) | 96.6 ± 1.3 (*n* = 9) | 99.9 ± 0.3 (*n* = 9) |
| Abnormal morphology (%) | 0.3 ± 0.3 (*n* = 13) | 0.1 ± 0.2 (*n* = 13) | 0.3 ± 0.4 (*n* = 12) | 0.2 ± 0.2 (*n* = 12) |

[a]Source: Bucci et al. (2003).
[b]Reported by study authors.
[c]Mean ± standard deviation.

**Table B.23. Hematologic Changes in F0 Female Ranch Wild Mink After Dietary Exposure to DIMP[a]**

| Parameter | | Exposure Group, % (Adjusted Daily Dose, mg/kg-d)[b] | |
|---|---|---|---|
| | | 0 | 2500 (460.72)[c] |
| **F0 Females** | | | |
| *N* | | 35 | 35 |
| Study initiation (9.5 mo of age) | RBC (× $10^6$µL) | 7.59 | 7.72 |
| | Reticulocytes (% of RBCs) | 3.1 | 3.3 |
| | MCV (µ$m^3$) | 62 | 61 |
| | Heinz bodies (% of RBC) | 0.0 | 0.0 |
| | Plasma cholinesterase (U/I) | 1109 | 1040 |
| | Whole blood cholinesterase (U/I) | 4378 | 4355 |
| | RBC cholinesterase (U/I) | 8118 | 8099 |
| Study termination (13.5 mo of age) | RBC (× $10^6$µL) | 7.79 | 7.38[d] |
| | Reticulocytes (% of RBCs) | 1.8 | 4.1[e] |
| | MCV (µ$m^3$) | 58 | 60[d] |
| | Heinz bodies (% of RBC) | 0.0 | 2.8[e] |
| | Plasma cholinesterase (U/I) | 1426 | 860[e] |
| | Whole blood cholinesterase (U/I) | 3725 | 3115[e] |
| | RBC cholinesterase (U/I) | 6479 | 6041[e] |
| | Brain cholinesterase (µmol/g/min) | 6.53 ($n$ = 10) | 7.13 ($n$ = 10) |

[a]Source: Bucci et al. (2003).
[b]Reported by study authors.
[c]All groups were measured, but only results for the high-dose group were reported.
[d]Statistically different from control ($p < 0.05$).
[e]Statistically different from control ($p < 0.01$).

**Table B.24. Hematologic Changes in F1 Female Ranch Wild Mink After Dietary Exposure to DIMP[a]**

| Parameter | | Exposure Group, % (Adjusted Daily Dose, mg/kg-d)[b] | |
|---|---|---|---|
| | | 0 | 2500 (329.47)[c] |
| **F1 Females** | | | |
| *N* | | 35 | 35 |
| 4.5 mo of age | RBC (× $10^6$µL) | 7.97 | 7.94 |
| | Reticulocytes (% of RBCs) | 3.1 | 3.1 |
| | MCV (µm$^3$) | 60 | 60 |
| | Heinz bodies (% of RBC) | 0.0 | 0.0 |
| | Plasma cholinesterase (U/I) | 1279 | 999[d] |
| | Whole blood cholinesterase (U/I) | 4589 | 4285[d] |
| | RBC Cholinesterase (U/I) | 8207 | 7859[e] |
| | Brain cholinesterase (µmol/g/min) | -- | -- |
| 7.5 mo of age | RBC (× $10^6$µL) | 8.45 | 6.36 |
| | Reticulocytes (% of RBCs) | 3.4 | 3.9 |
| | MCV (µm$^3$) | 60 | 61 |
| | Heinz bodies (% of RBC) | 0.0 | 0.2[e] |
| | Plasma Cholinesterase (U/I) | 1133 | 894[d] |
| | Whole blood Cholinesterase (U/I) | 4793 | 4572[d] |
| | RBC cholinesterase (U/I) | 8301 | 8174 |
| | Brain cholinesterase (µmol/g/min) | -- | -- |
| 13.5 mo of age | RBC (× $10^6$µL) | 8.29 | 6.20 |
| | Reticulocytes (% of RBCs) | 1.7 | 2.0 |
| | MCV (µm$^3$) | 61 | 61 |
| | Heinz bodies (% of RBC) | 0.1 | 1.3[d] |
| | Plasma cholinesterase (U/I) | 1310 | 905[d] |
| | Whole blood cholinesterase (U/I) | 4335 | 3966[e] |
| | RBC cholinesterase (U/I) | 7332 | 7103 |
| | Brain cholinesterase (µmol/g/min) | 7.24 ($n$ = 10) | 6.81 ($n$ = 10) |

[a]Source: Bucci et al. (2003).
[b]Reported by study authors.
[c]All groups were measured, but only results for the high-dose group were reported.
[d]Statistically different from control ($p < 0.01$).
[e]Statistically different from control ($p < 0.05$).

**Table B.25. Abnormal Clinical Responses in F1 Female Ranch Wild Mink After Dietary Exposure to DIMP[a]**

| Parameter | Exposure Group, % (Adjusted Daily Dose, mg/kg-d)[b] | | | | |
|---|---|---|---|---|---|
| | **0** | **0** | **150 (19.74)** | **450 (56.50)** | **2500 (329.47)** |
| Abnormality Level 1 | 2/4 (3)[c] | 1/5 (3) | 3/3 (6) | 2/3 (9) | 4/4 (9) |
| Abnormality Level 2 | 0/4 | 0/5 | 1/3 (1) | 2/3 (6) | 3/4 (6) |
| Abnormality Level 3 | 0/4 | 0/5 | 1/3 (1) | 1/3 (2) | 1/4 (4) |

[a]Source: Calabrese (2003a).
[b]Adjusted daily doses reported by Bucci et al. (2003).
[c]Number of mink with abnormal responses/number of mink that survived intervention (number of abnormal responses).

## APPENDIX C. BMD OUTPUTS

There are no BMD outputs for DIMP.

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