FINAL
4-1-2011

Provisional Peer-Reviewed Toxicity Values for

Phenothiazine
(CASRN 92-84-2)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

AUTHORS, CONTRIBUTORS, AND REVIEWERS

CHEMICAL MANAGER

Jeff Swartout
National Center for Environmental Assessment, Cincinnati, OH

DRAFT DOCUMENT PREPARED BY

ICF International
9300 Lee Highway
Fairfax, VA 22031

PRIMARY INTERNAL REVIEWERS

Dan D. Petersen, PhD, DABT
National Center for Environmental Assessment, Cincinnati, OH

Susan Makris, MS
National Center for Environmental Assessment, Washington, DC

This document was externally peer reviewed under contract to
Eastern Research Group, Inc.
110 Hartwell Avenue
Lexington, MA 02421-3136

Questions regarding the contents of this document may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

TABLE OF CONTENTS

COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMD	benchmark dose
BMCL	benchmark concentration lower bound 95% confidence interval
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
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
POD	point of departure
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 PHENOTHIAZINE (CASRN 92-84-2)

BACKGROUND

HISTORY

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1) EPA's Integrated Risk Information System (IRIS)
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in EPA's Superfund Program
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR);
   - California Environmental Protection Agency (CalEPA) values; and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by a panel of six EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

DISCLAIMERS

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

QUESTIONS REGARDING PPRTVS

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may 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), or OSRTI.

INTRODUCTION

Phenothiazine is used in the United States in the chemical industry, veterinary medicine, agricultural products, and as a psychopharmacological drug by clinicians (Integrated Laboratory Systems, 1997). The empirical formula for phenothiazine is $C_{12}H_9NS$ (see Figure 1). A table of chemicophysical properties is provided below (see Table 1). In this document, "statistically significant" denotes a *p*-value of <0.05.

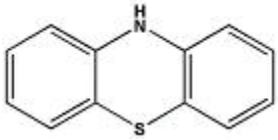

Figure 1. Phenothiazine Structure

Table 1. Chemicophysical Properties Table (Phenothiazine)	
Property (unit)	**Value[a]**
Boiling point (ºC)	371
Melting point (ºC)	184
Density (g/cm^3)	1.362
Vapor pressure (Pa at 25ºC)	Not available
pH (unitless)	Not available
Solubility in water (g/100 mL at 25ºC)	2
Relative vapor density (air = 1)	Not available
Molecular weight (g/mol)	199.27
Flash point (°C)	202
Log octanol/water partition coefficient (unitless)	4.2[b]

[a]http://www.chemicalbook.com/ChemicalProductProperty_EN_CB2272320.htm.
[b]NIOSH (1998).

The IRIS database does not list a chronic oral reference dose (RfD), a chronic inhalation reference concentration (RfC), or a cancer assessment for phenothiazine. No Drinking Water Standards and Health Advisories List values are reported. No RfD or RfC values are reported in the HEAST (U.S. EPA, 2010). The CARA list does not include a Health and Environmental Effects Profile (HEEP) for phenothiazine. The American Conference of Governmental Industrial Hygienists (ACGIH), the National Institute of Occupational Safety and Health (NIOSH), and the Occupational Safety and Health Administration (OSHA), respectively, have derived an 8-hour time-weighted average (TWA), 10-hour TWA, and a permissible exposure level (PEL), of 5 mg/m^3 (ACGIH, 1986; NIOSH, 1998).

The HEAST (U.S. EPA, 2010) has not reported an EPA cancer weight-of-evidence (WOE) classification for phenothiazine. The International Agency for Research on Cancer (IARC) has not reviewed the carcinogenic potential of phenothiazine. Phenothiazine is not included in the *11th Report on Carcinogens.* CalEPA (2008a,b) has not developed a quantitative estimate of carcinogenic potential for phenothiazine.

Literature searches were conducted on sources published from 1900 through October 22, 2010, for studies relevant to the derivation of provisional toxicity values for phenothiazine, CAS No. 92-84-2. 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 toxicity values: ACGIH, ATSDR, CalEPA, EPA IRIS, EPA HEAST, EPA HEEP, EPA OW, EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 2 provides information for all of the potentially relevant studies. Entries for the principal studies (PS) are bolded.

Table 2. Summary Of Potentially Relevant Data For Phenothiazine (CASRN 92-84-2)

Category	Number of Male/Female Species, Study Type, and Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a,b]	Reference (Comments)	Notes[c]
Human								
			1. Oral (mg/kg-day)[a]					
Acute	2 volunteers, sex not reported (at least one male), clinical, 3 doses, 12 hrs	750 mg total in one day	Photosensitization marked by increased hyperemia (no other endpoints examined)	Not determined	Not determined	Not determined	DeEds et al. (1940)	
	92 patients, sex not reported, clinical, one dose	3.12−42.9 g total for an unspecified duration	No dermal effects.	Not determined		Not determined		
Subchronic	None							
Chronic	None							
Developmental	None							
Reproduction	None							
Carcinogenic	None							
			2. Inhalation (mg/m^3)[a]					
Subchronic	None							
Chronic	None							
Developmental	None							
Reproduction	None							
Carcinogenic	None							

Table 2. Summary Of Potentially Relevant Data For Phenothiazine (CASRN 92-84-2)

Category	Number of Male/Female Species, Study Type, and Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a,b]	Reference (Comments)	Notes[c]
Animal								
			1. Oral (mg/kg-day)[a]					
Subchronic	0/49 rats (*N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide [FANFT] + phenothiazine), 0/16 rats (phenothiazine), diet, 7 d/wk for 20 wks, observed 40 wks	0, 22.5	No increase in tumor incidence with phenothiazine alone, but phenothiazine and FANFT together increased bladder carcinoma incidence, as compared to FANFT alone.	22.5	Not determined	None	Wang and Hayashida (1984)	
	4/4 dogs, diet, 7 d/wk, 13 wks	**Male: 0, 1.54, 6.06, 16.93, 69.30 Female: 0, 1.59, 6.82, 17.68, 67.05**	Increased SGOT (F).	**1.59**	**No acceptable fits**	**6.82**	**Hazleton Laboratories, Inc. (1974a).**	**PS NPR**
	4/4 dogs, diet, 7 d/wk, 13 wks	Male: 0, 69.30 Female: 0, 67.05	Decreased hematocrit, hemoglobin, and erythrocyte counts; increased spleen weight; lower blood sugar levels, particularly in females, were seen; congestion and hematopoiesis of the spleen; hemosiderin depositions in the spleen, liver, kidneys, and bone marrow; hyperplasia of the bone marrow.	None	Not determined	67.05	Hazleton Laboratories, Inc. (1974b).	NPR
Chronic	None							

Table 2. Summary Of Potentially Relevant Data For Phenothiazine (CASRN 92-84-2)

Category	Number of Male/Female Species, Study Type, and Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a,b]	Reference (Comments)	Notes[c]
Reproduction and Development	0/18−21 rats, gavage, one-generation reproduction study, Gestation Days (GDs) 6−15, GD 20	0, 15, 50, 150	Body weights and weight gains of dams treated with the highest dose were significantly reduced at GD 15; no other clinical signs of maternal toxicity; no significant fetotoxicity or teratogenicity.	>150	Not determined	None	Harris Laboratories, Inc. (1977a)	NPR
	0/10 rats, diet, developmental study, 7 d/wk, 22 d following mating	0, 50	Increased absorptions as compared to controls; no maternal toxicity, fetotoxicity, or teratology.	None	Not determined	1.25	Telford et al. (1962)	
	0/20−25 mice, gavage, developmental study, GDs 6−15, GD 17	0, 30, 100, 300	No clinical signs of maternal toxicity; an increase in the number of resorption sites, and the number of dams with one or more resorption sites was increased in each treated group of dams; the fetus weights were unchanged; structural abnormalities within expected range.	None	No fit	30	Harris Laboratories, Inc (1977b)	NPR
Carcinogenic	18/18 mice gavage followed by diet, 7 d/wk, 18 mos	0, 0.005	No increase in tumor incidence in any major tissue.	None	Not determined	None	Innes et al. (1969)	
2. Inhalation (mg/m^3)[a]								
Subchronic	None							
Chronic	None							
Developmental	None							
Reproduction	None							
Carcinogenic	None							

[a]Dosimetry, NOAEL, BMDL/BMCL, and LOAEL values are converted to human equivalent dose (HED in mg/kg-day), human equivalent concentration (HEC in mg/m^3), or average daily dose (ADD in mg/kg-day) units. Noncancer oral data are only adjusted for continuous exposure.
[b]Not reported by the study author, but determined from data.
[c]Notes: IRIS = Utilized by IRIS, date of last update; PS = Principal study; NPR = Not peer reviewed; SGOT = serum glutamic oxaloacetic transaminase.

HUMAN STUDIES

Oral Exposures

DeEds et al. (1940) reported photosensitization in two volunteer subjects (at least one male) who consumed 3 doses of 250 mg phenothiazine within 12 hours (approximately 10 mg/kg). The study was conducted by the USDA at the Stanford University Medical School in response to reported dermal irritation in workers who sprayed phenothiazine-based pesticides. The study authors did not mention any human study protocols that may have been in place at the time of the study. The authors also reported that there were no dermal effects in 92 patients who ingested a total of 3.12 to 42.9 grams of phenothiazine as a urinary antiseptic for an unspecified period. The authors hypothesized that the photosensitization was a result of metabolism of phenothiazine to leukothionol, which is a photosensitive compound. No other endpoints were examined in this study. There is too little detail in this study report to determine a NOAEL or LOAEL.

No other relevant studies of oral exposures to phenothiazine in humans were found in the literature. Two studies (Gilmour et al., 1971; Slone et al., 1977) of exposure to chlorpromazine, a phenothiazine derivative, were found but are not directly relevant for the assessment of chronic (Gilmour et al., 1971) and developmental (Slone et al., 1977) toxicity of phenothiazine.

Other toxicological information for phenothiazine exposure in humans comes from documentation of accidental overdose (HSDB, 1996). Historically, phenothiazine was used as an anthelmintic and a urinary antiseptic. In one case, phenothiazine was lethal when orally administered to a child at a dose of 425 mg/kg for 5 days. Other overdose scenarios have caused hemolytic anemia, toxic hepatitis, skin photosensitization, and intense pruritus. ACGIH (1986) also states that consuming average or large doses of phenothiazine orally can cause cramps, tachycardia, gastrointestinal and dermal irritation, kidney damage, and allergic skin reactions.

Inhalation Exposures

While some of the occupational exposure studies may include inhalation exposures, no studies in which inhalation was thought to be the primary route of phenothiazine exposure in humans could be identified.

ANIMAL STUDIES

Oral Exposures

The effects associated with oral exposure to phenothiazine in animals have been evaluated in subchronic (Wang and Hayashida, 1984; Hazelton Laboratories, 1974a,b), chronic (Innes et al., 1969), and reproductive and developmental (Harris Laboratories, Inc., 1977a,b; Telford et al., 1962) toxicity studies.

Subchronic Studies

Wang and Hayashida (1984) investigated the toxicity of phenothiazine (purity not reported) in 16 female Fisher rats by administering a diet containing 0.2% phenothiazine (22.5 mg/kg-day) for 20 weeks and then a control diet (powdered Wayne Lab-Blox) for the following 20 weeks. An additional 15 female Fisher rats were fed control diet for the entire 40-week duration of the study to constitute a control group. Additionally, the authors studied the joint carcinogenicity of phenothiazine and *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT) on 49 female Fisher rats by administering a diet containing 0.2% phenothiazine and 0.188% FANFT for 20 weeks and then the control diet for the following 20 weeks; this portion

of the study has relevance only in establishing a possible role of phenothiazine in the enhancement of FANFT-induced bladder cancer Animal weights were measured periodically (frequency unspecified). Histological examinations of the urinary bladders were performed, and microsomal fractions of the liver tissue of each test animal were prepared at 40 weeks. Statistical analysis was performed using the chi-square test and Student's *t*-test for their investigation of bladder carcinogenesis and hepatic microsomal nitroreductase, respectively.

Animals fed the 0.2% phenothiazine diet had final body weights slightly higher than the control group, and the authors found all of their bladders to be in normal condition, free of transitional cell carcinomas as shown in Appendix B, Table B.1. Rats fed the 0.2% phenothiazine and 0.188% FANFT diet had final body weights slightly lower than the control group, and the authors determined that only 4% of their bladders were in normal condition. Fifty-five percent of the rats fed both phenothiazine and FANFT exhibited bladder carcinoma, which was greater than the incidence in a group fed a 0.188% FANFT diet alone and was statistically significant. FANFT is a potent tumor initiator; phenothiazine may be a tumor promoter under these conditions. The study authors found a statistically significant increase in microsomal nitroreductase activity in the livers of animals fed 0.2% phenothiazine diet compared to the control group.

The increase in microsomal nitroreductase activity is not considered to be of toxicological significance. Because no other effects were noted following exposure to phenothiazine alone, a LOAEL cannot be determined. The NOAEL is 22.5 mg/kg-day.

The study by Hazelton Laboratories, Inc. (1974a) is selected as the principal study for deriving the screening subchronic p-RfD and screening chronic p-RfD. Hazelton Laboratories, Inc. (1974a) sponsored an oral toxicity study (not peer reviewed) in dogs. Phenothiazine (pharmaceutical grade, purity not specified) was administered to groups of four male and four female beagles in the diet at levels of 0, 50, 200, 500, or 2000 ppm. The basal laboratory diet for the control dogs and the compound/diet mixtures for the treated dogs were available ad libitum for 13 weeks. The adjusted daily doses were calculated by the study authors to be 1.54, 6.06, 16.93, or 69.30 mg/kg-day for males and 1.59, 6.82, 17.68, or 67.05 mg/kg-day for females. The study authors made daily observations about appearance, behavior, appetite, elimination, and signs of pharmacological effect. Clinical laboratory studies were performed on all dogs at Weeks 4 and 13. Hematocrit, hemoglobin, erythrocyte count, and total and differential leukocyte counts were measured. Biochemical studies included determinations of fasting blood sugar, blood urea nitrogen, bromsulphalein in liver function, serum glutamic pyruvic transminase, and serum glutamic-oxaloacetic transaminase. Urinalysis was performed and included specific gravity, pH, glucose, ketones, total protein, bilirubin, and microscopic examination of sediment. Following the 13-week study period, all animals were sacrificed; complete necropsies were performed, with organ-weight determination and comprehensive histopathological examination (brain, pituitary, thoracic, spinal cord, eyes, thyroids, lung, heart, liver, gallbladder, spleen, kidneys, adrenals, stomach, pancreas, small intestine, large intestine, mesenteric lymph node, urinary bladder, prostate, ovary, uterus, skin, rib junction, bone marrow, and nerve with skeletal muscle). Statistical analysis of results was not provided by the study authors, but the Fisher's exact test was performed for analysis of the incidence of specific effects (see Appendix B, Table B.2).

The study authors reported that all animals survived the study, and there was no indication of a compound-related effect among the test groups with regard to appearance, behavior, appetite, elimination, growth rate, or body weight. Although males and females from the 500-ppm dosage group showed lower relative weight gains over the 13-week treatment period, these animals had been initially heavier than their counterparts. The hair coat of the forelimbs, chest, and dorsal thoracic areas of all high-dose test animals was stained orange during the first week of study and continued until termination. The study authors concluded that this was probably the result of the oxidation of small amounts of phenothiazine adhering to the hair following feeding. Feed consumption was not adversely affected as a result of treatment.

Gross necropsy of the dogs after 13 weeks revealed no consistent gross tissue changes that could be attributed to test material except for dark-colored spleens in all of the animals from the 2000-ppm dose group (male and female) (see Appendix B, Tables B.2 and B.3, respectively). Study authors observed the following tissue alterations that were concluded to be related to the toxic effects of phenothiazine on the red blood cells (RBCs) and were present in all high-dose test animals: marked splenic congestion, with areas of increased extramedullary hematopoiesis; deposition of hemosiderin in the spleen, liver, kidney, and bone marrow; and increased cellularity of the bone marrow with a marked increase in erythroid elements (quantitative data not provided). Hemosiderin deposition was present, but to a lesser degree, in the liver and kidney sections of males (3/4) and females (1/4) from the 500-ppm dosage group. The other phenothiazine-induced effects (e.g., increased cellularity of the bone marrow as an adaptive response to the hematological effects) suggested to the study authors that the animals responded well physiologically, and, purportedly, the response of the animals at the 500-ppm dose is of minor biological significance.

Body weight was unaffected by phenothiazine treatment for both male and female dogs. Relative spleen weight for high-dose males was increased by 22.3% at 13 weeks, although not reaching statistical significance at the 5% level. Relative liver weight was increased for high-dose males by 13.6% and for females at 500 ppm and 2000 ppm by 11.5% and 15.7%, respectively; none of the increases were statistically significant. Other than a few anomalous relative organ-weight changes for males in the 50- and 200-ppm treatment groups (thyroid, kidney, adrenals) and in 500-ppm females (heart), other organ weights were unaffected (see Appendix B, Table B.4).

The results of pathological analysis show that both high-dose males and females were found to have statistically significant increases in the incidence of darkened spleens (see Appendix B, Tables B.2 and B.3).

At 4 weeks, examination of hematological data showed a lowering of the hematocrit, hemoglobin, and RBC count values in two male dogs and one female dog from the high-dose group. The RBC counts were also somewhat lower for the other two dogs in the high-dose group at that time period. At 13 weeks, the hematocrit, hemoglobin, and RBC count values were reduced for high-dose males by 16 to 18% and were statistically significant. At lower dose levels, the males showed statistically-significant increases in RBC counts (50 ppm) and white blood cell counts (200 ppm); the biological significance of the increased RBC counts at the low dose is uncertain but serves to accentuate the subsequent dose-related decline. All remaining hematological values were within normal limits (see Appendix B, Table B.5). The study authors reported a slight lowering of blood sugar values in one out of four females from the 200-ppm

group, one out of four females from the 500-ppm group, and all four females and one out of four males from the 2000-ppm group at 4 weeks. At 13 weeks, blood glucose levels were reduced by 8% for the two highest dose groups in males and by 4% in females; these changes are not statistically significant, and are considered to be within normal ranges. The 27% increase in serum glutamic pyruvic transaminase (SGPT) measured in 200-ppm males may be part of a trend of increasing values; however, there is a low mean value in the high-dose group, which is unexplained. This general trend in increasing SGPT, with a decrease in the high-dose group, is also seen in the treated females. The only statistically significant values for females are the serum glutamic oxaloacetic transaminase (SGOT) levels at 200 and 2000 ppm; however, there appears to be an overall trend of increasing SGOT values compared to the control group, with a 31% increase at 200 ppm. SGOT levels appear to increase with dose in the treated males as well, with a 21% increase at 2000 ppm (15% at 50 ppm) but do not reach the level of statistical significance. Both males and females in the high-dose group showed increases in bromsulphalein retention of 28% and 39%, respectively. All other clinical chemistry values were within acceptable normal limits and comparable with control values (see Appendix B, Table B.5).

The documentation of this study was missing some protocol details, particularly regarding measurement techniques. Otherwise, it appears to have been conducted according to good laboratory practice (GLP), despite being performed in 1987, prior to GLP establishment. While some of these endpoints, particularly the RBC effects, do not reach the level of statistical significance at all dose levels, a dose-related trend is observed beginning at the 200-ppm exposure level. The decreases in the hematocrit, hemoglobin, and RBC counts are supported by the findings of the histopathological analysis, which reported splenic congestion with increased extramedullary hematopoiesis; hemosiderin deposition in the spleen, liver, kidney, and bone marrow; and increased cellularity of the bone marrow with an increase in erythroid elements observed in the 2000-ppm dose group. Taken together, these results suggest hematological toxicity from exposure at the high dose. At lower exposure levels, the SGOT increases, beginning at 200 ppm for females and increased relative liver weights at 2000 ppm, suggest possible tissue damage, perhaps in liver or muscle, although there were no liver lesions reported in the histopathological analysis. A similar, but less-pronounced pattern is seen for males. Together, these endpoints support identification of a LOAEL of 6.82 mg/kg-day (200 ppm) in females for potential unspecified cellular toxicity, with a corresponding NOAEL of 1.59 mg/kg-day.

In a follow-up unpublished study sponsored by Hazelton Laboratories, Inc. (1974b), the toxicity of pharmaceutical-grade as compared to technical-grade[1] phenothiazine was investigated in male and female beagle dogs. Four animals per sex per dose were administered a control diet, or a diet containing 2000 ppm of either pharmaceutical-grade or technical-grade phenothiazine for 13 weeks. The control diet consisted of powdered Ground Wayne Dog Meal, and the study authors administered this to four animals per sex for 13 weeks to constitute a control group. Dogs were evaluated as described in the 5-dose, 13-week study by Hazelton Laboratories, Inc. (1974a) described above.

Animals fed the phenothiazine diet had body weights that were comparable to the control group, along with comparable behaviors and appetite (see Appendix B, Table B.6).

[1] Purity not specified for either formulation.

Discoloration of the coat in areas was observed and presumed to be a result of oxidation products of phenothiazine being stuck to the fur following feeding. The results of the hematological analysis show that two male dogs and one female dog exposed to the pharmaceutical-grade phenothiazine and three males and all females exposed to the technical-grade phenothiazine had lower hematocrit, hemoglobin, and erythrocyte counts at Week 4. This trend was seen to continue in Week 13 (see Appendix B, Table B.7), and one female treated with the technical-grade phenothiazine showed anemia in concordance with the hematocrit, hemoglobin, and RBC counts being reduced to roughly half of the normal levels, and WBC counts being roughly twice normal. Results of the biochemical analysis showed low blood sugar levels in one male and all female animals treated with technical-grade material, and one female additionally having elevated bromsulphalein levels. Necropsy showed all treated animals to have darkened spleens. Spleen weights and spleen-weight-to-body-weight ratios were increased in two females exposed to the pharmaceutical-grade phenothiazine, and three males and two females exposed to the technical-grade phenothiazine (see Appendix B, Table B.6). Other organ weights and corresponding ratios were found to be within normal range. Microscopic analysis showed RBC effects in all treated animals but were more pronounced in dogs treated with the technical grade material, which included incidences of increased extramedullary hematopoiesis; deposition of hemosiderin in the spleen, liver, kidney, and bone marrow; and increased cellularity in the bone marrow with increased erythroid elements (quantitative data not provided). Several incidental lesions were noted amongst the groups but were not treatment related.

Based on the RBC effects and the effects in the spleen of treated animals, a LOAEL of 67.05 mg/kg-day is identified. A NOAEL could not be identified because only one dose was examined in the study, and effects were seen at that dose level. While differences were seen between the technical-grade and pharmaceutical-grade preparations, these are related to exposure characteristics other then dose because the dose was the same between the two groups. There is no information described in the study report to suggest the characteristic responsible for the differences in response. This study will not be used to support the development of a subchronic p-RfD because this study examines the effects at only one dose.

Chronic Studies

Innes et al. (1969) published a study investigating the tumorigenicity of phenothiazine on male and female mice of two hybrid strains (18 per sex and per strain) by orally administering phenothiazine (purity and dosage not reported). The authors employed the chi-square test and found that mice in this group did not exhibit a statistically significant response in the incidence of bladder tumors compared to a positive control group (24 mice of each sex and each strain) to which the authors had administered ethyl carbamate. The authors did not report the method, vehicle, or dosage of phenothiazine, but some of this information was available in a review that described this study. Integrated Laboratory Systems (1997) reported that the study authors administered 0.1-mg/kg phenothiazine in 0.5% gelatin by gavage for the first 3 weeks (ages 7 to 28 days) at which time 0.20 ppm was administered in the diet until 18 months. The corresponding oral intake is 0.005 mg/kg-day.

This study is not well documented, and, as such, the methodology cannot be adequately assessed. The authors state that no effects were observed from administering the one dose employed, but no data are presented. The scope of the endpoints analyzed is narrowly focused on bladder tumors. The limitations in this study preclude its use as a principal study for

developing a chronic p-RfD or a provisional oral slope factor (p-OSF). It is not appropriate to identify a NOAEL or LOAEL given the study's deficiencies.

Inhalation Exposures

No studies could be located regarding the effects of subchronic or chronic duration inhalation exposures of animals to phenothiazine.

Developmental and Reproductive Toxicity Studies

Telford et al. (1962) published the results of a reproductive and developmental toxicity study in rats in which the study authors administered a total dose of 0.25 grams phenothiazine to each of 10 female Walter Reed-Carworth Farms rats in the diet for 22 days following mating and during gestation. One hundred and twenty-six untreated normal pregnant rats constituted the control group. Twenty-eight other compounds were also tested using the same protocol. The authors stated that the rats in the study weighed an average of 200 grams at the time of mating. Assuming an average body weight of 225 g over the study duration (allowing for an increase in body weight during gestation), an average intake of approximately 50 mg/kg-day is estimated (250 mg/0.225 kg/22 days). Twenty-two days after mating, the pregnant rats were euthanized, and the pups were delivered. The number and location of resorptions, and degree of resorption were recorded. Seventy percent of phenothiazine-treated rats had at least one resorption, as compared to 40.8% of control rats, and 15.7% of implantations in treated rats resulted in resorptions, as compared to 10.6% of control rats. The authors reported that the location and degree of resorptions were similar for all test substances but did not present individual compound details. In general, the degree was either Grade 3, representing complete resorption of the embryo but with small placenta still present, or Grade 4, which are cicatrized uterine plaques marking previous placental sites. A LOAEL of approximately 50 mg/kg-day for embryonic resorption is established in this study. A NOAEL was not established.

Harris Laboratories, Inc. (1977a) conducted a developmental study in rats; this study did not undergo peer review. Female albino Charles River rats were administered 0, 15, 50, or 150 mg/kg bw-day phenothiazine by gavage (purity and vehicle not reported) once per day on Gestation Days (GDs) 6−15. Twenty-one females in each dose group were treated, with the following numbers of pregnant dams: 20 controls, 18 at 15 mg/kg bw-day, 21 at 50 mg/kg bw-day, and 20 at 150 mg/kg bw-day. Body-weight data were taken daily, and mortality and behavioral reactions were noted as observed. On GD 20, dams were sacrificed, and resorptions and number of viable fetuses were noted. Each fetus was then weighed and examined for external, skeletal, and internal abnormalities. There was no information given regarding quality/possible contamination of the feed/water. The rats were not bred as part of the study, so breeding procedure information was not available.

The body weights of dams given 150 mg/kg-day were slightly less than control dams on GD 12 (not statistically significant) but were significantly lower than control dams on GD 15. There were no deaths or unusual behavioral reactions. No significant reproductive effects were seen. One control dam had excessive blood in both uterine horns, and one of the females dosed with 50 mg/kg-day had brown-green placentas and blood in the left uterine horn. However, numbers of corpea lutea, implantation sites, resorption sites, and fetuses were not significantly different between any dose group and the control group (see Appendix B, Table B.8). The body weights and sex ratios of the pups were not significantly different from controls for any dose group. Statistical evaluations for body-weight data were done using ANOVA with significant

effects further studied by Scheffe's Multiple Comparison. Analysis of numbers of corpea lutea, implantation sites, resorption sites, and fetuses (number and sex ratio) were conducted using the Chi-Square Test of Independence. No statistically-significant effects were found to be caused by exposure to phenothiazine using this protocol.

The body-weight loss in dams observed at GD 15 does not meet the 10% reduction threshold to be considered adverse. Furthermore, feed consumption was not reported, which could impact interpretation of the body-weight change data. A LOAEL cannot be identified; however, a NOAEL of 150 mg/kg-day is identified from this study. The lack of GLP certificates and missing data on purity and vehicle of the test substance were weaknesses of this study.

Harris Laboratories, Inc. (1977b) also conducted a developmental study in mice (not peer reviewed). The study authors administered, by gavage, 0, 30, 100, or 300 mg/kg-day phenothiazine in corn oil (purity not reported) once per day on GDs 6−15 to female albino Charles River CD-1 mice. One hundred and fifty virgin dams were mated with 100 males of the same age over a 32-day mating period. Copulations were confirmed by sperm-positive vaginal examinations. Day 0 was identified as the day of insemination. All females were assigned to treatments groups, with the following numbers of pregnancies: 20 controls, 20 in the 30-mg/kg group, 20 in the 100-mg/kg group, and 25 in the 300-mg/kg group. Body weights were recorded daily, and mortality and behavioral reactions were noted as observed. Feed and water was provided ad libitum. On GD 17, dams were sacrificed, and fetal swellings, implantation sites, resorption sites, and uterine abnormalities were noted. Corpora lutea were also counted. The number of fetuses was counted, and each fetus was then weighed and examined for external, skeletal, and internal abnormalities.

Mortalities in the dosed dams were not higher than control dams. An initially significant decrease in maternal body weight was observed in the two highest dose groups at GD 6, but a lasting effect was not found (see Appendix B, Table B.9). Feed consumption was not reported, which could impact interpretation of the body-weight change data. No unusual behaviors were noted in any of the animals. There was an increase in the number of resorption sites and number of dams with one or more resorption sites in all dose groups compared to controls (see Appendix B, Table B.9). The litter sizes were decreased by an average of 17% in all treatment groups but not reaching statistical significance at the 5% level. Fetal body weights and sex ratios did not differ significantly from controls. The abnormalities in the pups of treated dams were within the expected range. No other effects of exposure were noted. Statistical evaluations for body-weight data were done using One-Way Analysis of Variance with significant effects further studied by Scheffe's Multiple Comparison. Analysis of numbers of corpea lutea, implantation sites, resportion sites, and fetuses (number and male versus female) was conducted using the Chi-Square Test of Independence.

Phenothiazine was not found to be toxic to dams or to fetuses. Phenothiazine was not found to be teratogenic. However, the increase in the incidence of resorptions in treated dams establishes a LOAEL of 30 mg/kg-day. A NOAEL cannot be identified. The lack of GLP certificates and missing data on purity of the test substance are weaknesses of this study.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Acute and Short-Term Oral Studies

In a published study, Gershbein (1973) examined the effects of phenothiazine (purity not reported) on liver weight by feeding two groups of rats a diet consisting of 0.075% (750 ppm) phenothiazine for 7 days. The first exposed group consisted of 11 male Charles River rats. Test animals were weighed before and at the termination of the 7-day exposure period. Based on the results of a Student's *t*-test, a statistically–significant ($p < 0.01$) 12.7% increase in relative liver weight was observed in these animals when compared to a group of 11 male Charles River rats fed a control diet (Rockland rat meal); however, average body weight was also increased (27%; $p < 0.01$) in the treated animals. The second exposed group consisted of eight male Holtzman rats on which the author had performed a partial hepatectomy followed by a 3-day recovery before administering the 0.075% phenothiazine diet for the following 7 days. The study authors recorded that this group experienced a statistically significant (by the Student's *t*-test; $p < 0.01$) 22% increase in liver weight when compared to a control group of 14 male Holtzman rats whose livers had also been partially removed but were fed the control diet in the subsequent period. The author concluded that phenothiazine proved stimulatory to hepatic growth. The corresponding adjusted daily dose for both exposed groups is 67.7 mg/kg-day. The LOAEL for increased liver weight is 67.7 mg/kg-day; a NOAEL is not established.

Dow Chemical Company (1944) sponsored a comparison of different formulations of phenothiazine, which included three oral studies (not peer reviewed). In the first oral study, phenothiazine was suspended in a 5−10% gum arabic solution. Rats were given a single dose by stomach tube and were observed for at least 2 weeks following dosing. One preparation was purified phenothiazine, and one was phenothiazine tar (specific formulations could not be read). The second experiment repeatedly dosed rabbits with 0.1, 1.0, 2.0, or 5.0 g/kg of phenothiazine for an unspecified duration (purity not provided). Liver, spleen, kidney, adrenal, pancreas, and bone marrow were examined histopathologically. In another oral rat study, animals were given doses of 0.1, 0.5, 1.0, or 2.0 g/kg for an unspecified duration, and the same organs were examined following dosing. No GLP certificate is provided for these studies. No statistical analyses of results were presented. The study authors reported that both preparations showed low acute oral toxicity in rats and spleen and liver toxicity and bone marrow hyperplasia in rabbits at high doses. Because of the lack of detail on experimental design and results, these studies are not considered further for the determination of a POD for the p-RfD.

Eastman Kodak Company (1987) conducted a study (not peer reviewed) of acute oral toxicity in rats and mice. The animal strain, sex, and unit of weight measurements were not reported, nor were the animal husbandry, dose preparation, necropsy results, or length of studies. The study authors reported body-weight changes after 2 weeks, as well as animal survival and some clinical observations.

The study author exposed five rats and five mice orally to 200 to 3200 mg/kg-day phenothiazine—10% suspension in 2% sodium cellulose sulfate in water for 14 days. All rats exposed orally to 200 to 3200 mg/kg-day phenothiazine survived the study period and were reported to experience an increase in body weight after 2 weeks but were described as being moderately to quite weak. Mice exposed to 3200 mg/kg-day were reported to have died within 8 days after exposure. The mice experienced an increase in weight and were reported to be slightly or moderately weak. This study provides no useful information for derivation of the p-RfD.

Acute Inhalation Studies

Harris Laboratories, Inc. (1977c,d) sponsored a study (not peer reviewed) investigating the effects of acute inhalation exposure to phenothiazine (greater than 95% pure) in male albino rats (strain not specified). Ten male rats were exposed to 200 mg/L (200,000 mg/m^3) phenothiazine for 1 hour and were observed for 2 weeks. The corresponding human equivalent dose is 1158 mg/m^3. Animals were weighed prior to exposure and following the 2-week observation period. Gross observations were made at unreported intervals during the observation period and at autopsy. No effects were noted in the gross observations. Organs of the thorax and abdomen were found to be normal, despite the lack of control animals in the study for comparison. This study is not suitable (too short, no controls) for consideration in the derivation of the p-RfC.

Toxicokinetics

Due to the use of phenothiazine and its derivatives in human and veterinary medicine, many studies have examined its metabolism. A review of the toxicology literature funded by the National Institute of Environmental Health Science (NIEHS) is available (Integrated Laboratory Systems, 1997) that described the toxicokinetics, as well as results from other exposure studies. Phenothiazine is absorbed orally and dermally, although its oral absorption is limited by its low water solubility. It is known to enter the bloodstream and cross the blood-brain barrier. Furthermore, placental transfer is possible during fetal development. A significant portion of the original dose (30−38%) has been shown to accumulate in the liver in the form of phenothiazine sulfoxide (Analytical Development Corporation, 1987). Phenothiazine is primarily excreted from the body through urine as phenothiazine-*N*-glucuronide and leucophenothiazone sulfate. The half-life of phenothiazine in humans is 11 hours.

Mutagenicity

Phenothiazine generally tests negative for mutagenicity in bacteria, with and without metabolic activation (Mortelmans et al., 1986; Loveday and Seixas, 1980a,b), but positive in mammalian cells without metabolic activation. It has also been shown to induce DNA damage in mammalian cells (Integrated Laboratory Systems, 1997). Calle and Sullivan (1982) have demonstrated that under some circumstances, phenothiazine may have antimutagenic properties when administered in combination with known mutagens.

Intraperitoneal Injection Study

Eastman Kodak Company (1987) conducted a study (not peer reviewed) investigating the effect of a single dose of phenothiazine by intraperitoneal injection in rats and mice. The animal strain, sex, and unit of weight measurements were not reported, nor were the animal husbandry, dose preparation, necropsy results, or length of studies. Five rats and five mice were exposed intraperitoneally to 200−3200 mg/kg phenothiazine and were observed for 14 days. The rats were observed to be moderately to quite weak after 2 weeks. Additionally, exposed rats were reported to have rough coats. Rats exposed to the highest dose (3200 mg/kg) died on Day 1. The authors estimated the LD_{50} to be in the range of 1600−3200 mg/kg. The mice exposed intraperitoneally were also reported to be moderately weak. Mice exposed to 800 mg/kg were reported to expire within Day 1 and Day 2 of exposure. The LD_{50} was calculated to be approximately 400−800 mg/kg.

Dermal Studies

Dow Chemical Company (1944) sponsored a comparison study (not peer reviewed) of phenothiazine in which skin irritation tests were performed on rabbits using two formulations—purified phenothiazine and phenothiazine tar. Purity of the test substances, duration of application, number of animals used, and other experimental protocol details were not provided. The study report stated that these experiments were performed "in the usual manner." It is unclear how many animals were tested. No GLP certificate is provided for this study.

Pure phenothiazine caused little skin irritation, except after prolonged and repeated exposure. The phenothiazine tar did not cause irritation. The study authors stated that neither the pure phenothiazine nor phenothiazine tar was absorbed through the skin in toxic quantities and reported that neither product presented a skin absorption hazard. However, due to the irritation, the study authors concluded it would be wise to avoid prolonged exposures to pure phenothiazine. No statistical tests were performed. It is difficult to judge the quality of this study when so little description of the methodology is provided. However, dermal effects of phenothiazine appear to be relatively minor.

Eastman Kodak Company (1987) conducted a study (not peer reviewed) investigating the dermal toxicity and irritation of phenothiazine in guinea pigs. The animal strain, sex, and unit of weight measurements were not reported, nor were the animal husbandry, dose preparation, necropsy results, or study duration. Three guinea pigs were dermally exposed to varying amounts of solid phenothiazine (purity not reported), moistened with water, and held in contact with the depilated skin. The test animals were exposed in this manner for 24 hours at doses of 0.25−1.0 g/kg. Clinical observations were reported as slight-to-moderate edema, slight redness, and some necrosis and weight changes. The time period of these observations was not reported. The study authors reported some evidence of desquamation, some scattered eschars, and small areas of scar tissue after Week 1. At Week 2, there were some heavy scar tissues and a small narrow strip of secondary eschar surrounded by erythema. The study concluded that the limited weight gain at the largest doses applied provides some evidence of toxic effect caused by the dermal exposure and some evidence that absorption existed. No animals were reported to have died during the exposure period.

Eastman Kodak Company (1987) conducted a study (not peer reviewed) on skin sensitization of phenothiazine in guinea pigs. The animal strain, sex, and unit of weight measurements were not reported, nor were the animal husbandry, dose preparation, necropsy results, or length of studies. In the skin sensitization study, five guinea pigs were reported to be exposed via a "drop on" test method with a reported solution of 1% phenothiazine in guinea pig fat. Solvent controls and positive control using phenylhydrazine were also tested using the same "drop on" test method with five guinea pigs each. The study authors concluded that phenothiazine is a sensitizer of low-to-moderate activity in two out of five guinea pigs.

Table 3 provides a summary of selected acute, short-term, toxicokinetic, and mutagenicity studies.

Table 3. Other Studies

Tests	Materials and Methods	Results	Conclusions	References
Acute and short-term oral	Rabbits administered 0.1, 1.0, 2.0, and 5.0 g/kg in multiple doses (duration not reported). Rats administered 0.1, 0.5, 1.0, and 2.0 g/kg in a single dose or repeated doses (duration not reported).	Rabbits showed lack of weight gain, spleen and liver damage, bone marrow hyperplasia, and congestion of the kidneys. The single dose administered to rats showed no effects. Multiple doses resulted in spleen and liver damage and bone marrow hyperplasia.	Authors concluded that phenothiazine has a relatively low oral toxicity, especially when given in single doses. However, it is unclear what doses were administered, and no effects are described.	Dow Chemical Company (1944)
Acute oral	5 rats and 5 mice (unreported sex and strain) 200 to 3200 mg/kg for 14 days.	Weakness was observed in mice and rats, as well as body-weight changes (units not reported). Increased mortality in mice within 8 days of dosing (number of deaths not reported). No mortality observed in rats.	Rats: LD_{50} of >3200 mg/kg. Mice: LD_{50} of 1600 to 3200 mg/kg.	Eastman Kodak Company (1987)
short-term oral	0 or 750 ppm by diet for 7 days in 11 intact male rats, or 11 male rats with a partial hepatectomy.	Treated animals showed increased liver weight as compared to controls in groups with and without the partial hepatectomy.	The author concluded that phenothiazine proved stimulatory to hepatic growth.	Gershbein (1973)
Acute inhalation	200 mg/L for 1 hour followed by a 14-day observation period in rats.	Survival, body weights, and gross pathology were normal.	LC_{50} > 200,000 mg/m^3.	Harris Laboratories, Inc. (1977c,d)
Dermal irritation	An unreported dose of phenothiazine and phenothiazine tar was applied to the skin of an unreported number of rabbits for an unreported duration.	Pure phenothiazine caused little skin irritation, except after prolonged and repeated exposure. The phenothiazine tar did not cause irritation.	Authors reported that neither product presented a skin absorption hazard.	Dow Chemical Company (1944)
Dermal toxicity and irritation	0.25 to 1.0 g/kg phenothiazine applied to skin of 3 guinea pigs for 24 hours (sex and strain not reported). The observation period was not reported.	Slight-to-moderate edema, slight redness, and some necrosis and weight changes were initially noted. Scar tissues and secondary eschar surrounded by erythema were observed at Week 2. Treated animals showed limited weight gain.	Authors concluded limited weight gain at the largest doses is evidence of systemic toxic effect of exposure. Skin showed slight-to-moderate irritation.	Eastman Kodak Company (1987)
Skin sensitization	5 guinea pigs exposed via drop on skin with 1% phenothiazine.	The scores from the test solution did not exceed positive control results in either the 24- or 48-hour tests.	The authors concluded that phenothiazine is a sensitizer of low-to-moderate activity in 2 out of 5 guinea pigs.	Eastman Kodak Company (1987)

Table 3. Other Studies

Tests	Materials and Methods	Results	Conclusions	References
Intraperitoneal injection	5 mice and 5 rats (strains and sex not provided) exposed to 200−3200 mg/kg in a single dose, 14-day observation.	Weakness was observed in mice and rats; rats had rough coats; deaths occurred within 1−2 days.	Rats: LD_{50} of 1600−3200 mg/kg. Mice: LD_{50} of 400−800 mg/kg.	Eastman Kodak Company (1987)
Mutagenicity	*S. typhimurium* strains TA100, TA98, TA1535, TA1537, and TA1538, with and without metabolic activation, exposed to 5−500 µg/plate by the plate incorporation method or to 20 µg/mL via the liquid suspension method.	Negative results for all strains, with and without metabolic activation.	Not mutagenic in bacteria.	Loveday and Seixas, 1980a,b
Mutagenicity	*S. typhimurium* strains TA100, TA98, TA97, TA1535, and TA1537, with and without rat or hamster metabolic activation, exposed to 100, 333, 1000, 3333, and 10,000 µg/plate (0.5 to 50.2 µmol/plate) via the preincubation method.	Negative results for all strains, with and without metabolic activation.	Not mutagenic in bacteria.	Mortelmans et al. (1986)
Antimutagenicity	*S. typhimurium* strain TA98 with metabolic activation, exposed to 0.082 and 0.4 µmol/plate phenothiazine plus 8.2 nmol BaP.	The number of revertants per plate were 133 ± 21 at 0.082 µmol/plate and 181 ± 13 at 0.41 µmol/plate compared to 539 ± 54 for BaP alone.	Phenothiazine inhibited BaP's mutagenic activity.	Calle and Sullivan (1982)
Toxicokinetics	1.5 mg/kg was administered via gavage to male rats either once or as 5 daily doses.	Phenothiazine sulfoxide accounted for 30% (single dose) or 38% (multiple doses) of the administered phenothiazine dose in livers of rats 4 hours after treatment.	Phenothiazine can accumulate in the liver in the form of phenothiazine sulfoxide.	Analytical Development Corporation (1987)

DERIVATION OF PROVISIONAL VALUES

Table 4 presents a summary of noncancer reference values, if applicable. Table 5 presents a summary of cancer values, if applicable.

Table 4. Summary of Noncancer Reference Values for Phenothiazine (CASRN 92-84-2)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UF	Principal Study
Screening subchronic p-RfD (mg/kg-day)	Dog/F	Increased SGOT	5×10^{-3}	NOAEL	1.59	300	Hazleton Laboratories, Inc. (1974a).
Screening chronic p-RfD (mg/kg-day)	Dog/F	Increased SGOT	5×10^{-4}	NOAEL	1.59	3000	Hazleton Laboratories, Inc. (1974a)
Subchronic p-RfC (mg/m^3)	None						
Chronic p-RfC (mg/m^3)	None						

Table 5. Summary of Cancer Values for Phenothiazine (CASRN 92-84-2)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF	None			
p-IUR	None			

DERIVATION OF ORAL REFERENCE DOSES

Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

As indicated in Table 6, the Hazleton Laboratories, Inc. (1974a) study yields the lowest POD and would be chosen as the principal study for the derivation of the subchronic p-RfD. However, this study was not peer reviewed. Therefore, a subchronic p-RfD is not derived but a screening value is presented in Appendix A.

Table 6. Summary of Relevant Oral Systemic Toxicity Studies for Phenothiazine

References	# M/F, Species	Exposure (mg/kg-day)	Frequency/ Duration	$NOAEL_{ADJ}$[a] (mg/kg-day)	$LOAEL_{ADJ}$[b] (mg/kg-day)	Critical Endpoint
Telford et al., 1962	10 F (preg.), Walter Reed/Carworth Farms rats (126 controls)	50 (approx.), dietary	22 days during gestation	None	50	Embryonic resorption
Harris Laboratories, Inc., 1977a	20 F (preg.), albino Charles River rats	0, 15, 50, 150	daily, GDs 6–15	150	None	No maternal or developmental toxicity
Harris Laboratories, Inc. 1977b	20 F (preg.), albino Charles River CD-1 mice	0, 30, 100, 300	daily, GDs 6–15	None	30	Embryonic resorption
Hazleton Laboratories, Inc. (1974a)	4/4, dogs	Male: 1.54, 6.06, 16.93, 69.30 Female: 1.59, 6.82, 17.68, 67.05	7 d/wk, 13 wks	1.59	6.82	Increased SGOT

[a]$NOAEL_{ADJ}$ = NOAEL × (feeding schedule).
[b]$LOAEL_{ADJ}$ = LOAEL × (feeding schedule).

Derivation of Chronic Provisional RfD (Chronic p-RfD)

No chronic p-RfD can be derived because no chronic studies are available and the subchronic study that yields the lowest POD (Hazleton Laboratories, Inc., 1974a) and, as such, would be chosen as the principal study was not peer reviewed. Therefore, derivation of a screening value is provided in Appendix A.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

No studies investigating the effects of subchronic or chronic duration inhalation exposures to phenothiazine in humans or animals were identified. This precludes the derivation of subchronic and chronic inhalation toxicity values.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

Table 7 identifies the cancer WOE descriptor for phenothiazine.

Table 7. Cancer Weight-of-Evidence (WOE) Descriptor for Phenothiazine			
Possible WOE Descriptor	**Designation**	**Route of Entry (Oral, Inhalation, or Both)**	**Comments**
"Carcinogenic to Humans"	N/A	N/A	No human cancer studies are available.
"Likely to Be Carcinogenic to Humans"	N/A	N/A	No appropriate human or animal cancer data are available.
"Suggestive of Evidence of Carcinogenic Potential"	N/A	N/A	There is no evidence from human and animal studies that is suggestive of carcinogenicity.
"Inadequate Information to Assess Carcinogenic Potential"	**X**	**Oral administration by diet only.**	**Under the 2005 *Guidelines for Carcinogenic Risk Assessment* (U.S. EPA, 2005), the available evidence from exposure to phenothiazine is inadequate to assess carcinogenic potential. Only one study investigating the carcinogenic potential of phenothiazine over a chronic exposure period could be located. The Innes et al. (1969) study examined the effects of one dose in one species (mouse). Further investigation in corroboration of the finding of Innes et al. (1969) may be warranted.**
"Not likely to be Carcinogenic to Humans"	N/A	N/A	No appropriate evidence of noncarcinogenicity in humans or animals is available.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of Provisional Oral Slope Factor (p-OSF)

Neither of the two studies in the database that investigated the carcinogenic potential of phenothiazine is appropriate for derivation of a p-OSF. Both Innes et al. (1969) and Wang and Hayashida (1984) found no increase in tumor incidence following oral exposure to phenothiazine. Both studies were deficient in methodology, and, therefore, derivation of a p-OSF is precluded.

Derivation of Provisional Inhalation Unit Risk (p-IUR)

No human or animal studies examining the carcinogenicity of phenothiazine following inhalation exposure have been located. Therefore, derivation of a p-IUR is precluded.

APPENDIX A. PROVISIONAL SCREENING VALUES

DERIVATION OF SCREENING PROVISIONAL ORAL REFERENCE DOSES

Derivation of Screening Subchronic Provisional RfD (screening subchronic p-RfD)

For the reasons noted in the main document, it is inappropriate to derive a provisional subchronic p-RfD for phenothiazine. However, information is available that, although insufficient to support derivation of a provisional toxicity value, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an appendix and develops a screening value. Appendices receive the same level of internal and external scientific peer review as the main document to ensure their appropriateness within the limitations detailed in the main document. Users of the screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of a supplemental screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

The study sponsored by Hazleton Laboratories, Inc. (1974a) is selected as the principal study for derivation of the screening subchronic p-RfD because the effect observed in this study yields the lowest POD. The critical effect observed in the oral subchronic study of beagle dogs is increased SGOT in females (equivocal increase in males). The biological relevance of this endpoint is as an indicator of cellular toxicity, possibly in the liver. While this study was conducted prior to GLP and is not peer reviewed, the study appears to be well-conducted. Details are provided in the **Review of Potentially Relevant Data** section. The SGOT data for females from this study were subjected to BMD modeling (BMDS, version 2.1.1.55). An acceptable fit was found only for the Hill model after at least one parameter was fixed (specified). BMDS would not compute a BMDL until all parameters except the Hill coefficient (*n*) were specified. After specifying the parameters at their previously fitted values, a BMD and BMDL of 1.993 and 1.816 mg/kg-day, respectively, were found for a BMR of 1 standard deviation from the mean. The BMD modeling results are included in Appendix C. The male SGOT data were not amenable to BMD modeling. Given the modeling constraints needed to obtain a BMDL, the BMD results were not used for defining the POD. .

The POD in this study is a NOAEL of 1.59 mg/kg-day for SGOT levels in female dogs from Hazleton Laboratories, Inc. (1974a).

Adjustments for Daily Exposure

The study authors measured daily feed intake and reported average daily dose of phenothiazine. Because it is an oral study investigating noncancer endpoints, no further dosimetric adjustments were made.

A screening subchronic p-RfD is developed as follows:

$$\textbf{Screening Subchronic p-RfD} = \textbf{NOAEL} \div \textbf{UF}_C$$
$$= 1.59 \text{ mg/kg-day} \div 300$$
$$= \mathbf{5 \times 10^{-3} \text{ mg/kg-day}}$$

Table A.1 summarizes the uncertainty factors (UFs) for the screening subchronic p-RfD for phenothiazine.

Table A.1. Uncertainty Factors (UFs) for Screening Subchronic p-RfD of Phenothiazine (Hazleton Laboratories, Inc., 1974a)

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between dogs and humans. There are no data to determine whether humans are more or less sensitive than dogs to subchronic oral exposure to phenothiazine.
UF_D	3	A UF_D of 3 is selected because there is an acceptable developmental study but no acceptable multigeneration reproduction study. The available data do not suggest that additional studies may reveal sensitive effects not yet characterized.
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 in humans.
UF_L	1	A UF_L of 1 is applied because the POD was a NOAEL.
UF_S	NA	A UF_S is relevant only for the chronic p-RfD
UF_C	300	

Derivation of Screening Chronic Provisional RfD (screening chronic p-RfD)

Chronic toxicity studies for oral administration of phenothiazine are not available. Therefore, the screening chronic p-RfD is based on the NOAEL of 1.59 mg/kg-day derived for dogs exposed to phenothiazine for 13 weeks (Hazleton Laboratories, Inc., 1974a). The screening chronic p-RfD for phenothiazine is derived as follows:

$$\textbf{Screening Chronic p-RfD} = \textbf{NOAEL} \div \textbf{UF}_C$$
$$= 1.59 \text{ mg/kg-day} \div 3000$$
$$= \mathbf{5 \times 10^{-4} \text{ mg/kg-day}}$$

Table A.2 summarizes the UFs for the screening chronic p-RfD for phenothiazine.

Table A.2. Uncertainty Factors (UFs) for Screening Chronic p-RfD of Phenothiazine (Hazleton Laboratories, Inc., 1974a).

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between dogs and humans. There are no data to determine whether humans are more or less sensitive than dogs to subchronic oral exposure to phenothiazine.
UF_D	3	A UF_D of 3 is selected because there is an acceptable developmental study but no acceptable multigeneration reproduction study. The available data do not suggest that additional studies may reveal sensitive effects not yet characterized.
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 in humans.
UF_L	1	A UF_L of 1 is applied because the POD was a NOAEL.
UF_S	10	A UF_S of 10 is applied because the principal study was subchronic in duration.
UF_C	3,000	

APPENDIX B. DATA TABLES

Table B.1. Selected Incidence of Bladder Lesions in Female Fisher Rats Exposed to Phenothiazine in the Diet (with and without FANFT) for 20 Weeks Followed by a 20-Week Observation[a]

Parameter	Exposure Group (Human Equivalent Dose, mg/kg-day)			
	Control (0)	FANFT (0)	Phenothiazine (22.44)	FANFT and Phenothiazine (22.44)
Liver				
Sample size	15	47	16	49
Final body weight (g)[b]	198 ± 8	195 ± 12	203 ± 9	191 ± 15
Hyperplasia[c]	0/15 (0)	28/47 (60)	0/16 (0)	17/49 (35)
Papilloma[c]	0/15 (0)	6/47 (13)	0/16 (0)	3/49 (6)
Carcinoma[c]	0/15 (0)	8/47 (17)	0/16 (0)	27/49 (55)[d]

[a]Source: Wang and Hayashida (1984).
[b]Mean ± SD.
[c]Number of animals with endpoint/number of animals examined; () = percent of total.
[d]Statistically significantly different from control ($p < 0.0001$) by chi-square test performed by study authors.

Table B.2. Selected Pathologies of Male Beagle Dogs Exposed to Phenothiazine in the Diet for 13 Weeks[a,b]

Parameter	Exposure Group (mg/kg-day)				
	0 ppm (0)	50 ppm (1.54)	200 ppm (6.06)	500 ppm (16.93)	2000 ppm (69.30)
Heart					
Subendocardial brush stroke reddening in the left ventricle	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)
Two small firm nodes in right atrioventricular valve	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)
Heart worm in right ventricle	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)
Left auricle thickened with lumen partially closed	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)
Right atrioventricular valve thickened	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)
Spleen					
Black nodes at margin	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)
Gray discoloration on surface	0/4 (0)	0/4 (0)	3/4 (75)	0/4 (0)	0/4 (0)
Dark in color	0/4 (0)	0/4 (0)	1/4 (25)	0/4 (0)	4/4 (100)[c]
Enlarged	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)
Urinary Bladder					
Red area on neck	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	1/4 (25)
Small Intestine					
Round worms	0/4 (0)	0/4 (0)	1/4 (25)	1/4 (25)	2/4 (50)

[a]Source: Hazleton Laboratories, Inc., 1974a.
[b]Number of animals with endpoint/number of animals examined; () = percent of total.
[c]Statistically significantly different from control ($p < 0.05$) by Fisher's exact test in an independent statistical analysis performed for this review.

Table B.3. Selected Pathologies of Female Beagle Dogs Exposed to Phenothiazine in the Diet for 13 Weeks[a,b]

Parameter	Exposure Group (mg/kg-day)				
	0 ppm (0)	50 ppm (1.59)	200 ppm (6.82)	500 ppm (17.68)	2000 ppm (67.05)
Heart					
Subendocardial brush stroke reddening in the left ventricle	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	1/4 (25)
Two small firm nodes in right atrioventricular valve	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	1/4 (25)
Heart worm in right ventricle	0/4 (0)	0/4 (0)	0/4 (0)	1/4 (25)	0/4 (0)
Left auricle thickened with lumen partially closed	0/4 (0)	0/4 (0)	0/4 (0)	1/4 (25)	0/4 (0)
Right atrioventricular valve thickened	0/4 (0)	0/4 (0)	0/4 (0)	1/4 (25)	0/4 (0)
Spleen					
Black nodes at margin	0/4 (0)	2/4 (50)	0/4 (0)	0/4 (0)	0/4 (0)
Gray discoloration on surface	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)
Dark in color	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	4/4 (100)[c]
Enlarged	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	1/4 (25)
Urinary Bladder					
Red area on neck	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)
Small Intestine					
Round worms	0/4 (0)	1/4 (25)	1/4 (25)	0/4 (0)	1/4 (25)

[a]Source: Hazleton Laboratories, Inc., 1974a.
[b]Number of animals with endpoint/number of animals examined; () = percent of total.
[c]Statistically significantly different from control ($p < 0.05$) by Fisher's exact test in an independent statistical analysis performed for this review.

Table B.4. Body and Organ Weights in Beagle Dogs Exposed to Phenothiazine in the Diet for 13 Weeks[a,b]

Parameter	Exposure Group (mg/kg-day)				
	0 ppm (0)	**50 ppm (1.54)**	**200 ppm (6.06)**	**500 ppm (16.93)**	**2000 ppm (69.30)**
Male					
Final mean body weight (kg)	10.6 ± 1.7	11.9 ± 2.20	11.7 ± 2.4	11.6 ± 1.6	10.1 ± 0.5
Relative thyroid weight (%)	0.01 ± 0.002	0.790 ± 0.080[c]	2.42 ± 0.321[c]	0.010 ± 0.003	0.010 ± 0.002
Relative heart weight (%)	0.790 ± 0.080	0.765 ± 0.075	0.744 ± 0.150	0.833 ± 0.117	0.785 ± 0.064
Relative liver weight (%)	2.42 ± 0.321	2.27 ± 0.272	2.44 ± 0.436	2.54 ± 0.270	2.75 ± 0.240
Relative spleen weight (%)	0.229 ± 0.060	0.232 ± 0.044	0.225 ± 0.028	0.225 ± 0.14	0.280 ± 0.062
Relative kidney weight (%)	0.466 ± 0.051	0.407 ± 0.051	0.225 ± 0.028[c]	0.515 ± 0.041	0.447 ± 0.031
Relative adrenal weight (%)	0.010 ± 0.001	0.010 ± 0.002	0.456 ± 0.083[c]	0.011 ± 0.002	0.010 ± 0.001
Relative testes weight (%)	0.224 ± 0.052	0.182 ± 0.036	0.213 ± 0.020	0.214 ± 0.030	0.209 ± 0.029
Female					
	0 ppm (0)	**50 ppm (1.59)**	**200 ppm (6.82)**	**500 ppm (17.68)**	**2000 ppm (67.05)**
Final mean body weight (kg)	9.7 ± 2.6	10.2 ± 1.8	10.1 ± 1.5	9.5 ± 1.8	9.7 ± 1.4
Relative thyroid weight (%)	0.008 ± 0.001	0.009 ± 0.000	0.010 ± 0.002	0.008 ± 0.002	0.010 ± 0.003
Relative heart weight (%)	0.785 ± 0.044	0.790 ± 0.037	0.823 ± 0.070	0.886 ± 0.040[c]	0.814 ± 0.042
Relative liver weight (%)	2.463 ± 0.305	2.239 ± 0.245	2.430 ± 0.165	2.747 ± 0.430	2.849 ± 0.149
Relative spleen weight (%)	0.250 ± 0.048	0.250 ± 0.050	0.201 ± 0.037	0.288 ± 0.046	0.263 ± 0.154
Relative kidney weight (%)	0.464 ± 0.059	0.438 ± 0.020	0.481 ± 0.047	0.473 ± 0.060	0.491 ± 0.040
Relative adrenal weight (%)	0.011 ± 0.002	0.010 ± 0.001	0.009 ± 0.002	0.012 ± 0.002	0.012 ± 0.000

[a]Source: Hazleton Laboratories, Inc., 1974a.
[b]Mean ± SD.
[c]Statistically significantly different from control ($p < 0.05$) using a Fisher's exact test in an independent statistical analysis performed for this review.

Table B.5. Selected Hematological and Biochemical Values in Beagle Dogs Exposed to Phenothiazine in the Diet for 13 Weeks[a,b]

Parameter	Exposure Group (mg/kg-day)				
	0 ppm (0)	**50 ppm (1.54)**	**200 ppm (6.06)**	**500 ppm (16.93)**	**2000 ppm (69.30)**
Male					
Hematocrit (%)	51.63 ± 2.56	54.38 ± 1.70	48.88 ± 0.85	48.75 ± 2.72	42.63 ± 2.10[c]
Hemoglobin (g/dl)	17.32 ± 0.75	18.35 ± 0.49	16.50 ± 0.28	16.30 ± 0.94	14.22 ± 0.69[c]
RBC count	6.86 ± 0.28	7.53 ± 0.08[c]	6.68 ± 0.33	6.45 ± 0.50	5.80 ± 0.40[c]
WBC count	11.15 ± 1.06	11.70 ± 1.44	13.65 ± 1.37[c]	12.67 ± 3.74	11.75 ± 2.04
Glucose (mg/dl)	111.25 ± 8.77	104 ± 10.68	109.25 ± 4.99	102.5 ± 2.38	102.25 ± 8.77
BUN (mg/dl)	12.25 ± 3.69	13.25 ± 1.19	12.63 ± 1.25	13.13 ± 2.02	13.50 ± 1.29
SGPT (units/ml)	23.00 ± 2.12	23.25 ± 2.06	28.25 ± 1.89[c]	31.25 ± 6.65	22.25 ± 0.96
SGOT (K)	26.00 ± 4.69	28.00 ± 4.243	30.00 ± 5.354	27.00 ± 6.481	32.00 ± 4.24
Bromsulphalein retention (% in 30 min)	2.5 ± 0.3	2.7 ± 0.3	2.9 ± 0.3	1.9 ± 0.5	3.2 ± 0.3[c]
Female					
	0 ppm (0)	**50 ppm (1.59)**	**200 ppm (6.82)**	**500 ppm (17.68)**	**2000 ppm (67.05)**
Hematocrit (%)	51.88 ± 4.17	52.13 ± 2	48.88 ± 4.75	49.38 ± 3.30	47.38 ± 2.02
Hemoglobin (g/dl)	17.55 ± 1.49	17.60 ± 1.01	16.47 ± 1.79	16.47 ± 1.11	15.90 ± 0.75
RBC count	6.92 ± 0.66	7.03 ± 0.36	7.14 ± 1.15	6.65 ± 0.23	6.21 ± 0.20
WBC count	10.55 ± 1.81	11.47 ± 0.42	12.60 ± 0.94	10.17 ± 2.64	12.82 ± 3.01
Glucose (mg/dl)	97.50 ± 9.26	102.00 ± 5.35	107.25 ± 3.86	94.00 ± 8.60	93.75 ± 8.18
BUN (mg/dl)	14.00 ± 2.94	12.00 ± 1.92	12.25 ± 2.06	14.88 ± 2.39	12.50 ± 1.91
SGPT (units/ml)	23.50 ± 4.80	21.25 ± 1.71	22.00 ± 2.94	29.75 ± 6.18	21.00 ± 0.0
SGOT (K)	24.75 ± 2.5	25.00 ± 2.16	32.500 ± 4.51[c]	29.75 ± 5.68	34.25 ± 3.10[c]
Bromsulphalein retention (% in 30 min)	2.8 ± 0.6	2.8 ± 0.2	3.2 ± 0.4	2.6 ± 0.4	3.9 ± 1.1

[a]Source: Hazleton Laboratories, Inc., 1974a.
[b]Mean ± SD.
[c]Statistically significantly different from control ($p < 0.05$) by standard *t*-test in an independent statistical analysis performed for this review.

Table B.6. Body and Organ Weights in Beagle Dogs Exposed to Phenothiazine in the Diet for 13 Weeks[a,b]

Parameter	Exposure Group (mg/kg-day)		
	0 ppm (0)	**2000 ppm; Pharmaceutical Grade (69.30)**	**2000 ppm; Technical Grade (69.30)**
Male			
Final mean body weight (kg)	10.63 ± 1.73	10.18 ± 0.53	10.65 ± 1.22
Relative thyroid weight (%)	0.01 ± 0.00	0.01 ± 0.00	0.01 ± 0.00
Relative heart weight (%)	0.79 ± 0.08	0.79 ± 0.06	0.816 ± 0.06
Relative liver weight (%)	2.42 ± 0.32	2.75 ± 0.24	2.93 ± 0.32
Relative spleen weight (%)	0.229 ± 0.06	0.28 ± 0.062	0.40 ± 0.06[c]
Relative kidney weight (%)	0.47 ± 0.51	0.48 ± 0.03	0.49 ± 0.04
Relative adrenal weight (%)	0.01 ± 0.00	0.01 ± 0.00	0.01 ± 0.00
Relative testes weight (%)	0.22 ± 0.05	0.21 ± 0.03	0.21 ± 0.04
Female			
	0 ppm (0)	**2000 ppm; Pharmaceutical Grade (67.05)**	**2000 ppm; Technical Grade (67.05)**
Final mean body weight (kg)	9.73 ± 2.59	9.78 ± 1.44	9.78 ± 1.20
Relative thyroid weight (%)	0.001 ± 0.00	0.01 ± 0.00	0.01 ± 0.00
Relative heart weight (%)	0.79 ± 0.04	0.81 ± 0.04	0.85 ± 0.03
Relative liver weight (%)	2.46 ± 0.31	2.85 ± 0.15	3.02 ± 0.47
Relative spleen weight (%)	0.25 ± 0.05	0.26 ± 0.15	0.79 ± 0.85
Relative kidney weight (%)	0.46 ± 0.6	0.49 ± 0.04	0.49 ± 0.06
Relative adrenal weight (%)	0.01 ± 0.00	0.01 ± 0.00	0.01 ± 0.00

[a]Source: Hazleton Laboratories, Inc., 1974a.
[b]Mean ± SD.
[c]Statistically significantly different from control ($p < 0.05$) by standard *t*-test in an independent statistical analysis performed for this review.

Table B.7. Selected Hematological and Biochemical Values in Beagle Dogs Exposed to Phenothiazine in the Diet for 13 Weeks[a,b]

Parameter	Exposure Group (mg/kg-day)		
	0 ppm (0)	**2000 ppm; Pharmaceutical Grade (69.30)**	**2000 ppm; Technical Grade (69.30)**
Male			
Hematocrit (%)	51.63 ± 2.56	42.63 ± 2.10[c]	41.88 ± 3.6 [c]
Hemoglobin (g/dl)	17.32 ± 0.75	14.22 ± 0.69[c]	13.97 ± 1.26[c]
RBC count	6.86 ± 0.28	5.80 ± 0.40[c]	5.50 ± 0.29[c]
WBC count	11.15 ± 1.06	11.75 ± 2.04	15.70 ± 2.57[c]
Glucose (mg/dl)	111.25 ± 8.77	102.25 ± 8.77	96.75 ± 12.18
BUN (mg/dl)	12.25 ± 3.69	13.50 ± 1.29	12.75 ± 2.50
SGPT (units/ml)	23.00 ± 2.12	22.25 ± 0.96	29.75 ± 5.50[c]
SGOT (K)	26.00 ± 4.69	32.00 ± 4.24	36.25 ± 5.62
Bromsulphalein retention (% in 30 min)	2.5 ± 0.3	3.2 ± 0.3[c]	2.3 ± 0.5
Female			
	0 ppm (0)	**2000 ppm; Pharmaceutical Grade (67.05)**	**2000 ppm; Technical Grade (67.05)**
Hematocrit (%)	51.88 ± 4.17	47.38 ± 2.02	36.88 ± 8.64[c]
Hemoglobin (g/dl)	17.55 ± 1.49	15.90 ± 0.75	12.20 ± 3.13[c]
RBC count	6.92 ± 0.66	6.21 ± 0.20	4.77 ± 1.38[c]
WBC count	10.55 ± 1.81	12.82 ± 3.01	17.77 ± 5.73
Glucose (mg/dl)	97.50 ± 9.26	93.75 ± 8.18	101.50 ± 7.23
BUN (mg/dl)	14.00 ± 2.94	12.50 ± 1.91	13.00 ± 3.46
SGPT (units/ml)	23.50 ± 4.80	21.00 ± 0.0	29.50 ± 6.45
SGOT (K)	24.75 ± 2.5	34.25 ± 3.10[c]	36.00 ± 5.164[c]
Bromsulphalein retention (% in 30 min)	2.8 ± 0.6	3.9 ± 1.1	2.4 ± 0.5

[a]Source: Hazleton Laboratories, Inc., 1974a.
[b]Mean ± SD.
[c]Statistically significantly different from control ($p < 0.05$) by standard *t*-test in an independent statistical analysis performed for this review.

Table B.8. Body Weight and Reproductive Effects in Female Rats Exposed to Phenothiazine by Gavage During Gestation[a]

Parameter	Exposure Group (mg/kg-day)			
	0	**15**	**50**	**150**
Sample size	20	18	21	20
Mean body weight on GD 6 (g)[b]	214.4 ± 14.0	216.7 ± 14.0	209.0 ± 13.7	212.0 ± 14.0
Mean body weight on GD 15 (g)[b]	292.5 ± 30.6	286.2 ± 20.7	277.5 ± 16.1	266.6 ± 17.3[d]
Mean corpora lutea	10.7	10.5	10.9	11.5
Mean implantation sites	9.8	9.2	9.7	10.6
Mean resorption sites	1.0	0.4	0.1[e]	0.7
Mean fetus number	8.8	8.8	9.6	10.0
Number of females with one or more resorption sites[c]	8 (40)	6 (33.3)	3 (14.3)	10 (50)
Fetus sex ratio (males/females)	1.23	0.98	1.01	1.14
Mean fetus body weight (g)	3.6	3.7	3.7	3.8

[a]Source: Harris Laboratories, Inc. (1977a).
[b]Mean ± SD.
[c]Number of animals with endpoint/number of animals examined; () = percent of total.
[d]Statistically significant by One-Way Analysis of Variance and Scheffe's Multiple Comparison ($p < 0.05$) performed by study authors.
[e]Statistically significantly different from control ($p < 0.05$) by Fisher's exact test in an independent statistical analysis performed for this review.

Table B.9. Body Weight and Reproductive Effects in Female Mice Dams Exposed to Phenothiazine by Gavage During Gestation[a]

Parameter	Exposure Group (mg/kg-day)			
	0	30	100	300
Sample size	20	20	20	25
Mean body weight on GD 6 (g)[b]	33.7 ± 2.3	32.3 ± 2.3	31.4 ± 2.8[d]	31.0 ± 2.1[d]
Mean body weight on GD 17 (g)[b]	52.6 ± 3.8	48.7 ± 3.8	50.1 ± 3.8	48.9 ± 4.6
Mean corpora lutea	12.7	12.3	11.7	12.2
Mean implantation sites	12.2	12.1	11.4	11.9
Mean resorption sites	0.6	2.0	1.2	1.2
Mean fetus number	11.6	10.2	10.3	10.8
Number of females with one or more resorption sites[c]	7 (35)	17 (85)[e]	16 (80)[e]	17 (68)[e]
Fetus sex ratio (males/females)	0.79	1.0	1.04	1.14
Mean fetus body weight (g)	1.0	0.9	0.95	0.9

[a]Source: Harris Laboratories, Inc (1977b).
[b]Mean ± SD.
[c]Number of animals with endpoint/number of animals examined; () = percent of total.
[d]Statistically significant by One-Way Analysis of Variance and Scheffe's Multiple Comparison ($p < 0.05$) performed by study authors.
[e]Statistically significantly different from control ($p < 0.05$) by Chi-Square Test of Independence.

APPENDIX C. BMD MODELING OUTPUTS FOR PHENOTHIAZINE

Table C.1 is a summary of BMDS modeling results for increased SGOT in subchronic oral exposure of female dogs to phenothiazine. Because of the strong observed upper plateau value for SGOT, only the BMDS models with a maximum value parameter were fit to the data. Figure C.1 shows the fitted model graphically.

Table C.1. BMD Modeling Results for Increased SGOT in Female Rats[a]

Model	Homogeneity Variance *p*-Value	Goodness-of-Fit *p*-Value[b]	AIC for Fitted Model	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)	Comments
Hill (constant variance)	0.2706	0.4871	75.34	1.993	1.816	Acceptable fit only after specifying at least one parameter value. BMDL computed by BMDS only after specifying all parameter values except Hill coefficient (***n***)
Exponential (M3)	0.2706	0.0226	83.47	39.49	26.07	Poor fit[c]
Exponential (M5)	0.2706	0.0637	81.34	3.12	1.27	Poor fit[c]

[a]Source: Hazleton Laboratories, Inc., 1974a.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Statistically-significant lack of fit.

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose.

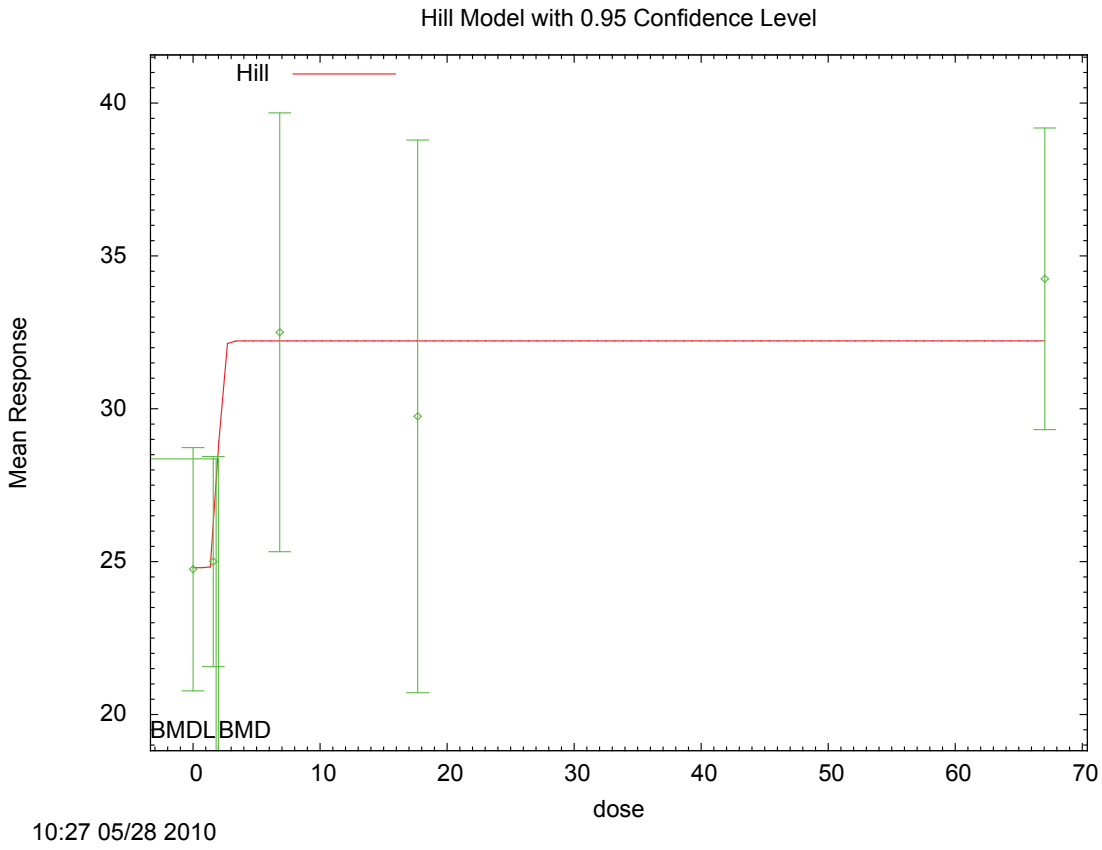

Figure C.1. Hill model fit to increased SGOT in female dogs treated with phenothiazine for 13 weeks Hazleton Laboratories, Inc., 1974a.

APPENDIX D. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). (1986) Documentation of the threshold limit values and biological exposure indices. Cincinnati, OH: ACGIH. 009017

Analytical Development Corporation. (1987) Thirteen studies on phenothiazine with attachments. U.S. Environmental Protection Agency, Washington, DC. 86-870000772. Available online at http://www.ntis.gov/search/product.aspx?ABBR=OTS0515211. 594357

CalEPA (California Environmental Protection Agency). (2008a) OEHHA acute, 8-hour and chronic reference exposure level (REL) summary. Office of Environmental Health Hazard Assessment. Available online at http://www.oehha.ca.gov/air/allrels.html. Accessed on 2/25/10. 595416

CalEPA (California Environmental Protection Agency). (2008b) Hot spots unit risk and cancer potency values. Office of Environmental Health Hazard Assessment. Available online at http://www.oehha.ca.gov/air/hot_spots/pdf/TSDlookup2002.pdf. 595417

Calle, LM; Sullivan, PD. (1982) Screening of antioxidants and other compounds for antimutagenic properties towards benzo[a]pyrene-induced mutagenicity in strain TA98 of Salmonella typhimurium. *Mutat Res* 101(2):99−114. 594556

DeEds, F; Wilson, RH; Thomas, JO. (1940) Photosensitization by phenothiazine. *J Am Med Assoc* 114(21):2095−2097. 594330

Dow Chemical Company. (1944) Comparative toxicity of crude Dow phenothiazine and a similar Dupont product. U.S. Environmental Protection Agency, Washington, DC. 86-870002124. 594306

Eastman Kodak Company. (1987) Studies on phenothiazine with cover letter dated 072787. U.S. Environmental Protection Agency, Washington, DC. 86-870001176. Available online at http://www.ntis.gov/search/product.aspx?ABBR=OTS0516079. 594349

Gershbein, LL. (1973) Psychotropic drugs and liver regeneration. *Res Comm Chem Pathol Pharmacol* 6(3):1005−1017. 594340

Gilmour, DG; Bloom, AD; Lele, KP; et al. (1971) Chromosomal aberrations in users of psychoactive drugs. *Arch Gen Psychiatr* 24(3):268−272. 594559

Harris Laboratories, Inc. (1977a). Teratogenic study with phenothiazine in albino rats (report to West Agro-Chemical, Inc, Kansas City MO, USA). Lincoln NE, USA: Harris Laboratories, Inc, project no T-1042. Available from NTIS, Springfield VA, USA; NTIS order no. NTIS/OTS0515213.

Harris Laboratories, Inc. (1977b). Teratogenic study with phenothiazine in albino mice (report to West Agro-Chemical, Inc, Kansas City MO, USA). Lincoln NE, USA: Harris Laboratories, Inc, project no T-1042. Available from NTIS, Springfield VA, USA; NTIS order no. NTIS/OTS0515213.

Harris Laboratories, Inc. (1977c). Acute inhalation LC50 study. Phenothiazine purified. Lot no. NB 36-145 (report to West Agro-Chemical, Inc, Kansas City MO, USA). Lincoln NE, USA: Harris Laboratories, Inc, project no T-1033 (available from NTIS, Springfield VA, USA; NTIS order no. NTIS/OTS0515213).

Harris Laboratories, Inc. (1977d). Acute inhalation LC50 study. Phenothiazine pharm. Lot no. 60927-R (report to West Agro-Chemical, Inc, Kansas City MO, USA). Lincoln NE, USA: Harris Laboratories, Inc, project no T-1043 (available from NTIS, Springfield VA, USA; NTIS order no. NTIS/OTS0515213).

Hazleton Laboratories, Inc. (1974a). 13-Week oral toxicity study in dogs. Phenothiazine (pharmaceutical grade). Final report (report to West Chemical Company, Long Island City NY, USA). Vienna VA, USA: Hazleton Laboratories, Inc, project no 872-100 (available from NTIS, Springfield VA, USA; NTIS order no. NTIS/OTS0515213).

Hazleton Laboratories, Inc. (1974b). 13-Week dietary administration dogs. Phenothiazine pharmaceutical and technical grades. Final report (report to West Chemical Company, Long Island City NY, USA). Vienna VA, USA: Hazleton Laboratories, Inc, project no 872-100 A (available from NTIS, Springfield VA, USA; NTIS order no. NTIS/OTS0515213).

HSDB (Hazardous Substances Data Bank). (1996) Phenothiazine. National Library of Medicine, Bethesda, MD. Available online at http://toxnet.nlm.nih.gov. Accessed on 3/24/2010. 597611

Innes, JR; Ulland, BM; Valerio, MG; et al. (1969) Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note. *J Natl Cancer Inst* 42(6):1101−1114. 062632

Integrated Laboratory Systems. (1997) Phenothiazine [92-84-2] review of toxicological literature. Prepared for the National Institute of Environmental Health Sciences, Research Triangle Park, NC. Available online at http://ntp.niehs.nih.gov/ntp/htdocs/Chem_Background/ExSumPdf/Phenothiazine.pdf. 594568

Loveday KS, Seixas GM. (1980a). Salmonella/mammalian microsome mutagenesis assay on phenothiazine,phenothiazone, and phenothiazine sulfoxide (prepared for West Agro-Chemical, Inc, Kansas City Mo, USA). Woburn MA, USA: Bioassay Systems Corporation, BSC project no 10411 (available from NTIS, Springfield VA, USA; NTIS order no. NTIS/OTS0515213).

Loveday KS, Seixas GM. (1980b). Salmonella liquid suspension mutant fraction assay on phenothiazine, phenothiazone, and phenothiazine sulfoxide (prepared for West Agro-Chemical, Inc, Kansas City Mo, USA). Woburn MA, USA: Bioassay Systems Corporation, BSC project no 10177 (available from NTIS, Springfield VA, USA; NTIS order no. NTIS/OTS0515213).

Mortelmans, K; Haworth, S; Lawlor, T; et al. (1986) Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. *Environ Mol Mutagen* 8(Suppl 7):1−119. 007315

NIOSH (The National Institute for Occupational Health and Safety). (1998) International chemical safety cards: Phenothiazine. Available online at http://www.cdc.gov/niosh/ipcsneng/neng0937.html. Accessed on 3/22/2010. 597531

Slone, D; Siskind, V; Heinonen, OP; et al. (1977) Antenatal exposure to the phenothiazines in relation to congenital malformations, perinatal mortality rate, birth weight, and intelligence quotient score. *Am J Obstet Gynecol* 128(5):486−488. 594547

Telford, IR; Woodruff, CS; Linford, RH. (1962) Fetal resorption in the rat as influenced by certain antioxidants. *Am J Anat* 110:29−36. 594549

U.S. EPA (U.S. Environmental Protection Agency). (2005) Guidelines for carcinogen risk assessment, Final Report. Risk Assessment Forum, U.S. Environmental Protection Agency. Washington, DC. EPA/630/P-03/001F. Available online at http://www.epa.gov/raf/publications/pdfs/CANCER_GUIDELINES_FINAL_3-25-05.PDF. 086237

U.S. EPA (Environmental Protection Agency). (2010) Health effects assessment summary tables (HEAST). Office of Emergency and Remedial Response, Washington, DC. Available online at http://epa-heast.ornl.gov/. Accessed on 4/8/2010. 595422

Wang, CY; Hayashida, S. (1984) Enhancement by phenothiazine and 2,5-di-O-acetyl-D-glucosaccharo-(1,4)(6,3)-dilactone of bladder carcinogenicity of N-[4-(5-nitro-2-furyl)-2-thiazolyl]-formamide in rats. *Cancer Lett* 24:37−43. 594553