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Provisional Peer Reviewed Toxicity Values for

Dimethylphenethylamine (Phentermine)
(CASRN 122-09-8)

Derivation of Subchronic and Chronic Oral RfDs

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Acronyms

bw - body weight
cc - cubic centimeters
CD - Caesarean Delivered
CERCLA - Comprehensive Environmental Response, Compensation, and Liability Act of 1980
CNS - central nervous system
cu.m - cubic meter
DWEL - Drinking Water Equivalent Level
FEL - frank-effect level
FIFRA - Federal Insecticide, Fungicide, and Rodenticide Act
g - grams
GI - gastrointestinal
HEC - human equivalent concentration
Hgb - hemoglobin
i.m. - intramuscular
i.p. - intraperitoneal
i.v. - intravenous
IRIS - Integrated Risk Information System
IUR - Inhalation Unit Risk
kg - kilogram
L - liter
LEL - lowest-effect level
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
m - meter
MCL - maximum contaminant level
MCLG - maximum contaminant level goal
MF - modifying factor
mg - milligram
mg/kg - milligrams per kilogram
mg/L - milligrams per liter
MRL - minimal risk level
MTD - maximum tolerated dose
MTL - median threshold limit

NAAQS - National Ambient Air Quality Standards
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-RfD - provisional Oral Reference Dose
p-RfC - provisional Inhalation Reference Concentration
p-OSF - provisional Oral Slope Factor
p-IUR - provisional Inhalation Unit Risk
PBPK - physiologically based pharmacokinetic
ppb - parts per billion
ppm - parts per million
PPRTV - Provisional Peer Reviewed Toxicity Value
RBC - red blood cell(s)
RCRA - Resource Conservation and Recovery Act
RGDR - Regional deposited dose ratio (for the indicated lung region)
REL - relative exposure level
RGDR - Regional gas dose ratio (for the indicated lung region)
RfD - Oral Reference Dose
RfC - Inhalation Reference Concentration
s.c. - subcutaneous
SCE - sister chromatid exchange
SDWA - Safe Drinking Water Act
sq.cm. - square centimeters
TSCA - Toxic Substances Control Act
UF - uncertainty factor
ug - microgram
umol - micromoles
VOC - volatile organic compound

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR DIMETHYLPHENETHYLAMINE (CASRN 122-09-8; Phentermine)
Derivation of Subchronic and Chronic Oral RfDs

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) 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 (PPRTV) 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 Integrated Risk Information System (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 two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program 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 science and available information evolve, PPRTVs are initially derived with a three-year life-cycle. However, EPA Regions or the EPA Headquarters Superfund Program sometimes request that a frequently used PPRTV be reassessed. 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 manuscripts 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 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 manuscript 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

Dimethylphenethylamine (1,1-dimethyl-2-phenylethylamine), commonly known as phentermine, is used as an appetite suppressant (anorectic) drug. Neither a subchronic nor chronic RfD for phentermine is listed on IRIS (U.S. EPA, 2003) or in the HEAST (U.S. EPA, 1997) or Drinking Water Standards and Health Advisories list (U.S. EPA, 2002). The CARA list (U.S. EPA, 1991, 1994) does not report any relevant documents for phentermine. ATSDR (2002), IARC (2002) and WHO (2002) have not published review documents for phentermine. The initial literature searches of TOXLINE (1965-1995), MEDLINE (1980-1995), CANCERLINE (1986-1995), CCRIS, TSCATS, RTECS, GENETOX, DART/ETICBACK, and EMIC/EMICBACK were conducted and screened in September 1995 to identify relevant data on phentermine. Update literature searches from 1995 to 2003 were performed in January, 2003 using the same databases, except for replacement of CANCERLIT with CANCERLINE and the addition of HSDB. The MEDLINE search strategy was unusually broad to facilitate identifying

pertinent clinical studies. The NTP (2002) status report was also searched for relevant information. Additional literature searches from January 2003 through September 2004 were conducted by NCEA-Cincinnati using MEDLINE, TOXLINE, Chemical and Biological Abstracts databases.

Phentermine acts on the nervous system by the same general mechanism as amphetamine (1-methyl-2-phenylethylamine) by stimulating sympathetic nerves via mimicking the action of catecholamine neurotransmitters (norepinephrine) and by stimulating the release of dopamine (Balcioglu and Wurtman, 1998; Baumann et al., 2000; Glazer, 2001; Hoffman and Lefkowitz, 1990; Silverstone, 1992; Sullivan and Comai, 1978). Stimulation of the sympathetic nervous system elicits various types of physiological and metabolic responses, although not all sympathomimetic amines produce each response and many differences in effects of these compounds are only quantitative. Effects of phentermine are mainly associated with the CNS, particularly appetite reduction and excitatory changes, and appetite suppression seems to be the main basis for phentermine-related weight loss.

REVIEW OF THE PERTINENT LITERATURE

Human Studies

Phentermine is usually administered by capsule in a single daily dose of 30 mg, often as the hydrochloride salt (equivalent to 24 mg phentermine base) complexed in a sustained release ion-exchange resin (Table 1). Assuming an average body weight of 90 kg for obese people based on typical values from clinical studies of phentermine (Table 1), the usual therapeutic dosage of 24-30 mg/day corresponds to approximately 0.3 mg/kg-day. Phentermine seems to be preferred for short-term therapeutic use (up to 6 months) in selected patients with significant obesity and medical risk, and there is currently limited information on efficacy or safety of prolonged use and possible development of tolerance, particularly in healthy individuals (Silverstone, 1992).

Numerous clinical trials of phentermine have been conducted to assess its efficacy as an appetite suppressant (i.e., an anorectic drug) and (in some studies) potential for adverse side effects (Table 1). The people tested in these trials are not representative of the general population in that they were markedly overweight (generally averaged 43-55% over ideal weight) and, in many of the studies, had calorie restricted diets (generally 1000-1500 cal/day). The preponderance of phentermine studies were double-blind and 3-6 months in duration and, when considered together, demonstrate that 0.3 mg/kg-day dosages of phentermine are effective in promoting weight loss. Body weight losses were quite variable but averaged 6-13% lower than placebo or pretreatment weights at the end of most of the studies, reflecting average weekly losses in the 0.2-0.4 kg range. Weekly losses tended to decrease after several weeks of treatment, but it is unclear if this was due to development of tolerance or a plateau effect

(maintenance weight). The anorectic effectiveness of phentermine appears to be similar following intermittent (alternate 4-week) or continuous exposure (Munro et al., 1968; Truant et al., 1972; Steel et al., 1973). There is a dearth of information on objective effects of phentermine other than weight loss; blood pressure and heart rate were reduced approximately 3% in one trial (Valle-Jones et al, 1983), but these cardiovascular effects were attributed to weight loss rather than directly to the chemical. Subjective side effects were reported in many of the clinical studies, with dry mouth and symptoms of CNS stimulation (e.g., insomnia, nervousness, irritability, mild hyperactivity) occurring most frequently (Table 1). Prevalences and incidences of subjective effects were often in the range of 20-30%; however, they were not reported by subjects in all studies (Langlois et al., 1974; Jackson and Vanik, 1976), and some of the studies were limited by lack of placebo comparisons and other data insufficiencies.

In a case-control analysis of a cohort of more than 8000 U.K. patients who received prescriptions for anorectic drugs (887 exposed to phentermine, 6091 exposed to dexfenfluramine, and 2355 exposed to fenfluramine) and 17,225 obese subjects without exposure to these drugs, no cases of stroke associated with phentermine use were identified (Derby et al., 1999).

The only information located regarding possible adverse human birth outcomes following exposure to phentermine during pregnancies was an abstract report that no pattern of offspring malformation or increase in spontaneous abortion rate was found among 86 women who used anorectic drugs (77 used phentermine) during the first trimester of pregnancy (McElhatton et al., 2000).

In weight-control therapy programs, phentermine has been used in combination with fenfluramine, an appetite suppressant which is thought to act via activation of serotonergic pathways (not via noradrenergic pathways as with phentermine). In September, 1997, however, fenfluramine was voluntarily withdrawn from the market as a result of a Food and Drug Administration (FDA) survey of reports that 32% of 271 users of the combination ("phen-fen") showed asymptomatic heart valve abnormalities (valvular regurgitation) and a report of 24 cases of symptomatic valvular heart disease associated with phen-fen use (Connolly et al., 1997; Glazer, 2001). The combined use of these drugs for weight control (each individually approved for weight control by the FDA) was based on placebo-controlled clinical trials and showed that a combination treatment with fenfluramine (30 mg once daily) and phentermine (15 mg once daily) was equally effective in inducing weight loss with fewer adverse effects (dry mouth, palpitations, or CNS symptoms including sleep difficulties, nervousness, depression, fatigue, or increased dreaming) compared with phentermine (30 mg once daily) alone or fenfluramine (20 mg, three times per day) alone (Weintraub et al., 1984, 1992). Since the withdrawal of

Table 1. DOUBLE-BLIND CLINICAL STUDIES OF PHENTERMINE

Population	Experimental Design	Results and Comments	Reference
23 women. Mean age 56 years, mean weight 202 lb (92 kg).	Capsules containing 30 mg phentermine as resin were ingested once daily for 12 weeks. Body weight was measured biweekly.	No placebo was used. Subjects initially averaged 43% over ideal weight and had 3% mean weight loss after 12 weeks. Most of the effect occurred during the first 4-8 weeks; cumulative mean weight loss was 2.0, 2.5 and 2.7 kg at week 4, 8 and 12, respectively. Mean rate of weight loss was 0.2 kg/week. Spontaneously reported subjective side effects included thirst (8/23), dry mouth (4/23), reduced appetite (4/23), nausea (3/23), increased energy (3/23) and constipation (2/23). Some of the phentermine subjects may have had mild diabetes mellitus controlled by diet alone (reported by 7 of 56 exposed to phentermine or dexamphetamine).	Seaton et al., 1964
108 women in 3 groups of 36. In Groups 1, 2 and 3, mean age was 42, 35 and 38 years, and mean body weight was 203, 207 and 214 lb (92, 94 and 97 kg), respectively.	Capsules containing phentermine as resin were ingested once daily in dosages of 0 mg (placebo) continuously (Group 1), 30 mg continuously (Group 2) or 30 mg intermittently (Group 3) for 36 weeks. The intermittent schedule involved alternate 4-week exposures to phentermine (5 periods) and placebo (4 periods). Body weight and symptoms were evaluated every 4 weeks.	Subjects in Groups 1, 2 and 3 had recommended diets providing ≈1000 calories/day (restricted carbohydrates), initially averaged 48, 58 and 55% higher body weight over ideal weight, and had 5, 13 and 13% mean total weight loss after 36 weeks. The rate of weight loss also was similar in Groups 2 and 3 and was greatest during the first 20 weeks. 25, 17 and 22 of the subjects in Groups 1, 2 and 3 respectively, completed the trial; of those that failed completion, 0, 8 and 11% were due to subjective side effects attributed to CNS stimulation. Effects in Groups 1, 2 and 3 included reduced appetite (20, 71, 82%), "troublesome" symptoms suggesting CNS stimulation (8, 24, 27%), and dry mouth (0, 0, 18%).	Munro et al., 1968

Table 1. (cont.) DOUBLE-BLIND CLINICAL STUDIES OF PHENTERMINE

Population	Experimental Design	Results and Comments	Reference
104 subjects in groups of 36 (Group 1; 26F, 10M), 34 (Group 2; 25F, 9M) and 34 (Group 3; 23F, 11M). Group mean ages were 37-38 years, and group mean baseline body weights were 175-179 lb (80-81 kg).	Capsules containing phentermine resin were ingested once daily in doses of 0 mg (placebo) continuously (Group 1), 30 mg continuously (Group 2) or 30 mg intermittently (Group 3) for 16 weeks. The intermittent schedule involved exposure to phentermine alternated with placebo during weeks 4, 8, 12 and 16. All groups were followed for 4 weeks post-treatment. Body weight, side effects, temperature, blood pressure, and pulse and respiration rates were evaluated weekly. Complete physical exams and laboratory tests were performed at beginning and end of study.	Diets had a fixed caloric content (provided 60% of the calories required to maintain ideal weight of each subject). Group body weights initially averaged 43-45% higher than ideal weight. Mean weight losses in Groups 2 and 3 were similar to each other and higher than in Group 1 during all treatment periods. Mean weight loss at the end of week 16 was 11.5, 20.3 and 18.4 lb (≈6.5, 10.3 and 11.6%) in Groups 1, 2 and 3, respectively. No clear indications of tolerance were found. Evaluation at the end of the 4-week observation period showed that ≈22% (5/23) and 48% (26/53) of the placebo and combined treated groups, respectively, had gained more than 1 pound. Success in attaining 16-week target weights and rate of weight loss also were more frequent in the treated groups than in controls. The most frequently reported complaints in Groups 1, 2 and 3 were dry mouth (≈19, 53 and 38%), constipation (≈17, 41 and 21%), insomnia (≈8, 32 and 27%) and nervousness (≈8, 29 and 15%).	Truant et al., 1972
32 women. Mean age 39 years, mean weight 206 lb (94 kg).	36-week intermittent schedule in which five 4-week exposure periods (one capsule containing 30 mg phentermine daily) were alternated with four 4-week non-exposure periods (placebo daily). Body weight and symptoms were evaluated every 4 weeks.	Diets providing approximately 1000 calories/day (restricted carbohydrates) were recommended. Subjects initially averaged 43.7% over ideal weight. Mean weight loss at the end of 36 weeks was 12.8% and mean rate of weight loss was 0.3 kg/week. Weight loss was greatest during the first half of the study, particularly during the treatment weeks. A side effect (dizziness) during the first 4 weeks excluded 2 subjects from the trial. Many (not quantified) subjects noted dry mouth, constipation or increased urinary frequency at beginning of the test but these effects were well tolerated. Other side effects included sleeplessness (20%), nausea and vomiting (14%), dizziness (9%) and drowsiness (8%). The side effects were attributed to CNS stimulation but not regarded as "clinically appreciable".	Steel et al., 1973

Table 1. (cont.) DOUBLE-BLIND CLINICAL STUDIES OF PHENTERMINE

Population	Experimental Design	Results and Comments	Reference
Groups of 30 (5M, 25F) control and 29 (24F, 5M) treated subjects. Mean age 35.1 years (control) and 39.7 years (treated). Mean weight 187 lb (85 kg) (same for both groups).	Phentermine was administered as the hydrochloride in capsule once daily in dosages of 0 mg (placebo) during weeks 1-2 (all subjects, pretreatment), 0 or 30 mg during weeks 3-16, and 0 mg during weeks 17-18 (all subjects, post-treatment). Patient history was evaluated pretreatment and at week 16. Clinical evaluations (body weight, vital signs, clinical symptoms) were performed pretreatment and at 2-week intervals for 18 weeks. Body weights were also determined at week 22 (27 controls, 25 treated, sex distribution not reported). Laboratory evaluations (hematology, clinical chemistry, urinalysis) were performed pretreatment and at weeks 4, 8, 12, 16 and 18. Physical examinations (systems evaluation, ophthalmologic examination, chest X-ray, EKG) were performed pretreatment and at week 16.	Subjects initially averaged 42.2% (controls) and 42.8% (treated) over ideal weight. 84% of the subjects (23 controls, 26 treated, sex distribution not reported) completed 18 weeks of evaluation. A 1000 calories/day diet was encouraged but not enforced. Mean body weight and mean weight loss after week 2 baseline were significantly ($p<0.05$-0.001) lower and higher, respectively, than the placebo group at each evaluation period. At week 16, body weight was ≈7% lower and weight loss was ≈313% higher than in the control group. Average weight loss per week was 1.2 and 0.3 lbs. in the treated and control groups, respectively. Both body weight and weight gain were increased in control and treated groups during post-treatment weeks 16-18, but the increases in the treated group were significantly greater than in the controls. Mean body weight increased in both groups during weeks 18-22, but was lower in the treated group than in controls (6.3%, $p<0.001$ at week 22). Mean body weight of the treated group, but not controls, was lower at week 22 than at the week 2 baseline (6.5%, $p<0.001$). No treatment-related differences in incidences of side effects (headaches, nervous, insomnia, dizzy, sweating, irritability) or other clinically significant inter- or intra-group changes were found.	Langlois et al., 1974

Table 1. (cont.) DOUBLE-BLIND CLINICAL STUDIES OF PHENTERMINE

Population	Experimental Design	Results and Comments	Reference
26 obese diabetics. Sex, age and weight not reported.	Phentermine in capsule was ingested once daily in dosages of 0 (placebo) or 30 mg on alternating months for 6 months. No continuous exposure to phentermine or placebo. Body weight, pulse rate, blood pressure, urine and blood glucose, plasma insulin, triglycerides and cholesterol were evaluated monthly.	Subjects lost a group total of 63.4 kg while taking phentermine and gained 21 kg while taking placebo. Mean weight loss per subject was 0.81 kg/month. Weight loss and weight gain occurred in 23 and 3 patients on phentermine, respectively, and in 8 and 18 patients on placebo, respectively; the difference between the median weights of the drug and placebo groups was significant ($p<0.01$). The 10 patients who left the study did so for reasons other than side effects, and no adverse or other side effects were reported by the subjects.	Jackson and Vanik, 1976.
66 obese diabetics (32 controls, 34 treated). The diabetes was controlled with insulin (Subgroup 1; 3 controls, 5 treated), diet alone (Subgroup 2; 14 controls, 15 treated) or an oral hypoglycemic agent (Subgroup 3; 15 controls, 14 treated). Sex, age and body weight not reported.	Capsules containing 0 (placebo) or 30 mg phentermine as resin were ingested once daily for 6 months. 14 subjects from the placebo group were then switched to 30 mg/day phentermine for 6 months; this new treated group was uncontrolled. Body weight, side effects, diabetic symptoms, urinary glucose (home tests), blood pressure, blood glucose and serum cholesterol were recorded or measured at 28-day intervals throughout the study.	Analysis of complete groups (i.e., not by diabetic therapy subgroup) showed that the subjects treated with phentermine lost significantly ($p<0.001$, test not reported) more weight than those on placebo [mean weight loss 11.6 lb. (obese group) compared to 3.2 lb (placebo group)]. Percent weight loss in the overweight subjects cannot be calculated due to lack of initial body weight data. The increased weight loss was not accompanied by appreciable reduction in insulin or oral hypoglycemic drug dosage or change in glycemia or glycosuria, and appears to be mainly due to responses in Subgroups 1 and 2. Mean weight loss also was significantly ($p<0.01$) greater during phentermine treatment (14.4 lb) than during placebo treatment (2.6 lb) in the group exposed to phentermine following exposure to placebo. Evaluation of the anorectic effect is complicated by lack of baseline body weight data (precluding calculating percent body weight loss) and information on matching of the exposed and placebo groups, although the 14 subjects given placebo followed by phentermine can be viewed as serving as their own controls. Slight mouth dryness and initial minor sleep disturbance were the only side effects noted.	Campbell et al., 1977

Table 1. (cont.) DOUBLE-BLIND CLINICAL STUDIES OF PHENTERMINE

Population	Experimental Design	Results and Comments	Reference
32 women and 18 men (mean age for all subjects, 49.9 years). Mean weight 181.9 lbs (82.7 kg) [170.5 lbs (77.5 kg) for women, 202.4 lbs (92.0 kg) for men].	Capsules containing 30 mg phentermine as resin were ingested once daily for 12 weeks. Body weight, blood pressure and heart rate were evaluated pretreatment. Subsequently, these endpoints and subjective side effects were evaluated every 4 weeks.	Study not double-blind or placebo controlled. Subjects initially averaged 33% over ideal weight. All subjects completed the study. A 1500 calories/day diet was encouraged but not enforced. Cumulative mean weight loss at week 12 was 18.2 lbs [16.8 lbs in males and 19.0 lbs in females (8.3% and 11.1% of initial weight, respectively]. Total weight loss as a percentage of initial overweight was 44.5% (43.4% in males and 48.1% in females). Other effects after 12 weeks treatment included reduced systolic blood pressure (2.8% lower than initial value, $p<0.05$), diastolic blood pressure (3.0%, $p<0.001$) and heart rate (3.3%, $p<0.01$); these were concluded to be almost certainly related to weight loss rather than directly to drug treatment. The reductions in blood pressure occurred mainly in subjects whose initial systolic values were $\geq$150 mm Hg. 20 subjective side effects were reported by 15 subjects; drowsiness/tiredness (6), dry mouth (4), constipation (4) and dizziness/giddiness (3) were most prevalent.	Valle-Jones et al., 1983.

Table 1. (cont.) DOUBLE-BLIND CLINICAL STUDIES OF PHENTERMINE

Population	Experimental Design	Results and Comments	Reference
50 women. Mean age 40.0 years, mean weight 228.1 lb (103.7 kg).	Phentermine as resin was ingested in a single mean daily dose of 36 mg (range 15-60 mg) for 20 weeks. The initial dose was 15 mg/day; this was increased in 5 mg increments (duration not specified) to 30 mg and subsequently, if weight loss was not produced, to a maximum of 60 mg unless precluded by side effects. Body weight, blood pressure, degree of appetite suppression and subjective side effects were recorded every two weeks. Plasma phentermine concentrations were assayed blind at weeks 6, 8, 16 and 18.	No placebo or other control group. Initially, an average of 68.4% excess body weight was reported as contrasted to normal body weight A 1000 kcal/day diet was recommended. 34 subjects completed the study with a 6.5% mean weight loss (6.7 kg) and wide individual variation (2.2 kg gain to 28.6 kg loss). Seven subjects withdrew from the study because of side effects after 4-8 weeks, including incapacitating headaches (3) and increased irritability with increased palpitations or increased blood pressure (2). Side effects in the 34 subjects that completed the study were mild and usually transient, including increased irritability (9), sleeplessness (8), occasional disturbing nightmares (5), increased energy (3) and palpitations on exertion (2). There was no correlation between plasma phentermine concentrations and daily dosage or weight loss; degree of obesity and plasma phentermine concentration, weight loss or daily dose; or plasma phentermine concentration and irritability, increased energy, sleeplessness or dreaming. The degree of subjective appetite suppression was related to weight loss but not to phentermine dosage or plasma phentermine concentration.	Douglas et al., 1983

Table 1. (cont.) DOUBLE-BLIND CLINICAL STUDIES OF PHENTERMINE

Population	Experimental Design	Results and Comments	Reference
Groups of 20 control (17F, 3M) and 20 treated (17F, 3M) subjects. Mean age 35.1 years (control) and 34.5 years (treated). Mean weight 35.1 years (control) and 34.5 years (treated).	Capsules containing 0 (placebo) or 30 mg phentermine as resin were ingested once daily for 16 weeks. This was followed by 4 weeks of dose tapering (week 17, 15 mg/day; week 18, 7.5 mg/day; week 19, 7.5 mg every other day; week 20, 7.5 mg every third day) and subsequently 4 weeks of follow-up with no treatment. Body weight was measured at weeks 4, 6 and 8 and thereafter every 4 weeks, and subjective complaints were used to assess adverse effects.	Subjects initially averaged 55% over their ideal body weight. Diets of 20 kcal/kg ideal body weight/day (range, 900-1800 kcal/day) were recommended. The treated group lost significantly ($p<0.01$) more weight than controls at all time points beginning at week 6. Weight loss at the end of week 16 (end of full dose treatment) was 4.9% and 11.0% of baseline in the control and treated groups, respectively. Compared to controls, treated subjects had significantly ($p<0.05$) more total complaints (241 vs. 79) and cardiovascular and CNS complaints (212 vs. 56). At the end of week 8 a total of 17 treated and 4 control subjects had complaints; these included dry mouth, CNS effects (sleep difficulties, nervousness, depression, fatigue and/or increasing dreaming) and palpitations in 12, 14 and 1 treated and 1, 4 and 0 control subjects, respectively. Of 10 treated and 2 control subjects with complaints at the end of week 16, dry mouth, CNS effects and palpitations were reported by 7, 7 and 1 treated and 0, 1 and 0 control subjects, respectively.	Weintraub et al., 1984
6 women. Age 24-28 years, moderately overweight (not quantified).	Each subject ingested one capsule containing 0 (placebo), 15 mg and 30 mg phentermine resin following overnight fast in three separate sessions. Order of dosing was randomized, but interval between doses was not reported. Anorectic effect was evaluated using a visual hunger rating scale before, 5 hours after and 10 hours after each dose. Calorie consumption was determined from amount of a standard sandwich meal ingested 5 and 10 hours post-dose.	Mean hunger ratings were significantly reduced at 15 mg and 30 mg when 5- and 10-hr values were combined (both $p<0.01$) and at 30 mg after 10 hours ($p<0.05$). Mean total calorie intake in the 5-hr, 10-hour and combined post-dose groups was 31, 18 and 25% lower than placebo at 15 mg, and 30, 38 and 33% lower than placebo at 30 mg. The decreases were significant at 15 and 30 mg when 5 and 10 hour values were combined (both $p<0.01$) and at 30 mg ($p<0.01$) after 10 hours. A significant correlation ($r=+0.68$, $p<0.01$) was found between pre-meal hunger ratings and calories consumed during the meal. Side effects were not discussed.	Silverstone, 1972

fenfluramine from the market, several other reports and studies (e.g., Burger et al., 1999; Gardin et al., 2000; Graham and Greene, 1997; Hensrud et al., 1999; Khan et al., 1998; Jick et al., 1998; Wee et al., 1998) have reported data on the prevalence of valvular regurgitation in patients who received phen-fen therapy. Each prevalence study found an association between phen-fen therapy and increased prevalence of valvular regurgitation. Among the studies, reported prevalences ranged from approximately 2% to 30% (see Gardin et al., 2000 and Glazer, 2001 for review). In addition, there are several case reports of pulmonary hypertension associated with phen-fen therapy (e.g., Dillon et al., 1999; Mark et al., 1997). A proposed mechanistic hypothesis involving serotonin agonistic effects of fenfluramine is supported by reports that endocardial fibroplasia seen in heart valves from phen-fen patients with valvular regurgitation was similar to changes associated with serotonin excess ("carcinoid syndrome") or exposure to ergotamine, a serotonin agonist, and the lack of reports of valvular abnormalities or other cardiovascular problems associated with phentermine monotherapy (Glazer, 2001).

Information regarding the possible developmental toxicity of phen-fen therapy is restricted to an abstract report of pregnancy outcome data for 100 women who used phen-fen, but discontinued use of the combined drug by the end of the first trimester of pregnancy (Johnson et al., 1998). Among 46 infants examined for gross abnormalities, one had a penile chordee and a second had a unilateral preauricular pit. The family of the second infant had a history of unilateral preauricular pits.

Animal Studies

Studies of phentermine in animals generally investigated anorectic and CNS behavioral effects. Most of these studies involved acute or short-term exposures by intravenous or parenteral injection, and all used dosages similar to or greater (most were substantially higher) than the 0.3 mg/kg-day therapeutic level. A few less-than-subchronic oral studies in animals were located, consisting of a 7-day study in rats showing anorectic effects at 4 and 8 mg/kg-day (Lawlor et al., 1969); a 35-day study in rats showing an anorectic effect, but no lung or heart histopathology at 27 mg/kg-day (Hasleton et al., 1977); and a 28-day study in mice showing an anorectic effect and associated increased metabolic energy expenditure at 25 mg/kg-day (Arch, 1981).

Developmental toxicity of phentermine was assessed in one study in rats which found that subcutaneous injection of 30 mg/kg-day on gestation days 16-20 did not cause any external abnormalities or effects on behavior, physical condition, body weight, crown-rump length, liver and lung weights, or lung histology and phospholipid content in neonates (Thoma-Laurie et al., 1982). Other developmental toxicity data are restricted to a study in which pregnant rats were infused with phentermine (10 mg/kg-day) plus dexfenfluramine (3 mg/kg-day) on gestation days 3 through 17; drug treatment did not affect the number of offspring, their birth weights, or their motor coordination assessed at 11 days of age (Bratter et al., 1999). Examination of 24 offspring hearts by light microscopy showed thickened mitral valves in 6 hearts, in contrast with no mitral valve thickening in an unspecified number of examined control offspring hearts (Bratter et al., 1999).

The effects of acute (single doses up to 2 weeks of exposure) parenteral administration of phentermine in combination with fenfluramine or dexfenfluramine have been examined on dopamine and/or serotonin release in rat striatum (Balcioglu and Wurtman, 1998), rat nucleus accumbens (Baumann et al., 2000; Rada and Hoebel, 2000), and rat anterior hypothalamus (Prow et al., 2001); brain serotonin levels in mice (Baumann et al., 1996) and rats (Lew et al., 1997; McCann et al., 1998); cocaine self-administration in rhesus monkeys (Glowa et al., 1997); conditioned reinforcement response in rats (Rea et al., 1998); and daily food intake in rats (Roth and Rowland, 1998). The doses of phentermine in these experiments were predominantly well above the therapeutic human dose of 0.3 mg/kg-day (≥3 mg/kg-day). Fluoxetine, a replacement drug for fenfluramine, increases the anorectic and long-term dopamine-depleting effects of phentermine. When administered i.p. in combination with phentermine (10 mg/kg, each), no effects on weight loss were reported despite reductions in brain monoamine. Phentermine administered i.p. alone did not cause any effect on weight loss or brain monoamines (Callahan et al., 2000). The results from these experiments are not directly related to the derivation of subchronic and chronic RfDs for phentermine, and are thus not further discussed in this issue paper.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC RfDs FOR PHENTERMINE

No data were located regarding adverse effects in overweight humans or laboratory animals following chronic oral exposure to phentermine. The human clinical data clearly indicate that subchronic exposure to 0.3 mg/kg-day dosages of phentermine is associated with 6-13% reductions in body weight and 0-30% prevalences of subjectively reported symptoms of mild CNS excitation and dry mouth. Effects such as these have been reported in obese patients and may be considered adverse when occurring in the general population (although they are not regarded as appreciable side effects of phentermine therapy), but the small magnitude of the body weight effect and the variable and generally low prevalences of side effects suggest that effects were only minimal in the phentermine studies.

The relevance of phentermine clinical trials to typical environmental exposures is somewhat unclear due to dissimilarities between the exposed subjects and the general population, specifically the significant obesity (and consequent medical risk) and low calorie diets of the subjects. The relevance of these potentially complicating factors to RfD derivation is not as problematic, however, as the limited ability of the available human data to describe subchronic dosage levels that produce no effects. Similarly, data from the available oral animal studies do not describe no-effect dosages.

Amphetamine (1-methyl-2-phenylethylamine) and chlorphentermine [1-methyl-2-(4-chlorophenyl)ethylamine] are structurally similar to phentermine, but appear to be unsuitable bases for derivation of an RfD for phentermine by analogy. The pharmacological properties of these potential surrogates markedly differ from those of phentermine in that chlorphentermine produces qualitatively different effects, particularly lipidosis of lung and other tissues (Lullmann

et al., 1973; Thoma-Laurie et al., 1982; Reasor, 1989; Elmaleh et al., 1993), and amphetamine has much more pronounced CNS activity, producing marked stimulant and euphoric effects (Sullivan and Comai, 1978; Silverstone, 1992). Amphetamine has been the most intensively studied anorectic sympathomimetic amine; however, it is unclear if its dose-effect relationships are well characterized (Silverstone, 1972).

The patient base for which weight loss was assessed was almost entirely overweight individuals, and the weight loss was nominal and occurred over a considerable length of time in most cases. The weight loss generally occurred during concomitant dieting, which is potentially confounding. Therefore, the weight loss, per se, in obese subjects should be considered a desired effect, not a toxic adverse effect.

Available human and animal data are considered inappropriate for development of either a subchronic or chronic p-RfD for dimethylphenethylamine.

REFERENCES

Arch, J.R.S. 1981. The contribution of increased thermogenesis to the effect of anorectic drugs on body composition in mice. Am. J. Clin. Nutr. 34: 2763-2769.

ATSDR (Agency for Toxic Substances and Disease Registry). 2002. Internet HazDat Toxicological Profile Query. U.S. Department of Health and Human Services, Public Health Service. Atlanta, GA. Online. http://www.atsdr.cdc.gov//qsql/toxprof.script

Balcioglu, A. and R.J. Wurtman. 1998. Effects of fenfluramine and phentermine (fen-phen) on dopamine and serotonin release in rat striatum: in vivo microdialysis study in conscious animals. Brain Res. 813:67-72.

Baumann, M.H., C.R. Schuster and R.B. Rothman. 1996. Effects of phentermine and cocaine on fenlfluramine-induced depletion of serotonin in mouse brain. Drug Alcohol Depend. 41: 71-74.

Baumann, M.H., M.A. Ayestas, C.M. Dersch et al. 2000. Effects of phentermine and fenfluramine on extracellular dopamine and serotonin in rat nucleus accumbens: therapeutic implications. Synapse. 36: 102-113.

Bratter, J., I.H. Gessner and N.E. Rowland. 1999. Effects of prenatal co-administration of phentermine and dexfenfluramine in rats. Eur. J. Pharmacol. 369: R1-R3.

Burger, A.J., H.B. Sherman, M.J. Charlamb et al. 1999. Low prevalence of valvular heart disease in 226 phentermine-fenfluramine protocol subjects prospectively followed for up to 30 months. J. Am. Coll. Cardiol. 34: 1153-1158.

Callahan, B.T., J. Yuan and G.A. Ricaurte. 2000. Fluoxetine increases phentermine-fluoxetine interatction in mice. Synapse. 38: 471-476.

Campbell, C.J., I.P. Bhalla, J.M. Steel and L.J.P. Duncan. 1977. A controlled trial of phentermine in obese diabetic patients. Practioner. 218: 851-855.

Connolly, H.M., J.L. Crary, M.D. McGoon et al. 1997. Valvular heart disease associated with fenfluramine-phentermine. N. Eng. J. Med. 337: 581-588.

Derby, L.E., M.W. Myers and H. Jick. 1999. Use of dexfenfluramine, fenfluramine and phentermine and the risk of stroke. Br. J. Clin. Pharmacol. 47: 565-569.

Dillon, K.A., K.G. Putman and J.L. Avorn. 1999. Death from irreversible pulmonary hypertension associated with short-term use of fenfluramine and phentermine. JAMA. 278: 1320.

Douglas, A., J.G. Douglas, C.E. Robertson and J.F. Munro. 1983. Plasma phentermine levels, weight loss and side effects. Int. J. Obes. 7: 591-595.

Elmaleh, D.R., H. Kizuka, R.N. Hanson, et al. 1993. Structure-localization relationships of ^{11}C-labeled phentermine derivatives: Effect of aromatic substitution. Appl. Radiat. Isot. 44: 821-829.

Gardin, J.M., D. Schumacher, G. Constantine et al. 2000. Valvular abnormalities and cardiovascular status following exposure to dexfenfluramine or phentermine/fenfluramine. JAMA. 283: 1703-1709.

Glazer, G. 2001. Long-term pharmacotherapy of obesity 2000: A review of efficacy and safety. Arch. Intern. Med. 161: 1814-1824.

Glowa, J.R., K.C. Rice, D. Matecka and R.B. Rothman. 1997. Phentermine/fenfluramine decreases cocaine self-administration in rhesus monkeys. Neuro Report. 8: 1347-1351.

Graham, D.J. and L. Green. 1997. Further cases of valvular heart disease associated with fenfluramine-phentermine. N. Eng. J. Med. 337: 635.

Hasleton, P.S., J.M. Kay and D. Heath. 1977. Phentermine resinate and the pulmonary vasculature of the rat. Arzneimittelforschung. 27(11): 2112-2113.

Hensrud, D.D., H.M. Connolly, M. Grogan et al. 1999. Echocardiographic improvement over time after cessation of use of fenfluramine and phentermine. Mayo Clin. Proc. 74: 1191-1197.

Hoffman, B.B. and R.J. Lefkowitz. 1990. Catecholamines and sympathomimetic drugs. In: Goodman and Gilman's. The pharmacological basis of therapeutics, 8th ed. A.G. Gilman, T.W. Rall, A.S. Nies and P. Taylor, Ed. Permagon Press, New York. p. 187-220.

IARC (International Agency for Research on Cancer). 2002. IARC Agents and Summary Evaluations. Online. http://193.51.164.11/cgi/iHound/Chem/iH_Chem_Frames.html

Jackson, W.P.U. and A.I. Vanik. 1976. Phentermine (duromine) for obese diabetics. S. Afr. Med. J. 50: 1351.

Jick, H., C. Vasilakis, L.A. Weinrauch et al. 1998. A population-based study of appetite-suppressant drugs and the risk of cardiac-valve regurgitation. N. Engl. J. Med. 339: 719-724.

Johnson, K.A., C.D. Chambers, L.M. Dick et al. 1998. Pregnancy outcome of women exposed to fen/phen. Teratology. 57: 188-189.

Khan, M.A., C.A. Herzog, J.V. St. Peter et al. 1998. The prevalence of cardiac valvular insufficiency assessed by transthoracic echocardiography in obese patients treated with appetite suppressant drugs. N. Eng. J. Med. 339: 713-718.

Langlois, K.J., J.A. Forbes, G.W. Bell and G.F. Grant, Jr. 1974. A double-blind clinical evaluation of the safety and efficacy of phentermine hydrochloride (fasting) in the treatment of exogenous obesity. Curr. Ther. Res. Clin. Exp. 16(4) 289-296.

Lawlor, R.B., M.C. Trivedi and J. Yelnosky. 1969. A determination of the anorexigenic potential of dl-amphetamine, d-amphetamine, l-amphetamine and phentermine. Arch. Int. Pharmacodyn. 179(2): 401-407.

Lew, R., B. Weisenberg, G. Vosmer and L.S. Seiden. 1997. Combined phentermine/fenfluramine administration enhances depletion of serotonin from central terminal fields. Synapse. 26: 36-45.

Lullmann, H., E. Rossen and K. U. Seiler. 1973. The pharmacokinetics of phentermine and chlorphentermine in chronically treated rats. J. Pharm. Pharmacol. 25: 239-243.

Mark, E.J., E.D. Patalas, H.T. Chang et al. 1997. Fatal pulmonary hypertension associated with short-term use of fenfluramine and phentermine. N. Eng. J. Med. 337: 602-606.

McCann, U.D., J. Yuan and G.A. Ricaurte. 1998. Neurotoxic effects of (±) fenfluramine and phentermine, alone and in combination, on monoamine neurons in the mouse brain. Synapse. 30: 239-246.

McElhatton, P.R., K.R. Pughe, C. Evans et al. 2000. Is exposure to amphetamine-like drugs in pregnancy associated with malformations? J. Toxicol. 38: 195-196.

Munro, J.F., A.C. MacCuish, E.M. Wilson and L.J.P. Duncan. 1968. Comparison of continuous and intermittent anorectic therapy in obesity. Br. Med. J. 1: 352-354.

NTP (National Toxicology Program). 2002. Management Status Report. Online. http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/Res_Stat/iH_Res_Stat_Frames.html

Prow, M.R., B. Lancashire, S. Aspley et al. 2001. Additive effects on rat brain 5HT release of combining phentermine with dexfenfluramine. Int. J. Obes. 25: 1450-1453.

Rada, P.V. and B.G. Hoebel. 2000. Supraadditive effect of *d*-fenfluramine plus phentermine on extracellular acetylcholine in the nucleus accumbens: possible mechanism for inhibition of excessive feeding and drug abuse. Pharmacol. Biochem. Behav. 65: 369-373.

Rea, W.P., R.B. Rothman and T.S. Shippenberg. 1998. Evaluation of the conditioned reinforcing effects of phentermine and fenfluramine in the rat: concordance with clinical studies. Synapse. 30: 107-111.

Reasor, M.J. 1989. A review of the biology and toxicologic implications of the induction of lysosomal lamellar bodies by drugs. Toxicol. Appl. Pharmacol. 97: 47-56.

Roth, J.D. and N.E. Rowland. 1998. Efficacy of administration of dexfenfluramine and phentermine, alone and in combination, on ingestive behavior and body weight in rats. Psychopharmacology. 137: 99-106.

Seaton, D.A., K. Rose and L.J.P. Duncan. 1964. A comparison of the appetite suppressing properties of dexamphetamine and phentermine. Scott. Med. J. 9: 482-484.

Silverstone, T. 1972. The anoretic effect of a long-acting preparation of phentermine (duromine). Psychopharmacologia (Berl.). 25: 315-320.

Silverstone, T. 1992. Appetite Suppressants. A Review. Drugs. 43: 820-836.

Steel, J.A., J.F. Munro and L.J.P. Duncan. 1973. A comparative trial of different regimens of fenfluramine and phentermine in obesity. Practioner. 211: 232-236.

Sullivan, A.C. and K. Comai. 1978. Pharmacological treatment of obesity. Int. J. Obes. 2: 167-189.

Thoma-Laurie, D., E.R. Walker and M.J. Reasor. 1982. Neonatal toxicity in rats following in utero exposure to chlorphentermine or phentermine. Toxicology. 24: 85-94.

Truant, A.P., L.P. Olon and S. Cobb. 1972. Phentermine resin as an adjunct in medical weight reduction: a controlled, randomized, double-blind prospective study. Curr. Ther. Res. 14: 726-738.

U.S. EPA. 1991. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. April.

U.S. EPA. 1994. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. December.

U.S. EPA. 1997. Health Effects Assessment Summary Tables. FY-1997 Update. Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. July. EPA-540-R-97-036. NTIS PB97-921199.

U.S. EPA. 2002. 2002 Edition of the Drinking Water Standards and Health Advisories. Office of Water, Washington, DC. EPA 822-R-02-038. Online. http://www.epa.gov/waterscience/drinking/standards/dwstandards.pdf

U.S. EPA. 2003. Integrated Risk Information System (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Online. http://www.epa.gov/iris

Valle-Jones, J.C., N.H. Brodie, H.O. O'Hara et al. 1983. A comparative study of phentermine and diethylpropion in the treatment of obese patients and general practice. Pharmatherapeutica. 3: 300-304.

Wee, C.C., R.S. Phillips, G. Aurigemma et al. 1998. Risk for valvular heart disease among users of fenfluramine and dexfenfluramine who underwent echocardiography before use of medication. Ann. Intern. Med. 129: 870-874.

Weintraub, M., J.D. Hasday, A.I. Mushlin and D.H. Lockwood. 1984. A double-blind clinical trial in weight control. Arch. Intern. Med. 144: 143-1148.

Weintraub, M., P.R. Sundaresan, M. Madan et al. 1992. Long-term weight control study. I (weeks 0 to 34): the enhancement of behavior modification, caloric restriction, and exercise by fenfluramine plus phentermine versus placebo. Clin. Pharmacol. Ther. 51: 586-594. (Cited in Glazer, 2001)

WHO (World Health Organization). 2002. Online Catalogs for the Environmental Criteria Series. Online. http://www.who.int/dsa/cat98/zehc.htm

SRC TR-03-046 / 12-21-04

Provisional Peer Reviewed Toxicity Values for

Dimethylphenethylamine (Phentermine)
(CASRN 122-09-8)

Derivation of Subchronic and Chronic Inhalation RfCs

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

Acronyms

bw - body weight
cc - cubic centimeters
CD - Caesarean Delivered
CERCLA - Comprehensive Environmental Response, Compensation, and Liability Act of 1980
CNS - central nervous system
cu.m - cubic meter
DWEL - Drinking Water Equivalent Level
FEL - frank-effect level
FIFRA - Federal Insecticide, Fungicide, and Rodenticide Act
g - grams
GI - gastrointestinal
HEC - human equivalent concentration
Hgb - hemoglobin
i.m. - intramuscular
i.p. - intraperitoneal
i.v. - intravenous
IRIS - Integrated Risk Information System
IUR - Inhalation Unit Risk
kg - kilogram
L - liter
LEL - lowest-effect level
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
m - meter
MCL - maximum contaminant level
MCLG - maximum contaminant level goal
MF - modifying factor
mg - milligram
mg/kg - milligrams per kilogram
mg/L - milligrams per liter
MRL - minimal risk level
MTD - maximum tolerated dose
MTL - median threshold limit

NAAQS - National Ambient Air Quality Standards
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-RfD - provisional Oral Reference Dose
p-RfC - provisional Inhalation Reference Concentration
p-OSF - provisional Oral Slope Factor
p-IUR - provisional Inhalation Unit Risk
PBPK - physiologically based pharmacokinetic
ppb - parts per billion
ppm - parts per million
PPRTV - Provisional Peer Reviewed Toxicity Value
RBC - red blood cell(s)
RCRA - Resource Conservation and Recovery Act
RGDR - Regional deposited dose ratio (for the indicated lung region)
REL - relative exposure level
RGDR - Regional gas dose ratio (for the indicated lung region)
RfD - Oral Reference Dose
RfC - Inhalation Reference Concentration
s.c. - subcutaneous
SCE - sister chromatid exchange
SDWA - Safe Drinking Water Act
sq.cm. - square centimeters
TSCA - Toxic Substances Control Act
UF - uncertainty factor
ug - microgram
umol - micromoles
VOC - volatile organic compound

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR DIMETHYLPHENETHYLAMINE (CASRN 122-09-8; Phentermine) Derivation of Subchronic and Chronic Inhalation RfCs

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) 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 (PPRTV) 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 Integrated Risk Information System (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 two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program 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 science and available information evolve, PPRTVs are initially derived with a three-year life-cycle. However, EPA Regions (or the EPA HQ Superfund Program) sometimes request that a frequently used PPRTV be reassessed. 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 manuscripts 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 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 manuscript 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

Dimethylphenethylamine (1,1-dimethyl-2-phenylethylamine), commonly known as phentermine, is used as an appetite suppressant (anorectic) drug that is orally administered. Neither a subchronic nor chronic RfC for phentermine is listed on IRIS (U.S. EPA, 2003) or in the HEAST (U.S. EPA, 1997). The CARA list (U.S. EPA, 1991, 1994) does not report any relevant documents for phentermine. ATSDR (2002), IARC (2002) and WHO (2002) have not published review documents for phentermine. Occupational exposure limits for phentermine have not been established by ACGIH (2002), NIOSH (2002), or OSHA (2002a,b). The initial literature searches of TOXLINE (1965-1995), MEDLINE (1980-1995), CANCERLINE (1986-1995), CCRIS, TSCATS, RTECS, GENETOX, DART/ETICBACK, and EMIC/EMICBACK were conducted and screened in September 1995 to identify relevant data on phentermine. Update literature searches from 1995 to 2003 were performed in January, 2003 using the same databases, except for replacement of CANCERLIT with CANCERLINE and the addition of

HSDB. The MEDLINE search strategy was unusually broad to facilitate identifying pertinent clinical studies. The NTP (2002) status report was also searched for relevant information. Additional literature searches from January 2003 through September 2004 were conducted by NCEA-Cincinnati using MEDLINE, TOXLINE, Chemical and Biological Abstracts databases.

REVIEW OF THE PERTINENT LITERATURE

Human Studies

No studies were located regarding inhalation exposure of humans to phentermine.

Animal Studies

No studies were located regarding inhalation exposure of animals to phentermine.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC RfCs FOR PHENTERMINE

In the absence of subchronic or chronic inhalation data on the toxicity of phentermine, derivation of a provisional subchronic or chronic RfC is precluded.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2002. 2002 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. Cincinnati, OH.

ATSDR (Agency for Toxic Substances and Disease Registry). 2002. Internet HazDat Toxicological Profile Query. U.S. Department of Health and Human Services, Public Health Service. Atlanta, GA. Online. http://www.atsdr.cdc.gov//qsql/toxprof.script

IARC (International Agency for Research on Cancer). 2002. IARC Agents and Summary Evaluations. Online. http://193.51.164.11/cgi/iHound/Chem/iH_Chem_Frames.html

NIOSH (National Institute for Occupational Safety and Health). 2002. Online NIOSH Pocket Guide to Chemical Hazards. Index of Chemical Abstract Numbers (CAS No.). Online. http://www.cdc.gov/niosh/npg/npgdcas.html

NTP (National Toxicology Program). 2002. Management Status Report. Online. http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/Res_Stat/iH_Res_Stat_Frames.html

OSHA (Occupational Safety and Health Administration). 2002a. OSHA Standard 1910.1000 Table Z-2. Part Z, Toxic and Hazardous Substances. Online. http://www.osha-slc.gov/OshStd_data/1910_1000_TABLE_Z-2.html

OSHA (Occupational Safety and Health Administration). 2002b. OSHA Standard 1915.1000 for Air Contaminants. Part Z, Toxic and Hazardous Substances. Online. http://www.osha-slc.gov/OshStd_data/1915_1000.html

U.S. EPA. 1991. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. April.

U.S. EPA. 1994. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. December.

U.S. EPA. 1997. Health Effects Assessment Summary Tables. FY-1997 Update. Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. July. EPA-540-R-97-036. NTIS PB97-921199.

U.S. EPA. 2003. Integrated Risk Information System (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Online. http://www.epa.gov/iris

WHO (World Health Organization). 2002. Online Catalogs for the Environmental Criteria Series. Online. http://www.who.int/dsa/cat98/zehc.htm

SRC TR-03-047 / 12-21-04

Provisional Peer Reviewed Toxicity Values for

Dimethylphenethylamine (Phentermine)
(CASRN 122-09-8)

Derivation of a Carcinogenicity Assessment

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

Acronyms

bw - body weight
cc - cubic centimeters
CD - Caesarean Delivered
CERCLA - Comprehensive Environmental Response, Compensation, and Liability Act of 1980
CNS - central nervous system
cu.m - cubic meter
DWEL - Drinking Water Equivalent Level
FEL - frank-effect level
FIFRA - Federal Insecticide, Fungicide, and Rodenticide Act
g - grams
GI - gastrointestinal
HEC - human equivalent concentration
Hgb - hemoglobin
i.m. - intramuscular
i.p. - intraperitoneal
i.v. - intravenous
IRIS - Integrated Risk Information System
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LEL - lowest-effect level
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
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MF - modifying factor
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MRL - minimal risk level
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NOAEL - no-observed-adverse-effect level
NOAEL(ADJ) - NOAEL adjusted to continuous exposure duration
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NOEL - no-observed-effect level
OSF - Oral Slope Factor
p-RfD - provisional Oral Reference Dose
p-RfC - provisional Inhalation Reference Concentration
p-OSF - provisional Oral Slope Factor
p-IUR - provisional Inhalation Unit Risk
PBPK - physiologically based pharmacokinetic
ppb - parts per billion
ppm - parts per million
PPRTV - Provisional Peer Reviewed Toxicity Value
RBC - red blood cell(s)
RCRA - Resource Conservation and Recovery Act
RGDR - Regional deposited dose ratio (for the indicated lung region)
REL - relative exposure level
RGDR - Regional gas dose ratio (for the indicated lung region)
RfD - Oral Reference Dose
RfC - Inhalation Reference Concentration
s.c. - subcutaneous
SCE - sister chromatid exchange
SDWA - Safe Drinking Water Act
sq.cm. - square centimeters
TSCA - Toxic Substances Control Act
UF - uncertainty factor
ug - microgram
umol - micromoles
VOC - volatile organic compound

PROVISIONAL PEER REVIEWED TOXICITY VALUE FOR DIMETHYLPHENETHYLAMINE (CASRN 122-09-8; Phentermine) Derivation of a Carcinogenicity Assessment

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) 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 (PPRTV) 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 Integrated Risk Information System (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 two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program 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 science and available information evolve, PPRTVs are initially derived with a three-year life-cycle. However, EPA Regions (or the EPA HQ Superfund Program) sometimes request that a frequently used PPRTV be reassessed. 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 manuscripts 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 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 manuscript 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

Dimethylphenethylamine (1,1-dimethyl-2-phenylethylamine), commonly known as phentermine, is used as an appetite suppressant (anorectic) drug that is orally administered. A carcinogenicity assessment for phentermine is not available on IRIS (U.S. EPA, 2003), in the HEAST (U.S. EPA, 1997), or in the Drinking Water Standards and Health Advisories List (U.S. EPA, 2002). The CARA list (U.S. EPA, 1991, 1994) does not report any relevant documents for phentermine. IARC (2002), ACGIH (2002), and NTP (2002) have not assessed the carcinogenicity of phentermine. ATSDR (2002) and WHO (2002) have not published review documents for phentermine. The initial literature searches of TOXLINE (1965-1995), MEDLINE (1980-1995), CANCERLINE (1986-1995), CCRIS, TSCATS, RTECS, GENETOX, DART/ETICBACK, and EMIC/EMICBACK were conducted and screened in September 1995 to identify relevant data on phentermine. Update literature searches from 1995 to 2003 were performed in January, 2003 using the same databases, except for replacement of CANCERLIT

with CANCERLINE and the addition of HSDB. The MEDLINE search strategy was unusually broad to facilitate identifying pertinent clinical studies. Additional literature searches from January 2003 through September 2004 were conducted by NCEA-Cincinnati using MEDLINE, TOXLINE, Chemical and Biological Abstracts databases.

REVIEW OF THE PERTINENT LITERATURE

Human Studies

No information was located regarding the carcinogenicity of phentermine in humans by any route of exposure.

Animal Studies

No information was located regarding the carcinogenicity of phentermine in animals by any route of exposure.

Supporting Studies

The genotoxicity of phentermine was evaluated in three *in vitro* assay systems that surveyed activity of various pharmaceutical drugs. These assays showed that phentermine induced reverse mutations in *Salmonella typhimurium* and *Streptomyces coelicolor* (Carere et al., 1975, reported as an abstract), and mitotic segregation (mainly non-disjunction) in diploid strains of *Aspergillus nidulans* (Bignami et al., 1974).

PROVISIONAL WEIGHT-OF-EVIDENCE CLASSIFICATION

As the available data are insufficient to assess carcinogenic potential in animals or humans, they are consistent with the hazard descriptor, "*inadequate information to assess carcinogenic potential*," as specified by the proposed U.S. EPA (1999) Guidelines for Cancer Risk Assessment.

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

Lack of human or animal cancer data precludes derivation of quantitative estimates of cancer risk for phentermine.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2002. 2002 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. Cincinnati, OH.

ATSDR (Agency for Toxic Substances and Disease Registry). 2002. Internet HazDat Toxicological Profile Query. U.S. Department of Health and Human Services, Public Health Service. Atlanta, GA. Online. http://www.atsdr.cdc.gov//qsql/toxprof.script

Bignami, M., G. Morpurgo, R. Pagliani et al. 1974. Non-disjunction and crossing-over induced by pharmaceutical drugs in *Aspergillus nidulans.* Mutat. Res. 26: 159-170.

Carere, A., G. Morpurgo, G. Cardamone et al. 1975. Point mutations induced by pharmaceutical drugs. Mutat. Res. 29: 235 (abstract).

IARC (International Agency for Research on Cancer). 2002. IARC Agents and Summary Evaluations. Online. http://193.51.164.11/cgi/iHound/Chem/iH_Chem_Frames.html

NTP (National Toxicology Program). 2002. Management Status Report. Online. http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/Res_Stat/iH_Res_Stat_Frames.html

U.S. EPA. 1991. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. April.

U.S. EPA. 1994. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. December.

U.S. EPA. 1997. Health Effects Assessment Summary Tables. FY-1997 Update. Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. July. EPA-540-R-97-036. NTIS PB97-921199.

U.S. EPA. 1999. Proposed Guidelines for Cancer Risk Assessment. July. Office of Research and Development, National Center for Environmental Assessment, Washington, DC.

U.S. EPA. 2002. 2002 Edition of the Drinking Water Standards and Health Advisories. Office of Water, Washington, DC. EPA 822-R-02-038. Online. http://www.epa.gov/waterscience/drinking/standards/dwstandards.pdf

U.S. EPA. 2003. Integrated Risk Information System (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Online. http://www.epa.gov/iris

WHO (World Health Organization). 2002. Online Catalogs for the Environmental Criteria Series. Online. http://www.who.int/dsa/cat98/zehc.htm