Provisional Peer Reviewed Toxicity Values for

Pentaerythritol tetranitrate (PETN)
(CASRN 78-11-5)

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## COMMONLY USED ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMC</td>
<td>benchmark concentration</td>
</tr>
<tr>
<td>BMD</td>
<td>benchmark dose</td>
</tr>
<tr>
<td>BMCL</td>
<td>benchmark concentration lower bound 95% confidence interval</td>
</tr>
<tr>
<td>BMDL</td>
<td>benchmark dose lower bound 95% confidence interval</td>
</tr>
<tr>
<td>HEC</td>
<td>human equivalent concentration</td>
</tr>
<tr>
<td>HED</td>
<td>human equivalent dose</td>
</tr>
<tr>
<td>IUR</td>
<td>inhalation unit risk</td>
</tr>
<tr>
<td>LOAEL</td>
<td>lowest-observed-adverse-effect level</td>
</tr>
<tr>
<td>LOAEL_ADJ</td>
<td>LOAEL adjusted to continuous exposure duration</td>
</tr>
<tr>
<td>LOAEL_HEC</td>
<td>LOAEL adjusted for dosimetric differences across species to a human</td>
</tr>
<tr>
<td>NOAEL</td>
<td>no-observed-adverse-effect level</td>
</tr>
<tr>
<td>NOAEL_ADJ</td>
<td>NOAEL adjusted to continuous exposure duration</td>
</tr>
<tr>
<td>NOAEL_HEC</td>
<td>NOAEL adjusted for dosimetric differences across species to a human</td>
</tr>
<tr>
<td>NOEL</td>
<td>no-observed-effect level</td>
</tr>
<tr>
<td>OSF</td>
<td>oral slope factor</td>
</tr>
<tr>
<td>p-IUR</td>
<td>provisional inhalation unit risk</td>
</tr>
<tr>
<td>p-OSF</td>
<td>provisional oral slope factor</td>
</tr>
<tr>
<td>p-RfC</td>
<td>provisional reference concentration (inhalation)</td>
</tr>
<tr>
<td>p-RfD</td>
<td>provisional reference dose (oral)</td>
</tr>
<tr>
<td>POD</td>
<td>point of departure</td>
</tr>
<tr>
<td>RfC</td>
<td>reference concentration (inhalation)</td>
</tr>
<tr>
<td>RfD</td>
<td>reference dose (oral)</td>
</tr>
<tr>
<td>UF</td>
<td>uncertainty factor</td>
</tr>
<tr>
<td>UF_A</td>
<td>animal-to-human uncertainty factor</td>
</tr>
<tr>
<td>UF_C</td>
<td>composite uncertainty factor</td>
</tr>
<tr>
<td>UF_D</td>
<td>incomplete-to-complete database uncertainty factor</td>
</tr>
<tr>
<td>UF_H</td>
<td>interhuman uncertainty factor</td>
</tr>
<tr>
<td>UF_L</td>
<td>LOAEL-to-NOAEL uncertainty factor</td>
</tr>
<tr>
<td>UF_S</td>
<td>subchronic-to-chronic uncertainty factor</td>
</tr>
<tr>
<td>WOE</td>
<td>weight of evidence</td>
</tr>
</tbody>
</table>
PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR PENTAERYTHRITOL TETRANITRATE (PETN, CASRN 78-11-5)

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

No RfD, RfC, or carcinogenicity assessments for pentaerythritol tetranitrate (PETN) were available on IRIS (U.S. EPA, 2008), in the Health Effects Assessment Summary Tables (HEAST; U.S. EPA, 1997), or in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006). The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994) did not include any relevant EPA documents. The Agency for Toxic Substances and Disease Registry (ATSDR, 2008) and the World Health Organization (WHO, 2008) had not assessed the health effects of PETN. The carcinogenicity of PETN had not been assessed by the International Agency for Research on Cancer (IARC, 2008), and PETN was not included in the National Toxicology Program’s 11th Report on Carcinogens (NTP, 2005). Occupational exposure limits for PETN had not been derived by the American Conference for Governmental Industrial Hygienists (ACGIH, 2007), the National Institute for Occupational Safety and Health (NIOSH, 2005), or the Occupational Safety and Health Administration (OSHA, 2008). CalEPA (2005, 2006, 2008a,b) had not derived noncancer or cancer risk values for PETN.

Literature searches for studies relevant to the derivation of provisional toxicity values for PETN were conducted in July 2007 in MEDLINE, TOXLINE special, and DART/ETIC (1960’s–July 2007); BIOSIS (2000–July 2007); TSCATS/TSCATS2, RTECS, CCRIS, HSDB, GENETOX (not date limited), and Current Contents (January–July 2007). Searches also were checked for updates in August 2008.

REVIEW OF PERTINENT DATA

PETN is a percussive explosive used in detonating fuses and as an admixture with TNT in small-caliber projectiles and grenades (Merck Index, 2001; NTP, 1989). PETN also has also been used therapeutically in the treatment of angina pectoris (Abrams, 1980; Murad, 1990). For this purpose, PETN was formulated with an inert ingredient, usually lactose, to decrease the potential explosion hazard (Murad, 1990; NTP, 1989). PETN is not on the Food and Drug
PETN is one of a number of organic nitrates (e.g., nitroglycerin) used therapeutically as a coronary vasodilator in the treatment of angina pectoris (Abrams, 1980; Murad, 1990). We located a limited amount of human health effects information specifically for PETN because its cardiovascular effects generally were grouped with the similar effects of the other nitrovasodilators. These organic nitrates, including PETN, are metabolized to their active intermediate in vasodilatory action, nitric oxide (Murad, 1990). Additional metabolic details have been summarized by Daiber et al. (2008).

The nitrovasodilators relax most smooth muscles, including those in arteries and veins, and selectively dilate large coronary vessels (Murad, 1990). Lower doses increase coronary blood flow without significantly affecting systemic arterial pressure. Higher doses, particularly if repeated at frequent intervals, decrease systolic and diastolic blood pressure and cardiac output, which can result in headache, weakness and dizziness, and the activation of compensatory sympathetic reflexes, such as tachycardia and peripheral arteriolar vasoconstriction. Smooth muscles in the bronchi, biliary tract, gastrointestinal tract, ureters, and uterus also can be relaxed by nitrovasodilators (Murad, 1990; Daiber et al., 2008). PETN seems to be unique among the long-acting nitrovasodilators in that patients do not appear to develop tolerance to treatment, resulting in continued induction of vasodilation in humans with ongoing PETN treatment (Fink and Bassenge, 1997; Jurt et al., 2001; Gori et al., 2003).

Adverse responses to the therapeutic use of PETN have been similar to those of other organic nitrates and generally secondary to actions on the cardiovascular system (Murad, 1990; Shrivastava et al., 1983). Headache has been common and can be severe, but it usually decreases over a few days if treatment is continued and often is controlled by temporarily decreasing the dose. Transient episodes of lightheadedness, dizziness, weakness, and other manifestations associated with postural hypotension have developed in patients, particularly when the patient was standing immobile. On occasion, these symptoms have progressed to loss of consciousness. All organic nitrates can cause skin rash, but it appears to occur most commonly with PETN (Murad, 1990).

The usual oral dosage of PETN was 10–40 mg as a tablet four times daily or 30–80 mg as a sustained release capsule every 12 hours (Murad, 1990; PDR, 1987); the total daily dose ranged from 40–160 mg/day or 0.6–2.3 mg/kg-day for a 70 kg adult. Doses above 160 mg/day (2.3 mg/kg-day) generally were not recommended due to the potential for severe hypotensive effects (Murad, 1990; PDR, 1987), although doses as high as 80 mg every 4–8 hours (3.4–6.9 mg/kg-day) were necessary to produce a therapeutic effect in some individuals (Alcocer et al., 1973; Abrams, 1980; Shrivastava et al., 1983).
Single oral doses of 100 mg PETN did not significantly change the resting heart rate, but it decreased resting systolic blood pressure 6 hours after ingestion by 6.1% ($p < 0.05$) in supine patients with stable angina and by 5.9% ($p < 0.05$) in standing patients. Kośmicki et al. (2005) observed no postural hypotension in any of the 15 treated patients. Diastolic blood pressure significantly decreased only in the standing position by 6.8% ($p < 0.05$) after 6 hours. During maximal exercise, no significant reduction of systolic blood pressure occurred, but there was a significant reduction in diastolic blood pressure 6 hours after ingestion. Kośmicki et al. (2005) reported no adverse effects after a single dose of 50 mg PETN. However adverse effects after ingestion of 100 mg PETN included headaches in 3 of 15 patients vs. 1/15 patients treated with a placebo.

**ANIMAL STUDIES**

**Oral Exposure**

The National Toxicology Program (NTP, 1989; Bucher et al., 1990) conducted subchronic and chronic studies in rats and mice using diets containing National Formulary Grade PETN, a 1:4 formulation of PETN and D-lactose monohydrate typically used in human therapeutics. Lactose also was present in the base diet (normal concentration approximately 1%) and the purity of the PETN was >99%. Due to low toxicity, the doses in most of these studies were based on the maximum dietary concentration of 5% (50,000 ppm) recommended by NTP conventions for 2-year studies. While NTP (1989; Bucher et al., 1990) conducted relatively comprehensive evaluations of the exposed animals, they did not report any tests related to cardiac function that might have revealed effects similar to those revealed in human subjects.

F344/N rats (10/gender/dose) were fed diets containing 0, 3100, 6200, 12,500, 25,000, or 50,000 ppm of the 1:4 PETN-lactose mixture, equivalent to 0, 620, 1240, 2500, 5000, or 10,000 ppm PETN, for 14 weeks (NTP, 1989; Bucher et al., 1990). Based on feed consumption data for Week 7, we estimated the average daily consumption of PETN as 39, 88, 190, 330, or 630 mg/kg-day, respectively, for males and 43, 86, 200, 370, or 830 mg/kg-day, respectively, for females. The endpoints investigated included clinical signs, body weight, feed consumption, whole-blood methemoglobin concentration, and urinary nitrate concentration. NTP (1989; Bucher et al., 1990) performed necropsies and measured weights for the brain, heart, right kidney, liver, lungs, and thymus of all sacrificed animals. NTP also conducted comprehensive histological examinations in the control and high-dose groups of both genders; evaluations at lower doses were limited to the Zymbal gland in females at 370 mg/kg-day. NTP (1989) reported no exposure-related effects in the male rats. Effects in treated female rats included

- 6−7% lower final body weights than controls and 17−18% lower body weight gains ($p$-values not reported) at $\geq$370 mg/kg-day
- 6−8% higher relative brain weights than controls ($p < 0.05$ or 0.01) at $\geq$200 mg/kg-day
- 6% higher relative kidney weights than controls ($p < 0.05$) at 830 mg/kg-day
- an adenoma of the Zymbal gland in one rat at 830 mg/kg-day.

Absolute organ weights were not reported. In male rats, this subchronic study identified a NOAEL of 630 mg/kg-day and no LOAEL, while in female rats, the NOAEL was 200 mg/kg-day and the LOAEL was 370 mg/kg-day, for reduced body weight gain.
NTP (1989; Bucher et al., 1990) fed F344/N rats (50/gender/dose) the 1:4 PETN-lactose mixture for 2 years in dietary concentrations of 0, 25,000, or 50,000 ppm (0, 5000, or 10,000 ppm PETN) for males and 0, 6200, or 12,500 ppm (0, 1240, or 2500 ppm PETN) for females. The lower dietary concentrations of the PETN-lactose mixture were selected for the female rats because higher concentrations caused 17–18% decreases in body weight gains in the 14-week study summarized above. The reported average daily consumption of PETN was approximately 240 or 490 mg/kg-day for males and 80 or 165 mg/kg-day for females. Clinical signs, body weights, and feed consumption were evaluated throughout the study. Necropsies were performed on each rat. Comprehensive histological examinations were performed on low-dose rats that died before Month 21 and on all control and high-dose rats. Histological examinations in the remaining low-dose rats were limited to the liver, kidneys, and gross lesions in both genders; the brain, pancreas, and testes in males; and the esophagus, lungs, thyroid, and uterus in females. NTP (1989) reported no exposure-related clinical signs, or effects on survival, or feed consumption. Mean body weights were 2–9% lower than controls throughout the study and 7% lower than controls at study termination in the 490 mg/kg-day males. However, the mean body weights for the low-dose males and all dosed females remained similar to controls throughout the study. No exposure-related nonneoplastic lesions were observed in either gender. This chronic study identified freestanding NOAELs of 490 mg/kg-day in male rats and 165 mg/kg-day in female rats.

Adenomas or carcinomas of the Zymbal gland occurred in all chronically treated groups of male and female rats, but the incidences were low and demonstrated neither statistical significance when compared with no incidence in controls, nor dose-related trends (see Table 1) (NTP, 1989; Bucher et al., 1990). The incidences of Zymbal gland neoplasms also exceeded the mean historical incidences for each gender, but they were within the upper ranges previously seen in the control groups (see Table 1). There were no increases in hyperplasia to suggest an increase of proliferative lesions of the Zymbal gland. Based on the occurrence of 9 total Zymbal gland neoplasms in dosed rats compared with none in controls and considering the occurrence of a Zymbal gland tumor in 1 high-dose female rat (1/10 compared to 0/10 in controls) in the 14-week study summarized above, NTP concluded that the results of the chronic study suggested a possible PETN-related effect.

Thyroid gland follicular cell adenomas or carcinomas (combined) occurred in 3/50 high-dose female rats. Although this incidence was not significantly higher than in controls (0/50), the incidence exceeded historical control incidences (see Table 1). Because there were no indications of increased follicular cell adenomas or carcinomas or increased follicular cell hyperplasia in males, NTP (1989; Bucher et al., 1990) considered the marginal increase in follicular cell tumors in females to be not PETN-related. Other findings included mononuclear leukemia in male rats that occurred with a negative trend due to an incidence in the high-dose group that was significantly lower than in controls.

NTP (1989; Bucher et al., 1990) fed B6C3F1 mice (10/gender/dose) diets containing 0, 3100, 6200, 12,500, 25,000, or 50,000 ppm of the 1:4 PETN-lactose mixture (0, 620, 1240, 2500, 5000, or 10,000 ppm PETN) for 13 weeks. Based on feed consumption data for Week 7, the estimated average daily consumption of PETN was 110, 303, 363, 925, or 2140 mg/kg-day, respectively, for males and 172, 306, 633, 1335, or 3120 mg/kg-day, respectively, for females. The endpoints evaluated included clinical signs, body weights, feed consumption, and whole-blood methemoglobin concentrations. Necropsies and measurements of brain, heart, right
kidney, liver, lungs, and thymus weights were performed on all animals. Comprehensive histological examinations were conducted in the control and high-dose groups of both genders; histological evaluations at lower doses were limited to the liver in females at 1335 mg/kg-day. There were no exposure-related clinical signs or effects on survival, body weight, or methemoglobin concentration, although dosed male mice consumed less feed than controls. Small, but statistically significant, increases in relative kidney weights (8% higher than controls) and relative liver weights (7% higher than controls) occurred in female mice at 3120 mg/kg-day, but there were no effects on organ weights in males or exposure-related nonneoplastic or neoplastic lesions in either gender. Because the increased kidney and liver weights were considered not to be adverse, this subchronic study identified freestanding NOAELs of 2140 mg/kg-day in male mice and 3120 mg/kg-day in female mice.

### Table 1. Incidences of Zymbal Gland and Thyroid Gland Tumors in Rats Exposed to PETN in the Diet for Two Years

<table>
<thead>
<tr>
<th>Male</th>
<th>0 mg/kg-day</th>
<th>240 mg/kg-day</th>
<th>490 mg/kg-day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zymbal Gland</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoma or Carcinoma</td>
<td>0/49 (0%)</td>
<td>3/45 (7%)</td>
<td>2/41 (4%)</td>
</tr>
<tr>
<td>Logistic Regression Tests</td>
<td><em>p</em> = 0.135</td>
<td><em>p</em> = 0.108</td>
<td><em>p</em> = 0.219</td>
</tr>
<tr>
<td>Cochran-Armitage Test</td>
<td><em>p</em> = 0.157</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Fisher Exact Test</td>
<td>NA</td>
<td><em>p</em> = 0.106</td>
<td><em>p</em> = 0.205</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Female</th>
<th>0 mg/kg-day</th>
<th>80 mg/kg-day</th>
<th>165 mg/kg-day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zymbal Gland</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoma or Carcinoma</td>
<td>0/36 (0%)</td>
<td>1/37 (3%)</td>
<td>3/35 (9%)</td>
</tr>
<tr>
<td>Logistic Regression Tests</td>
<td><em>p</em> = 0.055</td>
<td><em>p</em> = 0.492</td>
<td><em>p</em> = 0.116</td>
</tr>
<tr>
<td>Cochran-Armitage Test</td>
<td><em>p</em> = 0.055</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Fisher Exact Test</td>
<td>NA</td>
<td><em>p</em> = 0.507</td>
<td><em>p</em> = 0.115</td>
</tr>
</tbody>
</table>

| **Thyroid Gland**     |             |              |               |
| Follicular Cell Adenoma or Carcinoma | 0/50 (0%) | 0/48 (0%) | 3/50 (6%) |
| Logistic Regression Tests | *p* = 0.033 | NA        | *p* = 0.110 |
| Cochran-Armitage Test | *p* = 0.038 | NA        | NA            |
| Fisher Exact Test     | NA          | NA           | *p* = 0.121   |

*a*NTP, 1989; Bucher et al., 1990.

*b*Historical incidence at the study laboratory (mean ± SD): 4/599 (0.7% ± 1.0%); historical incidence in NTP studies: 19/1936 (1.0% ± 1.7%, range 0%–8%).

*c*Beneath the control incidence are *p*-values for the trend test. Beneath the dosed group incidence are the *p*-values for pairwise comparisons between that dose group and the controls. The logistic regression test regards tumors in animals dying prior to terminal kill as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates.

*d*Historical incidence at the study laboratory (mean ± SD): 1/649 (0.2% ± 0.6%); historical incidence in NTP studies: 11/1983 (0.6% ± 1.3%, range 0%–6%).

*e*Historical incidence at the study laboratory (mean ± SD): 5/627 (0.8% ± 1.3%); historical incidence in NTP studies: 19/1938 (1.0% ± 1.2%, range 0%–4%).
NTP (1989; Bucher et al., 1990) fed B6C3F1 mice (50/gender/dose) diets containing 0, 25,000, or 50,000 ppm of the 1:4 PETN-lactose mixture (0, 5000, or 10,000 ppm PETN) for 2 years. The reported average daily consumption of PETN was approximately 0, 810, or 1620 mg/kg-day, respectively, for males and 0, 1020, or 1936 mg/kg-day, respectively, for females. Clinical signs, body weights, and feed consumption were evaluated throughout the study. Necropsy was performed on each mouse. Comprehensive histological examinations were performed on low-dose mice that died before Month 21 and on all control and high-dose mice. Histological examinations in the remaining low-dose mice were limited to the stomach and gross lesions in both genders, and the liver and spleen in females. NTP (1989; Bucher et al., 1990) reported there were no exposure-related clinical signs, decreases in survival, effects on body weight or food consumption, or increases in nonneoplastic or neoplastic lesions. Combined tumors of the subcutaneous tissues (primarily fibromas and fibrosarcomas) occurred with a negative dose-related trend in male mice; incidences in both dosed groups were significantly lower than in controls. Tumors in the male mice control group occurred at a rate nearly five times higher than in historical controls, but NTP proposed no rationale for this discrepancy. This chronic study identified freestanding NOAELs of 1620 mg/kg-day in male mice and 1936 mg/kg-day in female mice.

Additional information on the chronic toxicity of PETN is available from a limited study in which groups of 45 albino rats of mixed genders were fed PETN in dietary doses of 0 or 2 mg/kg-day for one year (von Oettingen et al., 1944). Body weight was measured weekly; hematology (erythrocyte count, hemoglobin concentration, total and differential leukocyte counts) was evaluated monthly. Gross pathology, organ weights and volumes (liver, kidneys, spleen, heart with lungs, brain and testes), and histology (liver, kidneys, spleen, heart, lungs, brain and femur) were evaluated at the end of the study. Particular attention was paid to histological changes in the vascular walls of these tissues. An additional parameter reported was organ density calculated as the ratio of organ weight to volume. von Oettingen et al. (1944) noted a tendency for slightly higher erythrocyte and hemoglobin values in the dosed rats, but the values remained within the normal ranges. There were no clear PETN-related body weight changes, histopathology, or effects on any other endpoints. Mortality in both control and dosed groups (46.6 and 20%, respectively) was attributed to an infestation of parasitic tapeworm larvae in the livers of a large number of rats. This study identified a freestanding chronic NOAEL of 2 mg/kg-day in rats, although the results were compromised by the parasitic infestation and the resulting large numbers of premature deaths.

Effects of subchronic exposure to PETN on the cardiovascular system have been studied using animal models, including cholesterol-fed rabbits for atherosclerosis, and spontaneously hypertensive rats for hypertension. In the study in cholesterol-fed rabbits, dietary exposure to 6 mg/kg-day PETN for 15 weeks protected against the development of aortic atherosclerosis and endothelial dysfunction without affecting the vaso-relaxing potency of PETN in aortic rings (Kojda et al., 1995). The results of a subsequent study in cholesterol-fed rabbits indicated that dietary exposure to 6 mg/kg-day PETN for 16 weeks reduced the progression of aortic lesion formation, endothelial dysfunction, and low density lipoprotein (LDL) oxidation in established atherosclerosis (Hacker et al., 2001).

A study in spontaneously hypertensive rats (a genetic model of hypertension) found that exposure to 200 mg/kg-day PETN (100 mg/kg twice daily) by gavage for 6 weeks increased blood platelet cyclic guanosine 3c,5c-monophosphate (cGMP) content and decreased aortic
nitrates.

**Inhalation Exposure**

No information was located regarding effects of subchronic or chronic inhalation exposure to PETN.

**OTHER STUDIES**

“Military grade” PETN solutions in dimethylsulfoxide did not induce reverse mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, or TA1538 when tested without metabolic activation in a spot test or with metabolic activation in a plate incorporation assay (Whong et al., 1980). Similarly, the pharmaceutical-grade 1:4 PETN-lactose mixture used in the NTP toxicity and carcinogenicity studies was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested with or without metabolic activation in a preincubation assay (Mortelmans et al., 1986; NTP, 1989). The 1:4 PETN-lactose mixture caused a small increase in sister chromatid exchanges in cultured Chinese hamster ovary (CHO) cells in the presence or absence of metabolic activation, but the response was not clearly dose-related and cell cycle delay was not induced (NTP, 1989). The 1:4 PETN-lactose mixture did not induce chromosomal aberrations in CHO cells when tested with or without metabolic activation (NTP, 1989).

**DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RFD VALUES FOR PENTAERYTHRITOL TETRANITRATE**

**SUBCHRONIC p-RfD**

Information on the health effects of PETN in humans is available via clinical experience from its use as a venous dilator for the long-term treatment of angina pectoris. The recommended daily dose ranged from 40-160 mg/day (0.6–2.3 mg/kg-day for a 70 kg adult), usually administered as a 10–40 mg tablet 4 times a day (Murad, 1990; PDR, 1987). Adverse responses to the therapeutic use of PETN were similar to those of other nitrovasodilators and generally were secondary to effects on the cardiovascular system (Murad, 1990; Shrivastava et al., 1983). Doses in the recommended range have caused transient effects such as headache, lightheadedness, dizziness, weakness, and other manifestations associated with postural hypotension. Doses above 160 mg/day (~2.3 mg/kg-day) generally were not recommended due to the potential for more severe hypotensive effects, such as shortness of breath and unconsciousness. We located no additional information regarding the adverse effects of PETN in humans unrelated to its actions on the cardiovascular system.
Subchronic oral toxicity in rats exposed to PETN in the diet for 13–14 weeks (NTP, 1989; Bucher et al., 1990) resulted in small decreases in body weight gain (17% less than controls) and final body weight (6% less than controls), as well as small increases in relative brain and kidney weights (6–8% higher than controls) in females; no clear histopathological or other changes presented in either gender. A NOAEL of 200 mg/kg-day and LOAEL of 370 mg/kg-day were identified in rats based on the female body weight data. Effects in mice fed PETN in the diet for 13–14 weeks (NTP, 1989; Bucher et al., 1990) consisted of small increases in relative kidney and liver weights (7–8% higher than controls) in females. A NOAEL of 3120 mg/kg-day with no LOAEL was identified in mice. The small, but statistically significant, organ weight changes in mice were not considered to be toxicologically relevant and they were unaccompanied by any histopathological or other changes.

Because the hypotensive effects of PETN exposure could result in adverse consequences among people with normal and low blood pressure, we concluded that the minimum recommended human therapeutic dose of 0.6 mg/kg-day (Murad, 1990; PDR, 1987) provided the most conservative POD for deriving a subchronic RfD for PETN. Much higher doses in the subchronic animal studies were essentially nontoxic, as shown by the NOAELs of approximately 200 mg/kg-day in rats and 3120 mg/kg-day in mice, and the LOAEL of 370 mg/kg-day in rats at which only decreased weight gain was observed (NTP, 1989; Bucher et al., 1990). This suggested either that humans might be more sensitive to the effects of PETN than experimental rats and rabbits or that many adverse effects noted in humans (e.g., headache, lightheadedness, and other manifestations associated with postural hypotension) were difficult to observe in experimental animals.

The 0.6 mg/kg-day minimum recommended therapeutic dose of PETN in humans is considered a LOAEL because treated hypertensive patients have reported clinical symptoms, such as headache, dizziness, weakness, and other manifestations associated with postural hypertension at this dose (Murad, 1990; PDR, 1987). Vasodilation in normal, healthy adults is likely to lead to postural hypotension, as well, and potentially could cause more serious effects in humans who already are hypotensive. The human LOAEL of 0.6 mg/kg-day was divided by a composite uncertainty factor (UF) of 300, explained in the next paragraph, to derive a subchronic p-RfD as follows:

\[
\text{Subchronic p-RfD} = \frac{\text{NOAEL}}{\text{UF}} = \frac{0.6 \text{ mg/kg-day}}{300} = 0.002 \text{ or } 2 \times 10^{-3} \text{ mg/kg-day}
\]

The composite UF of 300 includes factors of 10 each for using a LOAEL point of departure (POD) and for human variability, and a factor of 3 for database deficiencies. A human variability UF of 3 was applied to account for variations in sensitivity within human populations. Although there is limited information on the degree to which humans of different genders, ages, health statuses, or genetic makeups might vary in the disposition of, or response to PETN, the lowest therapeutic dose already represents an extremely conservative POD in a population that could be considered sensitive (cardiac patients). The UF of 10 for extrapolation from a LOAEL to a NOAEL was not reduced, despite the mild nature of anticipated adverse effects because of the unknown slope of the dose-response curve. An UF of 10 for database deficiencies was applied due to the lack of information on reproductive and developmental toxicity.
Confidence in the human LOAEL is high because it is the minimum recommended therapeutic dose at which clinical experience has demonstrated adverse effects in treated patients (Murad, 1990; PDR, 1987). In addition, effects have been observed in experimental rats only at much higher doses (von Oettingen et al., 1944; NTP, 1989; Bucher et al., 1990; Kristek et al., 2003, 2007), and the rabbit studies (Kojda et al., 1995; Hacker et al., 2001) suggested potentially beneficial effects such as reduced serum cholesterol. Confidence in the database is medium. The database included 13–14 week studies in rats and mice that assessed systemic toxicity at doses much higher than the recommended human dose, but it lacked reproductive and developmental toxicity studies. Considering the levels of confidence in the human LOAEL and database, confidence in the subchronic p-RfD is medium.

**CHRONIC p-RfD**

PETN has been used as a coronary vasodilator for the long-term treatment of angina pectoris in humans (Abrams, 1980; Murad, 1990). As discussed for the subchronic RfD, the usual daily dose ranged from 0.6–2.3 mg/kg-day (Murad, 1990; PDR, 1987) and doses above 2.3 mg/kg-day generally were not recommended due to the potential for severe hypotensive effects (Murad, 1990; PDR, 1987). Although humans tend to develop tolerance to treatment with most organic nitrovasodilators, PETN seems to be unique in that patients experience continued induction of vasodilation with ongoing PETN treatment (Fink and Bassenge, 1997; Jurt et al., 2001; Gori et al., 2003).

Chronic oral toxicity was evaluated in rats exposed to PETN in the diet for one year (von Oettingen et al., 1944) and in rats and mice exposed to PETN in the diet for 2 years (NTP, 1989; Bucher et al., 1990). Body weight and limited hematology, organ weight, gross pathology, and histopathology evaluations were performed in the one-year rat study (von Oettingen et al., 1944). There were no clear exposure-related effects in the one-year study and a freestanding chronic NOAEL of 2 mg/kg-day was identified. The only nonneoplastic effect identified in the NTP (1989; Bucher et al., 1990) studies was a small decrease in final body weight (7% less than controls) in high-dose male rats; no adverse effects were observed in mice at any dose. Because the reduced final weight in rats was minimal, these studies identified chronic NOAELs of 490 mg/kg-day in rats and 3120 mg/kg-day in mice, with no LOAELs.

The minimum recommended human therapeutic dose of 0.6 mg/kg-day (Murad, 1990; PDR, 1987) was a LOAEL, and it provided the best basis for a chronic p-RfD for PETN, as it did for the subchronic derivation. Although the recommended human dose was based on hypotensive effects, the animal studies indicated that this dose is unlikely to cause chronic systemic toxicity unrelated to the effects of PETN on the cardiovascular system. In particular, similar and much higher doses in the chronic animal studies were nontoxic, as shown by the freestanding chronic NOAELs of 2 mg/kg-day (von Oettingen et al., 1944) and 490 mg/kg-day NTP (1989; Bucher et al., 1990) in rats, and 3120 mg/kg-day in mice (NTP, 1989; Bucher et al., 1990).
As was done for the subchronic p-RfD, the human LOAEL of 0.6 mg/kg-day PETN was divided by a composite UF of 300, which is explained in the next paragraph, to derive a chronic p-RfD as follows:

\[
\text{Chronic p-RfD} = \text{NOAEL ÷ UF} \\
= 0.6 \text{mg/kg-day ÷ 300} \\
= 0.002 \text{ or } 2 \times 10^{-3} \text{mg/kg-day}
\]

The composite UF of 300 included factors of 10 for extrapolating from a LOAEL to a NOAEL, a 3 for human variability, and a factor of 10 for database deficiencies. The UF for using a LOAEL for the POD was not reduced, despite the mild nature of anticipated adverse effects because of the unknown slope of the dose-response curve. The human variability UF of 3 was used to account for variation in sensitivity within human populations. Although there is limited information on the degree to which humans of different genders, ages, health statuses, or genetic makeups might vary in the disposition of, or response to PETN, the lowest therapeutic dose already represents an extremely conservative POD in a population that could be considered sensitive (cardiac patients). An UF of 10 for database deficiencies was applied due to the lack of reproduction and developmental toxicity studies. An UF for extrapolation from a less than chronic study was not needed because the adverse effects noted in human patients were considered to be reversible and appeared unlikely to increase with duration of exposure.

Confidence in the human LOAEL is high because it was the minimum recommended therapeutic dose based on clinical experience. In addition, effects have been observed in experimental animals only at much higher doses (von Oettingen et al., 1944; NTP, 1989; Bucher et al., 1990; Kristek et al., 2003, 2007), and the rabbit studies (Kojda et al., 1995; Hacker et al., 2001) suggested potentially beneficial effects (reduced serum cholesterol). Confidence in the database is medium. The database included 2-year studies in rats and mice that assessed systemic toxicity at doses much higher than the recommended human dose, but they lacked reproductive and developmental toxicity studies. Considering the levels of confidence in the human LOAEL and database, confidence in the chronic p-RfD is medium.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RFC VALUES FOR PENTAERYTHRITOL TETRANITRATE

No information was available on the subchronic or chronic inhalation toxicity of PETN, and no toxicokinetic data was available to inform extrapolation from the oral data, precluding derivation of p-RfC values for PETN.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR PENTAERYTHRITOL TETRANITRATE

WEIGHT-OF-EVIDENCE DESCRIPTOR

The carcinogenicity of PETN was evaluated by NTP (1989; Bucher et al., 1990) in 2-year dietary studies in F344/N rats and B6C3F1 mice. There were no exposure-related increases in neoplasms in male or female mice. Neoplastic findings in the rats included thyroid gland
follicular cell adenomas or carcinomas in a small number of high-dose females; incidences of combined tumors in the control, low-, and high-dose groups were 0/50, 0/48, and 3/50. The high-dose incidence was not statistically significantly higher than that in controls, but the incidence exceeded historical control incidences (see Table 1). Because there were no indications of increased thyroid follicular cell adenomas, carcinomas, or hyperplasia in chronically exposed males, the small increase in follicular cell tumors in females was not considered PETN-related by NTP.

The rats in the NTP (1989; Bucher et al., 1990) chronic study also had low incidences of Zymbal gland carcinomas or adenomas in all treated groups of both genders; incidences in the control, low-, and high-dose groups were 0/49, 3/45, and 2/41 in males and 0/36, 1/37, and 3/35 in females, respectively. The incidences did not reach statistical significance when compared with control group incidences, nor did they show statistically significant dose-related trends. However, they did exceed mean historical incidences for each gender (see Table 1). Considering the occurrence of Zymbal gland tumors in nine dosed rats compared with none in the controls, and a Zymbal gland tumor in one high-dose female rat in the NTP 14-week study, NTP concluded that the Zymbal gland tumors were possibly related to PETN exposure. Based on a marginal increase in neoplasms of the Zymbal gland, NTP (1989; Bucher et al., 1990) concluded that this study provided equivocal evidence of carcinogenic activity of PETN for male and female F344/N rats.

A limited amount of information was available on the genotoxicity and mutagenicity of PETN. In vitro studies found that PETN did not induce reverse mutations in various strains of Salmonella typhimurium (Mortelmans et al., 1986; NTP, 1989; Whong et al., 1980) or chromosomal aberrations in CHO cells (NTP, 1989). However, PETN exposure caused a small increase in sister chromatid exchanges in CHO cells in vitro, but the response was not clearly dose-related (NTP, 1989); the results suggested that PETN might have been weakly genotoxic in this assay.

As discussed above, the carcinogenicity of PETN was evaluated in chronic oral studies in rats and mice (NTP, 1989; Bucher et al., 1990). There was no evidence of carcinogenicity in mice. There was a marginal increase in Zymbal gland tumors in rats that suggests a possible PETN-related effect, but it did not provide unequivocal evidence of carcinogenicity. Genotoxicity studies of PETN were negative for mutagenicity (mutations in S. typhimurium and sister chromatid exchanges in CHO cells) or suggestive of other genotoxic activity (chromosomal aberrations in CHO cells). In accordance with the EPA (2005) Guidelines for Carcinogen Risk Assessment, there was “Suggestive Evidence of Carcinogenic Potential” for PETN, but the data were weak.

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK
Derivation of quantitative estimates of cancer risk for PETN was not supported by the existing data. However, the Appendix of this PPRTV document contains a Screening Value that might be useful in certain instances. Please see the attached Appendix A for details.
REFERENCES


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Bucher, J.R., J. Huff, J.K. Haseman et al. (1990) No evidence of toxicity or carcinogenicity of pentaerythritol tetranitrate given in the diet to F344 rats and B6C3F1 mice for up to two years. J. Appl. Toxicol. 10:353–357.


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


APPENDIX A. DERIVATION OF A SCREENING ORAL SLOPE FACTOR FOR PENTAERYTHRITOL TETRANITRATE (PETN)

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for PETN. However, information is available for this chemical which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, 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 PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix 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.

Data presented in Table 1 suggests female mice exhibited a slight dose-response relationship between dietary exposure to PETN and Zymbal Gland tumors and, possibly, also for thyroid follicular cell tumors (NTP, 1989; Bucher et al., 1990). Zymbal Gland tumors also were observed in treated male rats but without apparent dose-dependency. Although none of these relationships exhibited statistically significant trends, we attempted benchmark dose (BMD) modeling of these data to illustrate the relationships and to attempt to derive a Screening oral slope factor (OSF). This effort was justified, in part, because the rarity of Zymbal Gland tumors suggested potential biological relevance of their presence in every group of treated rats.

To determine the POD for derivation of the Screening OSF, BMD modeling was conducted using the BMD Modeling Software (BMDS Version 1.4.1a; U.S. EPA, 2000) on data sets for the incidence of Zymbal gland tumors and thyroid tumors in female rats. Applying the BMD multi-stage cancer model to the Zymbal gland tumor data generated the curves in Figures A-1 and A-2; applying this model to the thyroid tumor data generated the curves in Figures A-3 and A-4. Models for both data sets resulted in acceptable fit statistics (see Table A-1). The lowest BMDL\textsubscript{10} of 108 mg/kg-day from the Zymbal gland tumor data in female rats was chosen as the POD for deriving a Screening OSF for PETN.

We calculated the human equivalent dose (HED) of 26 mg/kg-day from the BMDL\textsubscript{10} of 108 mg/kg-day as follows:

\[
\text{BMDL}_{10\text{HED}} = \text{BMDL}_{10} \times \left( \frac{W_{\text{animal}}}{W_{\text{human}}} \right)^{1/4} \\
= 107.854 \text{ mg/kg-day} \times \left( \frac{0.229 \text{ kg}}{70 \text{ kg}} \right)^{1/4} \\
= 108 \text{ mg/kg-day} \times 0.24 \\
= 26 \text{ mg/kg-day}
\]

where

\[
W_{\text{human}} = 70 \text{ kg (human reference body weight)} \\
W_{\text{animal}} = 0.229 \text{ kg (average body weight for female F344 rats; NTP, 1989)}
\]
In the absence of a known mode of action (MOA) for carcinogenicity of oral PETN exposure, we assumed a linear approach to calculate the Screening OSF (U.S. EPA, 2005). To extrapolate cancer risks linearly from the BMDL_{10_{HED}} to the origin, we calculated a Screening OSF as the ratio \(0.1/\text{BMDL}_{10_{HED}}\). Taking the BMDL_{10_{HED}} of 26 mg/kg-day for the maximum incidence of adenoma or carcinoma in female mice as the POD that would be most protective of human health, we calculated a Screening OSF as follows:

\[
\text{Screening OSF} = \frac{0.1}{\text{BMDL}_{10_{HED}}} \\
= \frac{0.1}{26 \text{ mg/kg-day}} \\
= 0.0039 \text{ or } 4 \times 10^{-3} (\text{mg/kg-day})^{-1}
\]

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\(^{a}\)NTP, 1989; Bucher et al., 1990.
Figure A-1. BMD Analyses for Zymbal Gland Tumors in Female Rats Fed PETN for 2 Years (NTP, 1989; Bucher et al., 1990)—1 Degree Poly
Figure A-2. BMD Analyses for Zymbal Gland Tumors in Female Rats Fed PETN for 2 Years (NTP, 1989; Bucher et al., 1990)—2 Degrees Poly
Figure A-3. BMD Analyses for Thyroid Tumors in Female Rats Fed PETN for 2 Years (NTP, 1989; Bucher et al., 1990)—1 Degree Poly
Figure A-4. BMD Analyses for Thyroid Tumors in Female Rats Fed PETN for 2 Years (NTP, 1989; Bucher et al., 1990)—2 Degrees Poly