

Provisional Peer Reviewed Toxicity Values for

2-Nitrophenol
(CASRN 88-75-5)

Superfund Health Risk Technical Support Center
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Acronyms and Abbreviations

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
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
i.v.	intravenous
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-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration

p-RfD	provisional oral reference dose
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
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR 2-NITROPHENOL (CASRN 88-75-5)

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 new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a five-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 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

Neither a reference dose (RfD), reference concentration (RfC), nor carcinogenicity assessment is available for 2-nitrophenol in the Integrated Risk Information System (IRIS) database (U.S. EPA, 2007), the Health Effects Assessment Summary Table (HEAST) (U.S. EPA, 1997), or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006). The Chemical Assessments and Related Activities (CARA) database (U.S. EPA, 1991, 1994a) lists a Health Effects Assessment (HEA) (U.S. EPA, 1987) and a Health and Environmental Effects Profile (HEEP) (U.S. EPA, 1985) for Nitrophenols in which limited toxicity data for 2-nitrophenol are available. An Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile for Nitrophenols (2-Nitrophenol and 4-Nitrophenol) (ATSDR, 1992) also includes only limited toxicity data for 2-nitrophenol. Neither the American Conference of Governmental Industrial Hygienists (ACGIH, 2006), the National Institute of Occupational Safety and Health (NIOSH, 2006) nor the Occupational Safety and Health Administration (OSHA, 2006) has adopted occupational exposure limits for 2-nitrophenol. Health assessments for 2-nitrophenol are not available from CalEPA (2006) or the International Agency for Research on Cancer (IARC, 2006). Pertinent data was found for 2-nitrophenol after examining the Concise International Chemical Assessment Document (CICAD) for mononitrophenols (WHO, 2000). Relevant information for 2-nitrophenol from the National Toxicology Program (NTP, 2006) is limited to genotoxicity assays.

Literature searches covering the time period 1960's to August, 2006 were conducted in PUBMED, TOXLINE, and DART/ETIC to identify information relevant to 2-nitrophenol. TOXCENTER was searched for the time period August, 2001 to August 2006. Databases

searched without date limitations included TSCATS/TSCATS2, CCRIS, GENETOX, HSDB and RTECS. Search of Current Contents encompassed May to August, 2006.

REVIEW OF PERTINENT DATA

Human Studies

No data were located regarding the toxicity or carcinogenicity of 2-nitrophenol in humans following oral or inhalation exposure.

Animal Studies

Oral Exposure. Available repeated-dose oral studies consist of two limited 28-day gavage studies (Andrae et al., 1981; Koerdel et al., 1981; both in German) performed to evaluate OECD guideline 407 and a range-finding developmental toxicity study (IRDC, 1990).

Andrae et al. (1981) administered 2-nitrophenol to groups of Sprague-Dawley rats (10/sex/dose) at gavage doses of 0, 70, 210 or 630 mg/kg-day for 28 days. Because the original German report of this study was not available, information from the CICAD for mononitrophenols (WHO, 2000) was used to summarize the findings. Mid- and high-dose animals exhibited what was described by the WHO (2000) as locomotor inhibition for approximately 2 hours postdosing. Mortality rates were 1/10 in mid-dose males and 4/10 and 6/10 in high-dose males and females, respectively. Gross and histopathological examinations revealed pale liver in 7/20 low-dose rats (not reported by sex), hydropic liver cell swelling in 4/10 and 0/10 high-dose males and females, respectively, and vascular congestion of the liver in all high-dose male and female rats that died prior to terminal sacrifice. Fatty degeneration of the liver was noted in 6/20 control animals, 14/20 low-dose and 13/20 mid-dose rats, but not in high-dose rats. Other treatment-related effects, noted only at the highest dose level, included significantly increased alanine aminotransferase activity in males (data not reported), increased nephrosis in 2 and 5 males and females, respectively, testicular atrophy (1 male) and decreased spermatogenesis (2 males), and follicular atresia (4 females). This report did not contain information on hematological effects. WHO (2000) concluded that a NOAEL could not be determined for this study due to “unclear effects in the liver.”

Koerdel et al. (1981) administered 2-nitrophenol to groups of rats (5/sex/dose) at gavage doses of 0, 22, 67 or 200 mg/kg-day for 28 days. The summary from WHO (2000) was used as the source of study details because the original study was not available. Reported treatment-related effects included decreased food intake in high-dose males and mid- and high-dose females, non-significantly depressed final body weight in all dosed animals, decreased absolute liver and kidney weights in mid-dose groups, increased relative testes weight in low- and mid-dose males (decreased in high-dose males) and increased absolute and relative adrenal weight in all dosed groups. Hematology, clinical chemistry and histopathological examinations gave no indication of treatment-related effects. The study did not show a clear dose-response relationship for any of the endpoints examined.

In a range-finding developmental toxicity study, groups of Charles River COBS CD rats (5 dams/group) were administered 2-nitrophenol (in corn oil) at gavage doses of 0, 50, 125, 250, 500, or 1000 mg/kg-day on days 6-15 of gestation (IRDC, 1990). Body weights were determined during the treatment period and clinical signs were noted. Uterine examinations were performed on gestation day 20. A single high-dose dam died, but cause of death was not determined. Excessive salivation was observed in two high-dose dams. Mean maternal body weight gains in the 0, 50, 125, 250, 500 and 1000 mg/kg-day dose groups were 8, 7, 5, 6, 1 and -8 grams, respectively, for the initial 4 days of treatment (gestation days 6-9) and 52, 56, 54, 55, 45 and 39 grams, respectively, for the entire treatment period (gestation days 6-15). The appearance and behavior of the 50 mg/kg-day group of dams were comparable to the control group. Dose-related increases in the incidence of yellow staining around the nose, mouth and anogenital area were observed at doses ≥ 125 mg/kg-day. Dose-related increases in the incidence of darkly colored urine (probably due to the presence of the test chemical) occurred at doses ≥ 250 mg/kg-day. An increase in the number of early resorptions was observed in the highest dose group (2.3 versus 1.2 in controls), resulting in mean postimplantation loss of 13.8% compared to 8.2% in controls (statistical significance not reported). Among dams surviving until necropsy, no biologically significant treatment-related effects were seen. There were no biologically significant treatment-related effects on mean number of viable fetuses, implantations or *corpora lutea*. No data on hematological parameters were included in this study. This study assessed a limited number of potential adverse endpoints and is therefore of limited usefulness for risk assessment.

Inhalation Exposure. Available information for repeated inhalation exposure is restricted to results of a single 28-day study (Hazleton Laboratories, 1984). Groups of 7-week-old Sprague-Dawley rats (15/sex/group) were exposed to 2-nitrophenol vapors at target concentrations of 0, 5, 30 or 60 mg/m³ for 6 hours/day, 5 days/week for 4 weeks. All rats were subjected to ophthalmoscopic examinations prior to initiation of exposures and immediately preceding terminal sacrifice. Each animal was observed twice daily (pre- and postexposure during the week; morning and afternoon on weekends) for mortality and morbidity. Clinical signs and body weights and weight gains were assessed throughout the study. Following the 11th and 20th exposures, blood was collected by orbital sinus puncture from 10 rats/sex/group and analyzed for methemoglobin concentrations. At termination of the study (day 29), blood was collected via the abdominal aorta from 10 anesthetized rats/sex/group for hematology and serum chemistry. At necropsy, all rats were subjected to comprehensive gross examinations and organ weights were recorded. Comprehensive histopathological examinations were performed on 10 rats/sex in the 0 and 60 mg/m³ exposure groups. Nasal turbinates were examined histopathologically in 10 rats/sex of each exposure group.

Overall mean analytical concentrations deviated from the target concentrations by 0.0, +8.3 and +2.5% for the 5, 30 and 60 mg/m³ exposure groups, respectively (Hazleton Laboratories, 1984). The aerosol content of the exposure chambers was not significantly different from that present in room air. No significant exposure-related ocular lesions were apparent in any of the rats. No animals died during the study. No apparent exposure-related trends in clinical signs were apparent with the exception of yellow stains on the fur of all 2-nitrophenol exposed animals. There were no statistically significant exposure-related effects on mean body weight or weight gain. A statistically significant increase in methemoglobin

levels was noted in male and female rats of the 5 mg/m³ group analyzed on day 15 of the study. However, when animals were analyzed on day 28, the methemoglobin levels were similar to controls. No statistically significant increases were found in the higher dose groups. The change, compared with controls, in methemoglobin levels in treated animals of the low dose groups, while exhibited statistical significance, was not considered biologically significant. Hematology and clinical chemistry findings were unremarkable. Gross pathology revealed no consistent exposure-related trends. Small increases in liver weight, liver/brain weight ratio and spleen/brain weight ratio were seen in the 5 mg/m³ group females, but were not observed in females at higher doses or in any of the treated males. Histopathological examinations revealed squamous metaplasia in epithelium of the nasoturbinates and maxilloturbinates in 1/10, 0/10, 10/10 and 10/10 male rats and 1/10, 1/10, 9/10 and 10/10 female rats of the 0, 5, 30 and 60 mg/m³ exposure groups, respectively. No other apparent exposure-related effects were observed. On the basis of the nasal lesions, this study identified a NOAEL of 5 mg/m³ and a LOAEL of 30 mg/m³ for 2-nitrophenol in rats.

Other Studies

Limited genotoxicity data are available for 2-nitrophenol. The chemical produced negative results in the Ames test with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 both in the presence and absence of rat liver S9 metabolic activation (Chiu et al., 1978; Dellarco and Prival, 1989; Haworth et al., 1983; Kawai et al., 1987; Koerdel et al., 1981; Massey et al., 1994; Shimizu and Yano, 1986; Suzuki et al., 1983). 2-Nitrophenol did not induce DNA breakage in λ phage DNA (Yamada et al., 1987) or increase reversions from streptomycin dependence to independence in *Escherichia coli* strain Sd-4-73 (Szybalski, 1958). Negative results were reported for mutagenic activity in post-meiotic and meiotic germ cells of male *Drosophila melanogaster* exposed to 2-nitrophenol via feeding (400-500 ppm) or injection (2500 or 5000 ppm) (Foureman et al., 1994).

2-Nitrophenol did not exhibit skin tumor-promoting action in mice receiving dermal applications of a 20% solution twice weekly for 12 weeks (Boutwell and Bosch, 1959).

In rats and mice administered single oral doses of 2-nitrophenol, calculated LD₅₀ values were 2830 and 1300 mg/kg, respectively (Vernot et al., 1977). No information was located regarding the toxicity of 2-nitrophenol following acute inhalation exposure.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC RfD VALUES FOR 2-NITROPHENOL

Oral studies of 2-nitrophenol are limited to two 28-day studies from the German literature available only as brief summaries in WHO (2000) and a range-finding developmental toxicity study. None of these studies appear to have been adequate to derive NOAEL or LOAEL values. The lack of adequate oral data for humans or animals precludes the derivation of a provisional subchronic or chronic RfD for 2-nitrophenol.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC RfC VALUES FOR 2-NITROPHENOL

Subchronic p-RfC

Results of the only available repeated exposure (28-day) inhalation study of 2-nitrophenol (Hazleton Laboratory, 1984) provide marginally adequate information in rats to derive a provisional subchronic RfC for 2-nitrophenol. This study identified significantly increased incidences of squamous metaplasia of the nasal epithelium in rats as the critical effect following 4 weeks of exposure to 2-nitrophenol vapors for 6 hours/day, 5 days/week. The lowest concentration of 2-nitrophenol associated with squamous metaplasia of the nasal epithelium was 30 mg/m³ in both male and female rats; the associated NOAEL was 5 mg/m³. Because the NOAEL and LOAEL represent essentially 0 and 100% response, respectively, it is not feasible to apply meaningful benchmark dose analysis to the data set. Therefore, the NOAEL of 5 mg/m³ was selected as the point of departure for deriving a subchronic RfC for 2-nitrophenol.

The NOAEL of 5 mg/m³ from intermittent exposure was adjusted to account for a continuous exposure scenario as follows:

$$\begin{aligned} \text{NOAEL}_{[\text{ADJ}]} &= \text{NOAEL} \times 6 \text{ hours}/24 \text{ hours} \times 5 \text{ days}/7 \text{ days} \\ \text{NOAEL}_{[\text{ADJ}]} &= 5 \text{ mg}/\text{m}^3 \times 6/24 \times 5/7 = 0.89 \text{ mg}/\text{m}^3 \end{aligned}$$

According to U.S. EPA (1994b) methodology for respiratory effects of a category 1 gas (a systemic toxicant without significant portal of entry (lung) effects), such as 2-nitrophenol the NOAEL_[HEC] (human equivalent concentration) is calculated by multiplying the NOAEL_[ADJ] for upper respiratory effects by the regional gas dose ratio for extrathoracic effects (RGDR_{ET}). The default RGDR_{ET} is calculated according to the following equation:

$$\text{RGDR}_{\text{ET}} = \frac{\left[\frac{\dot{V}_E}{\text{SA}_{\text{ET}}} \right]_A}{\left[\frac{\dot{V}_E}{\text{SA}_{\text{ET}}} \right]_H} \quad (\text{Equation 4-18; U.S. EPA 1994b})$$

where:

\dot{V}_E = minute volume (cm³/minute)

SA_{ET} = surface area of the extrathoracic region (cm²), and

A, H = subscripts denoting laboratory animal and human, respectively.

Default surface area values for the extrathoracic respiratory region are 15 cm² for the rat and 200 cm² for the human (U.S. EPA (1994b). For the male Sprague-Dawley rat, a reference inhalation rate of 0.27 m³/day (270,000 cm³/day; U.S. EPA, 1988, standard default) produces a minute volume of 187.5 cm³/min (270,000 cm³/day ÷ 1440 min/day). The default minute volume for the human is 13,800 cm³/min (13.8 L/min or 20 m³/day; U.S. EPA, 1994b). Therefore:

$$RGDR_{PU} = \frac{\left[\frac{187.5}{15} \right]_A}{\left[\frac{13,800}{200} \right]_H} = 0.1812$$

The NOAEL_[HEC] is derived as follows:

$$NOAEL_{[HEC]} = NOAEL_{[ADJ]} \times RGDR_{ET} = 0.89 \text{ mg/m}^3 \times 0.1812 = 0.1613 \text{ mg/m}^3$$

The **subchronic p-RfC of 5E-4 mg/m³** based on squamous metaplasia of the nasal epithelium in rats (Hazleton Laboratories, 1984) is derived by dividing the NOAEL_[HEC] of 0.16 mg/m³ by a composite uncertainty factor (UF) of 300, which includes factors of 3 for interspecies extrapolation, 10 for interindividual human variability and 10 for data base deficiencies.

A 3-fold UF is used to account for uncertainty in extrapolating from laboratory animals to humans (i.e., interspecies variability). No information is available regarding the toxicity of 2-nitrophenol in humans. No comparative information is available regarding the toxicokinetics or toxicodynamics of 2-nitrophenol in animals and humans. However, the default dosimetric calculation for deriving an HEC accounts for the uncertainty in the variability in toxicokinetics of humans and rats. A 3-fold UF is applied to account for uncertainty in species differences for toxicodynamics (U.S. EPA, 1994b).

A 10-fold UF is used to account for variation in sensitivity among members of the human population (i.e., interindividual variability). This UF was not reduced due to the lack of human inhalation exposure data.

A 10-fold UF is used to account for uncertainty associated with data base deficiencies. A single 28-day inhalation toxicity study in one animal species (rat) is available (Hazleton Laboratories, 1984). The data base lacks studies of subchronic and chronic toxicity, inhalation neurotoxicity, developmental toxicity and reproductive toxicity (including 2-generation reproductive toxicity). Although the principal study (Hazleton Laboratories, 1984) was only a 28-day study (less than subchronic duration), the minor nature of the effects observed suggests that the 10-fold database UF is adequate to capture the uncertainties associated with use of the less-than-subchronic study in this instance.

Confidence in the principal study (Hazleton Laboratories, 1984) is low-to-medium. The study included comprehensive gross and histopathologic assessments. A major limitation of this study is the less-than-subchronic study duration of 28 days. Confidence in the data base is low because the data base lacks studies of subchronic and chronic toxicity, inhalation neurotoxicity, and developmental and reproductive toxicity (including 2-generation reproductive toxicity). Reflecting low-to-medium confidence in the principal study and low confidence in the data base, confidence in the provisional subchronic RfC is low.

Chronic p-RfC

The lack of adequate subchronic or chronic inhalation data for humans or animals precludes the derivation of a provisional chronic RfC for 2-nitrophenol. Use of the 28-day study (Hazleton Laboratories, 1984) was rejected because of uncertainties in exposure duration and toxicokinetics and dynamics in humans, and a lack of reproduction/developmental studies and which would result in five areas of uncertainties. According to the uncertainty in hematological effects which could become apparent in a chronic study, the database is insufficient to support derivation of chronic p-RfC (U.S. EPA, 1994b).

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 2-NITROPHENOL

Weight-of-Evidence Descriptor

No information was located regarding the carcinogenicity of 2-nitrophenol in humans. No lifetime assessments were located regarding the carcinogenicity of inhaled or ingested 2-nitrophenol in animals. 2-Nitrophenol did not exhibit skin tumor-promoting action in mice receiving dermal applications twice weekly for 12 weeks (Boutwell and Bosch, 1959). Available genotoxicity assays of 2-nitrophenol indicate that the chemical is not genotoxic (Chiu et al., 1978; Dellarco and Prival, 1989; Foureman et al., 1994; Haworth et al., 1983; Kawai et al., 1987; Koerdel et al., 1981; Massey et al., 1994; Shimizu and Yano, 1986; Suzuki et al., 1983; Szybalski, 1958; Yamada et al., 1987). In accordance with U.S. EPA (2005) cancer guidelines, there is *inadequate information to assess carcinogenic potential* for 2-nitrophenol, based on the lack of human or animal carcinogenicity data.

Quantitative Estimates of Carcinogenic Risk

There are no human or animal data from which to derive an oral slope factor or inhalation unit risk for 2-nitrophenol.

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