

Provisional Peer Reviewed Toxicity Values for

p- Nitrophenol
(CASRN 100-02-7)

Derivation of a Chronic Oral RfD

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 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
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-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
p-NITROPHENOL (CASRN 100-02-7)
Derivation of a Chronic Oral RfD**

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

An RfD for *p*-nitrophenol is not available on IRIS (U.S. EPA, 2002) or in the HEAST (U.S. EPA, 1997). The Drinking Water Standards and Health Advisory list reports an RfD of 8E-3 mg/kg-day (U.S. EPA, 2000), referenced to a Health Advisory (U.S. EPA, 1991a). The RfD was derived from a NOAEL of 25 mg/kg-day and LOAEL of 70 mg/kg-day for mortality and associated clinical signs and pathological changes in rats treated with *p*-nitrophenol by gavage for 13 weeks (Hazelton Laboratories, 1989). An uncertainty factor of 3000 (10 for intraspecies extrapolation, 10 for interspecies extrapolation, 10 to extrapolate from a subchronic study, and 3 for the lack of reproductive/developmental and chronic toxicity data) was applied to the NOAEL to calculate the RfD. Older U.S. EPA documents in the CARA list (U.S. EPA, 1991c, 1994), including a Health and Environmental Effects Profile (U.S. EPA, 1985) and a Health Effects Assessment (U.S. EPA, 1987), did not find relevant data on which to base an RfD.

ATSDR (1992) published a Toxicological Profile on 2- and 4-nitrophenol that declined to derive oral MRLs for *p*-nitrophenol due to the lack of adequate data. ATSDR (1992) did not use the Hazelton Laboratories (1989) study to derive an MRL “due to uncertainty regarding the monitoring of methemoglobin.” The above-mentioned documents, the NTP (2001) status report, the WHO (2001) Environmental Health Criteria series, the IARC (2001) monograph series, and a review on aromatic nitro and amino compounds (Weisburger and Hudson, 2001) were consulted for relevant studies. In 1995, TOXLINE, DART, and ETIC had been searched (from 1989) for studies relevant to toxicity resulting from oral exposure to *p*-nitrophenol. Updated literature searches (1994 - 2001) of TOXLINE, MEDLINE, CANCERLIT, EMIC/EMICBACK, DART/ETICBACK, TSCATS, RTECS, HSDB, GENETOX, and CCRIS were conducted in September, 2001.

REVIEW OF PERTINENT DATA

Human Studies

No data regarding human toxicity resulting from oral exposure to *p*-nitrophenol were identified in the available reviews or the literature search.

Animal Studies

Groups of 20 male and 20 female Sprague-Dawley rats were treated by gavage with 0, 25, 70, or 140 mg/kg-day of *p*-nitrophenol for 13 weeks (Hazelton Laboratories, 1989). Animals were bled at 7 and 14 weeks for hematology and clinical chemistry. Other endpoints measured were clinical observations, body weight, food consumption, hematology, clinical chemistry (including methemoglobin formation), ophthalmoscopy, organ weights, gross pathology, and histopathology of selected tissues. A dose-related increase in mortality was reportedly statistically significant at 140 mg/kg for both sexes (0/20, 0/20, 1/20, and 15/20 for males and 0/20, 1/20, 1/20 and 6/20 for females). Death was associated with clinical symptoms of languid behavior, pale appearance, prostration, wheezing, dyspnea, and congestion of the lungs, liver, kidney, and other organs. The authors note that gavage error was responsible for the premature death of one rat in the 140 mg/kg group (gender not specified). The authors also state that blood collection at week 7 “is suspected to have contributed to” the premature death of 1 male treated with 70 mg/kg and 2 males and 3 females treated with 140 mg/kg. Statistically significant elevations in lymphocyte counts and erythrocyte polychromasia were observed in rats treated with 140 mg/kg of *p*-nitrophenol. Analytical problems reportedly occurred with methemoglobin analysis at 7 weeks, and analysis was not performed at 14 weeks. The authors concluded that 25 mg/kg-day represents a NOEL.

Developmental toxicity studies of *p*-nitrophenol were also located. In a study reported by Kavlock (1990), groups of pregnant rats received a single gavage dose of *p*-nitrophenol on gestational day 11. Increased mortality (3/13) was observed in the dams dosed with 667 mg/kg; no deaths were observed in the dams exposed to 333 mg/kg. No significant alterations in litter size, perinatal loss, pup weight, or litter biomass, and no external malformations, were observed in the offspring of rats dosed with up to 1000 mg/kg (Kavlock, 1990). In another developmental toxicity study (Hardin et al., 1987; Plasterer et al., 1985), groups of 50 pregnant CD-1 mice were dosed via gavage with 400 mg/kg-day of *p*-nitrophenol on gestational days 6-13. Increased mortality (9/50 versus 0/50 for controls) was observed in the dams, and no effects on maternal weight gain were observed. No effects on the number of viable litters, number of live births per litter, percent survival of pups, pup birth weights, or pup weight gain were observed. Abu-Qare et al. (1999, 2000) indicate that a single oral dose of 100 mg/kg given to pregnant Sprague-Dawley rats did not alter maternal or fetal methemoglobin content, plasma butyrylcholinesterase, or brain acetylcholinesterase; other endpoints were not reported.

FEASIBILITY OF DERIVING A PROVISIONAL RfD FOR p-NITROPHENOL

The Hazelton Laboratories (1989) study is not suitable for derivation of a p-RfD. No statistically significant effects, including mortality, were observed in rats treated with either 25 or 70 mg/kg-day of *p*-nitrophenol compared to control-treated animals. Moreover, the incidences of *p*-nitrophenol-induced mortality are confounded by experimental error during blood collection: *p*-nitrophenol treatment may be related to as few as 1/20, 1/20, 3/30, and 13/20 mortalities in females dosed with 25, 70 or 140 mg/kg and males dosed with 140 mg/kg-day, respectively. On this basis, clear evidence of a statistically significant elevation in mortality is seen only in males treated with 140 mg/kg-day of *p*-nitrophenol. The non-mortality endpoints found to be elevated in animals treated with 70 or 140 mg/kg, clinical signs and organ congestion, were only seen in a subset of animals dying prematurely, and therefore cannot be considered independent indicators of toxicity. The authors report that animals were observed twice daily for mortality and moribundity; therefore, it is unclear the degree to which organ congestion represents post-mortem rather than *p*-nitrophenol-induced changes. Methemoglobin formation is a relatively sensitive marker of acute mononitrophenol toxicity (reviewed in ATSDR, 1992; U.S. EPA, 1980, 1985, 1987) and this endpoint was not evaluated due to analytical problems. Because mortality is the only independent measure of toxicity found to be related to *p*-nitrophenol exposure by Hazelton Laboratories (1989), use of this study to calculate a p-RfD might tend to underestimate risk to human health caused by oral exposure to *p*-nitrophenol.

REFERENCES

Abu-Qare, A.W., C.F. Brownie and M.B. Abou-Donia. 1999. Placental transfer pharmacokinetics and biochemical effects following a single oral dose of (14-C)p-nitrophenol in Sprague-Dawley rats. *Neurotoxicology*. 20: 122.

Abu-Qare, A.W., C.F. Brownie and M.B. Abou-Donia. 2000. Placental transfer and pharmacokinetics of a single oral dose of [14C]p-nitrophenol in rats. *Arch. Toxicol.* 74: 388-396.

ATSDR (Agency for Toxic Substances and Disease Registry). 1992. Toxicological Profile for Nitrophenols: 2-Nitrophenol, 4-Nitrophenol. U.S. Department of Health and Human Services, Atlanta, GA. TP-91/23.

Hardin, B.D., R.L. Schuler, J.R. Burg et al. 1987. Evaluation of 60 chemicals in a preliminary developmental toxicity test. *Teratog. Carcinog. Mutagen.* 7: 29-48.

Hazelton Laboratories. 1989. Subchronic toxicity study in rats with para-nitrophenol (final report) with cover letter. Submitted under TSCA Section 8(d) by Monsanto Company, St. Louis, MO. NTIS No. OTS0526338. EPA No. 40-8915314.

IARC (International Agency for Research on Cancer). 2001. Search IARC Monographs. Examined September 2001. Online.
http://193.51.164.11/cgi/iHound/Chem/iH_Chem_Frames.html

Kavlock, R.J. 1990. Structure-activity relationship in the developmental toxicity of substituted phenols: *In vivo* effects. *Teratology*. 41: 43-59. (Cited in ATSDR, 1991)

NTP (National Toxicology Program). 2001. Management Status Report. Examined September 2001. Online.
http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/ALL_SRCH/iH_ALL_SRCH_Frames.html

Plasterer, M.R., W.S. Bradshaw, G.M. Booth et al. 1985. Developmental toxicity of nine selected compounds following prenatal exposure in the mouse: naphthalene, p-nitrophenol, sodium selenite, dimethyl phthalate, ethylenethiourea and four glycol ether derivatives. *J. Toxicol. Environ. Health.* 15(1): 25-38.

U.S. EPA. 1980. Ambient Water Quality Criteria for Nitrophenols. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Planning Regulations and Standards, Washington DC. NTIS PB81-117749.

U.S. EPA. 1985. Health and Environmental Effects Profile (HEEP) for Nitrophenols. Prepared by the Office Health and Environmental Assessment, Environmental Criteria and Assessment Office for the Office of Solid Waste and Emergency Response, Washington DC.

U.S. EPA. 1987. Health Effects Assessment (HEA) for Nitrophenols. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1991a. Drinking Water Health Advisory for *p*-nitrophenol. Office of Science and Technology, Office of Water. NTIS PB92-135490.

U.S. EPA. 1991b. RfD/RfC Work Group Meeting Notes (with attachments) for the February 20, 1991 meeting. Office of Research and Development, National Center for Environmental Assessment, Washington, DC.

U.S. EPA. 1991c. 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 (HEAST). 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 PB 97-921199.

U.S. EPA. 2000. Drinking Water Standards and Health Advisories. Summer 2000. Office of Water, Washington, DC. Examined September 2001. Online. www.epa.gov/ost/drinking/standards/

U.S. EPA. 2002. Integrated Risk Information System (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Examined September 2001. Online. www.epa.gov/iris

Weisburger, E.K. and V.W. Hudson. 2001. Aromatic nitro and amino compounds. In: Patty's Toxicology, Vol 4, 5th ed., Bingham, E., B. Cofrancesco, and C.H. Powell, Ed. John Wiley and Sons Inc., p. 650-651.

WHO (World Health Organization). 2001. Environmental Health Criteria (EHC) Monographs International Programme on Chemical Safety, Geneva, Switzerland. Examined September 2001. Online. www.inchem.org/ehc.html

Provisional Peer Reviewed Toxicity Values for

p-Nitrophenol
(CASRN 100-02-7)

Derivation of a Chronic Inhalation RfC

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 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
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-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
p-NITROPHENOL (CASRN 100-02-7)
Derivation of a Chronic Inhalation RfC**

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

IRIS (U.S. EPA, 2002) lists the RfC for *p*-nitrophenol as not verifiable. The HEAST (U.S. EPA, 1997) includes a notation that data for nitrophenols are inadequate for quantitative risk assessment, referenced to a Health Effects Assessment (HEA) for nitrophenols (U.S. EPA, 1987). A Health and Environmental Effects Profile (HEEP) for nitrophenols (U.S. EPA, 1985), located in the CARA list (U.S. EPA, 1991a, 1994), also found an absence of relevant inhalation data. ATSDR (1992) published a Toxicological Profile on 2- and 4-nitrophenol that did not derive inhalation MRLs due to lack of adequate data. No occupational exposure limits for *p*-nitrophenol have been assigned by ACGIH (2001), OSHA (2001a,b) or NIOSH (2001). WHO (2001) and IARC (2001) have not produced documents on *p*-nitrophenol. The NTP (2001) status report and a review on aromatic nitro and amino compounds (Weisburger and Hudson, 2001) were consulted for relevant studies. In 1995, TOXLINE, DART, and ETIC had been searched

(from 1989) for studies relevant to toxicity resulting from inhalation exposure to *p*-nitrophenol. Updated literature searches (1994 - 2001) of TOXLINE, MEDLINE, CANCERLIT, EMIC/EMICBACK, DART/ETICBACK, TSCATS, RTECS, HSDB, GENETOX, and CCRIS were conducted in September, 2001.

REVIEW OF PERTINENT DATA

No new inhalation studies were identified in the literature search; two relevant papers, which appear to discuss the same study, were considered (Monsanto, 1989a,b). Monsanto (1989a) exposed groups of 15 male and 15 female Sprague-Dawley rats to 0, 1.09, 5.27, or 29.18 mg/m³ (target exposure 0, 1, 5, or 30 mg/m³) of *p*-nitrophenol 6 hours/day, 5 days/week for 4 weeks (20 days of exposure). Animals were evaluated for ophthalmology, clinical observations, mortality, moribundity, body weight, organ weights, clinical pathology, gross pathology, and histopathology of 41 tissues including the lungs and nasal turbinates. No mortalities were observed. The intensity of “yellow stains on the fur” was reported to be related to dose. The following statistically significant effects were reported: increased methemoglobin in males exposed to 5.27 mg/m³; increased hemoglobin and hematocrit in males exposed to 29.18 mg/m³; increased bilirubin in females exposed to 1.09 mg/m³; increased sodium in females exposed to 5.27 mg/m³; decreased liver weights in females at 29.18 mg/m³; increased relative lung weights in both male and female rats exposed to 29.18 mg/m³; increased body weight or body weight gain in males exposed to 5.27 or 29.18 mg/m³ at various time points; and decreased body weight or body weight gain in all *p*-nitrophenol-exposed females at various time points. However, Monsanto (1989a) concluded that none of these observed effects were consistently compound-related. Monsanto (1989a) did not report treatment-related effects on histopathology, but analysis of the raw data conducted by Syracuse Research Corporation using the Fisher exact test identified statistically significant differences in the incidences of ophthalmoscopic lesions (7/15 versus 1/15) and myocarditis (4/15 versus 0/15) in males exposed to 29.18 mg/m³ compared to controls, and hepatocytic vacuolization (6/15 versus 1/15 and 14/15 versus 8/15) and periocular polymorphonuclear leukocyte infiltration (11/15 versus 4/15 and 8/15 versus 3/15) in both males and females exposed to 29.18 mg/m³ versus controls. Histopathology incidence data were not provided for animals exposed to 1.09 or 5.27 mg/m³ of *p*-nitrophenol, and therefore could not be evaluated. Although Monsanto (1989a) concluded that no observed health effects were compound-related, a summary document (Monsanto, 1989b) reported a NOAEL of 5.27 mg/m³ and a LOAEL of 29.18 mg/m³ on the basis of cataracts, corneal and conjunctival drying, and ocular lesions. This inhalation experiment cannot be adequately evaluated because of the lack of histopathology data for intermediate concentrations, and high background incidences of lung lesions and mononuclear infiltration of the nasal turbinates, liver and kidneys.

Smith et al. (1988) investigated the short-term inhalation toxicity of *p*-nitrophenol sodium salt (CASRN 824-78-2) in male Crl:CD rats. Aerosol exposures up to 4.7 g/m³ for 4 hours did

not cause mortalities. Subsequently, male rats were exposed for 6 hours per day for 10 days to 0, 0.03, 0.13, 0.34, or 2.47 g/m³ of *p*-nitrophenol sodium salt aerosol, followed by a 14 day observation period. Urinalysis, hematology, and serum clinical chemistry were performed. No adverse effects were seen at 0.03 g/m³. Transient methemoglobinemia was observed at 0.13 g/m³ and higher. At 0.34 and 2.47 g/m³, transient weight loss, dark urine, proteinuria, increased creatine and serum glutamic-oxaloacetic-transaminase activity were observed. Exposure to 2.47 g/m³ also induced increased hematocrit, hemoglobin, and erythrocyte number. This study finds an acute inhalation LC₅₀ greater than 4.7 g/m³, a NOAEL of 0.03 g/m³ and a LOAEL of 0.13 g/m³. ATSDR (1992) chose not to derive an acute inhalation MRL from these data due to reporting inconsistencies, a lack of clearly toxic effects, and “the preliminary nature of the report.”

FEASIBILITY OF DERIVING A PROVISIONAL RfC FOR *p*-NITROPHENOL

A provisional RfC for *p*-nitrophenol cannot be derived because of a lack of human inhalation data and the inadequacy of the animal inhalation data. The RfD/RfC Work Group (U.S. EPA, 1991b) indicated that “an RfC for 4-nitrophenol is non-verifiable based on the lack of adequate subchronic or chronic inhalation toxicity data, a lack of data on portal-of-entry effects, and the fact that a route-to-route extrapolation cannot be performed due to the lack of pharmacokinetic data.” The Work Group also noted that because *p*-nitrophenol is a solid at room temperature, its aerosol nature and regional respiratory deposition are important considerations. It is not recommended to derive a provisional RfC for *p*-nitrophenol based on the provisional RfD, because sufficient information is not available regarding absorption of this chemical following oral or inhalation exposure and because it is not known whether this chemical will produce irritative respiratory effects when inhaled following subchronic or chronic exposure.

REFERENCES

- ACGIH (American Conference of Governmental Industrial Hygienists). 2001. TLVs and BEIs: Threshold Limit Values for Chemical Substances and Physical Agents, Biological Exposure Indices. Cincinnati, OH.
- ATSDR (Agency for Toxic Substances and Disease Registry). 1992. Toxicological Profile for Nitrophenols: 2-Nitrophenol, 4-Nitrophenol. U.S. Department of Health and Human Services, Atlanta, GA. TP-91/23.
- IARC (International Agency for Research on Cancer). 2001. Search IARC Monographs. Examined September 2001. Online.
http://193.51.164.11/cgi/iHound/Chem/iH_Chem_Frames.html

Monsanto Co. 1989a. Chemical listing subject to submission & a subacute dust inhalation toxicity study in rats with p-nitrophenol (final report) with attachments and cover letter dated 060889. Submitted under TSCA Section 8(d). NTIS No. OTS0520433. EPA Document No. 86-890000362.

Monsanto Co. 1989b. Health effects assessment for p-nitrophenol at the Krummrich plant (final report) with attachment and cover letter dated 122889. Submitted under TSCA Section 8(d). NTIS No. OTS0521595. EPA Document No. 86-900000046.

NIOSH (National Institute for Occupational Safety and Health). 2001. Online NIOSH Pocket Guide to Chemical Hazards. Index by CASRN. Examined September 2001. Online. www.cdc.gov/niosh/npg/npgdcas.html

NTP (National Toxicology Program). 2001. Management Status Report. Examined September 2001. Online. http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/ALL_SRCH/iH_ALL_SRCH_Frames.html

OSHA (Occupational Safety and Health Administration). 2001a. OSHA Standard 1910.1000 Table Z-2. Part Z, Toxic and Hazardous Substances. Examined September 2001. Online. www.osha-slc.gov/OshStd_data/1910_1000_TABLE_Z-2.html

OSHA (Occupational Safety and Health Administration). 2001b. OSHA Standard 1915.1000 for Air Contaminants. Part Z, Toxic and Hazardous Substances. Examined September 2001. Online. www.osha-slc.gov/OshStd_data/1915_1000.html

Smith, L.W., G.T. Hall and G.L. Kennedy. 1988. Acute and repeated dose inhalation toxicity of para-nitrophenol sodium salt in rats. Drug Chem. Toxicol. 11: 319-327.

U.S. EPA. 1985. Health and Environmental Effects Profile (HEEP) for Nitrophenols. Prepared by the Office Health and Environmental Assessment, Environmental Criteria and Assessment Office for the Office of Solid Waste and Emergency Response, Washington DC.

U.S. EPA. 1987. Health Effects Assessment (HEA) for Nitrophenols. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Solid Waste and Emergency Response, Washington, DC. .

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

U.S. EPA. 1991b. RfC for *p*-nitrophenol. Meeting notes of the RfD/RfC Workgroup. June 13, 1991. Office of Research and Development, National Center for Environmental Assessment, Washington, DC.

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 (HEAST). 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 PB 97-921199.

U.S. EPA. 2002. Integrated Risk Information System (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Examined September 2001. Online. www.epa.gov/iris

Weisburger, E.K. and V.W. Hudson. 2001. Aromatic nitro and amino compounds. In: Patty's Toxicology, Vol 4, 5th ed., Bingham, E., B. Cofrancesco, and C.H. Powell, Ed. John Wiley and Sons Inc., p. 650-651.

WHO (World Health Organization). 2001. Environmental Health Criteria (EHC) Monographs International Programme on Chemical Safety, Geneva, Switzerland. Examined September 2001. Online. www.inchem.org/ehc.html

Provisional Peer Reviewed Toxicity Values for

p-Nitrophenol
(CASRN 100-02-7)

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 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
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-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
p-NITROPHENOL (CASRN 100-02-7)
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 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

A carcinogenicity assessment for *p*-nitrophenol is not available on IRIS (U.S. EPA, 2002) or in the HEAST (U.S. EPA, 1997). The Drinking Water Standards and Health Advisory list (U.S. EPA, 2000) assigned *p*-nitrophenol to cancer group D, not classifiable as to human carcinogenicity. The source document for this assessment was a Health Advisory (U.S. EPA, 1991a). The CARA list (U.S. EPA, 1991b, 1994) includes a Health and Environmental Effects Profile (U.S. EPA, 1985) and Health Effects Assessment (U.S. EPA, 1987), both of which also assigned *p*-nitrophenol to cancer weight-of-evidence Group D. IARC (2001) has not assessed the carcinogenicity of *p*-nitrophenol. The NTP (2001) status report, the WHO Environmental Health Criteria series (2001), an ATSDR Toxicological Profile (ATSDR, 1992), and a review on aromatic nitro and amino compounds (Weisburger and Hudson, 2001) were consulted, and literature searches were conducted, to identify relevant studies. In 1995, TOXLINE, DART, and

ETIC had been searched (from 1989) for studies relevant to the carcinogenicity of *p*-nitrophenol. Updated literature searches (1994 - 2001) of TOXLINE, MEDLINE, CANCERLIT, EMIC/EMICBACK, DART/ETICBACK, TSCATS, RTECS, HSDB, GENETOX, and CCRIS were conducted in September 2001.

REVIEW OF PERTINENT DATA

Human Studies

No relevant data were located regarding the carcinogenicity of *p*-nitrophenol to humans by any route of exposure.

Animal Studies

No relevant data were located regarding the carcinogenicity of *p*-nitrophenol to animals following oral or inhalation exposure.

No carcinogenic alterations were observed in two repeated-exposure dermal studies (Boutwell and Bosch, 1959; NTP, 1991), although these studies had several design limitations. Application of 25 μ L of a 20% solution of *p*-nitrophenol in dioxane to the shaved back of 31 female Sutter mice twice weekly for 12 weeks did not induce skin tumors or lesions that could be considered precancerous in nature (Boutwell and Bosch, 1959). Clear limitations of this study include the fact that no control group was used, no other site was examined, and the duration of the study may have been too short for evaluating carcinogenic potential.

NTP (1991) conducted an 18-month skin painting study with *p*-nitrophenol in Swiss-Webster mice. In this study, *p*-nitrophenol in acetone was applied to the interscapular skin of mice (60/sex/group) at doses of 0 (vehicle), 40, 80, or 160 mg/kg 3 days/week for 80 weeks. Gross and microscopical examination of all major tissues and organs at necropsy revealed no significant neoplastic alterations that could be attributed to treatment with *p*-nitrophenol. However, high mortality occurred in all groups, including controls, starting at 60 weeks. Less than 50% of the animals in all dose groups were alive at 80 weeks. This study was reviewed by a peer review panel that concluded that under the conditions of the study there was no evidence of carcinogenic activity in male or female Swiss-Webster mice. However, the panel noted that a severe limitation of the study was the fact that Swiss-Webster mice were used, because this strain of mice has a lifespan of only approximately 1 year. The low survival rate severely limited the statistical power of the study.

Other Studies

Testing of *p*-nitrophenol for genotoxicity has produced primarily negative results, although there is some evidence that this chemical can produce clastogenic effects. *p*-Nitrophenol did not produce mutations in the *Salmonella typhimurium* plate incorporation assay with or without metabolic activation (ATSDR, 1992; NTP, 1991). No DNA damage was observed in *Escherichia coli*, *Proteus mirabilis*, and *S. typhimurium* without metabolic activation (ATSDR, 1992). DNA damage was observed in *Bacillus subtilis* without metabolic activation (ATSDR, 1992). A review of unpublished experiments (Hoechst Celanese Corporation, 1989) reported negative results for genotoxicity in *Salmonella*. Negative results were seen in a HGPRT assay in Chinese hamster ovary cells (Oberly et al., 1990) and forward mutation assays in mouse lymphoma cells with and without metabolic activation (ATSDR, 1992; Oberly et al., 1996), and in a DNA repair assay in rat hepatocytes without metabolic activation (ATSDR, 1992). A weakly positive result was observed for inhibition of DNA synthesis in Chinese hamster ovary cells without metabolic activation (ATSDR, 1992). At cytotoxic doses, *p*-nitrophenol induced DNA double strand breaks in primary rat hepatocytes (Elia et al., 1994; Storer et al., 1996), but not in V79 Chinese hamster cells or human white blood cells (Hartmann and Speit, 1997). Negative results were seen in a sister chromatid exchange assay in Chinese hamster ovary cells with or without metabolic activation (NTP, 1991); however, a positive result for chromosomal aberrations was observed in Chinese hamster ovary cells in the presence of metabolic activation at concentrations that delayed cell cycle (NTP, 1991). In cultured human peripheral lymphocytes, *p*-nitrophenol caused a dose-dependent and statistically significant increase in the incidence of chromosomal abnormalities (Huang et al., 1995, 1996). Negative results were observed in three *in vivo* assays: a dominant lethal assay and a host-mediated assay in mice (ATSDR, 1992), and germ cell assays in *Drosophila melanogaster* (NTP, 1991; Foureman et al., 1994).

PROVISIONAL WEIGHT-OF-EVIDENCE CLASSIFICATION

Based on the lack of information regarding the carcinogenicity of *p*-nitrophenol in humans or animals after oral or inhalation exposure, and no evidence of carcinogenicity in animals after dermal exposure, *p*-nitrophenol can be given a weight-of-evidence classification of Group D, *not classifiable as to human carcinogenicity*, according to U.S. EPA (1986) guidelines. Under the proposed guidelines (U.S. EPA, 1999) the *data are inadequate for an assessment of human carcinogenic potential*.

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

Derivation of quantitative estimates of cancer risk for *p*-nitrophenol is precluded by the absence of data demonstrating carcinogenicity associated with *p*-nitrophenol exposure.

REFERENCES

- ATSDR (Agency for Toxic Substances and Disease Registry). 1992. Toxicological Profile for Nitrophenols: 2-Nitrophenol, 4-Nitrophenol. U.S. Department of Health and Human Services, Atlanta, GA. TP-91/23.
- Boutwell, R.K., and D. K. Bosch. 1959. The tumor-promoting action of phenol and related compounds for mouse skin. *Cancer Res.* 19: 413-424.
- Elia, M.C., R.D. Storer, T.W. McKelvey et al. 1994. Rapid DNA degradation in primary rat hepatocytes treated with diverse cytotoxic chemicals: analysis by pulsed field gel electrophoresis and implications for alkaline elution assays. *Environ. Molec. Mutagen.* 24: 181-191.
- Fouremant, P., J.M. Mason, R. Valencia et al. 1994. Chemical mutagenesis testing in *Drosophila*. IX. Results of 50 coded compounds tested for the National Toxicology Program. *Environ. Molec. Mutagen.* 23: 51-63.
- Hartmann, A. and G. Speit. 1997. The contribution of cytotoxicity to DNA-effects in the single cell gel test (comet assay). *Toxicol. Lett.* 90: 183-188.
- Hoechst Celanese Corp. 1989. Dattenblatt altstoffe toxicological profiles for 3 chemicals with cover letter dated 031789. NTIS No. OTS0520433. EPA Document No. NTIS No. OTS0516686. EPA Document No. 86-890000362.
- Huang, Q., L. Wang, S. Han et al. 1995. The genotoxicity of substituted nitrobenzenes and the quantitative structure-activity relationship studies. *Chemosphere.* 30: 915-923.
- Huang, Q.G., L.R. Kong, Y.B. Liu et al. 1996. Relationships between molecular structure and chromosomal aberrations in in vitro human lymphocytes induced by substituted nitrobenzenes. *Bull. Environ. Contam. Toxicol.* 57: 349-353.

IARC (International Agency for Research on Cancer). 2001. Search IARC Monographs. Examined September 2001. Online.

http://193.51.164.11/cgi/iHound/Chem/iH_Chem_Frames.html

NTP (National Toxicology Program). 1991. Toxicology and Carcinogenesis studies of *p*-nitrophenol (CAS No. 100-02-7) in Swiss-Webster mice (dermal studies). Research Triangle Park, NC: U.S. Department of Health and Human Service, National Institutes of Health. NTP TR 417.

NTP (National Toxicology Program). 2001. Management Status Report. Examined September 2001. Online.

http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/ALL_SRCH/iH_ALL_SRCH_Frames.html

Oberly, T.J., M.A. Rexroat, B.J. Bewsey et al. 1990. An evaluation of the CHO/HGPRT mutation assay involving suspension cultures and soft agar cloning: results for 33 chemicals. *Environ. Mol. Mutagen.* 16: 260-271.

Oberly, T.J., W.P. Hoffman and M.L. Garriott. 1996. An evaluation of the twofold rule for assessing a positive response in the L5178Y TK[±] mouse lymphoma assay. *Mutat. Res.* 369: 221-232.

Storer, R.D., T.W. Mckelvey, A.R. Kraynak et al. 1996. Revalidation of the in vitro alkaline elution/rat hepatocyte assay for DNA damage: improved criteria for assessment of cytotoxicity and genotoxicity and results for 81 compounds. *Mutat. Res.* 368: 59-101.

U.S. EPA. 1985. Health and Environmental Effects Profile (HEEP) for Nitrophenols. Prepared by the Office Health and Environmental Assessment, Environmental Criteria and Assessment Office for the Office of Solid Waste and Emergency Response, Washington DC.

U.S. EPA. 1986. Guidelines for Carcinogen Risk Assessment. *Federal Register.* 51(185): 33992-34003.

U.S. EPA. 1987. Health Effects Assessment (HEA) for Nitrophenols. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1991a. Drinking Water Health Advisory for *p*-Nitrophenol. Office of Science and Technology, Office of Water. NTIS PB92-135490.

U.S. EPA. 1991b. 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 (HEAST). 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 PB 97-921199.

U.S. EPA. 1999. Guidelines for Carcinogen Risk Assessment. SAB Review Draft, July 1999. Office of Research and Development, National Center for Environmental Assessment. NCEA-F-0644. Online. <http://www.epa.gov/ncea/raf/crasab.htm>

U.S. EPA. 2000. Drinking Water Regulations and Health Advisories. Summer 2000. Office of Water, Washington, DC. Examined September 2001. Online. www.epa.gov/ost/drinking/standards/

U.S. EPA. 2002. Integrated Risk Information System (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Examined August 2001. Online. www.epa.gov/iris

Weisburger, E.K. and V.W. Hudson. 2001. Aromatic nitro and amino compounds. In: Patty's Toxicology, Vol 4, 5th ed., Bingham, E., B. Cohrssen, and C.H. Powell, Ed. John Wiley and Sons, Inc. p. 650-651.

WHO (World Health Organization). 2001. Environmental Health Criteria (EHC) Monographs International Programme on Chemical Safety, Geneva, Switzerland. Examined September 2001. Online. www.inchem.org/ehc.html