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Provisional Peer-Reviewed Toxicity Values for

o-Aminophenol
(CASRN 95-55-6)

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

AUTHORS, CONTRIBUTORS, AND REVIEWERS

CHEMICAL MANAGER

Q. Jay Zhao, PhD, MPH, DABT
National Center for Environmental Assessment, Cincinnati, OH

DRAFT DOCUMENT PREPARED BY

SRC, Inc.
7502 Round Pond Road
North Syracuse, NY 13212

PRIMARY INTERNAL REVIEWERS

Scott C. Wesselkamper, PhD
National Center for Environmental Assessment, Cincinnati, OH

Jeffry L. Dean II, PhD
National Center for Environmental Assessment, Cincinnati, OH

This document was externally peer reviewed under contract to:

Eastern Research Group, Inc.
110 Hartwell Avenue
Lexington, MA 02421-3136

Questions regarding the content of this PPRTV assessment should 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).

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COMMONLY USED ABBREVIATIONS AND ACRONYMS

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service Registry Number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line cells)
CL	confidence limit
CNS	central nervous system
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FEV_1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-S-transferase
Hb/g-A	animal blood-gas partition coefficient
Hb/g-H	human blood-gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MTD	maximum tolerated dose
NAG	N-acetyl-β-D-glucosaminidase
NCEA	National Center for Environmental Assessment
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OCT	ornithine carbamoyl transferase
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
PND	postnatal day
POD	point of departure
POD_{ADJ}	duration-adjusted POD
QSAR	quantitative structure-activity relationship
RBC	red blood cell
RDS	replicative DNA synthesis
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
SAR	structure activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	glutamic oxaloacetic transaminase, also known as AST
SGPT	glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_H	intraspecies uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
UF_D	database uncertainty factor
U.S.	United States of America
WBC	white blood cell

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR *o*-AMINOPHENOL (CASRN 95-55-6)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (http://www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

This document has been reviewed in accordance with U.S. EPA policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

QUESTIONS REGARDING PPRTVs

Questions regarding the content of this PPRTV assessment should 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).

INTRODUCTION

o-Aminophenol, CASRN 95-55-6, also known as *ortho*-aminophenol, 2-aminophenol, *o*-hydroxyaniline, 2-hydroxyaniline, 2-amino-1-hydroxybenzene, *o*-aminohydroxybenzene, or *o*-hydroxyphenylamine, is a white crystalline solid commonly used in the fur and leather industry (under the name Oxidation Base 17 or C.I. 76520) to convert leather, fur, and hair from shades of gray to yellow-browns (Mitchell and Waring, 2012). *o*-Aminophenol is also used as a chemical intermediate for a variety of substances including pharmaceuticals (HSDB, 2011), stains and dyes (Mitchell et al., 2003), and heterocyclic compounds such as oxyquinolines, phenoxamines, and benzoxazoles (Mitchell and Waring, 2012). In addition, *o*-aminophenol is a strong reducing agent used in photographic developers (Mitchell et al., 2003). It readily undergoes an oxidation/cyclization reaction in the presence of air (oxygen) and light to yield 2-aminophenoxazin-3-one (CASRN 1916-59-2) (Mitchell et al., 2003). To avoid this undesirable reaction, *o*-aminophenol is often converted to a salt, such as a hydrochloride (CASRN 51-19-4), an acetate, or a sulfate (CASRN 67845-79-8), to increase its stability (Mitchell et al., 2003).

The empirical formula for *o*-aminophenol is C_6H_7NO (see Figure 1). Table 1 summarizes the physicochemical properties of *o*-aminophenol. Although *o*-aminophenol can act as both an acid and a base, the basic dissociation constant is larger (Mitchell et al., 2003). As a result, it is more common to protonate the amine group than it is to remove a proton from the hydroxy group. *o*-Aminophenol does not exist as a dipolar ion (Mitchell et al., 2003).

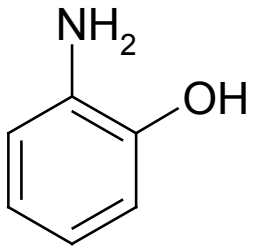


Figure 1. *o*-Aminophenol Structure

Table 1. Physicochemical Properties of *o*-Aminophenol (CASRN 95-55-6)

Property (unit)	Value
Physical state	White crystals that rapidly become yellow-brown when exposed to air and light[a]
Boiling point (°C)	267[b]
Melting point (°C)	173.5[b]; sublimes rapidly without decomposition at 153°C at a reduced pressure of 11 mm Hg[c,d]
Density (g/cm^3)	1.328[b]
Vapor pressure (mm Hg)	0.0031 (extrapolated)[e]
pH (unitless)	NV
pKa (at 25°C)	pKa_1 [$-NH_3^{(+)} \rightarrow -NH_2 + H^{(+)}$] = 4.66[a]; pKa_2 [$-OH \rightarrow -O^{(-)} + H^{(+)}$] = 9.71[a]
Solubility in water (g/L)	20[f]
Octanol-water partition constant (log K_{ow})	0.62[g]
Henry's law constant (atm m^3/mol at 25°C)	1.98×10^{-10} (estimated)[h]
Soil adsorption coefficient K_{oc} (mL/g)	92 (estimated)[h]
Atmospheric OH rate constant (cm^3/molecule-sec at 25°C)	74.2×10^{-12} (estimated)[h]
Atmospheric half-life (hr)	1.7 (estimated)[h]
Relative vapor density (air = 1)	NV
Molecular weight (g/mol)	109.13

[a]Mitchell et al. (2003).
[b]Haynes et al. (2014).
[c]Mitchell and Waring (2012).
[d]*o*-Aminophenol is often purified via sublimation under reduced pressure.
[e]The vapor pressure was extrapolated from the measured boiling point using a regression-derived equation.
[f]O'Neil et al. (2013).
[g]HSDB (2011).
[h]U.S. EPA (2012b).

NV = not available.

o-Aminophenol's moderate vapor pressure and estimated low Henry's law constant indicate that the compound could volatilize from dry surfaces but is unlikely to volatilize from water or moist surfaces. Its measured moderate water solubility and estimated low soil-adsorption coefficient indicate that *o*-aminophenol is likely to leach to groundwater or undergo runoff after a rain event. Thus, migration to groundwater is likely to compete with light-induced oxidation/cyclization in the environment depending on local conditions (wet, dry, shade, etc.).

A summary of available toxicity values for *o*-aminophenol from EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for *o*-Aminophenol (CASRN 95-55-6)

Source[a]	Value (applicability)	Notes	Reference
Noncancer			
IRIS	NV	NA	U.S. EPA (2016)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012a)
ATSDR	NV	NA	ATSDR (2016)
IPCS	NV	NA	IPCS (2016); WHO (2016)
Cal/EPA	NV	NA	Cal/EPA (2014); Cal/EPA (2016a); Cal/EPA (2016b)
OSHA	NV	NA	OSHA (2006); OSHA (2011)
NIOSH	NV	NA	NIOSH (2016)
ACGIH	NV	NA	ACGIH (2015)
Cancer			
IRIS	NV	NA	U.S. EPA (2016)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012a)
NTP	NV	NA	NTP (2014)
IARC	NV	NA	IARC (2015)
Cal/EPA	NV	NA	Cal/EPA (2011); Cal/EPA (2016a); Cal/EPA (2016b)
ACGIH	NV	NA	ACGIH (2015)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; Cal/EPA = California Environmental Protection Agency; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; IARC = International Agency for Research on Cancer; IPCS = International Programme on Chemical Safety; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration.

NA = not applicable; NV = not available.

Non-date-limited literature searches were conducted in June 2015 and May 2016 for studies relevant to the derivation of provisional toxicity values for *o*-aminophenol (CASRN 95-55-6). Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, ToxLine (including TSCATS1), and Web of Science. The following databases were searched outside of HERO for health-related values: ACGIH, ATSDR, Cal/EPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA Office of Water (OW), U.S. EPA TSCATS2/TSCATS8e, NIOSH, NTP, OSHA, and WHO.

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Tables 3A and 3B provide an overview of the relevant noncancer and cancer databases, respectively, for *o*-aminophenol and include all potentially relevant short-term-, subchronic-, and chronic-duration studies. The phrase "statistical significance" and the term "significant(ly)," used throughout the document, indicate a *p*-value of < 0.05 unless otherwise noted.

Table 3A. Summary of Potentially Relevant Noncancer Data for *o*-Aminophenol (CASRN 95-55-6)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (comments)	Notes[b]
Human								
1. Oral (mg/kg-d)								
ND								
2. Inhalation (mg/m^3)								
ND								
Animal								
1. Oral (mg/kg-d)[a]								
Short-term	5 M/0 F, rat (unspecified strain), diet, 12 d	0, 83, 586	Targets of toxicity include RBCs and potentially the liver and kidney.	NDr	NDr	NDr	Eastman Kodak (1979) (Inadequate reporting precludes independent identification of critical effect and NOAEL/LOAEL.)	NPR
2. Inhalation (mg/m^3)								
ND								

[a]Dosimetry: Values are converted to an ADD (mg/kg-day) for oral noncancer effects and an HEC (mg/m^3) for inhalation noncancer effects. All repeated exposure values are converted from a discontinuous to a continuous exposure, with the exception of values from animal developmental studies, which are not adjusted to a continuous exposure.
[b]Notes: NPR = not peer reviewed.

ADD = adjusted daily dose; BMCL = benchmark concentration lower confidence limit; BMDL = benchmark dose lower confidence limit; F = female(s); HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level; RBC = red blood cell.

Table 3B. Summary of Potentially Relevant Cancer Data for *o*-Aminophenol (CASRN 95-55-6)						
Category	**Number of Male/Female, Strain, Species, Study Type, and Duration**	**Dosimetry[a]**	**Critical Effects**	**BMDL/ BMCL[a]**	**Reference (comments)**	**Notes[b]**
Human						
1. Oral (mg/kg-d)						
ND						
2. Inhalation (mg/m^3)						
ND						
Animal						
1. Oral (mg/kg-d)[a]						
Carcinogenicity	25 M/0 F, F344 rat, drinking water, 52 wk (with or without initiation with EHEN 2 wk prior to exposure)	152	No evidence of hepatic or renal carcinogenicity or tumor promotion	NDr	Kurata et al. (1987)	PR
Carcinogenicity	6 M/0 F, S-D rat, 9 mo	14.5	No evidence of carcinogenicity	NDr	Miller and Miller (1948) (Study is considered inadequate due to lack of controls, low animal number, short exposure duration, limited endpoint evaluation, and a single low dose that did not approach the MTD.)	PR
2. Inhalation (mg/m^3)						
ND						

[a]Dosimetry: The units for oral exposures are expressed as HEDs (mg/kg-day); HEDs are calculated using species-specific DAFs based on the animal:human body-weight scaling to the 1/4 power (i.e., $BW^{1/4}$) ratio recommended by U.S. EPA (2011b): rat:human ratio = 0.24.
[b]Notes: PR = peer reviewed.

BMCL = benchmark concentration lower confidence limit; BMDL = benchmark dose lower confidence limit; DAF = dosimetric adjustment factor; EHEN = *N*-ethyl-*N*-hydroxyethylnitrosamine; F = female(s); HED = human equivalent dose; M = male(s); MTD = maximum tolerated dose; ND = no data; NDr = not determined; S-D = Sprague-Dawley.

HUMAN STUDIES

No data regarding the toxicity of *o*-aminophenol to humans following chronic or subchronic exposure by any route have been identified. No acute oral or inhalation studies have been located; however, methemoglobinemia was reported in humans following an intravenous injection of *o*-aminophenol [Kiese and Rachor (1964) as cited by Akazawa et al. (2000)]. The only other available human data are acute patch testing studies reporting positive reactions to *o*-aminophenol in 8.3−25% of test subjects (Matsunaga et al., 1989; Matsunaga et al., 1988; Katoh et al., 1986; Yasuno, 1985).

ANIMAL STUDIES

Oral Exposures

The only repeated-dose oral studies found in the literature are an unpublished 12-day dietary toxicity study in rats with limited data reporting (Eastman Kodak, 1979), a tumor-promotion drinking water study in rats that evaluated limited systemic endpoints (Kurata et al., 1987), and a 9-month dietary study in rats that evaluated liver carcinogenicity (Miller and Miller, 1948).

Short-Term-Duration Studies

Eastman Kodak (1979)

Groups of five male rats were fed diets containing 0, 0.1, or 1.0% *o*-aminophenol in diets containing 1% corn oil for 12 consecutive days. The study authors calculated daily intakes to be 0, 83, or 586 mg/kg-day. Blood was collected for hematology (hemoglobin concentration, hematocrit, red blood cell [RBC] morphology, white blood cell [WBC] count, and differential) and serum chemistry (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], lactate dehydrogenase [LDH], and glucose). At sacrifice, liver and kidney weights were recorded, and unspecified tissues were examined for histopathological lesions. No quantitative data were included in the study report.

No mortalities were reported. Clinical signs of toxicity observed at the 586-mg/kg-day dose included a yellowish cast to the fur and rust-colored urine; no clinical signs of toxicity were reported at the 83-mg/kg-day dose. Rats fed the 586 mg/kg-day diet consumed approximately half of the amount of food as controls and did not gain any weight, while rats in the 83-mg/kg-day dose group consumed slightly less than controls but had comparable body-weight gains. According to the study authors, decreased hemoglobin concentration and hematocrit, as well as RBC morphology, in rats fed 586 mg/kg-day were indicative of a chemical-induced anemia. Anemia was not observed at the 83-mg/kg-day dose. No changes in WBC counts or differential were observed in exposed rats relative to controls. Serum chemistry values were unaffected by treatment. Absolute liver and kidney weights were significantly reduced and relative weights were significantly increased in the 586-mg/kg-day group, compared with controls (percentage of changes were not reported); organ-weight effects were considered secondary to lack of body-weight gain. The only organ-weight change reported in the 83-mg/kg-day group was a significant increase in relative liver weight, compared with control. Histopathological changes attributed to treatment in the 586-mg/kg-day group were mild-to-moderate diffuse hyperkeratosis in the nonglandular portion of the stomach (due to irritation), minimal to moderate hypocellularity and congestion in the spleen, and atrophy of mesenteric fat (secondary to reduced food intake). None of these histopathological changes were observed in the 83-mg/kg-day group (control incidence not reported). The study authors

concluded that toxicity targets of *o*-aminophenol included the RBC and potentially the liver and kidney.

Data reporting is inadequate for independent analysis; therefore, a no-observed-adverse-effect level/lowest-observed-adverse-effect level (NOAEL/LOAEL) determination was not made for this study.

Subchronic-Duration Studies

No studies evaluating adverse effects following subchronic-duration oral exposure to *o*-aminophenol have been identified.

Chronic-Duration/Carcinogenicity Studies

Kurata et al. (1987)

Seventy-five male Fischer 344 rats were divided into three groups (25/group). Two groups were initiated with 0.1% *N*-ethyl-*N*-hydroxyethylnitrosamine (EHEN) in the drinking water for 2 weeks. Following the 2-week EHEN exposure, one of the groups was fed a diet containing 0.8% *o*-aminophenol for 50 weeks (EHEN + *o*-aminophenol); the other group continued to receive the basal diet (EHEN only). The third group was fed the 0.8% *o*-aminophenol test diet for 50 weeks without EHEN-pretreatment (*o*-aminophenol only). All rats were sacrificed in Week 52. At sacrifice, body, liver, and kidney weights were recorded. Kidney and liver sections were microscopically evaluated for neoplastic lesions. Additional liver sections were also evaluated for glutathione-*S*-transferase placental type (GST-P) positive foci using immunohistochemistry.

Based on terminal animal numbers, it appears that one rat from EHEN + *o*-aminophenol group, four rats from the EHEN-only group, and three rats from the *o*-aminophenol-only group died prior to study termination, but mortality details were not provided. Body weights were significantly decreased by 11−19% in the EHEN + *o*-aminophenol and *o*-aminophenol-only groups, compared with the EHEN-only group. Absolute liver weights were significantly decreased by 31−41% in the EHEN + *o*-aminophenol and *o*-aminophenol-only groups, compared with the EHEN-only group; relative liver weight was also significantly decreased by 35% in the *o*-aminophenol-only group, compared with the EHEN-only group. Absolute kidney weights were comparable among groups, but relative kidney weights were significantly increased by 20−29% in the EHEN + *o*-aminophenol and *o*-aminophenol-only groups, compared with the EHEN-only group. No neoplastic liver or kidney lesions were seen in the rats from the *o*-aminophenol-only group. The number of hepatocellular carcinomas in the liver of rats from the EHEN + *o*-aminophenol group (9/24) was significantly decreased compared with the incidence in the EHEN-only group (15/21), suggesting that *o*-aminophenol inhibited liver tumor development. Additionally, rats receiving EHEN + *o*-aminophenol showed significant decreases in the incidence of GST-P positive foci and the area of the foci, compared to rats that received EHEN alone. The incidence of neoplastic lesions in the kidney was comparable between the EHEN + *o*-aminophenol group and the EHEN-only group.

Based on these results, *o*-aminophenol was not a carcinogenic or tumor-promoting agent in the liver and kidneys under the conditions of this study. A NOAEL/LOAEL determination for non-neoplastic effects (body and organ weights) was not made due to lack of an untreated control. Based on reference body weights and water consumption values for male F344 rats in a chronic-duration study (U.S. EPA, 1988), the estimated daily intake of *o*-aminophenol is

632 mg/kg-day, which converts to a human equivalent dose (HED) of 152 mg/kg-day using the rat:human dosimetric adjustment factor (DAF) of 0.24 based on the animal:human body-weight scaling to the 1/4 power (i.e., $BW^{1/4}$) ratio recommended by the U.S. EPA (2011b).

Miller and Miller (1948)

A group of six male Sprague-Dawley (S-D) rats was fed a diet containing 0.117% *o*-aminophenol hydrochloride for up to 9 months. A positive control group of 12 male rats was fed a diet containing 0.06% 4-dimethylaminoazobenzene up to 9 months. It is unclear whether a negative control group was used. The rats were sacrificed at 9 months, and the liver was examined for gross evidence of cirrhosis and tumor incidence.

No gross evidence of liver cirrhosis or liver tumors was observed in the rats exposed to dietary *o*-aminophenol hydrochloride. *o*-Aminophenol was not carcinogenic under the conditions of this assay; however, confidence in this study is low due to lack of appropriate controls, low animal numbers, limited endpoint analysis, and use of a low dose that did not approach the maximum tolerated dose (MTD). Based on reference body weights and food consumption values for male S-D rats in a chronic-duration study (U.S. EPA, 1988), the estimated daily intake of *o*-aminophenol hydrochloride is 80.7 mg/kg-day. Based on molar-weight ratios (*o*-aminophenol accounts for 75% of total molecular weight of *o*-aminophenol hydrochloride), the estimated intake of *o*-aminophenol is 60.5 mg/kg-day, which converts to an HED of 14.5 mg/kg-day using the rat:human DAF of 0.24 based on the animal:human $BW^{1/4}$ ratio recommended by the U.S. EPA (2011b).

Reproductive/Developmental Studies

No studies evaluating the reproductive or developmental toxicity of *o*-aminophenol following oral exposure have been identified.

Inhalation Exposures

No studies evaluating the toxicity of *o*-aminophenol following inhalation exposure have been identified.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Genotoxicity

The genotoxicity of *o*-aminophenol was evaluated in vitro and in a limited number of in vivo studies. Available studies are summarized below in Table 4. In general, the data indicate that *o*-aminophenol is a weak mutagen that could cause deoxyribonucleic acid (DNA) damage and clastogenic effects.

Table 4. Summary of *o*-Aminophenol (CASRN 95-55-6) Genotoxicity, Mutagenicity, and Clastogenicity

Endpoint	Test System	Dose/ Concentration[a]	Results without Activation[b]	Results with Activation[b]	Comments	References (notes)
Genotoxicity studies in prokaryotic organisms						
Mutation	*Salmonella typhimurium* TA1535, TA1537, TA98, and TA100	0, 10, 33, 100, 166, 333, 666, 1,000 µg/plate	+ (TA100) – (TA1535, TA1537, TA98)	+ (TA100) – (TA1535, TA1537, TA98)	Preincubation assay: *o*-Aminophenol induced a 2−3-fold increase in revertant colonies in TA100 with and without S9 activation at ≥166 µg/plate. Cytotoxicity was noted at ≥666 µg/plate without activation.	Haworth et al. (1983) (Case Western Reserve University)
Mutation	*S. typhimurium* TA1535, TA1537, TA98, and TA100	0, 10, 33, 100, 333, 400, 666, 750 µg/plate	+ (TA100) – (TA1535, TA1537, TA98)	+ (TA100) – (TA1535, TA1537, TA98)	Preincubation assay: *o*-Aminophenol induced a 2−3-fold increase in revertant colonies in TA100 without activation at ≥333 µg/plate and a 2−6-fold increase with S9 activation at ≥100 µg/plate. Cytotoxicity was noted at ≥666 µg/plate without activation.	Haworth et al. (1983) (EG&G Mason Research Institute)
Mutation	*S. typhimurium* TA1535, TA1537, TA98, and TA100	0, 10, 33, 100, 333, 667, 1,000, 3,333, 6,667, 10,000 µg/plate	–	+ (TA100) – (TA1535, TA1537, TA98)	Preincubation assay: *o*-Aminophenol induced a 2-fold increase in revertant colonies in TA100 with S9 activation at ≥1,000 µg/plate. Cytotoxicity was noted at ≥667 µg/plate without activation and ≥6,667 µg/plate with activation.	Haworth et al. (1983) (SRI International)
Mutation	*S. typhimurium* TA98 and TA100	Concentrations not reported	+	+	Mutagenic activity was 2−3 times greater than controls; unclear whether the effect was observed in one or both strains.	Nishimura and Oshima (1983) as cited in U.S. EPA (1985) (Japanese study, abstract only)
Mutation	*S. typhimurium* TA98 and TA100	0, 25, 50, 100, 250, 500 µg/plate	–	+ (TA100) – (TA98)	Plate incorporation assay: *o*-Aminophenol induced a 2−3-fold increase over control in the number of revertant colonies in TA100 with S9 activation at ≥100 µg/plate. Cytotoxicity in TA100 was noted at ≥250 µg/plate without S9 activation.	Lavoie et al. (1979)

Table 4. Summary of *o*-Aminophenol (CASRN 95-55-6) Genotoxicity, Mutagenicity, and Clastogenicity

Endpoint	Test System	Dose/ Concentration[a]	Results without Activation[b]	Results with Activation[b]	Comments	References (notes)
Mutation	*S typhimurium* G46, TA1535, TA100, C3076, TA1537, D3052, TA1538, and TA98	Plate gradient ranges: 0.1−1, 1−10, 10−100, 100−1,000 µg/mL agar	+ (TA100) − (G46, TA1535, C3076, TA1537, D3052, TA1538, TA98)	+ (TA100) − (G46, TA1535, C3076, TA1537, D3052, TA1538, TA98)	Modified gradient plate test: *o*-Aminophenol was mutagenic at 7−100 µg/mL agar; reporting is inadequate to determine whether the compound was mutagenic with metabolic activation, without metabolic activation, or under both tested conditions.	Thompson et al. (1983)
Mutation	*S. typhimurium* TA1535, TA1537, TA1538, TA98, and TA100	Concentrations not reported	−	−	Plate incorporation assay.	De Flora et al. (1984)
Mutation	*S. typhimurium* TA98 and TA100	0, 0.5, 1.0, 2.0 µmol/plate (~0, 50, 100, 200 µg/plate)	+	−	Plate incorporation assay. No cytotoxicity was observed.	Degawa et al. (1979)
Mutation	*S. typhimurium* TA98 and TA100	15−150 µg/plate	−	−	Plate incorporation assay.	Yoshikawa et al. (1976) as cited in U.S. EPA (1985) (Japanese study)
Mutation	*S. typhimurium* TA98	10−30 µg/plate	−	−	NA	Watanabe et al. (1991) as cited in CCRIS (1993) (Japanese study)
Mutation	*Escherichia coli* WP2and WF2*uvrA*-	Plate gradient ranges: 0.1−1, 1−10, 10−100, 100−1,000 µg/mL agar	−	−	Modified gradient plate test.	Thompson et al. (1983)
DNA repair test	*E. coli* WP2 (wild-type), WP67 (*uvrA-, polA*-), and CM871 (*uvrA-, recA-, lexA*-)	Eight 2-fold dilutions starting from solubility or toxic concentration	+ (CM871, WP67)	−	MIC was 20 µg.	De Flora et al. (1984)

Table 4. Summary of *o*-Aminophenol (CASRN 95-55-6) Genotoxicity, Mutagenicity, and Clastogenicity

Endpoint	Test System	Dose/ Concentration[a]	Results without Activation[b]	Results with Activation[b]	Comments	References (notes)
DNA damage (SOS chromotest)	*E. coli* PQ37	Concentration not reported	+	NV	*o*-Aminophenol was tested after in vitro nitrosation via incubation with sodium nitrate at 37°C for 1 hr prior to conducting the SOS chromotest. The SOSIP of *o*-aminophenol was 5.9 compared with compounds that were not genotoxic (SOSIP <0.006).	Bartsch et al. (1991); Ohshima et al. (1989)
Genotoxicity studies in nonmammalian eukaryotic organisms						
Sex-linked recessive lethal mutations	*Drosophila melanogaster*	0, 200 (feeding); 0, 100 (injection)	− (feeding, injection)	− (feeding, injection)	NA	Yoon et al. (1985)
Genotoxicity studies in mammalian cells—in vitro						
CAs	CHO	0.1, 0.2, 0.5 mM	+	NV	*o*-Aminophenol induced a 4−17-fold increase in CAs. Observed CAs were predominantly chromatid exchanges and breaks, with a small percentage of dicentrics and rings.	Kanaya (1996)
SCE	Human lymphocytes	0, 1.6, 3.3, 6.6 µg/mL	+	NV	*o*-Aminophenol induced a 1.2−1.9-fold, dose-dependent increase in SCE frequency over control.	Kirchner and Bayer (1982)
SCE	Human fibroblasts	0, 0.01, 0.03, 0.10, 0.3 mM	+	NV	*o*-Aminophenol induced a 2-fold increase in SCE frequency at 0.10 mM. Cytotoxicity was noted at 0.30 mM.	Wilmer et al. (1981)
SCE	CHO	0.1, 0.2, 0.5 mM	+	NV	*o*-Aminophenol induced a 1.5−2-fold dose-dependent increase in SCE.	Kanaya (1996)
SCE	Chinese hamster V79	5−20 µM	+	NV	NA	Wild et al. (1981) (abstract)
UDS	Primary rat hepatocytes	0.5, 1.0, 5.0, 10, 50, 100, 500, 1,000 nmol/mL	−	NV	NA	Thompson et al. (1983)

Table 4. Summary of *o*-Aminophenol (CASRN 95-55-6) Genotoxicity, Mutagenicity, and Clastogenicity

Endpoint	Test System	Dose/ Concentration[a]	Results without Activation[b]	Results with Activation[b]	Comments	References (notes)
Genotoxicity studies in mammals—in vivo						
CAs	Ehrlich ascites tumor cells in the mouse	Concentration not reported	−	−	*o*-Aminophenol was "applied" to tumor cells; no further details provided.	Bogajewski and Bogajewska (1982) (abstract)
SCE	Chinese hamster bone marrow cells	5 mg/kg i.p.	−	−	Animal sacrificed 4 hr after injection.	Kirchner and Bayer (1982)
Mouse micronucleus test	Mouse bone marrow	0.5−2.0 mM/kg i.p.	+	+	NA	Wild et al. (1981) (abstract)
Genotoxicity studies with extracellular purified DNA						
DNA cleavage	^{32}P-5′-end-labeled DNA fragments from human *p53* tumor suppressing gene and c-Ha-*ras*-1 proto-oncogene	0, 5 µM (without Cu[II]); and 0, 1, 2, and 5 µM (with Cu[II])	− (without Cu[II]) + (with Cu[II])	− (without Cu[II]) + (with Cu[II])	*o*-Aminophenol incubated in the presence of Cu(II) caused DNA damage, but did not cause damage without Cu(II).	Ohkuma and Kawanishi (2001)
Oxidative DNA damage (8-oxodG formation)	Calf thymus DNA	0, 1, 2, 5 µM [with or without Cu(II)]	− (without Cu[II]) + (with Cu[II])	− (without Cu[II]) + (with Cu[II])	*o*-Aminophenol incubated in the presence of Cu(II) significantly increased the formation of 8-oxodG, compared with control. *o*-Aminophenol alone did not induce oxidative DNA damage.	Ohkuma and Kawanishi (2001)
DNA strand break	Double-stranded λDNA	250 µM	+	+	Exposure to *o*-aminophenol produced DNA fragments between 0.6 and 0.000004 daltons.	Yamada et al. (1985)

[a]Lowest effective dose for positive results, highest dose tested for negative results.
[b]+ = positive; − = negative.

8-oxoG = 8-oxo-7,8-dihydro-29-deoxyguanosine; CA = chromosomal aberration; CHO = Chinese hamster ovary (cell line cells); Cu = copper; DNA = deoxyribonucleic acid; i.p. = intraperitoneal; MIC = minimally inhibitory concentration; NA = not applicable; NV = not available; SCE = sister chromatid exchange; SOSIP = SOS-inducing potency factor; UDS = unscheduled DNA synthesis.

Available evidence from in vitro studies indicates that *o*-aminophenol is a weak mutagen. Several studies indicate that *o*-aminophenol is weakly mutagenic to *Salmonella typhimurium* strain TA100 with and without metabolic activation. In general, induction of revertant colonies was only two- to threefold greater than controls at noncytotoxic concentrations [Nishimura and Oshima (1983) as cited in U.S. EPA (1985); Haworth et al. (1983); Thompson et al. (1983); Lavoie et al. (1979)]. Other studies evaluating *o*-aminophenol found no evidence of mutagenicity in *S. typhimurium* strain TA100 with or without metabolic activation [Yoshikawa et al. (1976) as cited in U.S. EPA (1985); De Flora et al. (1984); Degawa et al. (1979)]. Mutagenicity was not reported in various other *S. typhimurium* strains or *Escherichia coli* strains WP2 or WF2*uvrA* [Watanabe et al. (1991) as cited in CCRIS (1993); Yoshikawa et al. (1976) as cited in U.S. EPA (1985); De Flora et al. (1984); Haworth et al. (1983); Nishimura and Oshima (1983); Thompson et al. (1983); Degawa et al. (1979); Lavoie et al. (1979)]. *o*-Aminophenol did not cause sex-linked recessive lethal mutations in *Drosophila melanogaster* following exposure via feeding or injection (Yoon et al., 1985).

o-Aminophenol caused clastogenic effects in several in vitro assays without metabolic activation, including chromosomal aberrations (CAs) in Chinese hamster ovary (CHO) cells and sister chromatid exchanges (SCEs) in human lymphocytes, human fibroblasts, CHO cells, and Chinese hamster V79 cells (Kanaya, 1996; Kirchner and Bayer, 1982; Wild et al., 1981; Wilmer et al., 1981). Micronuclei (MN) were induced in mouse bone marrow cells following intraperitoneal (i.p.) injections of *o*-aminophenol (Wild et al., 1981). However, in other in vivo assays, *o*-aminophenol did not induce CA in Ehrlich ascites tumor cells injected into mice (Bogajewski and Bogajewska, 1982) or SCE in Chinese hamster bone marrow cells (Kirchner and Bayer, 1982).

Available data indicate that *o*-aminophenol is capable of causing DNA damage in vitro; however, findings are inconsistent among different test systems. *o*-Aminophenol inhibited DNA repair in *E. coli* strains CM871 and WP67, but not wild-type WP2 at concentrations ≥20 µg/plate (De Flora et al., 1984). DNA damage was induced in *E. coli* strain PQ37 incubated with nitrosated *o*-aminophenol in the SOS chromotest; *o*-aminophenol was not tested prior to nitrosation (Bartsch et al., 1991; Ohshima et al., 1989). Unscheduled DNA synthesis was not induced in primary rat hepatocytes exposed to *o*-aminophenol (Thompson et al., 1983). In isolated DNA samples, *o*-aminophenol induced strand breaks in double-stranded λDNA (Yamada et al., 1985). *o*-Aminophenol also caused DNA damage in calf thymus DNA and ^{32}P-5′-end-labeled DNA fragments from human *p53* tumor-suppressing gene and c-Ha-*ras*-1 proto-oncogene in the presence, but not absence, of copper (Cu[II]), suggesting that oxidation of *o*-aminophenol to the *o*-aminophenoxyl radical in the presence of Cu(II) underlies the observed DNA damage in isolated DNA fragments (Ohkuma and Kawanishi, 2001).

Supporting Animal Toxicity Studies

Acute Toxicity

Acute studies indicate that *o*-aminophenol is a strong inducer of methemoglobinemia in rats, but not mice. Methemoglobinemia was reported in rats exposed once to *o*-aminophenol at an oral dose of 750 mg/kg, with methemoglobin formation of 50% in exposed rats compared with 0.71% in controls 2 hours post-treatment (Eastman Kodak, 1979). In an i.p. injection study, methemoglobin formation increased in a dose-related manner in rats exposed to *o*-aminophenol at doses of 0.15−1.0 mM/kg (55−110 mg/kg); methemoglobin formation was ~10% at the lowest dose and ~70% at the highest dose at 1 hour postinjection (data reported graphically, control data

not reported) (Harrison and Jollow, 1987). In contrast, methemoglobin formation rates were much lower in mice (2−3%) following an i.p. injection of 300 mg/kg (control data not reported); the study authors concluded that *o*-aminophenol was not a strong inducer of methemoglobin formation in mice (Itoh, 1987). Itoh (1987) also reported low Heinz body formation (<4%) in exposed mice following i.p. injection.

There is limited evidence from acute parenteral studies that *o*-aminophenol may cause mild kidney toxicity. Itoh (1987) reported mild tubular vacuolated degeneration and slight flattening of collecting tubules with dilatation in rat kidneys 1 week following an i.p. dose of 200 mg/kg (but not ≤150 mg/kg); however, no histological damage was observed in the kidneys of rats 48 hours after a single intravenous injection of 2.8 mM/kg (310 mg/kg) (Calder et al., 1971). Other parenteral studies reported no changes in kidney weight or serum blood urea nitrogen (BUN) levels (Rankin et al., 1996; Newton et al., 1982), although Rankin et al. (1996) reported a transient increase in urinary protein excretion in rats exposed to *o*-aminophenol.

Reported oral median lethal dose (LD_{50}) values include 951 mg/kg in male rats, 1,100 mg/kg in male and female rats, and 800 mg/kg in male mice (Eastman Kodak, 1979; University of Miami, 1975). Animals receiving single doses ≥940 mg/kg showed clinical signs of neurotoxicity, including tremors, convulsions, and central depression; it is unclear whether or not neurotoxic effects were limited to moribund animals (University of Miami, 1975). In anesthetized mice, the effective i.p. dose that caused 50% of mice (effective dose [ED_{50}]) to have a myoclonic convulsion (jerk) in response to a strong pinch was 3.42 mM/kg (376 mg/kg) (Angel and Rogers, 1972).

Carcinogenicity

No elevated incidences of squamous metaplasia or carcinoma of the bladder were observed in mice following implantation of cholesterol-based pellets containing *o*-aminophenol in the urinary bladder, compared with mice implanted with a cholesterol pellet containing no chemicals (Clayson et al., 1958).

In a dermal cancer bioassay, no evidence of carcinogenicity was observed in rats following skin exposure to a hair-dye formulation containing several chemicals, including 0.3% *o*-aminophenol, for 2 years (Burnett and Goldenthal, 1988).

Reproductive/Developmental Effects

A two-generation reproduction study conducted by dermal exposure found no adverse reproductive effects in rats following skin exposure to a hair-dye formulation containing several chemicals, including 0.3% *o*-aminophenol (Burnett and Goldenthal, 1988).

Developmental effects of *o*-aminophenol were studied only by parenteral exposure. Dose-related increases in frequency of litters with one or more malformed fetuses, number of fetuses presenting with one or more malformations, and number of fetal resorptions were observed in Syrian golden hamsters (LKV strain) following maternal exposure to 150−200 mg/kg via i.p. injection on Gestation Day (GD) 8, compared with controls; these effects were not observed at 100 mg/kg (Rutkowski and Ferm, 1982). Induced malformations included neural tube defects (encephalocele, exencephaly, and spina bifida), eye, limb, tail, and rib defects, and umbilical hernia (often involving eventration of the abdominal viscera).

o-Aminophenol was not toxic to the dams at these doses, suggesting that the fetus may be a sensitive target for *o*-aminophenol toxicity.

Metabolism/Toxicokinetic Studies

Oral absorption is very high (~95%) in laboratory animals (U.S. EPA, 1985). No evidence of percutaneous absorption was observed through depilated abdominal skin in guinea pigs during a 24-hour exposure in occluded conditions (Eastman Kodak, 1979). No distribution data were located for *o*-aminophenol. *o*-Aminophenol is metabolized primarily via conjugation at the phenolic group with sulfate or glucuronide, and the conjugated metabolites are excreted in the urine (Elder, 1988; U.S. EPA, 1985). *N*-acetylation can also occur, forming an acetamidophenol metabolite, which may be further conjugated with glucuronide prior to excretion in the urine (see Table 5) (U.S. EPA, 1985).

Table 5. Percent Recovery of Administered Dose in the Urine over 24 Hours Following a Single Oral Dose of *o*-Aminophenol in Rabbits (1,000 mg/Rabbit)[a]

Parent or Metabolite	Percent of Total
Parent	11
Aminophenylglucuronide	52
Aminophenolsulfate	15
Acetamidophenol	2−4
Acetamidophenylglucuronide	13
Acetamidophenylsulfate	0

[a]U.S. EPA (1985).

Mode-of-Action/Mechanistic Studies

Mode-of-action (MOA)/mechanistic data are consistent with the short-term-duration Eastman Kodak (1979) in vivo study regarding toxicity to RBCs, kidney, and liver. Limited evidence from acute human and animal studies suggests that methemoglobinemia may occur following *o*-aminophenol exposure [Kiese and Rachlor (1964) as cited in Akazawa et al. (2000); Harrison and Jollow (1987); Eastman Kodak (1979)]. *o*-Aminophenol also induces methemoglobin formation in erythrocyte suspensions in vitro (Akazawa et al., 2000; Harrison and Jollow, 1987; Eckert and Eyer, 1983; Smith et al., 1967).

The kidney (Rankin et al., 1996; Itoh, 1987; Newton et al., 1982; Eastman Kodak, 1979; Calder et al., 1971) and liver (Eastman Kodak, 1979) may be potential targets of *o*-aminophenol toxicity. In vitro, *o*-aminophenol was moderately toxic to renal slice cultures from male F344 and S-D rats, as evidenced by significantly reduced glutathione levels and decreased gluconeogenesis in response to stimulation with pyruvate or 1,6-diphosphate at concentrations of ≥0.1 mM (Valentovic and Ball, 1998; Valentovic et al., 1996). Significantly increased LDH leakage (indicative of cell death) was observed at 1 mM in slices from F344 rats only (Valentovic and Ball, 1998; Valentovic et al., 1996). Gluconeogenesis in response to stimulation with pyruvate was also observed in hepatic slices from F344 rats at 2 mM *o*-aminophenol, without evidence of cytotoxicity (Valentovic et al., 1996).

DERIVATION OF PROVISIONAL VALUES

Tables 6 and 7 present summaries of noncancer and cancer references values, respectively.

Table 6. Summary of Noncancer Reference Values for *o*-Aminophenol (CASRN 95-55-6)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value*	POD Method	POD (HED)	UF_C	Principal Study
Screening subchronic p-RfD (mg/kg-d)*	Rat/M	Increased severity of nephrosis	4×10^{-2}	NOAEL	12 (based on surrogate POD)	300	Burnett et al. (1989) as cited in U.S. EPA (2005b)
Screening chronic p-RfD (mg/kg-d)*	Rat/M	Increased severity of nephrosis	4×10^{-3}	NOAEL	12 (based on surrogate POD)	3,000	Burnett et al. (1989) as cited in U.S. EPA (2005b)
Subchronic p-RfC (mg/m^3)	NDr						
Chronic p-RfC (mg/m^3)	NDr						

*See detailed derivation in Appendix A.

HED = human equivalent dose; M = male(s); NDr = not determined; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; UF_C = composite uncertainty factor.

Table 7. Summary of Cancer Reference Values for *o*-Aminophenol (CASRN 95-55-6)

Toxicity Type (units)	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF $(mg/kg\text{-}d)^{-1}$	NDr			
p-IUR $(mg/m^3)^{-1}$	NDr			

NDr = not determined; p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor.

DERIVATION OF ORAL REFERENCE DOSES

No studies were located regarding toxicity of *o*-aminophenol to humans by oral exposure. Oral studies of *o*-aminophenol in animals were of inadequate duration and/or scope to support derivation of a subchronic or chronic provisional reference dose (p-RfD). The only repeated-dose study that evaluated non-neoplastic endpoints was conducted by Eastman Kodak (1979), in which five male rats per dose were fed diets with 0, 83, or 586 mg/kg-day *o*-aminophenol for 12 days. The study is limited by the use of a single sex (male), small animal groups (five/group), and short duration (12 days). As a result of the limitations of the available data for *o*-aminophenol, subchronic and chronic p-RfDs are not derived. Instead, screening p-RfDs are derived in Appendix A using an alternative surrogate approach.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

No subchronic- or chronic-duration inhalation studies of *o*-aminophenol in humans or animals have been located, precluding derivation of provisional reference concentrations (p-RfCs) for *o*-aminophenol based on chemical-specific data. An alternative surrogate approach was attempted, but screening p-RfCs could not be derived due to a lack of inhalation toxicity values for potential surrogates (see Appendix A).

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Table 8 identifies the cancer weight-of-evidence (WOE) descriptor for *o*-aminophenol.

Table 8. Cancer WOE Descriptor for *o*-Aminophenol (CASRN 95-55-6)

Possible WOE Descriptor	Designation	Route of Entry	Comments
"Carcinogenic to Humans"	NS	NA	There are no human data to support this.
"Likely to Be Carcinogenic to Humans"	NS	NA	Results from available animal studies are not sufficient to support this, and no human data are available.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	Results from available animal studies are not sufficient to support this, and no human data are available.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Inhalation and oral**	**No carcinogenicity studies are available that evaluated oral and inhalation exposure.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	The available data do not support this.

NA = not applicable; NS = not selected; WOE = weight of evidence.

No data in humans are available to assess the carcinogenic potential of *o*-aminophenol. *o*-Aminophenol did not cause liver tumors in rats in a 9-month dietary study by Miller and Miller (1948); however, this bioassay is considered inadequate due to lack of appropriate control group, low animal numbers, short duration, limited endpoint analysis, and use of a low dose that did not approach the MTD. The only other studies evaluating the carcinogenic potential of *o*-aminophenol included a drinking water tumor promotion assay and a bladder implantation assay; neither of these limited studies indicated that *o*-aminophenol was a carcinogenic or tumor-promoting agent (Kurata et al., 1987; Clayson et al., 1958). Genotoxicity data suggest that *o*-aminophenol is a weak mutagen and may cause DNA damage and clastogenic effects. Under the U.S. EPA cancer guidelines (U.S. EPA, 2005a), there is inadequate information to assess the carcinogenic potential of *o*-aminophenol.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of quantitative estimates of cancer risk for *o*-aminophenol is precluded by the absence of adequate carcinogenicity data for this compound.

APPENDIX A. SCREENING PROVISIONAL VALUES

For reasons noted in the main provisional peer-reviewed toxicity values (PPRTV) document, it is inappropriate to derive provisional toxicity values for *o*-aminophenol. 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 main 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.

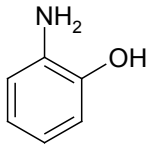
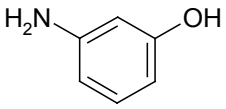
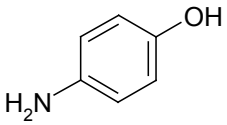
APPLICATION OF AN ALTERNATIVE SURROGATE APPROACH

The surrogate approach allows for the use of data from related compounds to calculate screening values when data for the compound of interest are limited or unavailable. Details regarding searches and methods for surrogate analysis are presented in Wang et al. (2012). Three types of potential surrogates (structural, metabolic, and toxicity-like) are identified to facilitate the final surrogate chemical selection. The surrogate approach may or may not be route-specific or applicable to multiple routes of exposure. In this document, it is limited to the oral noncancer effects only, based on the available toxicity data. All information was considered together as part of the final weight-of-evidence (WOE) approach to select the most suitable surrogate both toxicologically and chemically.

Structural Surrogates (Structural Analogs)

An initial surrogate search focused on the identification of structurally similar chemicals with toxicity values from the Integrated Risk Information System (IRIS), PPRTV, Agency for Toxic Substances and Disease Registry (ATSDR), or California Environmental Protection Agency (Cal/EPA) databases to take advantage of the well-characterized chemical-class information. This was accomplished by searching EPA's DSSTox database (DSSTox, 2016) and the National Library of Medicine's (NLM's) ChemIDplus database (ChemIDplus, 2016). Two structural analogs to *o*-aminophenol were identified that have oral toxicity values: *m*-aminophenol (U.S. EPA, 2006) and *p*-aminophenol (U.S. EPA, 2005b); no structural analogs with inhalation toxicity values were identified. Table A-1 summarizes the physicochemical properties and similarity scores of the structural analogs. The DSSTox similarity scores for both analogs were relatively high (>85% similar), while the ChemIDplus similarity scores were low (<50%). Comparison of physicochemical properties of the surrogates to *o*-aminophenol suggests that they will both behave in a manner analogous to *o*-aminophenol in the environment. Based on this finding, it may be expected that exposure pathways and bioavailability from environmental media might be comparable for the three compounds. Both *m*- and *p*-aminophenol are considered to be appropriate structural surrogates for *o*-aminophenol.

Table A-1. Comparison of Physicochemical Properties for *o*-Aminophenol (CASRN 95-55-6) and Candidate Analogs[a]

	***o*-Aminophenol**	***m*-Aminophenol**	***p*-Aminophenol**
Structure			
CASRN	95-55-6	591-27-5	123-30-8
Molecular weight	109.13	109.13	109.13
DSSTox similarity score (%)[b]	100	86	89
ChemIDplus similarity score (%)[c]	100	<50	<50
Melting point (°C)	173.5[d]	123	187.5
Boiling point (°C)	267[d]	164 (at 11 mm Hg)	284
Vapor pressure (mm Hg at 25°C)	0.0031 (extrapolated)[e]	0.0019 (estimated)[c]	0.00004 (extrapolated)
Henry's law constant (estimated) (atm-m^3/mole at 25°C)	2.0×10^{-10}	2.0×10^{-10}	2.0×10^{-10}
Water solubility (mg/L)	20,000[f]	27,000	16,000
Log K_{ow}	0.62[g]	0.21	0.04
pKa	$pKa_1 = 4.66$[h]; $pKa_2 = 9.71$[h]	4.37	5.48

[a]Data were gathered from the PHYSPROP database for each respective compound unless otherwise specified (U.S. EPA, 2012c).
[b]DSSTox (DSSTox, 2016).
[c]ChemIDplus Advanced, similarity scores (ChemIDplus, 2016).
[d]Haynes et al. (2014).
[e]The vapor pressure was extrapolated from the measured boiling point using a regression-derived equation.
[f]O'Neil et al. (2013).
[g]HSDB (2011).
[h]Mitchell et al. (2003).

Metabolic Surrogates

Oral absorption is high (78−100%) in laboratory animals for *o*-, *m*-, and *p*-aminophenol (U.S. EPA, 1985). In general, metabolism and elimination pathways are the same for the different aminophenol isomers. Each compound is conjugated at the phenolic group with sulfate or glucuronide, and conjugated metabolites are excreted in the urine (Elder, 1988; U.S. EPA, 1985). *N*-Acetylation also occurs, resulting in an acetamidophenol metabolite, which may be further conjugated with sulfate or glucuronide prior to excretion in the urine (Elder, 1988; U.S. EPA, 1985). Different rates for these processes lead to differences in the proportions of the resulting urinary metabolites produced, primarily minor, but also including absence of acetamidophenylsulfate following treatment with *o*-aminophenol and absence of aminophenylsulfate following treatment with *m*-aminophenol (see Table A-2).

Table A-2. Percent Recovery in the Urine over 24 Hours Following a Single Oral Dose in Rabbits (1,000 mg/Rabbit)[a]

Parent or Metabolite	*o*-Aminophenol	*m*-Aminophenol	*p*-Aminophenol
Parent	11	0	2
Aminophenylglucuronide	52	59	45
Aminophenolsulfate	15	0	8
Acetamidophenol	2–4	12–19	13–25
Acetamidophenylglucuronide	13	5	16
Acetamidophenylsulfate	0	15	4

[a]U.S. EPA (1985).

The proximal toxicant(s) of aminophenol isomers' toxicity have not been clearly identified, so it is unclear whether minor differences in the formation and distribution of metabolites observed for aminophenol isomers could result in differences in toxicity. It has been proposed that formation of an electrophilic compound, possibly a benzoquinone imine, is necessary for *p*-aminophenol to induce nephrotoxic effects (Elder, 1988). The acetylated metabolite of *p*-aminophenol is acetaminophen (*N*-acetyl-*p*-aminophenol) (Elder, 1988; U.S. EPA, 1985); however, it is unclear if the toxic metabolite of acetaminophen (*N*-acetyl-*p*-benzoquinone imine [NAPQ1]) is formed following *p*-aminophenol exposure. Renal macromolecule binding assays indicate that either *p*-aminophenol or a nonconjugated metabolite is involved in renal toxicity, and inhibition or alteration of conjugation processes (such as glucuronide formation) increases the severity of the renal lesions (Elder, 1988). Methemoglobin formation following exposure to *p*- and *o*-aminophenol is thought to be caused by cyclic oxidation-reduction transformation of ferro- to ferrihemoglobin via an oxidized quinone imine intermediate (Elder, 1988).

Due to a lack of significant differences in the absorption, distribution, metabolism, and elimination of the aminophenol isomers, as well as insufficient data to identify any difference in proximal toxicants, both *m*- and *p*-aminophenol are considered appropriate metabolic surrogates for *o*-aminophenol.

Toxicity-Like Surrogates

Table A-3 summarizes the available oral and inhalation human health assessment values and acute toxicity data for *o*-aminophenol and the compounds identified as potential surrogates. Acute lethality studies for *o*-aminophenol provide oral median lethal dose (LD_{50}) values in rats and mice. The rat LD_{50} data suggest that *p*-aminophenol may be more acutely toxic than *o*- or *m*-aminophenol.

Table A-3. Comparison of Available Human Health Assessment Values and Acute Toxicity Data for *o*-Aminophenol (CASRN 95-55-6) and Candidate Analogs

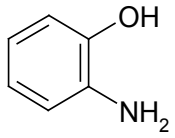
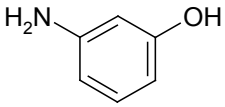
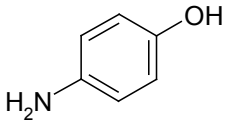
	***o*-Aminophenol**	***m*-Aminophenol**	***p*-Aminophenol**
Structure			
CASRN	95-55-6	591-27-5	123-30-8
Repeat-dose toxicity—oral, subchronic			
POD (mg/kg-d)	NA	80	50
POD type	NA	NOAEL	NOAEL
UF_C	NA	300	300
p-RfD (mg/kg-d)	NA	3×10^{-1}	2×10^{-1}
Critical effects	NA	Reduced body weight and tremors	Increased severity of nephrosis
Other effects	NA	Increased total bilirubin and reticulocyte ratio; thyroid follicular cell hypertrophy	Reduced body weight concomitant with reduced food intake, anemia
Species	NA	Rat (neonatal)	Rat (males, females)
Duration	NA	18 d	90 d
Route	NA	Oral (gavage)	Oral (diet)
Notes	NA	Newborn rats were more sensitive than older rats examined in 4- and 13-wk studies. Effects noted at higher doses in older rats included hemolytic anemia, potential liver toxicity (elevated ALT), and potential kidney toxicity (increased BUN in females, hyaline droplets in males)	Hyperactivity and convulsions, reductions in food consumption and body weight, mild hematological changes, and embryo/fetotoxic effects
Source	NA	U.S. EPA (2006)	U.S. EPA (2005b)
Repeat-dose toxicity—oral, chronic			
POD (mg/kg-d)	NA	240	50
POD type	NA	NOAEL	NOAEL
UF_C	NA	3,000	3,000
p-RfD (mg/kg-d)	NA	8×10^{-2}	2×10^{-2}
Critical effects	NA	Hemolytic anemia	Increased severity of nephrosis
Other effects	NA	Thyroid follicular cell hypertrophy; reduced body weight concomitant with reduced food intake	Reduced body weight concomitant with reduced food intake, anemia
Species	NA	Rat (female)	Rat (males, females)
Duration	NA	90 d	90 d

Table A-3. Comparison of Available Human Health Assessment Values and Acute Toxicity Data for *o*-Aminophenol (CASRN 95-55-6) and Candidate Analogs

	***o*-Aminophenol**	***m*-Aminophenol**	***p*-Aminophenol**
Route	NA	Oral (diet)	Oral (diet)
Notes	NA	NA	NA
Source	NA	U.S. EPA (2006)	U.S. EPA (2005b)
Acute toxicity			
Rat oral LD_{50} (mg/kg)	951	924	375
Toxicity target	Tremor, cyanosis	Excitement, spastic paralysis	Muscle weakness, cyanosis
Mouse oral LD_{50} (mg/kg)	800	401	NA
Toxicity target	Tremor, cyanosis	Excitement, spastic paralysis	NA
Rat inhalation LC_{50} (mg/m^3)	NA	1,162	>5
Toxicity target	NA	Excitement, spastic paralysis	NR
Mouse inhalation LC_{50} (mg/m^3)	NA	NA	NA
Toxicity target	NA	NA	NA
Reference	ChemIDplus (2016)	ChemIDplus (2016)	ChemIDplus (2016)

ALT = alanine aminotransferase; BUN = blood urea nitrogen; LC_{50} = median lethal concentration; LD_{50} = median lethal dose; NA = not applicable; NOAEL = no-observed-adverse-effect level; NR = not reported; POD = point of departure; p-RfD = provisional reference dose; UF_C = composite uncertainty factor.

The repeat-dose oral database for *o*-aminophenol consists of a single unpublished short-term-duration study in rats (Eastman Kodak, 1979); this study is of limited use for risk assessment due to the use of one sex (males), small group sizes (five/group), and short duration (12 days). Based on acute and short-term-duration animal studies, the red blood cells (RBCs) and potentially kidney and liver are targets of *o*-aminophenol toxicity (Rankin et al., 1996; Harrison and Jollow, 1987; Itoh, 1987; Eastman Kodak, 1979).

The critical effects identified following oral exposure to *m*-aminophenol included reduced body weight and tremors in neonatal rats exposed via gavage for 18 days (lowest-observed-adverse-effect level [LOAEL] 240 mg/kg-day) and hemolytic anemia in adult female rats exposed via diet for 90 days (LOAEL 900 mg/kg-day). Other effects noted with repeated oral exposure included increased total bilirubin and reticulocyte ratio and thyroid follicular cell hypertrophy, as well as potential liver and kidney toxicity thought to be secondary to hemolytic anemia (modest increases in alanine aminotransferase [ALT], slight increases in blood urea nitrogen [BUN] in females, and hyaline droplets in males) (U.S. EPA, 2006). The subchronic provisional reference dose (p-RfD) of 0.3 mg/kg-day is based on a point of departure (POD) of 80 mg/kg-day for neonatal effects in the 18-day gavage study, and the chronic p-RfD of 8×10^{-2} mg/kg-day is based on a POD of 240 mg/kg-day for hemolytic anemia in adult female rats (U.S. EPA, 2006).

The critical effect identified following oral exposure to *p*-aminophenol was increased severity of nephrosis in male and female rats exposed via diet for 90 days (LOAEL 150 mg/kg-day). Other effects noted at higher exposure levels included anemia and reduced body weight concomitant with reduced food intake (U.S. EPA, 2005b). Both the subchronic p-RfD of 0.2 mg/kg-day and the chronic p-RfD of 2×10^{-2} mg/kg-day are based on a POD of 50 mg/kg-day for nephrotoxic effects (U.S. EPA, 2005b).

In a comparison of relative toxicities, the subchronic POD value for *p*-aminophenol is fourfold lower than that of *m*-aminophenol. The lower reference value for *p*-aminophenol is based on adverse renal effects that occurred at lower doses than anemia following exposure for 90 days. In animals exposed to *m*-aminophenol for 90 days in the diet, anemia was observed in the absence of renal toxicity, and in young rats in a 28-day gavage study, doses that caused hemolytic anemia produced evidence of only mild kidney damage. Therefore, *p*-aminophenol appears to be a more potent renal toxicant than *m*-aminophenol. While the potency may differ among aminophenol isomers, evidence for similar toxicity targets (kidney and RBC) suggests that both *m*- and *p*-aminophenol are appropriate toxicity-like surrogates for *o*-aminophenol for oral exposure.

No repeat-exposure inhalation studies were available for *o*-, *m*-, or *p*-aminophenol and inhalation toxicity values were not derived.

Weight-of-Evidence Approach

A WOE approach is used to evaluate information from potential candidate surrogates as described by Wang et al. (2012). Commonalities in structural/physicochemical properties, toxicokinetics, metabolism, toxicity, or mode of action between potential surrogates and chemical(s) of concern are identified. Emphasis is given to toxicological and/or toxicokinetic similarity over structural similarity. Surrogate candidates are excluded if they do not have commonality or demonstrate significantly different physicochemical properties and toxicokinetic profiles that set them apart from the pool of potential surrogates and/or chemical(s) of concern. From the remaining potential surrogates, the most appropriate surrogate (most biologically or toxicologically relevant analog chemical) with the highest structural similarity and/or most conservative toxicity value is selected.

The structural surrogate analysis indicated that both *m*- and *p*-aminophenols have relatively high similarity scores (>85%) compared to *o*-aminophenol based on the DSSTox database search. A comparison of physicochemical properties of these surrogates to *o*-aminophenol suggests that these surrogate chemicals share similar physicochemical properties to *o*-aminophenol. Metabolic surrogate analysis indicated that, in general, the metabolism and elimination pathways are the same for the different aminophenol isomers. However, there are insufficient data to identify the proximal toxicant of aminophenols to inform a more refined selection of a particular metabolic surrogate. Based on the acute and short-term-duration animal studies with *o*-aminophenol, the RBC, liver, and kidney are potential toxicity targets. The two surrogate chemicals also share the same toxicity targets (i.e., RBC and kidney), and *m*-aminophenol also affects the liver; nevertheless, relative potency among the aminophenol isomers might differ in each of these target tissues. Thus, these analyses suggest that both candidate analogs, *m*- and *p*-aminophenol, are acceptable as structural, metabolic, and toxicity-like surrogates.

For this assessment, *p*-aminophenol was selected over *m*-aminophenol as the surrogate for *o*-aminophenol for both the subchronic and chronic oral toxicity values because the POD based on *p*-aminophenol will provide a more conservative/health-protective toxicity value for both subchronic and chronic oral exposure to *o*-aminophenol.

ORAL TOXICITY VALUES

Derivation of a Screening Subchronic Provisional Reference Dose

Based on the overall WOE presented in this PPRTV assessment, *p*-aminophenol is selected as the surrogate for *o*-aminophenol for the screening subchronic p-RfD. The study used for the subchronic p-RfD for *p*-aminophenol is a 13-week (90 days) dietary study in male and female weanling Sprague-Dawley (S-D) rats by Burnett et al. (1989) as cited in U.S. EPA (2005b). The PPRTV report for *p*-aminophenol (U.S. EPA, 2005b) described this study as follows:

> *In order to investigate the effects of longer-term oral exposure, a combined subchronic feeding, teratology, and dominant lethal study of p-aminophenol was conducted in rats. Groups of 40 male and 45 female weanling Sprague-Dawley rats were fed diets containing 0, 0.07, 0.20, or 0.70% of p-aminophenol (>98.1% purity) in their diet for 13 weeks (Burnett et al., 1989). At that time, 10 males and 10 females of each group were sacrificed for toxicity evaluation, and 25 females from each group were removed from the test diets and mated with untreated males. After mating, the pregnant females were returned to their test diets throughout gestation and sacrificed on gestation day 20 for fetal examinations. Males not sacrificed at week 13 were continued on their test diets until week 20, when 20 males from each group were removed from the test diets and mated with untreated females in a dominant lethal assay until their sacrifice on week 27. The remaining 10 males and 10 females from each group were maintained on their test diets until sacrifice on week 17. Based on food consumption and body weight data presented graphically in the paper, doses were approximately 0, 50, 150, and 560 mg/kg-day in males and 0, 60, 175, and 620 mg/kg-day in females.*
>
> *Animals were observed daily for general condition and monitored weekly for signs of toxicity, body weight, and feed consumption (Burnett et al., 1989). At 6 weeks, blood was collected from 5 males and 5 females from the high dose group (0.70%) for methemoglobin analyses. At week 12, urine was collected from 10 males and 10 females selected from each group for bacterial mutagenicity testing; and at week 13, the same 10 rats/group were sacrificed and blood collected for hematology and clinical chemistry analysis. At necropsy, the major organs were weighed, and a complete histopathological examination was performed for animals from the control and high dose groups. The liver, kidney, urinary bladder, and gross lesions were also examined from animals in the low- and mid-dose groups. The same procedures were used to collect blood and autopsy rats sacrificed at end of the 27 week study.*
>
> *Hyperactivity and convulsions were noted in a few of the females consuming the high-dose test diet after 6 weeks on study (Burnett et al., 1989). No treatment-related deaths occurred (one low-dose female died of unknown causes). Food consumption was markedly lower than controls in both males and females*

from the high-dose group during the first week of the study, and remained significantly lower than controls for most of the study in both sexes. Body weights of both males and females in this group were significantly lower than controls throughout the study, with deficits of 10−15% in males and 15−20% in females after week 5. Food consumption and body weight were similar to controls in the low and mid-dose groups. Hematology analyses showed statistically significant decreases in red blood cell counts (-10%) and hemoglobin level (-5%) in high-dose females at 13 weeks, but not at 27 weeks. Other hematology and clinical chemistry findings were reportedly unremarkable (data not presented in paper). The assay for methemoglobin in high-dose rats showed no difference from controls. Increased relative weights were observed for several organs in high-dose males and females, secondary to the decrease in body weight at this dose. Statistically significant changes in other organ weights (increased absolute and relative pituitary weight in low- and mid-dose females at 13 weeks, and increased absolute heart weight in low-dose males at 13 weeks) were not considered by the researchers to be treatment-related. No gross lesions were seen at autopsy. Microscopic evaluation revealed nephrosis characterized by cytoplasmic eosinophilic droplets in the tubular epithelial cells of male and female rats of all groups, but with a dose-related increase in incidence and/or severity (Table 1). In males, the lesions were similar to glomerulonephropathy typical of aging rats (albeit more severe in the treated groups), while in females the droplets were smaller and intensely brown. Statistical analysis of the data in Table 1 was performed for this review. The Jonckheere-Terpstra trend test for ordered categorical data showed statistically significant ($p<0.001$) increases in severity of nephrosis with increasing dose in both males and females, using the 13-week data for all 4 dose groups. Pairwise comparisons using the same test showed significant ($p<0.005$) differences from controls in mid- and high-dose males and high-dose females. No other treatment-related histopathological changes were noted. A LOAEL of 150 mg/kg-day (0.2%) and NOAEL of 50 mg/kg-day (0.07%) is identified from this study, based on increased severity of nephrosis in males.

A similar study (Re et al., 1984) with a combined subchronic-duration feeding and teratology of *m*-aminophenol reported similar effects, but these effects occurred at a higher dose level. In this study, four groups of 35 S-D female rats were fed diets containing 0, 0.13, 0.25, or 0.98% *m*-aminophenol. From reported body-weight and food consumption data, average doses are estimated to be about 0, 120, 240, or 900 mg/kg-day.

The PPRTV report for *m*-aminophenol (U.S. EPA, 2006) described findings from this study as follows:

This study identified a LOAEL of 900 mg/kg-day (0.98% in the diet) based on evidence of hemolytic anemia (increased incidence and/or severity of iron-positive pigmentation in the spleen, liver and kidneys, along with reduced red blood cell count and hemoglobin). Body weight was lower than controls in both the mid- and high-dose groups, but the change was minimal in the mid-dose group and was secondary to reduced food intake at both doses (suggesting an organoleptic, rather than toxic, effect). Histological changes in the thyroid consistent with hypertrophy (reduced follicle size and increased follicular

epithelial cell height) were reported in both the mid- and high-dose groups (incidence reported only as "several" animals in the mid-dose group). Thyroid hormone measurements were not made. However, reported changes in thyroid weight were not consistent with a hyperthyroid effect. There was an increase in relative, but not absolute thyroid weight in the high dose group, apparently secondary to the decrease in body weight at this dose. In the mid-dose group, absolute and relative thyroid weights were actually reduced. Therefore, the thyroid effects are considered to be adaptive rather than adverse. Thus, the 240 mg/kg-day dose (0.25%) is considered a NOAEL for m-aminophenol.

Therefore, a POD based on *p*-aminophenol will provide a more conservative/health-protective toxicity value for both subchronic and chronic oral exposure to *o*-aminophenol. The selection of a POD of 50 mg/kg-day is also supported by a 3-month oral toxicity study [Fournier (1981) as cited in SCCS (2010)] in rats treated with 50 mg/kg-day *o*-aminophenol. Based on a secondary report from the Scientific Committee on Consumer Safety (SCCS, 2010), clinical observation, body-weight gain, hematological parameters, blood biochemistry, and urine examination revealed no difference between the treated and the control group. Histopathological examination showed broncho-pulmonary injuries, which did not permit to affirm the toxicity of the *o*-aminophenol. In addition, a developmental toxicity study [Boutemy et al. (1981) as cited in SCCS (2010)] in rats treated with *o*-aminophenol identified a NOAEL of 70 mg/kg-day for maternal and developmental toxicity.

The SCCS report (SCCS, 2010) also reported two 30-day oral toxicity studies in rats treated with *o*-aminophenol. One study [Boutemy (1989) as cited in SCCS (2010)] identified a LOAEL of 20 mg/kg-day (the lowest dose tested) based on increased vacuolization of the urothelium of the bladder in males and females, and observed renal cells in the urine of male rats. The other study [Coleman et al. (1989) as cited in SCCS (2010)] identified a NOAEL of 5 mg/kg-day and a LOAEL of 15 mg/kg-day due to increased thyroid weight. These findings from 30-day studies were inconsistent with the no toxicity effect found in rats treated with 50 mg/kg-day *o*-aminophenol for 3 months [Fournier (1981) as cited in SCCS (2010)], which also included a pathological examination of these target organs/tissues. The toxicity data summarized in the SCCS report are only presented here as supportive evidence because the report has limited information available and makes no final conclusion on the safety of *o*-aminophenol (SCCS, 2010). Further, the studies cited in the SCCS report were not available for review.

Therefore, a POD based on *p*-aminophenol is considered appropriate for deriving screening p-RfDs. The critical effect for the subchronic toxicity portion of the study of *p*-aminophenol was increased severity of nephrosis in male rats; the NOAEL of 50 mg/kg-day for this effect was used as the POD. The subchronic p-RfD for *p*-aminophenol was derived using a composite uncertainty factor (UF_C) of 300 reflecting 10-fold uncertainty factor values for interspecies extrapolation (UF_A), a 10-fold for intraspecies variability (UF_H), and a 3-fold for database uncertainties (UF_D, reflecting lack of a second species in the study). Wang et al. (2012) indicated that the uncertainty factors applied in deriving a surrogate toxicity value for the chemical of concern should be the same as those applied to the selected analog unless additional information is available. However, the EPA endorses body-weight scaling to the 3/4 power (i.e., $BW^{3/4}$) as a default to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purpose of deriving an RfD from effects

that are not portal-of-entry (U.S. EPA, 2011b). Therefore the surrogate POD was converted into a human equivalent dose (HED) and the UF_A was reduced to a 3 (rather than 10-fold) for the derivation of a screening subchronic p-RfD for *o*-aminophenol. Additionally, a 10-fold UF_D (rather than 3-fold) was applied due to lack of useful repeat-dose toxicity studies for *o*-aminophenol (Table A-4).

Following U.S. EPA (2011b) guidance, the POD for the 13-week study in rats exposed to *p*-aminophenol is converted to an HED through the application of a dosimetric adjustment factor (DAF) derived as follows:

$$DAF = (BW_a^{1/4} \div BW_h^{1/4})$$

where:

DAF = dosimetric adjustment factor
BW_a = animal body weight
BW_h = human body weight

Using a reference BW_a of 0.25 kg for rats and a reference BW_h of 70 kg for humans (U.S. EPA, 1988), the resulting DAF is 0.24. Applying this DAF to the NOAEL identified in the 13-week rat study yields a NOAEL (HED) as follows:

POD (HED)	=	NOAEL (mg/kg-day) × DAF
	=	50 mg/kg-day × 0.24
	=	12 mg/kg-day

Using the surrogate POD (HED), the screening subchronic p-RfD for *o*-aminophenol is derived as follows:

Screening Subchronic p-RfD	=	Surrogate POD (HED) ÷ UF_C
	=	12 mg/kg-day ÷ 300
	=	**4×10^{-2} mg/kg-day**

Table A-4 summarizes the uncertainty factors for the screening subchronic p-RfD for *o*-aminophenol.

Table A-4. Uncertainty Factors for the Screening Subchronic p-RfD for *o*-Aminophenol (CASRN 95-55-6)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty associated with extrapolating from animals to humans when a cross-species dosimetric adjustment (HED calculation) is performed.
UF_H	10	A UF_H of 10 is applied for interindividual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of *o*-aminophenol in humans.
UF_D	10	A UF_D of 10 is applied. The repeat-dose oral database for *o*-aminophenol consists of a single study that is limited due to use of one sex (males), small group sizes (five/group), and short duration (12 d). Therefore, the POD is based on a surrogate chemical.
UF_L	1	A UF_L of 1 is applied because the POD is a NOAEL.
UF_S	1	A UF_S of 1 is applied because a subchronic-duration study was selected as the principal study.
UF_C	300	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$.

HED = human equivalent dose; NOAEL = no-observed-adverse-effect level; POD = point of departure; UF = uncertainty factor.

Derivation of a Screening Chronic Provisional Reference Dose

Based on the overall surrogate approach presented in this PPRTV assessment, *p*-aminophenol is selected as the surrogate for *o*-aminophenol for the screening chronic p-RfD. The chronic p-RfD for *p*-aminophenol was derived by adding an additional UF of 10 to extrapolate from subchronic to chronic duration (UF_S); the UF_C was 3,000. Similarly, the screening chronic p-RfD for *o*-aminophenol is derived by factoring in a UF_S of 10 to the screening subchronic p-RfD of 4×10^{-2} mg/kg-day derived above. The screening chronic p-RfD for *o*-aminophenol is derived as follows:

$$\begin{aligned} \textbf{Screening Chronic p-RfD} &= \text{Surrogate POD (HED)} \div UF_C \\ &= 12 \text{ mg/kg-day} \div 3{,}000 \\ &= \mathbf{4 \times 10^{-3} \text{ mg/kg-day}} \end{aligned}$$

Table A-5 summarizes the uncertainty factors for the screening chronic p-RfD for *o*-aminophenol.

Table A-5. Uncertainty Factors for the Screening Chronic p-RfD for *o*-Aminophenol (CASRN 95-55-6)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty associated with extrapolating from animals to humans when cross-species dosimetric adjustment (HED calculation) is performed.
UF_H	10	A UF_H of 10 is applied for interindividual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of *o*-aminophenol in humans.
UF_D	10	A UF_D of 10 is applied. The repeat-dose oral database for *o*-aminophenol consists of a single study that is limited due to use of one sex (males), small group sizes (five/group), and short duration (12 d). Therefore, the POD is based on a surrogate chemical.
UF_L	1	A UF_L of 1 is applied because the POD is a NOAEL.
UF_S	10	A UF_S of 1 is applied because a subchronic-duration study was selected as the principal study.
UF_C	3,000	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$.

HED = human equivalent dose; NOAEL = no-observed-adverse-effect level; POD = point of departure; UF = uncertainty factor.

Derivation of Screening Provisional Reference Concentrations

No subchronic- or chronic-duration inhalation studies examining the effects of candidate analogs for *o*-aminophenol in humans or animals have been located (U.S. EPA, 2006, 2005b), precluding derivation of provisional reference concentrations (p-RfCs) for *o*-aminophenol based on an alternative surrogate approach.

APPENDIX B. REFERENCES

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