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Provisional Peer Reviewed Toxicity Values for

p-Aminophenol
(CASRN 123-30-8)

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

8-8-2005

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR *p*-AMINOPHENOL (CASRN 123-30-8)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. EPA's Integrated Risk Information System (IRIS).

2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in EPA's Superfund Program.

3. Other (peer-reviewed) toxicity values, including:

   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's Integrated Risk Information System (IRIS). PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because science and available information evolve, PPRTVs are initially derived with a three-year life-cycle. However, EPA Regions (or the EPA HQ Superfund Program) sometimes request that a frequently used PPRTV be reassessed. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

No RfD, RfC, or cancer assessment for *p*-aminophenol is available in the HEAST (U.S. EPA, 1997). The source document for the HEAST, the Health and Environmental Effects Profile (HEEP) for Aminophenols (U.S. EPA, 1985), concluded that the data for *p*-aminophenol were inadequate for risk assessment. *p*-Aminophenol is not listed on IRIS (U.S. EPA, 2005a) or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2002). The HEEP is the only relevant document included in the CARA list (U.S. EPA, 1991, 1994). ATSDR (2003) has not produced a Toxicological Profile for *p*-aminophenol and no Environmental Health Criteria Document is available (WHO, 2003). Neither NTP (2003) or IARC (2003) has assessed the carcinogenicity of *p*-aminophenol. ACGIH (2003), NIOSH (2003), and OSHA (2003) have not recommended occupational exposure limits for *p*-aminophenol. Literature searches were conducted from 1984 through 2003 for studies relevant to the derivation of provisional toxicity

values for *p*-aminophenol. Databases searched included: TOXLINE (supplemented with BIOSIS and NTIS updates), MEDLINE, CANCERLIT, TSCATS, RTECS, CCRIS, DART, EMIC/ EMICBACK, HSDB, and GENETOX. An additional literature search from January 2002 through July 2005 was conducted by NCEA-Cincinnati using MEDLINE, TOXLINE, Chemical and Biological Abstracts databases and no additional information was found.

p-Aminophenol is a metabolite of the industrial chemical aniline, the pesticide isopropyl carbanilate, and analgesics such as acetaminophen (paracetamol, N-acetyl-p-aminophenol) and phenacetin (4-ethoxyphenyl-N-acetamide). It is also used in photographic processes, an intermediate in the manufacture of sulfur and azo dyes, in dyeing furs and feathers, and a component of oxidative hair color formulations (Budavari, 2001; Benya and Cornish, 1994; Elder, 1988).

REVIEW OF PERTINENT DATA

Human Studies

No data regarding the toxicity of *p*-aminophenol to humans following chronic or subchronic exposure by any route were located.

Animal Studies

Acute administration of *p*-aminophenol via the subcutaneous, intravenous, or oral routes in animals have been reported to cause nephrotoxicity (Calder et al., 1971; Kiese et al., 1975; Newton et al., 1982, 1983a,b,c; Cottrell et al., 1976; Gartland et al., 1989; Gyrd-Hansen, 1974; Crowe et al., 1979; Tange et al., 1977; Shao and Tarloff, 1996), methemoglobin formation (Cox and Wendel, 1942; Kiese et al., 1975; Miller and Smith, 1970; Fraser and Vesell, 1968; Wind and Stern, 1977; Harrison and Jollow, 1981, 1987), and convulsions (Angel and Rogers, 1972). The renal effects were characterized histologically by tubular necrosis, and associated with increased levels of enzymes indicative of renal damage in urine and serum (e.g., blood urea nitrogen) and measures of impaired renal function (e.g., decreased accumulation of organic ions of *p*-aminohippurate).

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 27. 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 analyses. 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 of 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 count (-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 at13 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 lesion was 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.

Table 1. Incidence and Severity of Nephrosis (Eosinophilic Droplets in Tubular Cells) in Sprague-Dawley Rats Exposed to *p*-Aminophenol in the Diet (Burnett et al., 1989)

Dietary Concentration (%)	Treatment period (wk)	Incidence of Nephrosis Graded as None (0), Minimal (1), Mild (2), Moderate (3), or Marked (4)									
		Males					Females				
		0	1	2	3	4	0	1	2	3	4
0	13	3/10[a]	5/10	2/10	0/10	0/10	8/10[a]	2/10	0/10	0/10	0/10
0.07	13	0/10	8/10	2/10	0/10	0/10	5/10	4/10	1/10	0/10	0/10
0.20	13	0/10[b]	2/10	8/10	0/10	0/10	6/10	3/10	1/10	0/10	0/10
0.70	13	0/10[b]	0/10	0/10	8/10	2/10	0/10[b]	4/10	4/10	2/10	0/10
0.70	20[c]	1/20	4/20	6/20	6/20	3/20			N/A		
0	27	0/10	6/10	4/10	0/10	0/10	5/10	2/10	3/10	0/10	0/10
0.70	27	1/10	0/10	2/10	5/10	3/10	1/10	6/10	3/10	0/10	0/10

[a] statistically significant trend for increasing severity of nephrosis with increasing dose ($p<0.001$, Jonckheere-Terpstra test conducted for this review)

[b] statistically significant increase in severity of nephrosis versus controls ($p<0.005$, Jonckheere-Terpstra test conducted for this review)

[c] male rats from the dominant lethal study, which were exposed for 20 weeks and then examined at 27 weeks after 7 weeks on control diet

For the teratogenicity portion of this study, 25 females were discontinued from the test diet after 13 weeks, replaced with basal diet, and mated with one untreated male rat (Burnett et al., 1989). Inseminated females were returned to their original test diets. Pregnant females were observed daily for condition and signs of toxicity. Body weights were recorded on gestation days 0, 6, 9, 12, and 20. Food consumption was measured on days 11 and 19 in 10 dams from each test diet group. All female rats were sacrificed on gestation day 20 and uterus and ovaries examined to determine the numbers of live and dead fetuses, early and late resorptions, and

corpora lutea. Live fetuses were removed, dried, weighed, and examined for external gross malformations and sex determination. One-half of the live fetuses of each litter were fixed for examination of soft tissue anomalies, and the remainder were fixed and stored for examination for skeletal anomalies. Maternal weight gain was significantly reduced throughout gestation in the high-dose group (about 30% lower than controls over all of gestation), although food consumption during gestation did not differ from controls. Numbers of live fetuses, implantation sites, and corpora lutea were similar in all dose groups, but the high- dose group showed statistically significant increases in the number of dams with resorptions and total resorptions, and a significant 13% decrease in mean pup weight when compared to controls. Examination of fetuses from this group found significant increases in the numbers of both fetuses and litters with fetuses showing unossified sternebrae and 14th rudimentary ribs (both considered minor skeletal variations). The incidence of 14th rudimentary ribs was also significantly increased (on the basis of both fetuses and litters) in the mid-dose group, although the incidence was much lower than in the high-dose group. The researchers noted that occurrence of this particular variation is highly variable, and that the incidence of litters with this variation in the mid-dose group was comparable to historical controls in their laboratory. The researchers also suggested that effects in the high-dose group were probably secondary to reduced maternal weight gain in this group. This study identified a LOAEL of 620 mg/kg-day and NOAEL of 175 mg/kg-day for both overt maternal toxicity in dams and embryo/fetotoxic effects of *p*-aminophenol.

The dominant lethal portion of this study was conducted using groups of 20 males from each dose group that were removed from the test diet after 20 weeks and placed on basal diet for the remainder of the study while being mated to two untreated females in each of two separate 6-day sessions (Burnett et al., 1989). Females were observed daily for pregnancy and weighed periodically during gestation. The females were sacrificed on day 17 of gestation and the uterine contents examined. There was a statistically significant increase in the total number of resorptions, but not the number of dams with resorptions, in the high-dose group in the first mating; neither endpoint was affected in the second mating. Other statistically significant changes were reported in the results of the first mating, but these were slight, not dose-related, and not duplicated in the second mating. In order to provide more conclusive results, the researchers conducted a second dominant lethal assay using the same protocol, but starting with rats fed the test diets for 8 weeks. No significant differences from controls were seen. Therefore, the high dose of 560 mg/kg-day in males was a NOAEL for this portion of the study. Results of the *Salmonella* mutagenicity study using urine of the treated rats were negative.

The results of another rat oral teratology study of *p*-aminophenol were briefly reported in an abstract (Spengler et al., 1986). In this study, maternal toxicity and teratogenicity (neither effect described in any more detail) were both observed at doses of 250 mg/kg-day, but not 85 or 25 mg/kg-day, in rats treated orally on days 6-15 of gestation. While these results are consistent with those of Burnett et al. (1989), the lack of available details regarding study methods and results prevents independent evaluation of this study.

Developmental effects were studied by multiple routes of exposure in hamsters. Groups of pregnant Syrian golden hamsters (LKV strain) were given *p*-aminophenol either by oral gavage (0, 100, or 200 mg/kg), intraperitoneal (*i.p.*) injection (0, 100, 150, or 200 mg/kg), or intravenous (*i.v.*) injection (0, 100, 150, 200, or 250 mg/kg) on gestation day 8 (Rutkowski and Ferm, 1982). Dams were sacrificed on gestation day 13 and the uteri removed and contents examined. *p*-Aminophenol produced statistically significant, dose-related increases in incidence of litters with resorptions, incidence of litters with malformed fetuses, and total number of malformed fetuses when administered *i.p.* or *i.v.* No effects were seen by oral exposure. 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). *p*-Aminophenol was not toxic to the dams at these doses.

Few studies were located that examined the carcinogenicity of *p*-aminophenol. As reviewed in IARC (1974), administration of diets containing 0.09-0.2% of *p*-aminophenol hydrochloride to groups of 12-15 rats for periods of 270 to 341 days did not result in any increased incidence of tumors (Ekman and Strömbeck, 1949a,b; Miller and Miller, 1948). No other study details were provided.

Kurata et al. (1987) investigated the ability of *p*-aminophenol to promote development of tumors induced by N-ethyl-N-hydroxyethylnitrosamine (EHEN). Three groups of 25 male Fischer 344 rats were studied over a 52-week period. Two groups were initiated with 0.1% EHEN in the drinking water for 2 weeks. Starting on week 3 and continuing through the end of the study, one of the groups was fed a diet containing 0.8% *p*-aminophenol; the other group received a basal diet throughout the study. The third group was fed the 0.8% *p*-aminophenol test diet without EHEN-pretreatment. The 0.8% dietary concentration is estimated to provide approximately 400 mg/kg-day of *p*-aminophenol, assuming a rat in a chronic study consumes a quantity of food equivalent to 5% of his body weight per day. All rats were sacrificed in week 52; the body, liver, and kidney weights were recorded. Liver and kidney sections were evaluated by histology and the liver by immunohistochemical determinations for glutathione S-transferase placental type (GST-P) positive foci. No liver or kidney lesions were seen in uninitiated rats treated with *p*-aminophenol. There was some evidence for weak promotional activity by *p*-aminophenol in the kidney. Full size renal adenomas were not seen in rats treated with EHEN alone, but occurred with statistically significant incidence in rats treated with both *p*-aminophenol and EHEN. An adenocarcinoma was noted in one animal treated with both compounds. In the liver, *p*-aminophenol appeared to weakly inhibit development of preneoplastic lesions in rats initiated with EHEN; rats receiving both compounds showed significant decreases in the number and area of GST-P positive foci, in comparison to rats that received EHEN alone. However, the incidence of hepatocellular carcinoma was similar in both groups.

Other Studies

p-Aminophenol was not mutagenic to *Salmonella typhimurium* or *Escherichia coli* with or without metabolic activation in all available studies (Watanabe et al., 1991; Zeiger et al., 1988; Thompson et al., 1983; DeFlora et al., 1984; Lavoie et al., 1979; Degawa et al., 1979; Sawamura et al., 1978; Garner and Nutman, 1977; Yoshikawa et al., 1976; McCann et al., 1975; Mamber et al., 1984), with the exception of a report by Wild et al. (1980) for a positive result in strain TA1535 without (but not with) metabolic activation. The urine of rats fed up to 0.7% of *p*-aminophenol in the diet for 12 weeks was also negative for mutagenicity in *Salmonella* (Burnett et al., 1989). Assays for DNA damage in *Escherichia coli* (differential survival in repair proficient and deficient strains) reported mixed results for *p*-aminophenol (positive: Hellmér and Bolcsfoldi, 1992 and DeFlora et al., 1984; negative: Mamber et al., 1983).

In mammalian cells *in vitro*, *p*-aminophenol tested positive in assays for forward mutation in L5178Y mouse lymphoma cells at the $tk^{+/-}$ locus (Amacher and Turner, 1982; Oberly et al., 1984; Majeska and Holden, 1995). However, tests for mutagenicity at the HGPRT locus were negative in both the mouse lymphoma cells (Majeska and Holden, 1995) and in Chinese hamster ovary (CHO) cells (Majeska and Holden, 1995; Oberly et al., 1993). The chemical induced chromosomal aberrations and single-strand DNA breaks in both types of cells (Majeska and Holden, 1995). Assays for sister chromatid exchange (SCE) were positive in Chinese hamster (V79) cells (Wild et al., 1981), mixed in human peripheral lymphocytes (positive: Takehisa and Kanaya, 1982; negative: Kirchner and Bayer, 1982), and negative in human fibroblasts (Wilmer et al., 1981), although cytotoxicity interfered with the results in the latter study. *p*-Aminophenol did not induce unscheduled DNA synthesis in cultured rat hepatocytes (Probst et al., 1981; Thompson et al.,1983), but did inhibit DNA synthesis in human lymphoblastoid cells (Hayward et al., 1982).

In vivo assays found that *p*-aminophenol induced chromosome breaks and micronucleus formation in mouse bone marrow cells (Mitra and Manna, 1971; Wild et al., 1980, 1981) and hepatocytes (Cliet et al., 1989), but not rat bone marrow cells (Hossack and Richardson, 1977). Administered *in vivo*, the chemical had no effect on SCE in Chinese hamster bone marrow cells (Kirchner and Bayer, 1982). *p*-Aminophenol induced sperm head abnormalities in treated mice (Topham, 1980; Wild et al., 1980, 1981), but was negative in a sex-linked recessive lethal test in *Drosophila melanogaster* (Eiche et al., 1990) and a dominant lethal test in rats (Burnett et al., 1989).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR *p*-AMINOPHENOL

No studies examining the effects of *p*-aminophenol in orally exposed humans were located. The oral subchronic and developmental toxicity of *p*-aminophenol was studied in rats by Burnett et al. (1989). This study identified the kidney as the most sensitive target for *p*-aminophenol. Gross neurological effects (hyperactivity and convulsions), marked reductions in food consumption and body weight, mild hematological changes, renal lesions (increased incidence/severity of eosinophilic droplets in tubule cells), and embryo/fetotoxic effects all occurred at the high dose of 0.7% (560 mg/kg-day in males and 620 mg/kg-day in females). The renal lesions, which were increased in both males and females at the high dose, were also increased in males at the mid-dose of 150 mg/kg-day. On this basis, the study defined a LOAEL of 150 mg/kg-day and NOAEL of 50 mg/kg-day for subchronic oral exposure to *p*-aminophenol. There is abundant evidence from acute studies that the kidney is an important target for *p*-aminophenol (e.g., Kiese et al., 1975; Newton et al., 1982, 1983a,b,c; Gartland et al., 1989; Shao and Tarloff, 1996). In the acute studies, the renal effects were characterized histologically by tubular necrosis, and associated with increased levels of enzymes indicative of renal damage in urine and serum (e.g., blood urea nitrogen) and measures of impaired renal function (e.g., decreased accumulation of organic ions of *p*-aminohippurate).

In the Burnett et al. (1989) study, developmental effects were seen only at the high dose of 620 mg/kg-day, which also produced overt maternal toxicity (marked decrease in body weight gain). The results of other oral developmental toxicity studies are consistent with this result (Spengler et al., 1986; Rutkowski and Ferm, 1982), although parenteral experiments have demonstrated that *p*-aminophenol has potential to selectively target the fetus and produce malformations when administered by *i.p.* or *i.v.* injection (Rutkowski and Ferm, 1982).

A provisional **subchronic RfD of 0.2 mg/kg-day** for *p*-aminophenol is derived by applying to the rat oral subchronic NOAEL of 50 mg/kg-day from the Burnett et al. (1989) study an uncertainty factor of 300 (10 for extrapolation from rats to humans, 10 for protection of sensitive individuals, and 3 for deficiencies in the data base including the lack of a second species in the study) as follows:

p-sRfD	=	NOAEL / UF
	=	50 mg/kg-day / 300
	=	0.2 or 2E-1 mg/kg-day

A provisional **chronic RfD of 0.02 mg/kg-day** for *p*-aminophenol is similarly derived by incorporating an additional uncertainty factor of 10 to extrapolate from subchronic to chronic duration (total UF = 3000):

p-RfD = NOAEL / UF
= 50 mg/kg-day / 3000
= 0.02 or 2E-2 mg/kg-day

Confidence in the principal study is medium. The study included an adequate number of animals and dose groups, and investigated an adequate array of endpoints, but not all results were reported in sufficient detail for independent evaluation in the paper. Both a NOAEL and LOAEL were identified. Confidence in the database is low. The principal study evaluated both subchronic and developmental toxicity, but no other adequate long-term oral studies were located. The results of the principal study were supported primarily by acute data, although some supporting developmental toxicity data were also located. Overall confidence in the provisional subchronic and chronic RfD values is low.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR *p*-AMINOPHENOL

No chronic or subchronic inhalation studies examining the effects of *p*-aminophenol in humans or animals were located, precluding derivation of provisional RfC values for *p*-aminophenol.

DERIVATION OF A PROVISIONAL CARCINOGENICITY ASSESSMENT FOR *p*-AMINOPHENOL

No data in humans are available to assess the carcinogenic potential of *p*-aminophenol. Studies in animals were negative, but were not adequate bioassays. *p*-Aminophenol weakly promoted development of renal, but not liver, tumors initiated by EHEN. Genotoxicity data suggest the chemical has some potential to produce effects on DNA, although study results were mixed. Under the U.S. EPA (2005b) Guidelines for Carcinogen Risk Assessment, there is inadequate information to assess the carcinogenic potential of *p*-aminophenol.

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