10-25-2006

Provisional Peer Reviewed Toxicity Values for

m-Aminophenol
(CASRN 591-27-5)

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
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
i.v.	intravenous
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level
MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration

p-RfD	provisional oral reference dose
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR *m*-AMINOPHENOL (CASRN 591-27-5)

Background

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

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

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

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

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

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

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

Disclaimers

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

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

Questions Regarding PPRTVs

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

INTRODUCTION

m-Aminophenol is not listed on IRIS (U.S. EPA, 2006) or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2004). The HEAST (U.S. EPA, 1997) lists a subchronic RfD value of 7E-1 mg/kg-day and a chronic RfD of 7E-2 mg/kg-day for *m*-aminophenol based on altered weights for both the whole body and thyroid in rats exposed to *m*-aminophenol in their diet for 13 weeks. The source document for this assessment was a Health and Environmental Effects Profile (HEEP) for Aminophenols (U.S. EPA, 1985). No RfC or carcinogenic assessment for *m*-aminophenol is available in the HEAST (U.S. EPA, 1997) or HEEP (U.S. EPA, 1985). The HEEP is the only relevant document included in the CARA list (U.S. EPA, 1991, 1994). ATSDR (2006) has not produced a Toxicological Profile for *m*-aminophenol and no Environmental Health Criteria document is available (WHO, 2006). Neither NTP (2006) nor IARC (2006) has assessed the carcinogenicity of *m*-aminophenol. ACGIH (2005), NIOSH (2006), and OSHA (2006) have not recommended occupational exposure limits for *m*-aminophenol. Literature searches were conducted from 1984 through 2003 in TOXLINE (supplemented with BIOSIS and NTIS updates), MEDLINE, CANCERLIT, TSCATS, RTECS, CCRIS, DART, EMIC/ EMICBACK, HSDB, and GENETOX. Update literature searches from

2003 through October 2005 were conducted in MEDLINE, TOXLINE (NTIS subfile), TOXCENTER, TSCATS, CCRIS, DART/ETIC, GENETOX, HSDB, RTECS, and Current Contents. An additional update literature search of Medline (October 2005 to April 2006) was conducted in April, 2006.

REVIEW OF PERTINENT DATA

Human Studies

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

Animal Studies

No data were located on the toxicity to animals of inhaled *m*-aminophenol. Studies on the oral toxicity of *m*-aminophenol are discussed below.

A combined subchronic toxicity and developmental toxicity study of *m*-aminophenol was conducted in rats. Four groups of 35 Sprague-Dawley female rats were fed diets containing 0, 0.13, 0.25 or 0.98% *m*-aminophenol for 90 days (Re et al., 1984). From reported body weight and food consumption data, average doses are estimated to be about 0, 120, 240 or 900 mg/kg-day. Animals were observed daily for mortality and signs of toxicity. Food consumption and body weights were recorded weekly. After 13 weeks, 10 females from each group were randomly selected for sacrifice, necropsy and histopathology. Prior to necropsy, blood samples were collected for hematology and clinical chemistry analyses (not further described). Organ weights were recorded for the adrenals, kidneys, ovaries, liver, heart, thyroid, brain and pituitary. Organs from rats in the high exposure (0.98%) and control groups that were prepared for histologic examination were the following (organs with * were also evaluated from the low and middle exposure groups): brain, thyroids with parathyroids*, heart, kidney*, intestines, urinary bladder, skeletal muscle, uterus, pituitary, lungs, spleen, pancreas, ovaries*, adrenals*, eyes, salivary gland, peribronchial lymph node, liver*, stomach, bone with marrow, mammary gland and all gross abnormalities.

The remaining 25 rats from each group were mated to untreated male rats during week 14 (Re et al., 1984). Confirmed pregnant females (designated gestation day 0) were moved to individual cages to resume test diet. Dams were observed daily for physical condition and signs of toxicity; body weights were recorded on days 0, 6, 9, 12, 15 and 20 of gestation. Feed consumption was determined for 10 dams per treatment group on gestation days 11 and 19. Each female was sacrificed on gestation day 20 and uterus and ovaries were examined. The numbers of live and dead fetuses and early and late resorptions were recorded, as were the total number of corpora lutea on both ovaries. Live fetuses were removed, dried, weighed and examined for external gross malformations and sex determination. One-third of the live fetuses

of each litter were fixed for examination of soft tissue anomalies and the remaining two-thirds were fixed and stored for examination for skeletal anomalies.

Dose-related reductions in food intake and body weight were noted in treated rats (Re et al., 1984). Weekly food intake was 20% lower than controls during the first week of the study in the high-dose group and similar deficits occurred throughout the study in this group. As a result, body weights in this group were significantly reduced throughout the study, with the deficit from controls increasing from 12% at the end of the first week to 21% after 13 weeks. Statistically significant, but much less severe (on the order of 5%), reductions in food consumption and body weight were also seen in the mid-dose group. Food intake and body weight in the low-dose group were similar to controls. Hematological changes were found only in the high-dose group, including significant decreases in red blood cell count (10%) and hemoglobin levels (4%). Clinical chemistry variables were unaffected at any dose. Organ weight changes were observed only in the thyroid, although the data were not presented in the publication. Relative thyroid weight was reportedly increased in the high-dose group, probably secondary to the reduced body weight in this group (absolute thyroid weight was apparently unchanged from controls in this group). On the other hand, both relative and absolute thyroid weights were reported to be significantly decreased in the low- and mid-dose groups. Gross changes were not seen in the thyroid or other tissues at necropsy. Histopathological examination revealed reduced follicle size and increased height of follicle epithelial cells (consistent with hypertrophy) in thyroids from 9/10 rats in the high-dose group. Similar changes were also seen in several animals from the mid-dose group (incidence not reported), but not in the low-dose group. Deposits of iron-positive pigment were found in the spleen, liver and kidneys in a dose-related fashion. Pigmentation in the liver was noted in 8/10 high-dose, 2/10 low- and mid-dose and 3/10 control animals. Renal tubular pigmentation was observed in 8/10 high-dose, 1/10 mid-dose, 2/10 low-dose and 1/10 control animals. Deposits in the spleen were seen in all control and high-dose animals (not evaluated in low- or mid-dose groups), but the severity was only slight-to-moderate in controls versus moderately severe-to-severe in the high-dose rats. The increased deposition of iron pigments, together with the reductions in red blood cell count and hemoglobin in the high-dose group, indicate a hemolytic anemia at this dose.

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.

In the teratology portion of the study, as in the pre-mating period described above, body weights were significantly decreased in the high- and mid-dose groups (Re et al., 1984). The deficit from controls was 16-20% in the high-dose group, but only 5-6% in the mid-dose group. Food consumption was reduced in the high-dose group; food consumption data were not reported for the mid-dose group. None of the dams died during the study and no other signs of maternal toxicity were observed. No significant differences between control and treated groups were seen for fertility, incidence of corpora lutea, total implantation sites, live fetuses, resorptions, dead fetuses, male/female ratios, fetal weight or fetal variations or malformations. The high dose of 900 mg/kg-day is a NOAEL for developmental effects of *m*-aminophenol in this study.

Koizumi et al. (2002) compared the toxicity of *m*-aminophenol administered by gavage to newborn and young Sprague-Dawley rats. Study protocols differed for the newborn and young rats and are described independently here. Newborn rats (6/sex/dose) were given *m*-aminophenol by gavage at doses of 0, 30, 80 or 240 mg/kg-day (range-finding study) or 0, 24, 80 or 240 mg/kg-day (main study) on postnatal days 4-21. In the range-finding study, rats were examined during the exposure period for behavior, body weight, and physical development (including abdominal fur appearance, incisor eruption and eye opening). The animals were sacrificed on postnatal day 22 and evaluated for hematology effects [red blood cell (RBC) count, hemoglobin (Hb), hematocrit (Ht), white blood cell count and platelet count], blood biochemistry changes [total protein, total cholesterol, glucose, urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP)], gross findings and organ weight changes (organs not specified). In the main study, two groups of rats were assigned to each dose. One group was sacrificed on postnatal day 22, while the other group was withdrawn from treatment, maintained for a 9-week recovery period and sacrificed at 12 weeks of age. In the main study, the rats were subjected to the same clinical, hematological, biochemical and gross pathology examinations as conducted in the range-finding study, as well as the following evaluations: physical development parameters (preputial separation, vaginal opening, reflex ontogeny); hematology [mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and hemoglobin concentration (MCHC), platelet count, reticulocyte ratio, differential leukocyte count and blood clotting parameters]; blood biochemistry [albumin, albumin-globulin ratio, triglycerides, creatinine, gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), phospholipid, calcium, inorganic phosphorus, sodium, potassium, chloride], organ weights (brain, pituitary, heart, thymus, liver, kidneys, spleen, adrenals, thyroids, lungs, testes, epididymides, ovaries and uterus) and histopathology (all weighed organs, as well as trachea, pancreas, lymph node, esophagus, submandibular gland, sublingual gland, stomach, intestine, urinary bladder, eyeballs, spinal cord, sciatic nerve, seminal vesicles, prostates, vagina, mammary gland, bone and bone marrow, skeletal muscle and skin).

Effects on treated animals were the same in both the range-finding and main studies. Newborn rats receiving the highest dose showed clinical signs of toxicity (tremors in all animals in the main study from dosing days 2 to 12, with incidence decreasing to 0 by days 16 and 17) and significantly reduced body weight (when compared with controls) beginning on dosing day 8

in males and on dosing day 4 in females. Terminal body weight in the high dose animals was 10% lower than controls in males and 13% lower in females. Because the newborn rats were suckled by foster mothers, it is not possible to determine whether decreased food intake may have contributed to the lower body weights. Hematological findings were unremarkable; the only effect reported was a slight increase in reticulocyte ratio in high dose males (21.7% in treated vs. 18.0% in controls; statistical significance not reported). Serum chemistry did not reveal changes in ALT or AST. Total bilirubin was significantly increased in high-dose animals of both sexes (26% increase over controls in males; 50% increase in females). Other findings included a dose-related decrease in blood glucose in females (10% decrease from controls at 80 mg/kg-day; 21% decrease at 240 mg/kg-day), and a 25% decrease in BUN in high-dose females. Weight changes were observed in several organs (brain, liver, kidney, spleen), but the changes were seen primarily in the high-dose group and appeared to reflect decreased body weight in this group. Histological evaluation revealed slight hypertrophy of thyroid follicular cells (in 4/6 males and 2/6 females) at 240 mg/kg-day (incidence, if any, in controls and other dose groups not reported), with no other histology findings. Despite the evidence for hypertrophy, there were no changes in thyroid weight in any group. Among the recovery groups sacrificed 9 weeks after treatment ended, the only findings were slightly increased RBC (6%), Hb (5%) and Ht (7%) in females in the 240 mg/kg-day group.

This study identified a NOAEL of 80 mg/kg-day and a LOAEL of 240 mg/kg-day for newborn rats. The researchers considered the 240 mg/kg-day dose to be "unequivocally toxic." Effects in the 240 mg/kg-day group included reduced body weight, tremors, changes in serum bilirubin and reticulocyte ratio, and slight hypertrophy of thyroid follicular cells. Because the rats were suckled by foster mothers and food consumption could not be monitored, it is uncertain to what extent the reduction in body weight may have been related to an effect on food consumption. The incidence of tremors, while high at the beginning of exposure (all rats affected), decreased over the course of exposure and had declined to 0 by day 16 or 17 of treatment, suggesting that the animals had developed tolerance to the exposure. The mild change in reticulocyte ratio and elevated bilirubin at the high dose could be signs of mild or compensated hemolytic anemia; however, no other hematology changes were noted in these animals (RBC, Hb and Ht were not different from controls), nor was there evidence of hemosiderin deposition. The mild thyroid follicular cell hypertrophy observed in this study may reflect an adaptive response to m-aminophenol exposure, rather than an adverse effect. No corresponding changes in thyroid weight were found, and other endpoints that would more clearly identify a toxic effect on the thyroid (thyroid activity and thyroid hormone levels in serum) were not monitored.

In a separate series of experiments, young (5-week old) rats were treated with *m*-aminophenol by gavage for either 14 days (range-finding study) or 28 days (main study) (Koizumi et al., 2002). In the range-finding study, groups of 5 rats/sex/dose were given 0, 80, 200 or 500 mg/kg-day *m*-aminophenol and sacrificed 24 hours after the last exposure. General behavior, body weight and food consumption were monitored. Upon sacrifice, hematology (RBC, Hb, Ht, MCV, MCH, MCHC, white blood cell count and platelet count), blood chemistry (total protein, total cholesterol, glucose, triglycerides, BUN, creatinine, AST, ALT, ALP, sodium, potassium, chloride), gross findings and organ weights (organs unspecified) were

evaluated. In the main study, groups of 7 rats/sex/dose were administered daily doses of 0, 80, 240 or 720 mg/kg-day. Animals were sacrificed one day after the last treatment. Separate control and high-dose recovery groups were maintained for 2 weeks after the 28-day exposure and sacrificed at 11 weeks of age. Rats in the main study were examined for general behavior, body weight and food consumption, and subjected to urinalysis, hematology, blood biochemistry, necropsy, organ weight and histopathological evaluations. These evaluations were not detailed, but were reported to comply with the Test Guideline of the Japanese Chemical Control Act under Good Laboratory Practice conditions.

Rats exposed to 720 mg/kg-day in the main experiment exhibited tremors and salivation sporadically throughout the study. Timing of these effects in relation to daily dose administration was not reported. Terminal body weights were significantly ($p<0.01$) lower than controls in males at 720 mg/kg-day (12%). Body weights in females at this dose were also lower than controls (10%), although the difference did not reach statistical significance. Females treated at 720 mg/kg-day and sacrificed upon termination of exposure in the main study showed signs of anemia, including significantly ($p<0.05$) decreased RBC (10% lower than control) and Hb (8% reduction) and increased reticulocyte ratio (77% increase). These effects were not observed at doses up to 500 mg/kg-day in the range-finding study. Clinical chemistry evaluations revealed significantly ($p<0.05$) increased ALT in animals of both sexes treated at 720 mg/kg-day (59% increase in males; 46% increase in females), increased total cholesterol in high dose males (21% higher than controls) and decreased triglycerides in high dose males (47% lower), potentially indicating effects on the liver. High dose animals of both sexes had increased total bilirubin (2.2-fold higher than controls in males; 1.6-fold in females), likely resulting either from liver toxicity or from hemolytic anemia. BUN was increased (24%) in high dose females, suggesting possible renal toxicity.

Relative liver and kidney weights were significantly ($p<0.01$) increased in both sexes at 720 mg/kg-day only (22% and 16%, respectively, in males; 17% and 18%, respectively, in females). However, absolute liver and kidney weights were not significantly different from controls in either sex, so the relative organ weight changes may reflect only reduced body weight at this dose. Similarly, relative brain and testes weights were increased in high dose males (18% and 19%, respectively, $p<0.01$), but these changes were likely associated with body weight reductions. In contrast, both absolute and relative thyroid weights were substantially increased in both sexes treated at 720 mg/kg-day (54% and 77%, respectively, in males; 67% and 85%, respectively, in females), suggesting a specific effect on the thyroid. In addition, absolute and relative spleen weights were increased in females treated at this dose (39% and 50%, respectively), possibly in response to the hemolytic anemia. Histopathology evaluation revealed changes consistent with hemolytic action (pigment or hemosiderin deposition) in the liver, kidneys and spleen (all 720 mg/kg-day animals of both sexes). Slight deposition of pigment in the renal proximal tubular epithelium was observed in 6 of 7 females treated at 240 mg/kg-day. Hypertrophy of thyroid follicular cells (5/7 females and 3/7 males) was observed in the 720 mg/kg-day animals and is consistent with the increase in thyroid weight in both sexes. Also at this dose, the incidence of hyaline droplets in the proximal tubule epithelium of the kidney was increased over controls in males (7/7 treated vs. 2/7 controls).

Animals in the 720 mg/kg-day recovery group, sacrificed 2 weeks after treatment ended, showed no thyroid follicular cell hypertrophy. Males in the recovery group had significantly ($p<0.05$) decreased RBC (4% less than control), Hb (3%), and MCHC (2%), and increased MCV (3% more than control) and reticulocyte ratio (41%). Females in the recovery group did not have reduced RBC or Hb, but had significantly ($p<0.05$) increased hematocrit (8%), MCV (5%) and MCH (4%) and decreased MCHC (2%). The incidence of pigment deposition in the liver and kidneys of male rats in the 720 mg/kg-day recovery group was much lower than in the same dose group sacrificed immediately after treatment ended (1/7 with deposits in liver and 0/7 in kidney of recovery group compared with 7/7 each for liver and kidney in the immediate sacrifice group). Similarly, the incidence of liver pigmentation in females was lower in the recovery group (2/7 vs. 7/7 in the immediate sacrifice group). However, both males and females of the recovery group had hemosiderin deposition in the spleen (6/7 males and 7/7 females). The hematological findings and histopathology suggest that the hemolytic effects persisted in the recovery group.

This study identified a NOAEL of 240 mg/kg-day and a LOAEL of 720 mg/kg-day. The researchers considered the 720 mg/kg-day dose to be "unequivocally toxic." Effects at 720 mg/kg-day included anemia, liver and kidney toxicity, tremors, decreased body weight and thyroid changes. Evidence of hemolytic anemia included hematological findings (decreased RBC and Hb, increased reticulocyte ratio in females), serum chemistry (significantly increased bilirubin in both sexes) and histopathology (pigment deposition in liver and kidney, hemosiderin deposits in spleen). Liver toxicity was suggested by modest increases in ALT, while slightly increased BUN in females and tubular lesions in males (hyaline droplets) suggested possible kidney effects. The authors suggested that the liver and kidney effects may have occurred secondary to hemolytic toxicity. Although there was an increased incidence of pigment deposition in the kidneys of females at 240 mg/kg-day, there were no accompanying hematological findings, nor was serum bilirubin increased.

Kurata et al. (1987) investigated the ability of *m*-aminophenol to promote development of tumors induced by N-ethyl-N-hydroxyethylnitrosamine (EHEN). Over a 52-week period, three groups of 25 male Fischer 344 rats were studied; 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% *m*-aminophenol; the other group received a basal diet throughout the study. The third group was fed the 0.8% *m*-aminophenol test diet without EHEN-pretreatment. The 0.8% dietary concentration is estimated to provide approximately 400 mg/kg-day of *m*-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 *m*-aminophenol. *m*-Aminophenol did not promote development of preneoplastic lesions in the liver of rats initiated with EHEN; rats receiving both compounds showed significant decreases in the number of GST-P positive foci, in comparison to rats that received EHEN alone. The incidence of hepatocellular carcinoma was similar in both groups.

Other Studies

A teratology study conducted by parenteral exposure failed to find developmental effects of *m*-aminophenol. Groups of pregnant Syrian golden hamsters (LKV strain) were given *m*-aminophenol at dose levels of 0, 100, 150 or 200 mg/kg by intraperitoneal injection on gestation day 8 (Rutkowski and Ferm, 1982). Dams were sacrificed on gestation day 13 and the uteri removed and contents examined. *m*-Aminophenol was not toxic to the dams at these doses and produced no clear evidence of a teratogenic effect. There were six malformed fetuses that were observed at 150 mg/kg, but all were from the same litter and no malformations were seen at the 200 mg/kg dose.

m-Aminophenol was not mutagenic to *Salmonella typhimurium* or *Escherichia coli* (Watanabe et al., 1991; Lavoie et al., 1979; Thompson et al., 1983; Hayashi, 1981; Elder, 1988; Zeiger et al., 1988). In mammalian cells *in vitro*, *m*-aminophenol did not increase the frequency of sister chromatid exchanges (SCE) in Chinese hamster (V79) cells (Wild et al., 1981; Elder, 1988) or human lymphocytes (Kirchner and Bayer, 1982) and did not induce unscheduled DNA synthesis in cultured rat hepatocytes (Thompson et al., 1983). An abstract from a recent study published in Chinese reported DNA damage (as measured by the comet assay) to human peripheral blood lymphocytes and mouse spleen cells treated with *m*-aminophenol *in vitro* (Qu et al., 2004). *In vivo*, *m*-aminophenol did not increase the incidences of micronuclei in bone marrow cells in mice (Wild et al., 1981) or rats (Hossack and Richardson, 1977), SCE in Chinese hamster bone marrow cells (Kirchner and Bayer, 1982) or sperm-head abnormalities in mice (Wild et al., 1981). Results of a dominant lethal assay in rats were negative (CTFA, 1982; Elder, 1988).

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

No studies examining the effects of *m*-aminophenol in orally exposed humans were located. A long-term oral study reported no liver or kidney lesions in rats fed a diet containing 400 mg/kg-day for 52 weeks, but did not investigate other endpoints (Kurata et al., 1987). Re et al. (1984) found no developmental effects produced by *m*-aminophenol in rats at oral doses up to 900 mg/kg-day. A teratology study conducted by parenteral exposure in hamsters also found no evidence of developmental effects by *m*-aminophenol at i.p. doses up to 200 mg/kg-day (Rutkowski and Ferm, 1982).

There were three studies considered for use in developing the provisional RfD (p-RfD) values for *m*-aminophenol: a 90-day diet study in rats (Re et al., 1984), a 28-day gavage study in young rats (Koizumi et al., 2002) and an 18-day gavage study in newborn rats (Koizumi et al., 2002). In the 90-day rat study, Re et al. (1984) identified a NOAEL of 240 mg/kg-day and LOAEL of 900 mg/kg-day for hemolytic anemia. Other effects in the 900 mg/kg-day group were decreased body weight (associated with reduced food intake) and thyroid histological changes (hypertrophy) suggestive of hyperactivity but not clearly adverse. Findings of the 28-day gavage study (Koizumi et al., 2002) were similar. In this study, the NOAEL was 240

mg/kg-day and the LOAEL was 720 mg/kg-day. Effects at 720 mg/kg-day included hemolytic anemia, some evidence of liver and kidney toxicity that may have been secondary to the anemia, decreased body weight, and thyroid changes (hypertrophy together with increased thyroid weight) indicative of hyperactivity. This study also found clinical signs (salivation and tremors) in the treated animals that probably reflected the bolus dosing used in this study.

The 18-day newborn rat study (Koizumi et al., 2002) identified a NOAEL of 80 mg/kg-day and a LOAEL of 240 mg/kg-day. Effects at 240 mg/kg-day included reduced body weight and tremors. The decrease in body weight started early in the study, achieving statistical significance at 8-11 days. The deficit from controls was 10-13% over most of the study. Tremors seen at this dose were likely associated with the gavage route of exposure and were seen less often as the study progressed, suggesting the animals developed tolerance. The results of this study suggest that the newborn rats were more sensitive to m-aminophenol than the older rats used in the 24-day and 90-day studies. The 240 mg/kg-day dose that produced body weight effects and tremors in the 18-day newborn study was a NOAEL in the 24-day and 90-day studies. Therefore, the 18-day newborn study was chosen as the critical study for both the subchronic and chronic p-RfDs. The body weight and tremor data from the newborn rat study are not amenable to benchmark dose modeling, because the authors did not provide adequate information for modeling of the data (in-life body weight data were only presented graphically and with no measure of variance; terminal body weight data were collected after overnight starvation following the last dosing and this seems to have increased variability in the data [body weight differences were of similar magnitude to in-life measures but were no longer statistically significant]; terminal body weights were presented as mean plus some measure of variance, but the latter was not identified [e.g., standard error vs. standard deviation] and this information is needed to perform the modeling; tremors were seen in all animals at the high dose and (presumably) none at any lower doses, so the data provide no indication of the dose-response beyond that provided by the NOAEL/LOAEL). Because the data were not suitable for modeling, the NOAEL (80 mg/kg-day) from the newborn rat study was chosen as the point of departure for both the subchronic and chronic p-RfDs.

The **subchronic p-RfD of 0.3 mg/kg-day** for *m*-aminophenol is derived by dividing the newborn rat oral NOAEL of 80 mg/kg-day from the Koizumi et al. (2002) newborn study by an uncertainty factor of 300 as follows:

Subchronic p-RfD	=	NOAEL / UF
	=	80 mg/kg-day / 300
	=	0.3 or 3E-1 mg/kg-day

The uncertainty factor of 300 includes a factor of 10 for extrapolation from rats to humans, 3 for protection of sensitive individuals, and 10 for deficiencies in the subchronic toxicity database, including lack of longer-term or developmental toxicity data in a second species, absence of a systematic study of neurotoxicity, and lack of a multigeneration reproduction study. A reduced, 3-fold uncertainty factor for protection of sensitive individuals is applied because the point of departure was identified in a sensitive subpopulation (newborn rats).

A **chronic p-RfD of 0.08 mg/kg-day** for *m*-aminophenol is similarly derived, but uses a higher uncertainty factor of 10 for deficiencies in the chronic toxicity database (total UF = 3000):

Chronic p-RfD	=	NOAEL / UF
	=	240 mg/kg-day / 3000
	=	0.08 or 8E-2 mg/kg-day

A single long-term oral study was conducted as part of a tumor promotion assay, but investigated only liver and kidney pathology and no other endpoints (Kurata et al., 1987). Therefore, the 90-day study of Re et al (1984) is selected as the basis for the provisional chronic RfD. The NOAEL in this study is 240 mg/kg-day, with a LOAEL of 900 mg/kg-day for hemolytic anemia and possible thyroid effects (equivocal). An aggregate uncertainty factor (UF) of 3000 is applied, yielding an RfD of 0.08 mg/kg-day. The UF of 3000 includes factors of 10 for interspecies extrapolation (UF_A), 3 ($10^{0.5}$) for extrapolation to sensitive humans (UF_H), 10 for data base deficiencies (UF_D) and10 for subchronic-to-chronic exposure duration extrapolation (UF_S). The reduced factor of 3 for UF_H is the same as for the provisional subchronic RfD. A full 10-fold database factor is applied because of the lack of a multi-generation reproductive toxicity study, a second developmental study and an adequate longer-term toxicity in a second species. A full 10-fold factor is required for UF_S because the chronic study (Kurata et al, 1987) does not address the effect of continued exposure duration on either hemolytic anemia or thyroid effects. Also, the neonatal rat study (Koizumi et al., 2002) is not used as the basis for the chronic p-RfD because the NOAEL of 80 mg/kg-day is not, in itself, subject to a duration adjustment factor (i.e., UF_S), as it is only relevant for neonates. The subchronic NOAEL, although higher, results in a lower RfD when adjusted for chronic exposure.

Confidence in the principal study is low. The study included an adequate number of dose groups, and an adequate array of endpoints was investigated. However, the number of animals per dose group was minimal, a single sex was tested, and the thyroid effects were not evaluated or described fully. Confidence in the database is low for the subchronic data and low for the chronic data. Only a single subchronic toxicity study, one developmental study and one neonatal toxicity study are available. The chronic study evaluated only liver and kidney effects. No adequate chronic oral studies were located, and no systematic studies of neurotoxicity or reproductive effects are available. Overall confidence in both the subchronic and chronic p-RfD is low.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR *m*-AMINOPHENOL

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

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR *m*-AMINOPHENOL

Under the 2005 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), there is *inadequate information to assess the carcinogenic potential* of *m*-aminophenol. No data in humans are available to assess the carcinogenic potential of *m*-aminophenol. *m*-Aminophenol has not been tested for complete carcinogenicity in animals, but did not promote development of tumors initiated by EHEN in rats. *m*-Aminophenol tested negative in mutagenicity assays using *S. typhimurium* and *E. coli*, and in assays for induction of SCE and unscheduled DNA synthesis *in vitro*. In *in vivo* assays, m-aminophenol has tested negative for micronuclei in mice and rats, induction of SCE in hamster, sperm-head abnormalities in mice and dominant lethal mutagenicity in rats. There is a single report of DNA damage (as measured by comet assay) in human lymphocytes and mouse spleen cells after *m*-aminophenol treatment *in vitro* (Qu et al., 2004).

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2005. TLVs® and BEIs®: Threshold Limit Values for Chemical Substances and Physical Agents, Biological Exposure Indices. Cincinnati, OH.

ATSDR (Agency for Toxic Substances and Disease Registry). 2006. Toxicological Profile Information Sheet. U.S. Department of Health and Human Services, Public Health Service. Online. http://www.atsdr.cdc.gov/toxpro2.html

CTFA (Cosmetic, Toiletry and Fragrance Association). 1982. Submission of data by CTFA. Study no. 81/39/007. Final report. Combined 90-day feeding, teratology, and dominant lethal study on meta-aminophenol in the Sprague-Dawley rat. (Cited in Elder, 1988)

Elder, J. 1988. Final report on the safety assessment of p-aminophenol, m-aminophenol, and o-aminophenol. J Am. Coll. Toxicol. 7 (3): 279-334.

Hayashi, K. 1981. Effects of harman and norharman on the metabolism of aniline and *p*-dimethylaminobenzene. Nippon Eiseigaku Zasshi. 36(2): 495-505. (Japanese; Cited in Elder, 1988)

Hossack, D.J.N. and J.C. Richardson. 1977. Examination of the potential mutagenicity of hair dye constituents using the micronucleus test. Experientia. 33(3): 377-378.

IARC (International Agency for Research on Cancer). 2006. Search IARC Monographs. Online. http://monographs.iarc.fr/

Kirchner, G. and U. Bayer. 1982. Genotoxic activity of the aminophenols as evidenced by the induction of sister chromatid exchanges. Hum. Toxicol. 1(4): 387-392.

Koizumi, M., N. Nishimura, T.Enami, et al. 2002. Comparative toxicity study of 3-aminophenol in newborn and young rats. J. Toxicological Sciences 27(5):411-421.

Kurata, Y., H. Tsuda, T. Sakata, et al. 1987. Reciprocal modifying effects of isomeric forms of aminophenol on induction of neoplastic lesions in rat liver and kidney initiated by N-ethyl-N-hydroxyethylnitrosamine. Carcinogenesis. 8(9): 1281-1285.

Lavoie, E., L. Tulley, E. Fow and D. Hoffman. 1979. Mutagenicity of aminophenyl and nitrophenyl ethers, sulfides, and disulfides. Mutat. Res. 67(2): 123-131.

NIOSH (National Institute for Occupational Safety and Health). 2006. Online NIOSH Pocket Guide to Chemical Hazards. Online. http://www.cdc.gov/niosh/npg/npgdcas.html

NTP (National Toxicology Program). 2006. Management Status Report. Online. http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/ALL_SRCH/iH_ALL_SRCH_Frames.html

OSHA (Occupational Safety and Health Administration). 2006. OSHA Standard 1910.1000 Table Z-1. Part Z, Toxic and Hazardous Substances. Online. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992

Re, T.A., R.F. Loehr, S.C. Rodriguez, et al. 1984. Results of teratogenicity testing of *m*-aminophenol in Sprague-Dawley rats. Fundam. Appl. Toxicol. 4: 98-104.

Rutkowski, J.V. and V. H. Ferm. 1982. Comparison of the teratogenic effects of the isomeric forms of aminophenol in the Syrian Golden hamster. Toxicol. Appl. Pharmacol. 63: 264-269.

Qu M., L. Sun, Z. Kang, et al. 2004. Comparison of DNA damage on human peripheral blood lymphocytes and mouse blood spleen cells induced by aminophenols. Huanjing Yu Jiankang Zazhi 21(4):218-220. (English abstract).

Thompson, C.Z., L.E. Hill, J.K. Epp and G.S. Probst. 1983. The induction of bacterial mutation and hepatocyte unscheduled DNA synthesis by monosubstituted anilines. Environ. Mutagen. 5(6): 803-811.

U.S. EPA. 1985. Health and Environmental Effects Profile for Aminophenols. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC. EPA 600/X-85/398. NTIS PB88-173612/AS.

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

U.S. EPA. 1994. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. December.

U.S. EPA. 1997. Health Effects Assessment Summary Tables. FY-1997 Update. Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati OH for the Office of Emergency and Remedial Response, Washington, DC. July. EPA/540/R-97/036. NTIS PB97-921199.

U.S. EPA. 2004. 2004 Edition of the Drinking Water Standards and Health Advisories. Office of Water, Washington, DC. Winter, 2004. EPA 822-R-02-038. Online. http://www.epa.gov/waterscience/drinking/standards/dwstandards.pdf

U.S. EPA. 2005. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001B. Available at http://www.epa.gov/iriswebp/iris/cancer032505.pdf.

U.S. EPA. 2006. Integrated Risk Information System (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Online. http://www.epa.gov/iris/

Watanabe, T., M. Kusumoto, M. Ishihara, et al. 1991. The modulating effect of hair dye components on the formation of mutagenic oxidized products from m-phenylenediamine with hydrogen peroxide. Eisei. Kagaku. 37(6): 512-521. (CCRIS database: Online. http://toxnet.nlm.nih.gov/)

WHO (World Health Organization). 2006. Online catalogs for the Environmental Health Criteria Series. Online. http://www.inchem.org/pages/ehc.html

Wild, D., M.T. King, K. Eckhardt and E. Gocke. 1981. Mutagenic activity of aminophenols and diphenols, and relations with chemical structure. Mutat. Res. 85: 456. (Abstract)

Zeiger, E., B. Anderson, S. Haworth, et al. 1988. *Salmonella* mutagenicity tests. IV. Results from the testing of 300 chemicals. Environ. Mol. Mutagen. 11 (Suppl. 12): 1-158.