United States
Environmental Protection
Agency

EPA/690/R-07/008F
Final
7-03-2007

Provisional Peer Reviewed Toxicity Values for

2-Chlorophenol
(CASRN 95-57-8)

Superfund Health Risk Technical Support Center
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Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
i.v.	intravenous
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level
MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value

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

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR 2-CHLOROPHENOL (CASRN 95-57-8)

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 new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a five-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and

circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

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

Questions Regarding PPRTVs

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

INTRODUCTION

A chronic reference dose (RfD) value of 5E-3 mg/kg-day is available for 2-chlorophenol on IRIS (U.S. EPA, 1988a) and in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2004). The HEAST (U.S. EPA, 1997) lists a subchronic RfD for 2-chlorophenol of 5E-2 mg/kg-day. Both RfD values were based on a no-observed-adverse-effect level (NOAEL) of 5 mg/kg-day for reproductive effects in a drinking water study that exposed rats to 2-chlorophenol for 10 weeks prior to mating and during mating, gestation and weaning (Exon and Koller, 1982). Uncertainty factors of 100 and 1000 were used to derive the subchronic and chronic RfDs, respectively. The source documents for the RfD assessments included a Drinking Water Criteria Document (DWCD) (U.S. EPA, 1986a), a Health Effects Assessment (HEA) (U.S. EPA, 1987a), and two Health and Environmental Effects Documents (HEEDs) (U.S. EPA, 1987b, 1990). The Chemical Assessments and Related Activities (CARA) lists (U.S. EPA, 1991, 1994) do not include any additional relevant EPA documents. The Agency for Toxic Substances and Disease Registry (ATSDR, 1999) and the World Health Organization (WHO, 1989) have assessed the health effects of chlorophenols, but did not derive any oral risk assessment values specifically for 2-chlorophenol.

An RfC for 2-chlorophenol is not available on IRIS (U.S. EPA, 1988a) nor in the HEAST (U.S. EPA, 1997). The Agency for Toxic Substances and Disease Registry (ATSDR) and the World Health Organization (WHO) have not derived any inhalation risk assessment values for 2-chlorophenol. Occupational exposure limits for 2-chlorophenol have not been derived by the American Conference for Governmental Industrial Hygienists (ACGIH), the National Institute

for Occupational Safety and Health (NIOSH) or the Occupational Safety and Health Administration (OSHA).

A cancer assessment for 2-chlorophenol is not available on IRIS (U.S. EPA, 1988a). The HEEDs (U.S. EPA, 1987b, 1990) assigned 2-chlorophenol to U.S. EPA (1986b) Cancer Group D (not classifiable as to human carcinogenicity); this classification is also included in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2004). The carcinogenicity of 2-chlorophenol has not been assessed by NTP or IARC.

Literature searches were conducted from the 1960's through August, 2006 for studies relevant to the derivation of provisional toxicity values for 2-chlorophenol. Data bases searched included: TOXLINE/TOXCENTER (including BIOSIS, NTIS and Chemical Abstracts subfiles), MEDLINE (including PubMed cancer subset), TSCATS/TSCATS 2, CCRIS, DART/ETIC, GENETOX, HSDB, RTECS, and Current Contents.

REVIEW OF PERTINENT DATA

Human Studies

Relevant information regarding the toxicity of 2-chlorophenol in humans was not located.

Animal Studies

Oral Exposure. In a 14-day study performed in conjunction with EPA, groups of 12 male and 12 adult female CD-1 ICR mice were administered 2-chlorophenol in corn oil by gavage in doses of 0, 35, 69 or 175 mg/kg-day (Borzelleca, 1983; Borzelleca et al., 1985). The highest dose level was approximately 50% of the acute oral LD_{50} of 347 and 345 mg/kg in male and female CD-1 mice, respectively. Endpoints evaluated during the study included clinical observations, body weight (days 1, 8 and 15), and food and water intake. Endpoints evaluated at the end of the treatment period included hematology [red blood cells (RBC), total and differential white blood cells (WBC), platelets, hematocrit (Hct), hemoglobin (Hgb) and coagulation], serum chemistry [lactate dehydrogenase (LDH), alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), bilirubin, protein, glucose, cholesterol, albumin/globulin, phosphorus, potassium, calcium, sodium and chloride], hepatic microsomal activities (cytochrome P_{450}, cytochrome b_5, protein, aminopyrine demethylase, aniline hydroxylase, and arylhydrocarbon hydroxylase), immune response and behavioral measurements. The earlier report of the study (Borzelleca, 1983) implies that the immunology endpoints included cell-mediated response (Delayed-type hypersensitivity (DTH) response to sheep RBC, response to concanavalin A), humoral response [splenic Immunoglobulin mu (IgM) antibody forming cells (AFC) to sheep RBC, serum antibody levels to sheep RBC, lymphocyte response to lipopolysaccharide (LPS)], and reticuloendothelial system (RES) function (vascular clearance and uptake of ^{51}Cr sheep RBC). The Borzelleca (1983) report also implies that the behavioral endpoints included inverted screen test, swimming endurance, locomotor activity, pain sensitivity, olfactory sensitivity, passive avoidance learning, and forepaw grip strength. Other endpoints included sister-chromatid exchange (bone marrow

and/or testes, not otherwise specified), *in vitro* fertilization capability (penetration of ova, fertilization, blastula formation), absolute and relative organ weights, and gross pathology. Histopathological examinations were not performed. The results of this study are qualitatively reported in tabular summaries. Effects included 100% mortality at 175 mg/kg-day, hyperactivity at 35 and 69 mg/kg-day, reduced body weight at 69 mg/kg-day, and reduced brain, liver and spleen weights (effect levels not indicated); additional information on these effects was not reported. No biologically or statistically significant compound-related adverse effects were reported for the other endpoints as indicated by the authors. The 100% mortality in the high-dose animals indicates that 175 mg/kg-day was a FEL for short-term repeated gavage exposures in mice. The authors (Borzelleca et al., 1985) referred to the effects at the lower doses as "slight toxic effects", but apparently concluded that they were not biologically significant, indicating that 69 mg/kg-day was a NOAEL. Results of acute studies reported by Borzelleca et al. (1985) include an ED_{50} of 63 mg/kg for reversible motor impairment in mice exposed to a single oral dose of 2-chlorophenol; additional information was not provided.

Gavage studies (10-day and 90-day) of 2-chlorophenol in Sprague-Dawley rats were conducted by the EPA (Daniel et al., 1993). In the 10-day study, groups of 10 male and 10 female 8-week-old Sprague-Dawley rats were administered 2-chlorophenol in corn oil by daily gavage at doses of 0, 13, 64, 129 or 257 mg/kg-day. The highest dose level was approximately 38% of the reported acute LD_{50} of 670 mg/kg for a rat. Endpoints evaluated during the study included clinical signs (observed for physiological and behavioral responses and mortality), body weight and food and water consumption. Evaluations at the end of the exposure period included hematology [RBC, WBC, Hct, Hgb and mean corpuscular volume (MCV)], serum chemistry (ALP, AST, ALT, LDH, cholesterol, BUN, creatinine, glucose, and calcium), absolute and relative organ weights (brain, liver, spleen, lungs, thymus, kidneys, adrenal glands, heart, and gonads), and gross pathology. Comprehensive histological examinations were performed in the control and high-dose groups; target organs were also histologically evaluated at the lower dose levels. Tissues that were examined included liver, kidneys, urinary bladder, heart, aorta, skin, skeletal muscle, bone, sciatic nerve, spleen, thymus, lymph nodes, respiratory tract (nasal turbinates, trachea, lung with bronchi), gastrointestinal tract (esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum), endocrine system (adrenals, pancreas, pituitary, thyroid/parathyroid), and reproductive system (testes, epididymis, seminal vesicles, prostate, preputial gland, ovaries, uterus, clitoral gland).

There were no treatment-related deaths, significant clinical observations or significant changes in food or water consumption or body weight gain (Daniel et al., 1993). The hematology evaluations found significantly ($p \leq 0.05$) increased RBC count (12% higher than controls) and Hct (28% higher than controls) in the high-dose (257 mg/kg-day) males; these effects were not clearly dose-related and there were no significant changes in hematologic values in females. Serum chemistry changes that were statistically significant included increased glucose levels in females at 129 and 257 mg/kg-day (45 and 42% higher than controls, respectively) and males at 257 mg/kg-day (21% higher than controls); decreased ALP in females at 129 and 257 mg/kg-day (15 and 16% lower than controls); and decreased AST, cholesterol, and LDH in males at 257 mg/kg-day (25, 27 and 55% lower than controls, respectively). Serum LDH values were significantly decreased in females at 64 and 129 mg/kg-day, but not at 257 mg/kg-day. The only serum chemistry changes that appeared to be dose-related were the

increased glucose and decreased ALP in female rats, but the authors reported that these values were within the normal ranges for laboratory rats. Statistically significant organ weight changes consisted of decreases in absolute kidney and heart weights in females at 129 mg/kg-day, but not at other dose levels, and decreases in absolute and relative lung weights in females at all dose levels; quantitative data were not reported. Necropsy findings included enlarged mandibular lymph nodes, reddened lungs and reduced thymus size in all groups of both sexes; these were minimal to mild changes not considered to be treatment-related by the authors. The histological examinations similarly showed lymphoid hyperplasia, mild congestion of the lungs, and mild thymic atrophy in all groups; these effects did not appear to be treatment-related to the authors because they were not significant in severity or incidence (data not reported). Histopathological changes in kidneys, heart, lungs or other tissues were not reported. The lack of any clear treatment-related or biologically significant hematology, clinical chemistry, organ weight or pathological changes indicates that the highest dose level, 257 mg/kg-day, is a NOAEL for 10-day gavage exposure in male and female rats although it is difficult to ascertain the significance of the reported effects due to a lack of data reporting.

In the 90-day study, groups of 10 male and 10 female 8-week-old Sprague-Dawley rats were administered 2-chlorophenol in corn oil by daily gavage at doses of 0, 17, 50, or 150 mg/kg-day (Daniel et al., 1993). Study endpoints were the same as in the 10-day study summarized above; evaluations included clinical signs, body weight, food and water consumption, hematology, serum chemistry (with the addition of triglycerides, total protein, albumin and globulin), organ weights and gross pathology in all groups, and histopathology in the control and high-dose groups. There were no clinical signs of toxicity, unscheduled deaths, or significant changes in food or water consumption or body weight gain. Hematology changes that were statistically significant included increased RBC count in females at 17 and 150 mg/kg-day (3 and 6% higher controls), but not at 50 mg/kg-day; increased Hct in females at 150 mg/kg-day (5% higher than controls); and increased MCV in males at 150 mg/kg-day (3% higher than controls). Serum chemistry changes that were statistically significant included decreased ALP in males at 50 and 150 mg/kg-day (31 and 28% less than controls), decreased AST in males at 50 and 150 mg/kg-day (22 and 19% less than controls), decreased ALT in males at 50 and 150 mg/kg-day (18 and 18% less than controls), and increased glucose at 50 mg/kg-day (16% higher than controls; similar increases occurred at 17 and 150 mg/kg-day but were not statistically significant). Although statistically significant changes were observed for these and several other hematology and clinical chemistry indices, no responses were clearly dose-related, consistent between sexes or, according to the authors, outside normal ranges or biologically significant. There were no clear effects on organ weights; the only statistically significant changes were increased relative liver weight in females at 17 mg/kg-day, increased absolute spleen weight in males at 17 and 50 mg/kg-day, and increased absolute brain weight in males at 50 mg/kg-day; quantitative data were not reported. There were no gross or histopathological changes in either sex. The lack of any clear treatment-related or biologically significant hematology, clinical chemistry or organ weight changes, as well as the lack of any pathological effects, indicates that the highest dose level, 150 mg/kg-day, is a NOAEL for 90-day gavage exposure in rats.

The oral toxicity of 2-chlorophenol was also assessed in 18-day studies with preweanling rats and in 14- and 28-day studies with juvenile rats (Hasegawa et al., 2005). Preweanling Sprague-Dawley SPF rats were administered 2-chlorophenol in olive oil by gavage on postnatal

days (PNDs) 4-21 in dose-finding and main studies. In the 18-day dose-finding study with preweanling rats, groups of 4 males and 4 females were exposed to dose levels of 0, 20, 100 or 500 mg/kg-day. General behavior and body weight were evaluated during the study, and hematology, blood chemistry, gross pathology and organ weights were evaluated on PND 22; histopathology was not assessed. Although not specifically reported, it is assumed that the scope of these evaluations was the same as in the main study with newborn rats summarized below. Effects were limited to 100% mortality by the 9th day of dosing at 500 mg/kg-day; clinical signs were not observed at 20 and 100 mg/kg-day, and no other results were reported. This study identified a FEL of 500 mg/kg-day for lethality in preweanling rats. The next lowest dose level of 100 mg/kg-day is a NOAEL based on the lack of clinical signs and systemic effects, but confidence in this effect level is low due to the small numbers of animals and lack of histological examinations.

In the main 18-day study with preweanling rats, groups of 12 male and 12 female Sprague-Dawley SPF rats were administered 2-chlorophenol in olive oil by gavage in doses of 0, 8, 50 or 300 mg/kg-day on PNDs 4-21 (Hasegawa et al., 2005). Half of the animals were sacrificed on PND 22, and the remaining 6 rats/sex/group were observed without treatment for the following 9 weeks and then sacrificed (on PND 85). Endpoints evaluated during the study included general behavior, body weight and postnatal developmental parameters, including surface righting and visual placing reflex for reflex ontogeny, fur appearance, incisor eruption and eye opening for external development, and preputial separation, vaginal opening and estrous cycle for sexual development. Comprehensive hematology and blood biochemistry evaluations were conducted at the end of the treatment period on PND 22 (6 rats/sex/dose) and end of the observation period on PND 85 (6 rats/sex/dose). Hematology indices included RBC, Hct, Hgb, MCV, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, total and differential WBC, platelet count, and reticulocyte count. Blood biochemistry indices included total protein, albumin, albumin/globulin ratio, glucose, total cholesterol, triglycerides, phospholipid, total bilirubin, BUN, creatinine, AST, ALT, ALP, γ-glutamyl transpeptidase, calcium, inorganic phosphorus, sodium, potassium and chloride. Prothrombin time, activated thromboplastin time, and urine indices (color, pH, occult blood, protein, glucose, ketone bodies, bilirubin, urobilinogen, sediment, volume and osmotic pressure) were evaluated only at the end of the observation period. Organ weights (brain, pituitary, thymus, thyroids, heart, lungs, liver, spleen, kidneys, adrenals, testes, epididymides, ovaries and uterus) and histopathology (organs that were weighed as well as macroscopically abnormal organs) were evaluated on PND 22 (6 rats/sex/dose); it was not indicated if these evaluations were performed on PND 85.

Effects included tremors in 11/12 males and 12/12 females at 300 mg/kg-day; the tremors appeared within 5 minutes of dosing and disappeared within 4 hours in most animals. At 50 mg/kg-day, 1/12 females showed tremors once from 15-30 minutes following dosing on treatment day 9. No tremors were observed in males at 50 mg/kg-day or in either sex at 0 or 8 mg/kg-day. The only other reported effects occurred at 300 mg/kg-day; these consisted of other signs of neurotoxicity (hypoactivity in 2/12 males and 3/12 females and abnormal gait in 1/12 males and 1/12 females), transiently decreased body weight in both sexes (additional information not reported), and histological changes in the kidneys (slight to moderate basophilic renal tubules in 4/6 males and 5/6 females) with increases in relative kidney weight (8% in males and 4% in females). The biological significance of the basophilic renal tubular changes was not discussed.

No results were reported for the 9-week observation period. The 300 mg/kg-day dose is a FEL for preweanling rats based on the occurrence of tremors in 23/24 of the exposed males and females; other signs of neurotoxicity (hypoactivity and abnormal gait) were also observed at this dose level. The next lowest dose of 50 mg/kg-day is a NOAEL because tremors were only observed in 1/12 females once on exposure day 9; the incidence is not statistically different from the control group (0/12) and the occurrence was isolated. Additionally, there were no clinical signs of neurotoxicity in the males exposed to 50 mg/kg-day, or in the 4 males and 4 females exposed to 100 mg/kg-day in the dose-finding study summarized above.

The studies with juvenile rats included a 14-day dose-finding study and a 28-day main study (Hasegawa et al., 2005). In the 14-day dose-finding study, 5-week-old male and female Sprague-Dawley SPF rats were administered 2-chlorophenol in olive oil by gavage in doses of 0, 100, 200 or 500 mg/kg-day; group sizes were 3 per sex at 500 mg/kg-day and were not reported for the other dose levels. General behavior, body weight and food consumption were evaluated during the study, and hematology, blood chemistry, gross pathology and organ weights were evaluated the day after the last treatment; histopathology was not assessed. Although not specifically reported, it is assumed that the scope of these evaluations was the same as in the study with newborn rats summarized above. The only information regarding the results is a statement that no toxic signs were observed, indicating that 500 mg/kg-day is a NOAEL in juvenile rats. Confidence in this effect level is low due to the apparent small numbers of animals and lack of histological examinations.

In the 28-day main study, groups of 12 male and 12 female 5- to 6-week old Sprague-Dawley SPF rats were exposed to 2-chlorophenol in olive oil by gavage in doses of 0, 8, 40, 200 or 1000 mg/kg-day (Hasegawa et al., 2005). It appears that half of the animals were sacrificed following the last treatment and the remaining 6 rats/sex/group were observed without treatment for the following 2 weeks and then sacrificed. Evaluations included general behavior, body weight, food consumption, urinalysis, hematology, blood biochemistry, gross pathology, organ weights and histopathology. Although not specifically reported, it is implied that the scope and schedule of these evaluations are the same as in the 18-day study with preweanling rats summarized above. The only effects in this study were clinical signs of neurotoxicity and histological changes in the liver in most animals only at 1000 mg/kg-day. The clinical signs occurred sporadically in both sexes within 3 hours of dosing and included tremors (4/12 males and 5/12 females), hypoactivity (8/12 males and 5/12 females) and abnormal gait (4/12 males and 7/12 females). The liver effects consisted of slight centrilobular hypertrophy of hepatocytes (6/6 males and 5/6 females); the authors indicated that this suggested a compensatory response for hepatic metabolism. None of the animals showed basophilic renal tubules as observed in the preweanling rats exposed to 300 mg/kg-day on PNDs 4-21 (see above). No results were reported for the 2-week observation period. This study identified a FEL of 1000 mg/kg-day based on the clinical signs of neurotoxicity; the NOAEL is 200 mg/kg-day.

Additional information on effects of repeated oral exposures to 2-chlorophenol is available from a series of reproductive toxicity, immunotoxicity and carcinogenicity studies in Sprague-Dawley rats that were exposed prenatally, postnatally, or both pre- and postnatally to concentrations of 0, 5, 50 or 500 ppm 2-chlorophenol in drinking water (Exon and Koller, 1982, 1983a,b, 1985). Offspring produced in the reproductive study were used in the immunotoxicity

and carcinogenicity studies. In the reproductive study, groups of 12-14 females were exposed to the treated drinking water from 3 weeks of age through breeding (to untreated males) at 90 days of age and subsequently until 3 weeks post-parturition (Exon and Koller, 1982, 1983b, 1985). Table 1 shows the statistically significant reproductive endpoints that were reported by Exon and Koller (1982). The values found in Exon and Koller (1983b, 1985) agree with each other but are slightly different from those found in Exon and Koller (1982), and differ in their statistical evaluation. The reason for the differences is unknown. Maternal and pup weight, percent conception, litter size, and number of stillbirths were evaluated at parturition. Pup survival, body weight and hematology (red and white cell counts, hemoglobin, packed cell volume, and mean corpuscular volume) were evaluated at weaning.

Table 1. Reproductive effects of 2-Chlorophenol in Rats

Effect	Dose (ppm)			
	0	**5**	**50**	**500**
Litter Size (mean ± SD)	11.4 ± 1.2 n=12	11.7 ± 3.5 n=12	10.1 ± 2.3 n=12	9.2 ± 4.3[b] n=14
Stillborn (incidence)	0/91	2/105	0/91	6/110[b]

[a] Female rats were exposed to 2-chlorophenol in drinking water from 3 weeks of age through mating at 90 days of age and subsequently through pregnancy and lactation.
[b]Significantly different from control group ($p \leq 0.05$).
Source: Exon and Koller (1982)

Statistically significant ($p \leq 0.05$) changes included 19% reduced mean litter size (live and stillborn pups) at 500 ppm (9.2 ± 4.3 compared to 11.4 ± 1.2 in controls) and 5% increased incidence of stillbirths at 500 ppm (6/110 compared to 0/91 in controls) (Exon and Koller, 1982).

Based on the evidence of decreased litter size and an increase in stillbirth incidence, this study identified a NOAEL of 50 ppm and a LOAEL of 500 ppm for reproductive toxicity. The conversion factor for converting the amount of 2-chlorophenol ingested in drinking water (ppm) to a dose (mg/kg-day) was calculated by dividing the reference water consumption of 0.031 L/day for female Sprague Dawley rats in a subchronic study by the corresponding reference body weight in female Sprague Dawley rats (0.031 L/day/0.204 kg = 0.15 L/kg-day) (U.S. EPA, 1988b). Thus, the 5, 50 and 500 ppm doses correspond to estimated drinking water doses of 0.75, 7.5 and 75 mg/kg-day, respectively, and the NOAEL and LOAEL correspond to 7.5 and 75 mg/kg-day, respectively.

In the immunotoxicity studies, offspring from female rats described in the above studies that were exposed to 0, 5, 50 or 500 ppm 2-chlorophenol in drinking water from 3 weeks of age through mating at 90 days until 3 weeks post-parturition were continued on treatment for 10 weeks (Exon and Koller, 1983a) or 15 weeks (Exon and Koller, 1985), at which time immune responses were evaluated. Tests were conducted for humoral immunity (measured as the ratio of serum Immunoglobulin gamma (IgG) antibody levels to bovine serum albumin or keyhole limpet hemocyanin), cell-mediated immunity (measured as delayed-type hypersensitivity response in ears injected with oxazolone), and macrophage function (measured as the ability of peritoneal exudate cells to phagocytize sheep red blood cells *in vitro*) in 4 male and 4 female offspring from each exposure group. Body, liver, spleen, and thymus weights were also evaluated in these

offspring. There were no statistically significant ($p \leq 0.05$) differences between the treated and control groups for any of the immune responses or other end points, indicating that a NOAEL of 500 ppm was identified. Using conversion factors of 0.14 and 0.15 L/kg-day based on subchronic values for water consumption and body weight in male and female Sprague Dawley rats (U.S. EPA, 1988b), respectively, the NOAEL of 500 ppm identified in these studies corresponds to estimated drinking water doses of 70 mg/kg-day in males and 75 mg/kg-day in females.

In the carcinogenicity studies (Exon and Koller, 1983b, 1985), groups of 24-32 male and 24-28 female rats received combined pre- and postnatal exposures to 0, 5, 50 or 500 ppm of 2-chlorophenol in drinking water. Three-week-old females were exposed continuously through mating (90 days of age), pregnancy and lactation, and the offspring received treated drinking water from weaning for 24 months. All rats were observed daily for gross signs of morbidity, and moribund or tumor-bearing rats were sacrificed. Body weight was measured monthly in all rats, and hematology (RBC, WBC, Hct, Hgb and MCV) was evaluated every 2 weeks (Exon and Koller, 1983b) or every 2 months (Exon and Koller, 1985) in 5 males and 5 females per group. Gross and microscopic examinations of major organs and tumor tissues were conducted in all animals. There were no effects on body weight at 15 weeks (Exon and Koller, 1985) or 7 months (Exon and Koller 1983b), the only times for which data were reported. A significant decrease in body weight ($p \leq 0.10$) was observed at 7 months in females at doses of 5 and 500ppm (7.6 and 5.2% less than controls respectively). Exon and Koller (1985) noted that red blood cell count, packed cell volume and blood hemoglobin concentrations were "generally increased" in both sexes at 500 ppm. These effects were most evident after 14 months of exposure, when the RBC, packed cell volume (PCV) and hemoglobin values were 15, 19 and 16% higher than controls ($p \leq 0.05$), respectively; no other quantitative hematology data were reported. In an earlier report of interim (15-month) findings, however, Exon and Koller (1983b) indicated that 2-chlorophenol did not affect any of the measured hematology parameters. Noncancer histopathologic observations were not reported. Although there were no clear treatment-related or biologically significant body weight or hematology changes, the lack of noncancer histopathology data precludes identification of a NOAEL or LOAEL for chronic toxicity. There were no statistically significant ($p \leq 0.10$) differences between exposed and control groups in tumor incidence, latency or type in either sex. Incidences of total tumors in the 0, 5, 50 and 500 ppm groups were 13, 17, 8 and 18% in males, and 5, 0, 13, and 18% in females, respectively; no other incidence data were reported.

Inhalation Exposure. Relevant information regarding the inhalation toxicity of 2-chlorophenol in animals was not located.

Other Studies

Co-carcinogenicity and Tumor Promotion. In a co-carcinogenicity study (Exon and Koller, 1983b, 1985), groups of 24-32 male and 24-28 female Sprague-Dawley rats were exposed prenatally, postnatally, or both pre- and postnatally to 0, 5, 50 or 500 ppm 2-chlorophenol in drinking water, with prenatal exposure to the known carcinogen ethylnitrosourea (ENU). Comparison groups received prenatal exposure to ENU alone; comparisons were not made to offspring unexposed to ENU or 2-chlorophenol. Rats were exposed to ENU as its precursors,

ethylurea (0.316% in feed) and sodium nitrite (1 ppm in drinking water), on days 14-21 of gestation. Prenatal exposure to 2-chlorophenol involved exposing 3-week-old females through mating (90 days of age) and pregnancy; the dams were not exposed during lactation, and the offspring were observed without treatment from weaning for 24 months. Postnatal exposure to 2-chlorophenol involved exposing offspring from unexposed dams to the treated water from weaning for 24 months. Combined pre- and postnatal exposure to 2-chlorophenol involved exposing 3-week-old females continuously through mating (90 days of age), pregnancy and lactation, and subsequent exposure of the offspring to the treated water from weaning for 24 months. Histological examinations were performed on major organs and grossly observed tumors, but data were only reported for total tumors.

Male offspring of rats treated with ENU and combined pre- and postnatal exposure to 2-chlorophenol, at all treatment levels, had significantly ($p \leq 0.10$) increased incidences of total tumors when compared to the group exposed to ENU alone (Table 2). Significantly higher incidences of total tumors also occurred in male offspring exposed to ENU and 2-chlorophenol given prenatally at 5 and 500 ppm (but not 50 ppm), male offspring exposed to ENU and 2-chlorophenol given postnatally at 5 ppm, and female offspring exposed to ENU and 2-chlorophenol given prenatally or postnatally at 500 ppm. Tumor latency (mean days to tumor) was significantly decreased in rats exposed to ENU with combined pre- and postnatal exposure to 2-chlorophenol at all treatment levels when compared to the group exposed to ENU alone. Although total tumor incidence was increased and time-to-tumor latency was decreased in all groups of male rats with combined pre- and postnatal exposure to 2-chlorophenol compared with those exposed to ENU alone, interpretation of the findings is complicated by a high tumor incidence in the group exposed to ENU alone, lack of a dose-response relationship, and lack of similar effects in females (Table 2). The authors concluded that the results suggest that 2-chlorophenol may act as a co-carcinogen or promoter of carcinogenesis.

Table 2. Tumor Incidence and Latency in Rats Exposed Pre- and Postnatally to 2-Chlorophenol with Prenatal Exposure to ENU (Exon and Koller, 1983b)

2-Chlorophenol (ppm) (Pre-and Postnatal + ENU)	Total Tumor Incidence (%)			No. Rats/Group		Days to Tumor (mean ± SE)
	Total	Male	Female	Male	Female	
Unexposed	3	7	0	30	30	422 ± 40
ENU only	58	54	63	28	24	302 ± 16
5	85[a]	92[a]	79	24	24	245 ± 14[a]
50	63	75[a]	50	24	24	256 ± 17[a]
500	68	77[a]	60	30	30	259 ± 14[a]

[a]$p \leq 0.10$ compared to ENU positive control group by chi-square test (incidence data) or analysis of variance (least-square means) (latency data).

The skin tumor-promoting ability of 2-chlorophenol was assessed in 2- to 3-month old female albino Sutter mice (Boutwell and Bosch, 1959). When 25µl of a 20% solution of 2-chlorophenol in benzene was applied to shaved back skin twice weekly for 15 weeks following initiation with a single 25µl application of 0.3% DMBA (9,10-dimethyl-1,2-benz[a]anthracene) in benzene, 31/35 mice survived compared to 15/20 similarly initiated vehicle control mice. Of the survivors, 61% had skin papillomas compared to 7% in controls, and 10% had skin

carcinomas compared to 0% in controls. When 2-chlorophenol was applied as a 20% solution in dioxane to uninitiated mice twice weekly for 12 weeks, 28/30 mice survived; 46% of the survivors had papillomas and 0% developed carcinomas. A dioxane-treated vehicle control group was not reported.

Genotoxicity. A limited amount of information is available on the genotoxicity of 2-chlorophenol. 2-Chlorophenol did not induce reverse mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 when tested with or without exogenous metabolic activation (Haworth et al., 1983). 2-Chlorophenol did not induce DNA-repairing genes (*umuDC*) in *S. typhimurium* TA1535/pSK1002 (Ono et al., 1992), or DNA damage in *Escherichia coli* as shown by the induction of prophage lambda (DeMarini et al., 1990), when tested with or without exogenous metabolic activation. Sister-chromatid exchanges were not increased in mice that were exposed to 2-chlorophenol in corn oil by gavage in doses of 35-175 mg/kg-day for 14 days (Borzelleca et al., 1985); bone marrow and testicular cells (specific cell types not indicated) were examined.

DERIVATION OF A PROVISIONAL SUBCHRONIC ORAL RfD FOR 2-CHLOROPHENOL

Subchronic RfD

Information relevant to the derivation of a subchronic oral RfD for 2-chlorophenol is available from one 14-day study in mice (Borzelleca, 1983; Borzelleca et al., 1985) and several studies in rats ranging in exposure duration from 10 days to approximately 16-21 weeks (Daniel et al., 1993; Exon and Koller, 1982, 1983a, 1985; Hasegawa et al., 2005). The preponderance of these studies used gavage exposure and showed frank toxic effects, particularly mortality and clinical signs of neurotoxicity, as summarized in Table 3. The gavage studies identified FELs of 175 mg/kg-day for mortality in mice exposed for 14 days (Borzelleca, 1983; Borzelleca et al., 1985), 300 mg/kg-day for overt neurotoxicity (tremors) and 500 mg/kg-day for mortality in preweanling rats exposed for 18 days on PNDs 4-21 (Hasegawa et al., 2005), and 1000 mg/kg-day for overt neurotoxicity (tremors, hypoactivity and abnormal gait) in rats exposed for 28 days (Hasegawa et al., 2005). Although these are generally well-designed studies with comprehensive evaluations that included clinical signs, body weight, hematology, clinical chemistry, organ weights, histology and, in the study with preweanling rats, postnatal developmental indices, they did not identify more subtle indicators of toxicity and actual data were not supplied in some instances. NOAELs in the gavage studies were 69 mg/kg-day in mice exposed for 14 days (Borzelleca, 1983; Borzelleca et al., 1985), 50 and 100 mg/kg-day in preweanling rats exposed for 18 days on PNDs 4-21 (Hasegawa et al., 2005), 150 mg/kg-day in rats exposed for 90 days (Daniel et al., 1993), and 200 mg/kg-day in rats exposed for 28 days (Hasegawa et al., 2005).

Table 3. Summary of Effect Levels from Oral Toxicity Studies of 2-Chlorophenol

Species	Exposure Duration	NOAEL[a]	LOAEL[a]	FEL[a]	Effects	Reference
mouse	14 days (gavage)	69	ND	175	100% mortality at 175 mg/kg-day. No biologically significant effects at 69 mg/kg-day[b,c].	Borzelleca, 1983; Borzelleca et al., 1985
rat	10 days (gavage)	257	ND	ND	No clear treatment-related or biologically significant effects[b].	Daniel et al., 1993
rat	90 days (gavage)	150	ND	ND	No clear treatment-related or biologically significant effects[b,d].	Daniel et al., 1993
rat	18 days (PND 4-21) (gavage)	100	ND	500	100% mortality at 500 mg/kg-day. No effects at 100 mg/kg-day but small numbers of rats were tested. Dose-finding study with no histology[b].	Hasegawa et al., 2005
rat	18 days (PND 4-21) (gavage)	50[e]	ND	300	Tremors in 23/24 males and females at 300 mg/kg-day. No clear treatment-related effects at 50 mg/kg-day[b,d].	Hasegawa et al., 2005
rat	14 days (gavage)	500	ND	ND	No clinical signs or other effects but small numbers of rats were tested. Dose-finding study with no histology[b].	Hasegawa et al., 2005
rat	28 days (gavage)	200	ND	1000	Tremors, hypoactivity, abnormal gait and centrilobular hepatocellular hypertrophy at 1000 mg/kg-day. No reported effects at 200 mg/kg-day[b,d].	Hasegawa et al., 2005
rat	16 weeks[f] (drinking water)	7.5	75	ND	Reduced litter size (19%) and increased incidence of stillbirths.	Exon and Koller, 1982, 1985
rat	16-21 weeks[g] (drinking water)	75	ND	ND	No effects on immune responses[h] or body, liver, spleen or thymus weights. Other endpoints not evaluated.	Exon and Koller, 1983a, 1985

ND = not determined
[a]mg/kg-day
[b]Endpoints included clinical signs, body weight, hematology, serum chemistry, organ weights and gross pathology.
[c]Endpoints included immune responses and behavioral tests.
[d]Endpoints included histopathology.
[e]The only reported effect was tremors in 1/12 females that occurred once on treatment day 9.
[f]Female rats were exposed from 3 weeks of age through mating to untreated males at 90 days of age and subsequently through pregnancy and lactation.
[g]Offspring of female rats that were exposed from 3 weeks of age through mating to untreated males at 90 days of age and subsequently through pregnancy and lactation were continued on treatment for 10-15 weeks.
[h]Tests for humoral immunity, cell-mediated immunity and macrophage function were conducted.

Drinking water studies (Exon and Koller, 1982, 1983a and b, 1985) investigated reproductive and immunological toxicity in rats. There were no effects on immune function in rats that were exposed to 75 mg/kg-day via maternal drinking water during gestation and lactation and subsequently by direct consumption for 10-15 weeks (Exon and Koller, 1983a, 1985). Exposure to 75 mg/kg-day in drinking water during pregnancy and lactation significantly ($p \leq 0.05$) affected litter size (19% reduced) and stillbirths (5% increased) in rats (Exon and Koller 1982, 1985); no effects on litter size occurred at 7.5 mg/kg-day. Therefore, reproductive toxicity as evidenced by decreased litter size and an increase incidence in stillbirths was chosen for the development of the subchronic RfD for 2-chlorophenol based on a NOAEL of 7.5 mg/kg-day (Exon and Koller, 1982).

The NOAEL of 7.5 mg/kg-day is divided by a composite uncertainty factor of 1000 to derive a provisional **subchronic RfD of 8E-3 mg/kg-day**, as follows:

sRfD	=	NOAEL / UF
	=	7.5 mg/kg-day / 1000
	=	**0.0075 or 8E-3 mg/kg-day**

The composite UF of 1000 includes a factor of 10 for animal-to-human extrapolation, 10 for interindividual variability and 10 for database deficiencies.

The animal-to-human UF of 10 reflects a factor of three ($10^{1/2}$) for pharmacokinetic differences across species and a factor of three ($10^{1/2}$) for pharmacodynamic considerations.

The intraspecies UF of 10 is used to account for variation in sensitivity within human populations because there is limited information on the degree to which humans of varying gender, age, health status or genetic makeup might vary in the disposition of, or response to, the chemical.

An UF for extrapolation from a LOAEL to a NOAEL is not necessary because a NOAEL was chosen for the point of departure for the derivation for the sRfD.

The UF of 10 for database deficiencies is applied due to the lack of comprehensive reproductive and developmental toxicity studies, including a two-generation reproductive toxicity study and a subchronic study in mice (see below).

Confidence in the key study is low because a limited number of reproductive/ developmental endpoints (maternal and pup weight, percent conception, litter size and number of stillborn) were evaluated and the adequacy of the reporting is marginal. Confidence in the database is also low. The database includes 18-day, 28-day and 90-day studies in rats that assessed systemic toxicity and postnatal developmental toxicity at doses that include the range of those tested in the key study. Deficiencies in the database include the lack of comprehensive reproductive and developmental toxicity studies (especially important because reproductive effects have been identified as critical for this chemical) and a subchronic toxicity study longer than 14 days in duration in mice, which appeared to be more sensitive than rats to the subchronic effects of the chemical. In addition, a two-generation reproductive toxicity study is not

available. Considering the levels of confidence in the key study and data base and the lack of supporting data for the critical effects, confidence in the provisional RfD is low.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR 2-CHLOROPHENOL

No information is available on the subchronic or chronic inhalation toxicity of 2-chlorophenol, precluding derivation of RfC values for this chemical.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 2-CHLOROPHENOL

Weight-of-evidence Classification

Information regarding the carcinogenicity of 2-chlorophenol mainly consists of the negative results of a drinking water study in which rats were exposed to 0, 5, 50 or 500 ppm via maternal consumption during pregnancy and lactation and subsequently by direct consumption for 24 months (Exon and Koller 1983b, 1985). There were no significant increases in tumor incidence, latency or type in either sex, but a definitive conclusion regarding carcinogenicity is precluded by the use of marginal numbers of animals for a cancer bioassay (24-32/sex/dose level) and the apparent lack of a MTD, because the only observed effects (body weight and hematology changes) were not clearly treatment-related or biologically significant.

The ability of 2-chlorophenol to act as a promoter or co-carcinogen was investigated in a study with the known carcinogen ENU (Exon and Koller 1983b, 1985). Male rats that were exposed to 0, 5, 50 or 500 ppm of 2-chlorophenol in drinking water via maternal consumption during pregnancy and lactation and subsequently by direct consumption for 24 months, combined with prenatal exposure to ENU, had increased total tumor incidences and decreased time-to-tumor latencies compared to rats exposed to ENU alone. Another study found that dermal application of 2-chlorophenol promoted the formation of DMBA-initiated skin tumors in mice (Boutwell and Bosch, 1959).

2-Chlorophenol has been studied in several short term *in vitro* and *in vivo* animal studies. 2-Chlorophenol did not induce reverse mutations or DNA-repair in *S. typhimurium* (Haworth et al., 1983; Ono et al., 1992), DNA damage in *E. coli* (DeMarini et al., 1990), or sister-chromatid exchanges in orally-exposed mice (Borzelleca et al., 1985).

In accordance with current EPA cancer guidelines (U.S. EPA, 2005), the available data are inadequate for an assessment of human carcinogenic potential.

Quantitative Estimates of Carcinogenic Risk

Derivation of quantitative estimates of cancer risk for 2-chlorophenol is precluded by the lack of data demonstrating carcinogenicity associated with 2-chlorophenol exposure.

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