

Provisional Peer Reviewed Toxicity Values for

2, 4, 5-Trichlorophenol (CASRN 95-95-4)

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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 2,4,5-TRICHLOROPHENOL (CASRN 95-94-4)

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 oral reference dose (RfD) for 2,4,5-trichlorophenol is available in the Integrated Risk Information System (IRIS) database (U.S. EPA, 1987a; accessed 2007). The source document for the assessment was a Health Effects Assessment (HEA) for the chemical (U.S. EPA, 1984). The chronic oral RfD of 0.1 mg/kg-day in IRIS was derived from a no observed effect level (NOEL) of 100 mg/kg-day (1000 ppm in the diet, food consumption was assumed to be 10% of body weight), based on liver and kidney pathology observed in a 98-day dietary study (McCollister et al., 1961). A composite uncertainty factor (UF) of 1000 was applied to account for interspecies and interindividual differences and the use of a subchronic study to derive the chronic oral RfD. The Health Effects Assessment Summary Table (HEAST) references the chronic oral RfD for 2,4,5-trichlorophenol listed on IRIS and provides a subchronic RfD of 1 mg/kg-day, based on liver and kidney effects in the 98-day dietary study (U.S. EPA, 1997). The source documents referenced in the HEAST include the 98-day dietary study in rats (McCollister et al., 1961), the HEA for 2,4,5-trichlorophenol (U.S. EPA, 1984), and a Health and Environmental Effects Document (HEED) for Chlorinated Phenols (U.S. EPA, 1987b). In addition to the HEA (U.S. EPA, 1984) and the HEED (U.S. EPA, 1987b), IRIS (U.S. EPA, 1987a) identifies a Drinking Water Criteria Document (DWCD) for Chlorinated Phenols (U.S. EPA, 1986) that did not evaluate 2,4,5-trichlorophenol and an Ambient Water Quality Criteria Document (AWQCD) for Chlorinated Phenols (U.S. EPA, 1980) that derived an AWQC from the NOEL of 100 mg/kg-day for liver and kidney pathology observed in the 98-day dietary study (McCollister et al., 1961). The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994) does not identify additional reports that may contain toxicological

information on 2,4,5-trichlorophenol. Drinking Water Standards and Health Advisories are not available for 2,4,5-trichlorophenol (U.S. EPA, 2006).

No inhalation reference concentration (RfC) value is available for 2,4,5-trichlorophenol on IRIS or in the HEAST (U.S. EPA 1987a,b). An Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile is available for chlorinated phenols (ATSDR, 1999), but Minimal Risk Levels (MRLs) were not derived for 2,4,5-trichlorophenol. Occupational exposure standards and guidelines for 2,4,5-trichlorophenol are not available from the American Conference of 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 2,4,5-trichlorophenol is not available on IRIS (U.S. EPA, 1987a) or in the HEAST (U.S. EPA, 1997). A U.S. EPA (1988a) Carcinogenicity Assessment concluded that this compound could not be assessed as a potential human carcinogen and classified it as weight-of-evidence Group D, due to inadequate evidence from both animal and human studies (U.S. EPA, 1988a). The International Agency for Research on Cancer (IARC) indicated that 2,4,5-trichlorophenol has not been adequately tested for carcinogenicity (IARC, 1979). The World Health Organization (WHO) Environmental Health Criteria document on Chlorophenols other than Pentachlorophenol (WHO, 1989) indicated that there was limited evidence of carcinogenicity from occupational exposure to chlorophenols; however the potential carcinogenicity of 2,4,5-trichlorophenol was not specifically evaluated. 2,4,5-Trichlorophenol is not included in the NTP (2005) 11th Report on Carcinogens.

Literature searches were performed for the time period of 1965 to August, 2006 in TOXLINE, MEDLINE (plus PubMed cancer subset) and DART/ETICBACK. An updated search of the TOXCENTER (BIOSIS) database was performed for the time period of January 2000 to August, 2006. Databases searched without date limitations included TSCATS, RTECS, GENETOX, HSDB and CCRIS. Search of Current Contents encompassed February 2006 to August 2006.

REVIEW OF PERTINENT DATA

Human Studies

Oral Exposure. No data were located regarding the oral toxicity or carcinogenicity of 2,4,5-trichlorophenol in humans.

Inhalation Exposure. No information is available regarding the potential effects of inhalation exposure to 2,4,5-trichlorophenol as a single agent in humans. Several epidemiology studies were conducted of workers exposed to chlorinated phenols, 2,4,5-trichlorophenoxyacetic acid and chlorinated dioxins in combination (reviewed in ATSDR, 1999; WHO, 1989). 2,3,7,8-Tetrachlorodibenzodioxin (TCDD) is a common contaminant generated during the production of phenoxy herbicides from 2,4,5-trichlorophenol. Effects that were attributable to TCDD exposure were seen in exposed workers (e.g., chloracne) (Bleiberg et al., 1964). The literature search did

not identify any studies regarding carcinogenicity of 2,4,5-trichlorophenol as a single agent in humans. Mortality studies conducted on occupational workers involved in the manufacture of 2,4,5-trichlorophenoxyacetic acid using 2,4,5-trichlorophenol as a feedstock did not show increased mortality from any cause, as compared to unexposed controls (Ott et al., 1987, 1980). Several case control and cohort studies have evaluated cancer risks in pesticide production workers exposed to chlorinated phenols, phenoxy herbicides, and chlorinated dibenzodioxins and furans (reviewed in ATSDR, 1999; WHO, 1989). Because workers were exposed to several chemicals simultaneously, the studies do not provide information about a possible association between 2,4,5-trichlorophenol and cancer.

Animal Studies

Oral Exposure. No chronic oral studies were available for 2,4,5-trichlorophenol in animals.

McCollister et al., 1961

A subchronic dietary study was performed in male and female Wistar rats (10/sex/group). Rats were given diets containing 0, 0.01, 0.03, 0.1, 0.3 or 1% 2,4,5-trichlorophenol for 98 days. Daily dose estimates for 2,4,5-trichlorophenol were calculated to be 0, 10, 30, 100, 300 and 1000 mg/kg-day for male and female rats, assuming a body weight of 0.186 kg and a food consumption rate of 0.018 kg/day (average for male and female Wistar rats from a subchronic study, U.S. EPA, 1988b). Animals were weighed twice a week for the first month and once a week for the remainder of the study. Food consumption was recorded for the first month (frequency not specified) and rats were examined for clinical signs of toxicity (frequency not specified). Blood samples were obtained at study termination for hematology analysis in a subset of female rats (5/group) and blood urea nitrogen (BUN) in a subset of male rats (3/group). Animals were sacrificed and lungs, heart, liver, kidney, spleen, testes and brain were removed and weighed. Histopathology evaluation was performed for these organs, as well as for the pancreas and adrenal glands (organ weights were not measured for pancreas and adrenals).

2,4,5-Trichlorophenol administration in the diet did not produce clinical signs of toxicity or induce mortality at any dose level. No effect was observed on food consumption, hematology or BUN analyses, organ to body weight ratios or gross examination of tissues. Body weight gain was reduced by 24% in high-dose female rats (1000 mg/kg-day) and the mean terminal body weight for this group was 9% lower than control female rats. No other changes in body weight were observed in this study. Male and female rats from the two highest dose groups (300 and 1000 mg/kg-day) experienced a diurnal effect, observed as a wetness of the abdominal area throughout the study. Histopathological lesions were also observed in the liver and kidney of rats given 300 or 1000 mg/kg-day. In high-dose rats, the kidney lesions were described as moderate degenerative changes in the epithelial lining of the convoluted tubules and early proliferation of interstitial tissue. Mild degenerative changes were observed in the centrilobular portion of the liver, consisting of cloudy swelling and areas of focal necrosis. Slight proliferation of the bile duct and early portal cirrhosis were also observed. Kidney and liver alterations in the 300 mg/kg-day dose group were described as similar to, but milder than, the effects seen in rats from the 1000 mg/kg-day dose group. Incidence data were not provided in

this study. The NOAEL and LOAEL values for this study were 100 and 300 mg/kg-day, respectively, based on liver and kidney lesions and diuresis observed in male and female rats.

McCollister et al. (1961) also evaluated the acute oral toxicity, skin irritation and sensitization, and short-term (24-28 day) oral toxicity of 2,4,5-trichlorophenol in rats and rabbits. The acute oral toxicity of 2,4,5-trichlorophenol was assessed in male rats (5/dose, strain not specified) after administration of a single oral gavage dose (20% solution in corn oil) at dose levels of 0, 1, 1.26, 1.58, 2, 2.52, 3.16 or 3.98 g/kg. The acute oral LD₅₀ was calculated to be 2.96 g/kg. Skin irritation tests in rabbits showed that high concentrations of 2,4,5-trichlorophenol in solution produced a mild erythema (no further details were provided). Dry 2,4,5-trichlorophenol was not shown to be irritating to rabbit skin. In a 28-day oral study in rabbits, animals (1-3/dose group) were given daily gavage doses of 1, 10, 100 or 500 mg/kg (in 5% gum acacia solution) for 5 days/week (20 doses). Histopathology evaluation (tissues not specified) showed very slight liver and kidney alterations at 500 mg/kg-day, very slight kidney changes at 100 mg/kg-day, and no changes at 1 or 10 mg/kg-day 2,4,5-trichlorophenol. No further information was provided. NOAEL and LOAEL values were not derived for this study in rabbits because detailed information regarding the nature and severity of liver and kidney effects was not reported. Groups of male rats (5/group) were given 18 oral gavage doses of 0, 30, 100, 300 or 1000 mg/kg-day (in olive oil) over a 24 day period. 2,4,5-Trichlorophenol administration did not affect survival, terminal body weight, hematology or BUN analyses, organ to body weight ratios, or histopathological examination of lung, heart, liver, kidney, spleen, adrenals, pancreas or testes. Rats given doses of 1000 mg/kg-day lost an average of 10 g of body weight during the first 10 days of the study, but body weight loss was recovered during the remainder of the study and terminal body weights were similar to controls. A 15% increase in kidney weight was observed in rats given 1000 mg/kg, as compared to control rats. The reported changes in body and kidney weights in high-dose rats are not clearly adverse effects. A NOAEL value of 1000 mg/kg-day was therefore derived for this short-term rat study.

Chernoff and Kavlock, 1982, 1983; Gray et al., 1983, 1986; Gray and Kavlock, 1984

Pregnant CD-1 mice (30 treated, 40 controls) were given 0 or 800 mg/kg-day 2,4,5-trichlorophenol by corn oil gavage on gestation days (GD) 8 to 12. The change in maternal weight was measured during the treatment period (frequency not given). The dams gave birth on gestation day 19. The authors of this report considered the next day as postnatal day 1 (PND 1). Dams were allowed to give birth and litters were counted and weighed on postnatal days (PND) 1 and 3. Dead pups were necropsied and abnormalities were recorded. Dams that had not given birth by PND 3 were euthanized and uterine implantation sites were counted. All pups were combined in a pool from which six were randomly assigned to 4-12 dams that had given birth and selected for nursing of the pups on PND 6. Litter viability and pup weight were measured on PND 30. Locomotor activity in a figure eight maze was measured for 60 minutes using one male and one female mouse pup per litter on PND 21. This locomotor activity test was repeated for male mice on PNDs 58 and 210. Female mice were not retested because many were pregnant by PND 58 (male and female mice were housed together post-weaning). Female mice that became pregnant were removed and housed individually through parturition (number not specified). No further information was provided on the breeding of offspring exposed prenatally to 2,4,5-trichlorophenol. The study report indicated that offspring litter size and the age of these dams at parturition were recorded; however, these data were not clearly presented or discussed in

study reports. Necropsy was performed for male mice on PND 250. Body and organ weights (liver, testes, seminal vesicles, right kidney) were measured and gross pathology was recorded.

Eighty percent of control mice (32/40) became pregnant, while only 60% of treated mice became pregnant (18/30). Four dams given 2,4,5-trichlorophenol died prior to giving birth. The cause of death was not specified in the study reports. 2,4,5-Trichlorophenol administration produced a 13% decrease in the number of pups alive/litter on PND 1. No change was seen in maternal weight gain during treatment, average pup weight on PND 1, or the number or average weight of pups alive on PND 3 or 30. A 21% increase in locomotor activity was seen in treated mice as compared to controls on PND 21; however, this finding was not seen when the same mice were retested on PND 58. No gross abnormalities were observed in 2,4,5-trichlorophenol-treated offspring and organ weights were similar to controls.

Chernoff et al., 1990

Pregnant female Sprague-Dawley rats (25-30/group) were given 0 or 650 mg/kg-day 2,4,5-trichlorophenol by corn oil gavage on GD 6 to 15. Dams were weighed every other day during the treatment period. Groups of rats were killed on GD 8 (n=1), GD 12 (n=4), GD 16 (n=3) and GD 20 (n=15). Thymus, spleen and adrenal weights were measured for dams in all groups. Litters were removed from dams sacrificed on GD 20. Half of the fetuses from each litter were fixed in formalin for examination of soft tissue anomalies and half were stained with alizarin red for skeletal evaluation. Measured developmental endpoints included mean fetal weight, mean fraction dead or resorbed, and mean proportion of fetuses with supernumerary ribs. Lateral and fourth cerebral ventricles and the renal pelvis lumina were scored using a scale from 1 (no visible space) to 4 (apparent hydrocephaly or hydronephrosis).

2,4,5-Trichlorophenol administration caused 12% mortality in dams. Deaths occurred throughout the treatment period, with dams dying prior to GD 8, GD 12 and GD 16. Maternal weight gain was not affected by 2,4,5-trichlorophenol administration. A 20% increase in spleen weight was observed in a single treated dam sacrificed on GD 8, as compared to control dams. Spleen weights were similar to controls for treated dams sacrificed on GD 12, GD 16 and GD 20 and adrenal and thymus weights were similar to controls throughout the study. 2,4,5-Trichlorophenol administration did not cause developmental toxicity, as assessed by fetal weight, fraction dead or resorbed and evaluation of visceral and skeletal anomalies. A LOAEL value of 650 mg/kg-day was derived from this study, based on maternal mortality. A NOAEL value was not available from this study.

Hood et al. 1979

Pregnant CD-1 mice (8 or more/group) were given 0 or 800-900 mg/kg of 2,4,5-trichlorophenol via oral gavage (1:1 honey and water solution as vehicle) on a single day between GD 8 and GD 15. Separate groups of pregnant mice (8 or more/group) were administered 0 or 250-300 mg/kg 2,4,5-trichlorophenol via oral gavage (1:1 honey and water solution as vehicle) for three consecutive days during gestation (GD 7-9, GD 10-12, GD 13-15). Dams were sacrificed on GD 18 and the number of live, dead or resorbed fetuses was recorded. Live fetuses were weighed and examined for gross malformations. Two fetuses per litter were dissected and examined for gross visceral anomalies and malformations of the brain, oral and nasal cavities. Additional fetuses from each litter (number not given) were fixed in formalin for

examination of soft tissue anomalies or were eviscerated and stained with alizarin red for skeletal evaluation.

No results regarding maternal toxicity were reported. 2,4,5-Trichlorophenol administration, given as a single gavage dose or on three consecutive days, did not reduce mean fetal weight, or increase the incidence of gross malformations, or visceral or skeletal anomalies. The incidence of prenatal deaths and resorptions (25.4% of total, not calculated on a per litter basis) was significantly increased compared to solvent controls (9.2%), but not untreated controls (10.3%) in mice given a single dose (800-900 mg/kg) on GD 14. The incidence of prenatal deaths and resorptions was similar to control mice for groups receiving 2,4,5-trichlorophenol on other days (single or multi-dose). The study authors did not consider this isolated result to indicate a significant developmental effect of 2,4,5-trichlorophenol. Although 800 mg/kg-day appears to be a NOAEL, deficiencies in study methodology and reporting make interpretation of this study uncertain.

Inhalation Exposure. No studies were located regarding the toxicity of 2,4,5-trichlorophenol by inhalation exposure in animals.

Other Studies

Genotoxicity Information is available regarding the genotoxicity of 2,4,5-trichlorophenol (see Table 1). 2,4,5-Trichlorophenol produced both positive and negative results in the reverse mutation assay using several strains of *Salmonella typhimurium* (George et al., 1992; Rasanen et al., 1977; Strobel and Grummt, 1987). The differing results for reverse mutagenicity in *Salmonella typhimurium* did not appear to be related to the applied concentration or bacterial strain. Positive results were observed for mutagenicity in the *Umu* test system (error-prone repair assay in *Salmonella typhimurium*) with and without metabolic activation (Ono et al., 1992) and in the *E. Coli* prophage induction assay with metabolic activation (George et al., 1992; De Marini et al., 1990). The prophage induction assay is based on lambda excision which occurs during an SOS response to DNA damage. 2,4,5-Trichlorophenol did not produce forward mutations in Chinese hamster V79 cells (6-thioguanine resistance) (Jansson and Jansson, 1986), or chromosomal aberrations or sister chromatid exchanges in human peripheral lymphocytes exposed *in vitro* (Blank et al., 1983). Chromosome aberrations were seen in Chinese hamster ovary (CHO) cells following incubation with 2,4,5-trichlorophenol, but only at concentrations that produced significant cytotoxicity (cell counts <60% of controls) (Armstrong et al., 1993). 2,4,5-Trichlorophenol administration to rats (164 mg/kg-day by gavage) did not produce DNA damage in the blood or liver, as measured by the alkaline elution assay for single-strand breaks (Kitchin and Brown, 1988). The genotoxicity findings for 2,4,5-trichlorophenol were mixed.

Table 1. Genotoxicity Studies with 2,4,5-Trichlorophenol						
Test system	Endpoint	Test conditions	Results ^a		Dose ^b	Reference
			Without activation	With activation		
Prokaryotic organisms						
<i>S. typhimurium</i> strains TA98, TA100, TA102, TA104	Reverse mutation	Plate incorporation assay	-	-	5 mg/plate	George et al., 1992
<i>S. typhimurium</i> strains TA97, TA98, TA100, TA104	Reverse mutation	Plate incorporation assay	+	+	10 µg/plate	Strobel and Grummt, 1987
<i>S. typhimurium</i> strains TA98, TA100, TA1535, TA1537	Reverse mutation	Plate incorporation assay	-	-	50 µg/plate	Rasanen et al., 1977
<i>S. typhimurium</i> strain TA1535/pSK1002	<i>Umu</i> test	Error-prone repair	+	+	100 µg/mL	Ono et al., 1992
<i>E. coli</i> (WP2,λ strain derived from <i>E. coli</i> B/r; indicator strain TH008 derived from <i>E. Coli</i> C)	Prophage lambda induction	Microsuspension assay	-	+	0.8 µM	George et al., 1992
<i>E. coli</i> (WP2,λ strain derived from <i>E. coli</i> B/r; indicator strain <i>E. coli</i> C)	Prophage lambda induction	Microsuspension assay	-	+	3.99 µM	DeMarini et al., 1990
Mammalian cells						
V79 Chinese hamster cells	Forward mutation to 6-thioguanine resistance	Plate incorporation assay	-	ND ^c	12.5 µg/mL	Jansson and Jansson, 1986
Chinese hamster ovary (CHO) cells	Chromosome aberrations	Measured 20 hours after a 3 hour treatment	+T	ND ^c	140 µg/mL	Armstrong et al., 1993
Human peripheral lymphocytes	Chromosome aberrations, sister chromatid exchange	10 years after industrial accident (inhalation and dermal exposure assumed)	-	ND ^c	Not given; exposure categories were controls, possibly exposed and known to be exposed (with chloracne)	Blank et al., 1983
<i>In vivo</i> mammalian test systems						
Female Sprague-Dawley rat	DNA damage in blood and liver cells; single-strand breaks measured by alkaline elution	Single gavage dose given 4 hours prior to sacrifice; vehicle was 16% acetone/ 84% corn oil	-	ND ^c	164 mg/kg	Kitchin and Brown, 1988
^a + = positive, - = negative, T = toxicity, ND = no data ^b Lowest effective dose for positive results/highest dose tested for negative results; ND = no data. ^c Exogenous metabolic activation not used, due to endogenous metabolic activity in mammalian cells.						

Tumor Promotion

The tumor promoting activity of 2,4,5-trichlorophenol was evaluated in mouse skin (Boutwell and Bosch, 1959). The fur was shaved from the backs of mice one week prior to chemical application. 9,10-Dimethyl-1,2-benz[a]anthracene (0.3% DMBA in acetone, 25 μ L application, 75 μ g) was applied as a single application to the mid-dorsal region of mice (20/group, gender not specified). 2,4,5-Trichlorophenol (21% in acetone) was applied to the backs of mice (25 μ L application, 5.25 mg) twice weekly for 16 weeks following DMBA treatment. Typical papillomas larger than 1 mm were counted and the gross observation of benign and malignant tumors was confirmed by microscopic examination. The survival of mice treated with 2,4,5-trichlorophenol (19/20) was similar to acetone treated controls (18/20) at 16 weeks (both groups received DMBA application). 2,4,5-Trichlorophenol increased the incidence of surviving mice with papillomas, as compared to acetone treated controls (42% incidence in treatment mice, 0% incidence in control mice).

DERIVATION OF A PROVISIONAL SUBCHRONIC RfD FOR 2,4,5-TRICHLOROPHENOL

A chronic oral reference dose (RfD) for 2,4,5-trichlorophenol (0.1 mg/kg-day) is available in IRIS (U.S. EPA, 1987). This value is based on liver and kidney pathology observed in a 98-day dietary study (McCollister et al., 1961). Chronic oral toxicity studies were not available for 2,4,5-trichlorophenol. McCollister et al. (1961) is the only study that evaluated the subchronic oral toxicity of this compound. The NOAEL and LOAEL values for this study (100 and 300 mg/kg-day, respectively) were based on liver and kidney lesions and a diurnal effect (i.e., wet abdomen) observed in male and female rats exposed to 2,4,5-trichlorophenol in the diet for 98 days. Kidney lesions consisted of degeneration of the tubule epithelium and proliferation of interstitial tissue. Cloudy swelling and areas of focal necrosis were observed in the centrilobular portion of the liver. Liver and kidney effects were also seen in a 28-day gavage study in rabbits at doses of ≥ 100 mg/kg-day; however, the nature and severity of these effects was not indicated (McCollister et al., 1961). In a 24-day dietary study in rats by the same authors, no effects were observed on survival, terminal body weight, hematology or histopathology at doses of ≤ 1000 mg/kg-day.

Developmental toxicity assays were conducted using 2,4,5-trichlorophenol at oral gavage doses of ≥ 650 mg/kg-day (Chernoff et al., 1990; Chernoff and Kavlock, 1982, 1983; Gray et al., 1983; Gray and Kavlock, 1984; Gray et al., 1986; Hood et al. 1979). Decreased maternal survival was seen in mice given 800 mg/kg-day 2,4,5-trichlorophenol on GD 8 to 12 (Chernoff and Kavlock, 1982, 1983; Gray et al., 1983, 1986; Gray and Kavlock, 1984) and in rats given 650 mg/kg-day 2,4,5-trichlorophenol on GD 6 to 15 (Chernoff et al., 1990). 2,4,5-Trichlorophenol administration reduced pup survival in mice on PND 1 (800 mg/kg-day, GD 8 to 12) (Chernoff and Kavlock, 1982, 1983; Gray et al., 1983, 1986; Gray and Kavlock, 1984), but this effect may have been secondary to maternal toxicity in the same study.

The **subchronic p-RfD of 0.3 mg/kg-day** is based on degenerative histopathological changes in the liver (cloudy swelling and focal necrosis) and kidney (degeneration of tubule

epithelium) and a diurnal effect observed in male and female rats exposed to 2,4,5-trichlorophenol in the diet for 98 days (McCollister et al., 1961). Incidence data were not provided in this study; therefore, benchmark dose (BMD) modeling could not be performed and the NOAEL was chosen as the point of departure for the subchronic RfD.

The subchronic p-RfD is derived by dividing the NOAEL of 100 mg/kg-day by a composite uncertainty factor (UF) of 300 as follows:

$$\begin{aligned} \text{Subchronic p-RfD} &= \text{NOAEL/ UF} \\ &= 100 \text{ mg/kg-day} / 300 \\ &= \mathbf{0.3 \text{ mg/kg-day}} \end{aligned}$$

The composite UF of 300 includes factors of 10 for animal-to-human extrapolation and interindividual variability and a factor of 3 for database uncertainty. The interspecies UF of 10 was used to account for pharmacokinetic and pharmacodynamic differences across species. The interindividual variability 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 2,4,5-trichlorophenol. A database UF of 3 was selected due to the absence of supporting subchronic or chronic oral toxicity studies and lack of a multigeneration reproductive toxicity study. Available developmental toxicity studies were limited and were at high single doses, but indicate that the developing organism may not be a sensitive target for 2,4,5-trichlorophenol.

Confidence in the critical study is medium. McCollister et al. (1961) was a well-conducted, 13-week dietary study; however, a relatively small number of animals were used (10/group) and data reporting was minimal. Hematology analysis was only performed for a small subset of female rats (5/group) and clinical chemistry tests were not performed (with the exception of BUN in 3 male rats/group). Histopathology examination was performed for lungs, heart, liver, kidney, spleen, testes, brain, adrenals and brain and both NOAEL and LOAEL values were derived from the study based on liver and kidney toxicity. Confidence in the database is low-to-medium. No supporting subchronic or chronic oral toxicity studies were available; however, supporting short-term studies were conducted in rats and rabbits (McCollister et al., 1961). Single-dose developmental toxicity studies were available using oral gavage doses of ≥ 650 mg/kg-day; although limited, these studies suggest that the developing organism may not be particularly sensitive to the oral toxicity of 2,4,5-trichlorophenol. A multigeneration reproductive toxicity study is not available. Overall, confidence in the subchronic p-RfD is low-to-medium.

FEASIBILITY OF DERIVING PROVISIONAL CHRONIC AND SUBCHRONIC RfC VALUES FOR 2,4,5-TRICHLOROPHENOL

No inhalation toxicity studies are available for 2,4,5-trichlorophenol. The data are therefore inadequate to support derivation of a provisional inhalation subchronic or chronic RfC for 2,4,5-trichlorophenol.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 2,4,5-TRICHLOROPHENOL

Weight-of-evidence Classification

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is *inadequate evidence to assess the carcinogenic potential* of 2,4,5-trichlorophenol, based on limited data in both humans and animals. This compound was previously classified as weight-of-evidence Group D, due to inadequate evidence from both animal and human studies (U.S. EPA, 1988a). The International Agency for Research on Cancer (IARC) indicated that 2,4,5-trichlorophenol has not been adequately tested for carcinogenicity (IARC, 1979, 1987).

Human studies have not evaluated cancer risks of exposure to 2,4,5-trichlorophenol as a single agent. Studies in pesticide production workers consider simultaneous exposure to chlorinated phenols, phenoxy herbicides and chlorinated dibenzodioxins and furans (reviewed in ATSDR, 1999; WHO, 1989). Genotoxicity findings were mixed for reverse mutation in *S. typhimurium*, but were positive for mutagenicity in the *Umu* test system (error-prone repair assay in *Salmonella typhimurium*) and the *E. Coli* prophage induction assay (see Table 1). No conclusion could be derived from the available genotoxicity studies. No other studies were available that evaluated the carcinogenic potential of 2,4,5-trichlorophenol.

Quantitative Estimates of Carcinogenic Risk

There are no human or animal data on which to base an oral or inhalation cancer assessment for 2,4,5-trichlorophenol.

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