2,4-DICHLOROPHENOL

Document History
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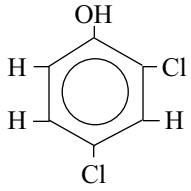
I. IDENTIFICATION[1]

Chemical Name: 2,4-Dichlorophenol
Synonyms: 2,4-DCP; DCP; Phenol: 2,4-Dichloro
CAS Number: 120–83–2
Molecular Formula: $Cl_2C_6H_3OH$
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[1-3]

Physical State: White solid at room temperature; colorless liquid when melted
Odor Description: Pungent or sharp phenolic odor
Odor Threshold: 1.4 mg/m³ (0.21 ppm)
Molecular Weight: 163
Conversion Factors: 1 mg/m³ = 0.15 ppm
1 ppm = 6.7 mg/m³
Vapor Pressure: 0.1 mm Hg at 20°C (68°F)
0.116 mm Hg at 25°C (77°F)
1 mm Hg at 53°C (127.4°F)
1 mm Hg at 76.5°C (169.7°F)
Boiling Pt: 210°C (410°F)
Melting Point: 40–45°C (104–113°F) at 760 mm Hg
pH: Slightly acidic in water
Saturated Atmosphere: 131 ppm at 20°C (68°F)
Solubility in Water: 4000 mg/L in water at 25°C; soluble in alcohol, ether, chloroform, and carbon tetrachloride
Flash Point: 103.9°C (219°F) (TCC)
Flammability Limit: No Data Found
Stability and Reactivity: Relatively stable; HCl evolved on combustion
pKa: 7.85 at 25°C (77°F)
Log Octanol/Water Partition Coefficient (K_{ow}): 3.08

III. USES AND VOLUME

Vulcan Chemical, Helena Chemical, Dow Chemical, Rhone-Poulenc (now Rhodia), and Sandoz produce or use 2,4-dichlorophenol (2,4-DCP). It is used as an intermediate in the manufacture of herbicides such as 2,4-dichlorophenoxyacetic acid (2,4-D); A.H. Marks (UK) and Inui (Japan) also use 2,4-DCP.[4] This chemical may be transported via normal transportation routes such as rail and highways in various containers including 55-gallon drums, isotainers and other bulk containers.[1]

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity

1. Oral Toxicity

The acute oral LD_{50} values of 2,4-DCP range from about 580–4500 mg/kg for rats and mice and are summarized in Table 1. Animals generally exhibited rapid onset of symptoms within 10–15 minutes after dosing and signs of toxicity were generally consistent with CNS involvement and included slight tremors, loss of righting reflex, salivation, labored breathing, depression, lethargy and ataxia.

Table 1

Acute Oral LD_{50} Values for 2,4-DCP

LD_{50} (mg/kg)	Species/Strain	Sex	#/Group
580[5]	Rat	M	
3670[2, 6, 7]	Sprague-Dawley Rat	M	6
4500[2, 6, 7]	Sprague-Dawley Rat	F	6
1630[2, 6, 7]	ICR Mice	M/F	6
1630[8]	CF-1 Mice	M	
2830[8]	Sprague-Dawley Rat	M	
1276[7, 9-11]	CD-1 ICR Mice	M	10
1352[7, 9-11]	CD-1 ICR Mice	F	10
2000–2400[12]	F344 Rats	F	5

With the exception of a 1943 study[5] indicating an acute oral LD_{50} of 580 mg/kg in rats (administered in fuel oil)[9], the oral LD_{50} values reported in the other 4 studies were at least 2000 mg/kg for rats. The data from the Wil study[12] using F344 rats (5 females/group) demonstrated a steep slope in the response data with 0/5 deaths at 500, 1000, and 2000 mg/kg; 5/5 deaths at 2400 mg/kg; 4/5 deaths at 2800 mg/kg; and 5/5 deaths at 3200 and 4000 mg/kg. In another study[13] using F344/N rats and $B6C3F_1$ mice, only the highest dose of 5200 mg/kg was lethal in mice with 1/10 males succumbing, while no deaths were observed in female mice or both sexes of rats during the 14-day study.[13]

Mild catarrhal enteritis was observed in female Sprague-Dawley albino rats given a single gavage dose of 316–5000 mg/kg/day 2,4-DCP in alcohol and sacrificed 24 hours later.[14]

Lung hemorrhaging occurred in Fischer-344 rats treated with a single gavage dose of 2,4-DCP at the lethal doses of 2400, 2800, 3200, and 4000 mg/kg. Gross necropsy revealed reddened hindstomach and intestines at the 2400–4000 mg/kg doses.[12]

2. *Eye Toxicity*

Based on a rabbit eye irritation test, contact with 2,4-DCP may result in slight pain, moderate to severe conjunctival redness and swelling, moderate reddening of the iris, and severe corneal injury which may lead to permanent impairment of vision.[15]

Rats exposed to aerosols of 2,4-DCP ranging from 0.77–1.13 mg/L (115–169 ppm) exhibited closed eyelids, tears and corneal opacity which was reversed within 24 hours after exposure.[16]

Severe corneal damage occurred in the eyes of rabbits after a single direct application of 0.1 mL 2,4-DCP. Careful washing of the eye 30 seconds after application did not prevent this damage.[14]

3. *Skin Toxicity*

a. Irritation

2,4-DCP is considered corrosive based on a U.S. Dept. of Transportation standard test.[15, 17]

A single 4-hour application of 500 mg of 2,4-DCP (solid form) to skin of rabbits produced skin injury characterized as slight to moderate erythema and edema and superficial to moderate necrosis; the moderate burns healed with a scar indicating the skin lesions were irreversible. Ten applications of 500 mg of 2,4-DCP (solid form) to skin of rabbits over 14 days caused a similar response leading to irreversible slight scarring.[14] Application of 2,4-DCP as a solid or as a 50% solution in Dowanol™ DPM (propylene glycol methyl ether) at doses up to 4000 mg/kg to skin of rabbits resulted in moderate to marked erythema and slight to marked edema and skin necrosis.[18, 19]

Application of undiluted 2,4-DCP melted at 40°C (liquid form) to skin of rats at doses of 200, 300, 1400 and 2000 mg/kg in a semi-occluded manner produced marked to severe skin irritation resulting in skin necrosis at all doses tested.[20] The skin injury was only slightly reversed 2 weeks after dosing. 2,4-DCP was considered corrosive to the skin.

The corrosive properties of 2,4-DCP noted in the studies described above were consistent with a 1945 study which reported skin necrosis within 15 seconds after application of powder, alcohol solution, and aqueous suspension treatment regimes to shaved skin of rabbits.[21]

b. Absorption

The dermal LD_{50} in rabbits for the solid material was 4000 mg/kg (occluded for 24 hours)[19], and 1414 mg/kg for a 50% solution (occluded for 24 hours) in Dowanol™ DPM (propylene glycol methyl ether) in male rabbits.[18] Signs of generalized toxicity in test animals included lethargy and anorexia that was not accompanied by gross pathology. Because there were only two rabbits per dose group, the 95% confidence interval on these values is very large (236–8455 mg/kg).[18,19]

The dermal LD_{50} in male Sprague-Dawley rats following application of undiluted 2,4-DCP melted at 40°C (liquid form) was 780 mg/kg with a 95% confidence interval of 369–1599 mg/kg.[20] The application was by means of a semi-occluded hypoallergenic adhesive bandage, which was removed after 24 hours

and excess product wiped off.[20] The minimal lethal dose in this study was 300 mg/kg. A slight decrease in motor activity was seen at 200 mg/kg while doses of 300 mg/kg and above caused marked depression in motor activity and respiratory function that remained present 9 days after treatment.[20] Mortality for male rats in this study was 0, 20, 60, and 80% for doses of 200, 300, 1400, and 2000 mg/kg, respectively; female rat mortality was 0 and 80% for doses of 200 and 2000 mg/kg, respectively.[20] Two deaths (of 30 animals tested) occurred during the first day, one male and one female, both at the 2,000 mg/kg dosing.[20]

Evaluation for chloracnegenesis following application of 10% suspensions of 2,4-DCP in chloroform to ears of rabbits was negative.[22-24]

A study of permeability of 2,4-DCP in a liquid carrier across human cadaver epidermis resulted in a calculated permeability coefficient for 2,4-DCP of 0.060 cm/hr, much higher than phenol at 0.008 cm/hr, and higher still than 17 other phenols ranging from 0.00024–0.059 cm/hr [50% of the phenols were less than 0.03 cm/hr].[25]

In addition, phenol is known to increase in permeability as temperature increases. For instance, phenol's permeability constant has been measured at 0.016, 0.019, 0.029, and 0.044 cm/hr at 10, 20, 30, and 37°C, respectively in one study and[26] 0.024, 0.039, 0.159, 0.159, and 0.160 cm/hr at 60, 70, 80, 90, 100°C.[27] Therefore, it is expected that 2,4-DCP would increase permeability in a similar fashion, beginning with 0.115 cm/hr at 37°C.[26] Furthermore, an increase in phenol concentration of applied product greater than ≥5% has been shown to cause an enhancement of the permeability coefficient by 10-fold resulting in an adsorption rate increase from 1% solution to 5% solution of 50-fold versus a predicted 5-fold.[28] It is postulated that the known corrosive effects of phenol, also present in 2,4-DCP, may be the causative factor for this increase.[28]

c. Sensitization

No information found.

4. Inhalation

A 4-hour inhalation LC_{50} in Sprague-Dawley rats was calculated at 0.97 mg/L (145 ppm; 970 mg/m^3) for a <4 um aerosol of 2,4-DCP created by increasing the temperature of the 2,4-DCP to 55°C immediately prior to aerosolization.[16] The results indicated a very sharp dose-response curve.[16] Death occurred within 3 hours after initiation of exposure and was preceded by spasms, loss of righting reflex and cyanosis.[16] Irritation, tearing, and spasms were noted at all doses. Weights returned to normal by Day 4 for the 770 mg/m^3 exposure group, by Day 7 for the 840 mg/m^3 exposure group, and by Day 7 for the survivors of the remaining exposure groups. No macroscopic evidence of anomalies was noted in the low dose group at the Day 14 autopsy. Dark red spots in the inferior lung lobes of the autopsied animals were observed sporadically.[16]

5. Other

One study in mice and a second in rats involving intraperitoneal administration of 2,4-DCP resulted in LD_{50} values of 153 and 430 mg/kg, respectively. CNS disorders paralleling those of the previously discussed acute oral tests were described as symptoms.[29,30] One study in rats demonstrated an LD_{50} value of 1730 mg/kg using a 20% solution of 2,4-DCP in fuel oil via the subcutaneous route. CNS effects were observed at lethal doses.[5]

B. Genotoxicity and Mutagenicity

2,4-DCP was negative in the Ames test using *S. typhimurium* strains TA98, TA100, TA1535, and TA 1537.[31]

The oral administration of 1 × 160 and 2 × 800 mg/kg of 2,4 DCP to Swiss Carworth Farm Lane Petter(CFLP) mice did not show a statistically significant increase in the mean percentage of erythrocyte polychromatophiles bearing miconuclei (the micronucleus technique of Schmid). The absence of clastogenic character was considered by the authors, after interpretation in consideration of the technique used, to be an absence of mutagenic effect. Two clastogenic substances (methylmethanesulfonate and cis-platine) were used as positive controls.[32]

Results of genotoxicity tests conducted by NTP are:[13]

1. Negative without S9 activation in *S. typhimurium* strain TA 1535, equivocal with hamster S9[33];

2. Positive without S9 in mouse L5178Y lymphoma cells, (not tested with S9)[34];

3. Positive for sister-chromatid exchanges both with and without S9 in Chinese hamster ovary cells, negative for aberrations with and without S9[13,35]; and

4. No increases in revertant colonies in strains TA98, TA100, or TA1537 with or without exogenous metabolic activation.

2,4-DCP was also negative in an unscheduled DNA synthesis (UDS) assay.[36] In CD-1 mice (12 males and females per group), daily gavage administration of 64, 128, and 638 mg/kg/day 2,4-DCP in corn oil for 14 days did not increase sister chromatid exchange (SCE) rates in testicular or bone marrow cells. No further details were provided.[7]

Ninety-day exposure of CD-1 mice (20 males and females per group) to 2,4-DCP in drinking water at doses of 50, 150, and 500 mg/kg/day also had no effect on SCE in bone marrow and testicular cells.[7]

C. Metabolism

Due to its high lipid solubility and low ionization at physiological pH, 2,4-DCP is expected to be readily absorbed after oral administration.[37] Findings from acute dermal toxicity tests indicate 2,4-DCP is rapidly absorbed when applied to skin as the liquid form at 40°C.[20] The mechanism of action of 2,4-DCP appears to be as a strong uncoupler of oxidative phosphorylation[2,38], a biochemical mechanism of toxicity similar to that of phenol. Of the di-, tri-, tetra-, and penta-chlorophenols, 2,4-DCP appears to have the second lowest potential of uncoupling oxidative phosphorylation based on testing of rat-liver mitochondria.[38]

A study in which rats were given intravenous 2,4-DCP showed the agent rapidly distributes to kidney, liver, fat, and brain tissues, with the highest concentrations in the kidney and liver. After a bolus intravenous injection in rats of a 10 mg/kg dose, 2,4-DCP was rapidly eliminated from the brain (½-life 6 min), from plasma and fat (½-life 10 min), from liver (½-life 15 min), and from kidneys (½-life 30 min). The levels of 2,4-DCP in plasma decreased from 1.64 mg/L at 10 minutes after administration to 0.04 mg/L at 30 minutes after injection.[39]

D. Developmental and Reproductive Toxicity

In repeat-dose studies with 2,4-DCP in corn oil, 2,4-DCP was not teratogenic in rats when given at doses of 200–750 mg/kg/day during days 6–15 of gestation. However, 4 out of 34 pregnant Fischer rats treated by gavage at 750 mg/kg/day died. There were neither post-implantation losses nor changes in the numbers of resorptions of viable fetuses at any dose level.[40,41] Maternal toxicity occurred at all dose levels; the slight increase in early embryonic death at the high dose level was considered secondary to the maternal toxicity. Oral exposure of pregnant rats to 750 mg/kg/day 2,4-DCP for 10 gestational days induced a slight decrease in fetal weight and delayed ossification of sternal and vertebral arches and led to a slight non-significant increase in early embryonic deaths (average 0.8/ litter controls; 1.2/litter at 750 mg/kg/day).[40, 41]

An increase in the incidence of the number of fetuses with skeletal abnormalities associated with reduced fetal body weight has been reported in mice treated with 74 mg/kg 2,4-DCP administered subcutaneously on Days 6–15 of gestation.[42]

No reproductive organ pathology was observed in rats or mice of either sex (10 groups of each sex, each species) at 2000 or 2600 mg/kg/day 2,4-DCP in the diet, respectively for 13 weeks. Reproductive organ pathology was not observed in male rats fed 440 mg/kg/day and female rats fed 250 mg/kg/day 2,4-DCP and male mice fed 1300 and female mice fed 8210 mg/kg/day for 2 years.[13]

The reproductive toxicity of 2,4-DCP was assessed in a one-generation reproduction study in rats.[43] Continuous treatment with 3, 30, or 300 ppm 2,4-DCP in drinking water prior to mating, during gestation and postnatally up to 13 weeks, did not alter reproductive performance (conception, litter size, pup birth weight, number of live births and survival to weaning).[43]

A total of 10 randomly chosen male and female CD-1 mice from dosing groups of 50, 150, and 500 mg/kg 2,4-DCP for 90-days prior to mating and throughout gestation did not produce any adverse effects on fertility and fetotoxicity.[7]

E. Subacute Toxicity (5–14 days)

Groups of ten (each sex) of male and female rats and mice were given diets containing 2,4-DCP at concentrations of 0, 2500, 5000, 10,000, 20,000, or 40,000 ppm. One male mouse died before the end of the studies (two weeks) at the 40,000 ppm dose, while no deaths occurred in any other group and no compound-related lesions were seen at necropsy in rats or mice.[13]

Groups of 12 male and 12 female CD-1 mice administered at doses of 64, 128, and 638 mg/kg/day 2,4-DCP once daily by gavage for 14 days failed to produce any significant compound-related toxicity.[13]

F. Subchronic Toxicity (15 days–179 days)

An NTP study consisted of the dietary administration of 2500–40,000 ppm (325–5200 mg/kg/day) 2,4-DCP to groups of 10 F344/N rats and 10 B6C3F_1 mice of each sex. Diets containing 0, 2500, 5000, 10,000, 20,000, or 40,000 ppm 2,4-DCP for up to 13 weeks did not cause mortality in rats of either sex. At 2600 mg/kg/day and 5200 mg/kg/day, body weights were decreased 11–40% from control values. All rats at doses of 2600 mg/kg/day and 5200 mg/kg/day and female rats at 1300 mg/kg/day exhibited bone marrow atrophy that resulted in depletion of both erythroid and myeloid elements. Dietary treatment of mice with 2600 mg/kg/day for 13 weeks also did not affect survival, but ingestion of 5200 mg/kg/day resulted in death of all of the treated mice within 3 weeks. Histopathological examinations of the heart did not revealed any effects in the rats fed 2,500 mg/kg/day or the mice fed 2600 mg/kg/day for 13 weeks. Renal tubular necrosis was seen in mice that died following treatment at 5200 mg/kg/day. At dietary levels of 325–2600 mg/kg/day, minimal liver injury (necrosis and syncytial alteration in the form of multinucleated hepatocytes) was observed in male mice. No histopathological changes were observed in the gastrointestinal tracts of Fischer-344 rats fed 2000 mg/kg/day or mice fed 2600 mg/kg/day for the 13 weeks.[13]

In a subchronic studies, dietary concentrations of 0.02–0.2% (resulting in doses of 20, 45, 100, 230 mg/kg/day) to ICR mice (7 males/group) for 6 months caused no observable adverse effects on growth or organ weight, hematology or histology.[2,6]

Progeny of Sprague-Dawley rats derived from dams (10 per group) treated with 3, 30, or 300 ppm 2,4-DCP in drinking water from 3 weeks of age through mating, gestation and lactation, and with continued treatment of progeny up to 13 weeks of age, had significantly increased liver and spleen weights, enhanced humoral immune responsiveness, and depressed cell-mediated immunity only in the 300 ppm dose group. Histopathologic changes were not observed in any treatment group.[43]

2,4-DCP fed to CD-1 mice in drinking water at doses of 50, 150, or 500 mg/kg/day for 90 days produced no treatment-related effects including standard hematological parameters, including total and differential white blood cells, red blood cells, platelets, hematocrit, hemoglobin, and coagulation measures relative to unexposed controls.[10]

G. Chronic Toxicity (>180 days)

Two-year studies were conducted by feeding diets containing 0, 5000 or 10,000 ppm 2,4-DCP to groups of 50 male F344/N rats and 50 male and 50 female B6C3F_1 mice for 103 weeks. Groups of 50 female rats received diets containing 0, 2500, or 5000 ppm. Mean body weights of the highest dose male and female rats, highest dose male mice, and both dosed groups of female mice were generally lower than those of controls. No significant differences in survival were observed between any groups of rats or mice of either sex. The average daily feed consumption by the rats and mice in this study are found in Table 2 along with mortality data.[13]

Nasal lesions were noted in male but not female Fischer-344 rats exposed to 210 mg/kg/day for

Table 2

Species	Average Dose for 103 Weeks (mg/kg/day)	Survival Rate	Lesions
Male Rats	Control	33/50	31/50 Mononuclear cell Leukemia
	210	25/50	17/50 Mononuclear cell Leukemia
	440	32/50	17/50 Mononuclear cell Leukemia
Female Rats	Control	34/50	12/50 Malignant lymphomas
	120	43/50	12/50 Malignant lymphomas
	250	40/50	4/50 Malignant lymphomas
Male Mice	Control	33/50	11/50 Syncytial alteration of hepatocytes
	800	32/50	33/49 Syncytial alteration of hepatocytes
	1,300	31/50	42/48 Syncytial alteration of hepatocytes
Female Mice	Control	45/50	
	430	40/50	
	820	43/50	

103 weeks (groups of 10 rats each sex). Nasal lesions were not observed in mice fed as much as 1300 mg/kg/day for the same exposure period. The incidence of mononuclear cell leukemia was decreased in dosed male rats relative to that in controls (see Table 2).[13] No histopathological changes were observed in the gastrointestinal tracts of Fischer-344 rats fed 440 mg/kg/day or mice fed 1300 mg/kg/day for the 103 weeks. The NOAEL for kidney effects in rats in this study is 440 mg/kg/day and 1300 mg/kg/day in mice.[13]

A NTP bioassay reported no evidence of carcinogenicity in male rats fed diets containing 210 and 440 mg/kg/day 2,4-DCP, in female rats maintained on diets containing 120 and 250 mg/kg/day, or in male mice at levels of 800 or 1300 mg/kg/day, and female mice at 430 and 820 mg/kg/day.[13]

2,4-DCP also was not carcinogenic in rats treated with 3, 30 or 300 ppm in drinking water for 2 years (treatment commenced with parents from weaning through mating and gestation and continued in offspring for 2 years).[43]

ICR male mice (7 /dose group) were dosed in feed at approximately 18, 45, 100, and 230 mg/kg. One of seven in the high dose group exhibited liver cell enlargement, and two of seven with round cell infiltration, indicating a NOAEL of 100 and a LOAEL of 230 mg/kg.[2,6]

One study suggested that 2,4-DCP may promote skin carcinogenesis in mice after initiation with dimethylbenzanthracene when applied at a concentration high enough to damage skin.[37,44] The interpretation of this finding was confounded, however, by the use of benzene as the vehicle for 2,4-DCP.[45]

IARC has classified the group "chlorophenols" as 2B (agent possibly carcinogenic to humans) but did not present any data specifically for 2,4-dichlorophenol.[46] A review of the epidemiology data concluded that information is insufficient to associate this material with soft tissue sarcoma and lymphoma incidence.[47]

H. Other

No specific neurotoxicity evaluations have been identified. However, signs of CNS involvement have been observed in acute LD_{50} evaluations.[2]

V. HUMAN USE AND EXPERIENCE

2,4-DCP is suspected to be involved in chloracne and porphyria induction in workers.[37] Porphyria cutanea tarda and hyperpigmentation, folliculitis, keratosis, and hirsutism have been reported in workers employed in the manufacture of 2,4-DCP. Exposure to chlorophenols and intermediates was probably through inhalation and dermal contact. Eleven cases of porphyria were identified, based on urinary porphyrin excretion, in a survey of 29 workers. Elevated serum transaminase levels, an evidence of liver damage (e.g. regeneration and hemofuscin deposition) were detected from liver biopsies in two cases that were studied in detail. The authors stated that the porphyria was probably related to liver injury.[48] A number of other limitations and confounding factors were associated with this study limiting its usefulness.[4]

Clinical assessment of two patients occupationally exposed during the manufacture of 2,4-dichlorophenoxyacetic acid herbicides revealed hematology and blood chemistry parameters (blood counts, bleeding and clotting time, serum bilirubin, blood urea nitrogen, and others) to be within normal ranges.[48]

A review of the medical records of 28 cases of 2,4-dichlorophenol exposure showed primarily first and second degree skin burns, varying from minor 1–2 cm areas which healed within several days to 10 × 32 cm on the forearm or 12 × 25 cm on both lower legs, which healed in 2.5 weeks to 2.5 months. Typically the burns were less severe if exposure was limited to small areas at ambient temperatures and with rapid showering (within 1 minute). The burns were more severe and slower to heal with larger areas exposed at elevated temperatures (molten, with steam condensate etc.) despite rapid showering (within 30–60 seconds). Nearly all cases were showered within 1 minute; with the exceptions in this group involving minor exposures that were not immediately apparent (leak around gloves, etc.).[49]

A series of cases involving fatalities believed to be from 2,4-DCP exposure were reviewed. In one, a worker in France in 1991 splattered pure 2,4-DCP on portions of his arm and leg while disposing of industrial waste. The man walked away from the exposure incident and washed without undressing, collapsed and experienced a seizure within 20 minutes of the accident and died shortly thereafter.[50] One source on this incident states that it involved melted 2,4-DCP at 60°C, on approximately 10% of the body surface.[2] A second states that less than 10% of the body was exposed.[50] Postmortem examination revealed blood and urine 2,4-DCP concentrations of 24.3 and 5.3 mg/L, respectively.[50,51] The identity of 2,4-DCP was confirmed by mass spectrometry. A screen for other drugs including ethanol, organic solvents, tranquilizers, and drugs of abuse was negative.[50, 51] For comparison, lethal blood phenol concentrations reported in the literature are as follows: 56 and 27 mg/L[52] 4.7 mg/L[53], 130 mg/L[54], and 60 and 90 mg/L.[55] It has been hypothesized that the low level of 4.7 mg/L may have resulted from resuscitation activities.[55]

In 1985, a worker apparently suffered dermal exposure to 2,4-DCP (as well as possibly some monochloroacetic acid), and bypassed the nearby safety shower and collapsed in the locker room shower where he was observed to be unconscious and convulsing, and could not be revived.[51] Serum total 2,4-DCP concentration at postmortem was 67 mg/L. The final pathologic diagnosis was "acute chlorinated phenolic exposure and 60% chemical burns".[51]

In 1948, a suspected 2,4-DCP fatality due to burns to both lower legs was reported. Another fatality due to burns to the face, neck, back, and thighs was reported at the same facility in 1980.[49] Another fatality occurred in this facility in 1998, where circumstances involved apparent exposure to molten 2,4-DCP without proper protective equipment. The individual bypassed the nearby safety shower, subsequently collapsed and had a cardiac arrest. He exhibited burns to the face, one knee and thigh, and both forearms. Significant exposure to 2,4-DCP, confirmed by testing of blood levels (free 2,4-DCP 7.2 mg/L, total 2,4-DCP 13.1 mg/L), resulted in death of the worker.[49] Also notable in this case was the absence of edema in the throat or lungs suggesting dermal absorption was the prevalent route of exposure.[56]

Another occupational fatality occurred in England in 1992 where a pump seal failure allowed steam and 2,4-DCP to contact a man's face and neck. Death occurred 20 minutes after exposure.[51]

An epidemiology study was completed on employees who manufactured or formulated 2,4-dichlorophenoxyacetic acid (2,4-D) anytime from 1945 through 1994. Since 2,4-DCP is an intermediate in the 2,4-D process, these employees also had the opportunity for exposure to molten 2,4-DCP. A total of 1,437 employees were tracked. Upon detailed review of the death certificates, it was noted that death was attributed to amyotrophic lateral sclerosis (ALS) for three cohort members. Based on the mortality experience among the more than 40,000 other employees who worked at this same general manufacturing location during the comparable period, the relative risk was 3.45 (95 percent confidence interval 1.11–11.11). The cases were employed in the manufacture or formulation of 2,4-D at different periods (1947–1949, 1950–1951, and 1968–1986), and for varying lengths of time (1.3, 1.8 and 12.5 years). In summary, there was no evidence of a causal association between working in the 2,4-D plant and mortality due to all causes, total malignant neoplasms, or non-Hodgkins Lymphoma. The etiology of ALS in the general population is largely unknown, and this study had limited information on risk factors to be able to control for possible confounding. The rates of ALS in this study are unstable due to the small numbers, which suggests that this may be a chance observation.[57]

Results of industrial hygiene surveys indicate that historical personal exposure concentrations of 2,4-DCP ranged from 0.049–0.13 ppm for 8 hour TWAs, 0.07–0.3 ppm for personal excursion samples, and 0.01–0.1 ppm for area sampling. In these surveys, no complaints of respiratory or eye irritation have been reported in workers exposed up 0.3 ppm 2,4-DCP.[58, 59]

VI. RATIONALE

An inhalation exposure OEL value of 1 ppm [6.7 mg/m^3] provides an appropriate margin of safety relative to the known 4-hour inhalation LC_{50} value of 145 ppm [970 mg/m^3] in rats with a sharp response curve[16] as well being protective of respiratory and eye irritation resulting from exposure to 2,4-DCP vapor. A continuous 8-hour inhalation exposure to 1 ppm 2,4-DCP approximates a human dose of 1 mg/kg/day for an 8-hour workday using a standard 55 kg woman breathing 8 m^3. This dose is over 100-fold below the acute lethal oral or dermal doses in animals. By comparison, other occupational exposure limits for phenolic compounds are 0.1–10 ppm for those listed with on a v/v basis (with only two less than 1 ppm); and 0.1 to 5 mg/m^3 for those on a mass basis only.[60,61] In addition, a relative comparison of pentachlorophenol (PCP) at 0.5 mg/m^3 which has oral LD_{50} values of 27–100 mg/kg[62] with 2,4-DCP which has oral LD_{50} values of approximately 580–4500 mg/kg suggests an equivalent 2,4-DCP concentration of approximately 2 ppm, compared to an OEL of 1 ppm.

A "skin" notation should be emphasized because of general permeability of 2,4-DCP through the skin, which is typical of phenolic compounds. 2,4-DCP has shown significant potential for permeation through the skin[25,26] and a material with a dermal LD_{50} value of 780 mg/kg in rats can be considered to be absorbed in toxicological significant amounts.

Additional care should be exercised with this chemical because of multiple case reports of rapid death in workers accidentally splashed on the skin with the molten or liquid form of 2,4-DCP. The rapid onset on life-threatening toxicity is consistent with acute toxicity findings in animals, as well as the known mechanism of toxicity of 2,4-DCP as a general uncoupler of oxidative phosphorylation, similar to phenol.[2,38] It is also consistent with increased permeation with respect to increased temperature and concentration.[26–28] Importantly, 300 mg/kg was a minimally lethal dose in rats following skin application of the liquid form of 2,4-DCP at 40°C.[20] This lethal dose in rats equates to a potentially lethal dose of 21 grams for a 70-kg person, or an approximate skin splash of 15 ml of molten 2,4-DCP. These findings indicate that strong caution must be exercised to avoid skin exposure to 2,4-DCP, particularly to the liquid form at temperatures above 40°C.

VII. RECOMMENDED OEL

8-Hour Time-Weighted-Average (TWA): 1 ppm (6.7 mg/m^3), SKIN*

*Absorbed rapidly through the skin in molten or heated liquid form in amounts that have caused rapid death in humans.

VIII. REFERENCES

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