MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for 2-Chlorophenol [CAS# 95-57-8]

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: January 13, 2017

SUBJECT: 2-Chlorophenol [CAS# 95-57-8] remaining at 24 hours

The current initial threshold screening level (ITSL) for 2-chlorophenol is 18 µg/m^3 based on a 24 hour averaging time. The ITSL was established on 6/2/2006 based on the EPA's oral reference dose (RfD) of 0.005 mg/kg-day (5 µg/kg). The EPA's RfD was derived from a rat subchronic drinking water study by Exon and Koller (1982) where groups of 12-20 female rats were exposed to 0, 5, 50, or 500 ppm of 2-chlorophenol in drinking water for 10 weeks and then were bred. The dosing was continued during breeding, gestation, and weaning. Reproductive effects included an increase in the number of stillborns and a decrease in litter size. EPA used the NOAEL of 5 mg/kg/day to derive the oral RfD of 0.005 mg/kg/day. In the 2006 review the averaging time was set at 24 hours. As 2-chlorophenol is a reproductive toxicant, it is appropriate for the ITSL to remain at a 24-hour averaging time.

References:

APCR. 2016. Air Pollution Control Rules, Promulgated pursuant to Part 55, Air Pollution Control, of the Natural Resources and Environmental Protection Act, Michigan Department of Environmental Quality. 1994. Act 451, as amended (NREPA).

EPA. 2006. Integrated Risk Information System. 2-Chlorophenol (CASRN 95-57-8). Available online at: https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=303

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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June 2, 2006

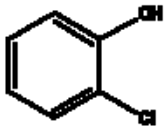
TO: **File for 2-Chlorophenol, CAS# 95-57-8**

FROM: **Margaret M. Sadoff, AQD Toxics Unit**

RE: **Development of Screening Level**

The ITSL for 2-chlorophenol (2-CP) is 18 ug/m3 with a 24-hour averaging time.

A search of the literature and the following databases was performed for information regarding 2-chlorophenol: American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values, National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Integrated Risk Information System (IRIS), Registry of Toxic Effects of Chemical Substances (RTECS), Environmental Protection Bureau Library, International Agency for Research on Cancer (IARC) Monographs, CAS Registry Online, Hazardous Substance Data Bank (HSDB), National Library of Medicine/Toxline, Health Effects Assessment Summary Tables (HEAST), National Toxicology Program (NTP) Study Database, Entrez PubMed, and CalEPA's Toxicity Values Database.



2-Chlorophenol MW = 130

Description

Unlike other chlorophenols which are solids, 2-CP is a liquid at room temperature which imparts greater potential for volatility. 2-CP falls under the general group of monochlorophenols. Monochlorophenols, as a group, are by-products of chlorine disinfection processes and are also produced during the bleaching of wood pulp with chlorine in paper production. Other chlorophenols are used as intermediates in the production of dyes and chlorinated pesticides. (Source: ATSDR Tox Profile for Chlorophenols, updated July 1999)

Acute & Subchronic Oral Toxicity in Experimental Animals

Reported oral LD50s in rats and mice are 670 mg/kg (Source: Toxline, HSDB). Another study reported an LD50 of 345 mg/kg/day in F CD-1 ICR mice given a single dose of 2-CP by gavage. In addition, results of acute inhalation studies were reported in ATSDR Tox Profile. Wistar rats

were exposed via inhalation to 2-CP for 4-hours resulting in a NOAEL of 104 ppm for lack of respiratory and neurological effects. Nose-only exposure of M/F Wistar rats to 2-CP for 4 hours at 908 ppm did not result in any deaths but tachypnea was observed in one of five exposed male rats. Whole body exposure of Sprague-Dawely rats to 2-CP for 6 hours at 620 ppm did not result in any deaths. (Source: ATSDR Tox Profile for Chlorophenols, updated July 1999)

The only known toxicity study involving repeated dosing of monochlorophenols in ICR mice involved daily gavage doses of 35, 69, or 175 mg/kg/day of 2-CP in corn oil for 14 days. No exposure-related deaths occurred at the two lower treatment levels but all mice exposed to 175 mg/kg/day died. The table below gives some other effect levels from oral studies in experimental animals.

Species	Duration	NOAEL mg/kg/day	LOAEL mg/kg/day	Effect
Mice	14 d	69		blood, immune, renal
		35		body weight decrease
			35	hyperactivity
Rat	16 wk	50		Immune
Rat	13 wk	5		reproductive
Rat	31 wk	50		developmental
Rat	27 mo	50		blood

EPA's RfD for 2-CP
(Source: EPA, IRIS)

The RfD is set at 0.005 mg/kg based on a NOAEL of 5 mg/kg-d (50 ppm) for lack of reproductive effects in a rat drinking water study (Exon and Koller, 1982). Groups of 12-20 weanling female Sprague-Dawley rats were exposed to 0, 5, 50 or 500 ppm of 2-chlorophenol in drinking water. Rats were bred after 10 wks of treatment. Treatment continued during breeding, gestation and weaning. Parameters evaluated included percent conception, litter size, birth weight, weaning weight, number of stillbirths, and hematology. The LOAEL was 500 ppm (50 mg/kg-d) based on number of stillborns and decreases in litter size. A total UF of 1,000 was applied to the NOAEL: 10 for interspecies variation, 10 for intraspecies variation, and 10 for use of subchronic data. There are no chronic or subchronic oral or inhalation toxicity data to support this NOAEL. There is no teratogenicity data. Therefore, confidence in the database is rated low. Confidence in the key study is also rated low because it only evaluated reproductive and hematologic effects. Consequently, overall confidence in the RfD is low. The last literature review by EPA in 2002 did not identify any new key studies.

Dermal & Ocular Exposure in Experimental Animals
(Source: ATSDR Tox Profile for Chlorophenols, updated July 1999)

Two out of two albino New Zealand rabbits died after a 24 hr dermal application of 2-CP. A serious LOAEL of 1580 mg/kg/day was reported.

Monochlorophenols produce effects ranging from slight hyperemia to severe corrosion when applied to the corneas of rabbits at relatively low concentrations. Severe discomfort and corrosion was reported to occur 1 minute after the application of 33 mg/kg undiluted 2-CP to rabbit eyes. In 15 week mouse initiation-promotion studies, 2-CP showed tumor promoting activity. In a study in which no initiator was used, 2-CP applied to the backs of mice 2 times per week for 12 weeks resulted in papillomas in 46% of the mice. No carcinomas were observed. The significance of these results is limited by the lack of appropriate vehicle control groups, irritation, and reporting of only gross pathological effects.

Absorption
(Source: ATSDR Tox Profile for Chlorophenols, updated July 1999)

Absorption via inhalation is a possible route of exposure in the workplace but the vast majority of exposure is by the dermal route. For the general population, exposure is predominantly through drinking water as 2-CP is a chlorination by-product. Inhalation exposure is more likely with monochlorophenols as compared to higher chlorinated phenols, based on potential for volatility. Given the high lipophilicity of chlorophenol compounds in general, absorption may be more limited by inhalation as compared to oral and dermal uptake, but there are very few studies of inhalation exposure to 2-CP from which to draw such conclusions.

Mechanism of Toxicity
(Source: ATSDR Tox Profile for Chlorophenols, updated July 1999)

Chlorophenols uncouple mitochondrial oxidative phosphorylation and thus interfere with respiration at the cellular level. Toxic manifestations of chlorophenol exposure include lethargy, tremors, convulsions and/or CNS depression followed by increased respiration, hyperthermia, elevated blood pressure, progressive neuromuscular weakness and cyanosis. The mechanism by which chlorophenols produce convulsions is unknown, but seems to decrease with increasing chlorination. Conversely, the ability of chlorophenols to uncouple oxidative phosphorylation increases with increasing chlorination.

Repro/Developmental/Genotoxicity
(Source: ATSDR Tox Profile for Chlorophenols, updated July 1999)

The data on higher chlorinated phenols having reproductive and/or developmental effects has been equivocal and only shown at doses producing maternal toxicity. Limited evidence suggests that chlorophenols are not teratogenic in experimental animals. As a class, chlorophenols are not directly genotoxic although a limited number of in vitro studies with eukaryotic cells have been positive for chromosomal aberrations.

Human Data
(Source: ATSDR Tox Profile for Chlorophenols, updated July 1999)

There are no human studies of inhalation exposure to 2-CP. One occupational study of workers exposed to sodium trichlorophenol and its derivatives showed no increased incidence of chronic bronchitis, chronic OPD or other alterations in pulmonary function. Two occupational studies with exposure to trichlorophenols and other unspecified chemicals report increased respiratory irritation and altered pulmonary function but these studies are confounded by multiple chemical exposures and lack of control for lifestyle factors such as smoking status. Other occupational studies of other chlorophenols have reported altered liver enzymes, porphyria (disturbance in red blood cell metabolism indicative of altered liver function), headaches, skin and eye irritation but, again, these studies are confounded by multiple exposure scenarios and are not specific to 2-CP.

Carcinogenicity
(Source: ATSDR Tox Profile for Chlorophenols, updated July 1999)

Numerous cohort and case-control studies of wood finishing and chlorophenoxy herbicide workers exposed to higher chlorophenols are available. Results of these studies vary, but some suggest a relationship between chlorophenol exposure and increased incidence of soft tissue sarcomas, lung cancers, malignant lymphomas, non-Hodgkins' lymphomas, and nasal/nasopharyngeal cancers. The conclusions from these studies are limited by small cohort

size, exposure to multiple contaminants including dioxins, and the lack of adequate control groups.

IARC has classified the chlorophenols, as a group, as 2B carcinogens (probable human carcinogens). This classification is based on limited evidence in humans and sufficient animal evidence of cancer effects upon exposure to 2,4,6-TCP. EPA has developed a unit risk of 3.1 E-6 per ug/m3 for 2,4,6-TCP. There has been considerable interest in the potential association between chlorophenol-based pesticides and cancer but these studies are not focused on the inhalation route, are not specific to 2-CP or lower chlorinated phenols, and are confounded by simultaneous exposures to dioxin.

One oral carcinogenicity study (Exon & Koller, 1985) exists for groups of Sprague-Dawley rats receiving prenatal, postnatal or prenatal & postnatal exposures to 0, 5, 50 and 500 ppm 2-CP in drinking water (0, 0.5, 5, 50 mg/kg/day). 2-CP alone had no effect on incidence of tumors relative to untreated controls. In a separate substudy, additional groups of rats received ethylurea and nitrite, (precursors of the cancer initiator ethylnitrosurea) in addition to 2-CP under the various exposure conditions. Findings in the combined-exposure male treatment groups indicated that 2-CP may have been either a co-carcinogen or a tumor promoter under the conditions of the study, but the effects were not concentration dependent. It is unclear whether a maximum tolerated dose was achieved in these studies.

There is insufficient data from which to derive a quantitative risk value for cancer effects from either oral or inhalation exposure to 2-CP. Therefore, an IRSL/SRSL will not be developed at this time.

Screening Level Development Rationale

Texas has a 30 minute acceptable ambient air concentration of 19 ug/m3 for 2-CP (ATSDR Tox Profile for Chlorophenols).

ATSDR has established an oral intermediate MRL of 0.003 mg/kg/day for 2,4-DCP and other chlorophenols (mixture) which is based on a NOAEL of 0.3 mg/kg/day for lack of effect on delayed type hypersensitivity. This is very close to the EPA RfD for 2-CP of 0.005 mg/kg/day based on a NOAEL of 5 mg/kg/day for lack of reproductive effects.

An ITSL could be derived based on the 4-hour inhalation study, but this study reported a NOAEL rather than an LC50. The ITSL would therefore be conservative at 11 ug/m3, annually.

Based on the rules hierarchy, an RfD based ITSL of **18 ug/m3 with a 24-hour average** is most appropriate. The calculation pursuant to R232(1)b is as follows:

$$\text{ITSL} = \text{Oral RfD} \times \frac{70\ \text{kg}}{20\ \text{m3}}$$

$$= 0.005\ \text{mg/kg/d} \times (70\text{kg}/20\text{m3})$$

$$= 0.0175\ \text{mg/m3 or } 17.5\ \text{ug/m3}$$

$$= \textbf{18 ug/m3 (rounded)}, \textbf{24-hr average}$$