MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for 2,4-Dichlorophenol (CAS # 120-83-2)

FROM: Keisha Williams, Air Quality Division

DATE: December 29, 2016

SUBJECT: Screening Level Review 2,4-Dichlorophenol (2,4-DCP)

The ITSL for 2,4-dichlorophenol is being set at 11 µg/m^3 (24 hour averaging time) based on the Michigan Department of Environmental Quality (MDEQ), Air Quality Division (AQD) Rule 336.1229 (2) (a) and (b) and 336.1232 (1) (b).

In 1986, the initial threshold screening level (ITSL) for 2,4-DCP was established at 77 µg/m^3 (annual averaging time). The objective for the present review was to determine if the screening level for 2,4-DCP should be changed in light of new information.

The following references or databases were searched to identify data to determine the screening level: United States Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the Registry of Toxic Effects of Chemical Substances (RTECS), the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, MDEQ Library, International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) Online, National Library of Medicine (NLM), Health Effects Assessment Summary Tables (HEAST), National Toxicology Program (NTP) Status Report, EPA Aggregated Computational Toxicology Resource (ACToR) Database, EPA TSCATS database, EPA Superfund Provisional Peer Reviewed Toxicity Values, EPA Acute Exposure Guideline Levels for Airborne Chemicals, EPA High Production Volume Database, United States Department of Labor Occupational Safety and Health Administration Permissible Exposure Limits, Spacecraft Maximum Allowable Concentrations, California Office of Environmental Health Hazard Assessments Reference Exposure Levels, Chemical Safety Program Protective Action Criteria, Texas Commission on Environmental Quality Effects Screening Levels, and European Chemicals Agency Registered Substances Dossiers.

Background Information

2,4-DCP (Figure 1.) is mainly used in the production of herbicides. It has a strong medicinal odor, and at room temperature, it is a white solid. Chemical properties are listed in Table 1 and reference values are listed in Table 2.

Figure 1. Chemical structure for 2,4-DCP

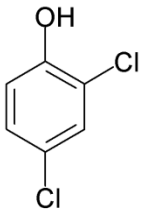

Table 1. Chemical properties of 2,4-DCP

Molecular weight: 163 grams/mole
Melting point: 45 °C
Boiling point: 210 °C
Vapor pressure: 0.14 mmHg at 25°C
Vapor density: 5.6, where air=1

Reference: PubChem database, https://pubchem.ncbi.nlm.nih.gov/compound/8449

Table 2. Benchmark values for 2,4-DCP

Agency	Reference Value
United States Environmental Protection Agency (EPA)	Reference dose (RfD): 0.003 mg/kg-day (EPA, 1988)
Agency for Toxic Substances and Disease Registry (ATSDR)	Minimal risk level (MRL) for an acute, oral dose: 0.01 mg/kg-day and for an intermediate, oral dose: 0.003 mg/kg-day (ATSDR, 1999)
Provisional Peer Reviewed Toxicity Values (PPRTVs)	The sub-chronic provisional RfD: 0.02 mg/kg-day (EPA, 2007)
Texas Commission on Environmental Quality (TCEQ)	Health effects screening levels for long-term exposure: 7 µg/m^3 and for short-term exposure: 67 µg/m^3 (TCEQ, 2014)
American Industrial Hygiene Association (AIHA)	Emergency Response Planning Guidelines (ERPGs), where ERPG-1 is approximately 1.3 mg/m^3, ERPG-2 is approx.13 mg/m^3, ERPG-3 is approx.130 mg/m^3 (AIHA, 2013)

Note: ATSDR regulates 2,4-DCP within the group of chlorophenols

Case studies of chlorophenol-induced health effects have been reported. One human case study was presented in the ATSDR toxicological profile of chlorophenols; and reported potential inhalation toxicity from 2,4-DCP (ATSDR, 1999; Bleiberg et al., 1964). It is important to note that this report also indicates the possibility of dermal or oral exposures as well as multi-pollutant exposures with other chlorophenols, so it is impossible to identify effects caused by 2,4-DCP inhalation alone. Still, this case study investigated potential 2,4-DCP-induced chloroacne, acquired porphyria and liver damage. Five human case studies have shown that dermal exposure to small amounts of concentrated 2,4-DCP “can cause rapid death” (Carra, personal communication, February 16, 2000; CDC, 2000). However, no controlled human studies were identified that are adequate for ITSL derivation.

Within the ATSDR toxicological profile of chlorophenols, it was noted that animal to human extrapolation was supported since there are interspecies similarities in health effects, like liver toxicity. Considering this, the animal studies on mono and dichlorophenols-induced toxicities were considered for ITSL derivation. However it is important to note that, "[the cases] of human death following dermal exposure indicates that animals may be more resistant to the toxic effects" (ATSDR, 1999).

Evaluation of Cancer Risk

The National Toxicology Program (NTP) evaluated 2,4-DCP for carcinogenicity in mice and rats (NTP, 1989). They found no increased tumors associated with chronic feed ingestion up to 5000 ppm given to female rats or 10000 ppm 2,4-DCP given to male rats. Considering feed consumption per day and average body weight, these concentrations were found to be approximately 240 and 420 mg/kg of body weight per day for female and male rats respectively. They also found no increased tumors associated with chronic feed ingestion in mice up to 10000 ppm 2,4-DCP, where these concentrations were found to be approximately 1500 and 1300 mg/kg body weight per day for female and male mice, respectively. Moreover, there was a significantly lower incidence of mononuclear cell leukemia and lymphomas in male rats and high dose female mice, respectively. With consideration for the aforementioned NTP study, the International Agency for Research on Cancer (IARC) has concluded that "there is evidence suggesting lack of carcinogenicity of 2,4-dichlorophenol in experimental animals" (IARC, 1999).

In a separate study which involved both prenatal exposure and a 2 year postnatal exposure to 2,4-DCP in drinking water, there was no significant increase in tumor incidence in male or female rats given up to 300 ppm 2,4-DCP, which is approximately 30 mg/kg per day assuming that a rat drinks a daily amount of water which equals 10% of its body weight (EPA, 1993; Exon and Keller, 1985; ATSDR, 1999). As a result, 2,4-DCP is not considered a human carcinogen.

Review of relevant studies

Study formerly used to derive the ITSL

An ITSL was derived in 1986 using the Kobayashi et al. study (1972) where a no observed adverse effect level (NOAEL) was found at 100 mg/kg per day for changes in liver histology (MDNR, 1986). The previously established ITSL was calculated thusly:

$$former\ ITSL = NOAEL\ x\ mouse\ body\ weight\ \ x \frac{1}{mouse\ daily\ ventilation\ rate}\ x \frac{1}{uncertainty\ factors}$$

where 30 grams was used for mouse body weight, 0.039 m^3 of air per day was used for the daily ventilation rate, and uncertainty factors (UFs) are 10 for intraspecies extrapolation, 10 for interspecies extrapolation and 10 for sub-chronic to chronic extrapolation

$$former\ ITSL = 100 \frac{mg}{kg} per\ day\ x\ 30\ g\ \ x \left(\frac{1}{0.039\ m^3 of\ air\ per\ day}\right) x \left(\frac{1\ kg}{1000\ grams}\right) x \frac{1}{10\ x\ 10\ x\ 10}$$

$$former\ ITSL \approx 77 \frac{\mu g}{m^3}, \text{annual averaging time}$$

Inhalation studies and studies assessing applicability of oral to inhalation extrapolation

Only one animal inhalation study was found: at 600 mg/m^3 2,4-DCP exposure for 6 hours, there was not found to be any toxicological effects on Sprague-Dawley Albino male rats, where

toxicological effects considered included death and behavioral abnormalities (Monsanto, 1975). Since this study only provides a free standing NOAEL, and there are several well conducted oral studies, oral studies were considered for ITSL derivation.

Inhalation absorbencies have not been studied, so relative absorbency efficiency of inhalation compared to oral exposure cannot be readily determined; however, studies show rapid absorption via dermal exposure and also suggest rapid absorption via the gastrointestinal tract (ATSDR, 1999; NTP, 1989). It is important to note that gastrointestinal tract toxicity, in particular, has not been found to be a major toxicity target. However, in the NTP study (1989), multifocal degeneration of the nasal respiratory epithelium was found to be increased in male rats fed approximately 200 or 400 mg/kg per day 2,4-DCP for two years as compared to time matched controls. This suggests that the respiratory system is a target organ, and may be significantly affected when inhalation is the route of exposure.

Study currently used to derive the proposed ITSL

As part of a larger toxicity study, dams were exposed to be 0, 3, 30 or 300 ppm 2, 4-DCP in drinking water from the age of 3 weeks old to parturition and lactation. EPA has noted that this exposure can be calculated as 0, 0.3, 3, or 30 mg/kg per day using the water consumption calculation given above (EPA, 1988; EPA, 1993; ATSDR, 1999). Randomly-selected 3 week old rat pups from each respective dosing group (N=10 per group) were likewise given 0, 0.3, 3 or 30 mg/kg per day of 2,4-DCP in drinking water for 15 weeks (Exon and Keller, 1985). An alteration in cell-mediated immunity was evaluated via the delayed-type hypersensitivity (DTH) response of footpad swelling after bovine serum albumin sensitization and challenge. There was a significant decrease in the DTH response in Sprague-Dawley rats given 3 or 30 mg/kg per day 2,4-DCP as compared to the control group (Exon and Keller, 1985). The NOAEL for this response was observed at 0.3 mg/kg per day. This was a well conducted study, and it is appropriate for use in ITSL derivation.

In fact, this key study and critical effect has been used for RfD derivation for 3 different health benchmarks (ATSDR, 1999; EPA, 1988; EPA, 2007). In deriving the EPA Integrated Risk Information System (IRIS) RfD of 0.003 mg/kg-day from a NOAEL of 0.3 mg/kg-day, EPA applied a total UF of 100 based on a factor of 10 for extrapolation from animal data to humans and a factor of 10 for protection of sensitive populations (EPA, 1988). Although this was a subchronic study, a 24 hour averaging time will be applied because of the early life exposure.

Using the IRIS RfD, a potential ITSL would be calculated thusly:

$$potential\ ITSL = RfD\ x\ \frac{70kg}{20m^3}$$

$$potential\ ITSL = 0.003\frac{mg}{kg}per\ day\ x\ \frac{70kg}{20m^3} = 0.0105\frac{mg}{m^3}$$

$$potential\ ITSL \approx 0.011\frac{mg}{m^3}\ x\frac{10^3\mu g}{mg} \approx 11\frac{\mu g}{m^3}, 24\ hr\ averaging\ time$$

Immune responses are some of the most sensitive chemical-induced responses; but, as noted by the EPA, they are also less commonly used for toxicity evaluation. Furthermore, it can be difficult to determine whether a given immune response is an adverse effect or not. For this reason, along with a lack of supporting studies, the confidence in the IRIS RfD is rated as “low”.

However, as noted by Exon and Keller (1985), “altered immunocompetence could result in decreased resistance to infectious diseases and oncogenesis or increased incidence of autoimmune or immunodeficiency disorders.” As a result of the possible health implications, the altered immune responses will remain the basis for the critical effect.

2,4-DCP-induced changes in immune responses were seen in male mice that had chronic consumption of 2,4-DCP (NTP, 1989). Specifically, there was a decrease in diffused angiectasis from 21% of controls to 6% of mice given the highest dose, as well as a decrease in diffuse hematopoietic cell proliferation from 20% of controls to 6% of mice given the highest dose. Moreover, there was an increase in multifocal lymphoid depletion from 2% of controls to 21% of mice given the highest dose, as well as an increase in thymocyte necrosis from 3% of the controls to 21% of mice given the highest dose. All these results suggest increased propensity for immunodeficiency in the high dose group.

While there were no significant hematopoietic changes in male or female rats in the chronic study, there were significant changes seen in rats given higher concentrations of 2,4-DCP for 13 weeks. Bone marrow atrophy, where “erythroid and myelocytic elements were depleted”, occurred in 60% of the female rats given 10,000 ppm 2,4-DCP (approximately 630 mg/kg per day) and all rats given the two highest doses (20,000 and 40,000 ppm). Indeed, this bone marrow atrophy was one of the reasons the researchers chose lower dosing concentrations in the female rats as compared to the mice and even the male rats. Moreover, the aforementioned decrease in mononuclear cell leukemia and lymphomas observed in the highest dose group as compared to controls in the chronic exposure group suggests decreases in immune responses. Altogether, these results suggest chemical-induced immunodeficiency, and these results support the immune responses observed by Exon and Keller (1985).

Although portal of entry effects have not been seen in the oral studies, the respiratory system may be a specific target for 2,4-DCP toxicity. As a result, this evaluation should be revisited when data from inhalation studies become available.

The ITSL for 2,4-dichlorophenol is now 11 µg/m^3 (24 hour averaging time).

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MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

June 18, 1986

TO: File

FROM: Catherine Simon, Toxicologist

SUBJECT: 2,4—Dichlorophenol (CAS No. 120—83—2)

Only one subchronic animal study adequate for deriving an acceptable ambient concentration (AAC) for 2,4—dichlorophenol was available. No chronic animal studies or human epidemiology studies were available for this purpose. In the subchronic animal study, groups of seven male ICR mice were fed 2,4—dichlorophenol in the diet for 6 months (Kobayashi, 1972). The dietary concentrations were equivalent to daily doses of 0, 45, 100, and 230 mg/kg. The only effect observed was in the highest dose group where slight histopathological changes of the liver were seen. These changes were described as infiltration of round cells, swelling of hepatocytes, and "dark cells." The no observable effect level (NOEL) from this study is 100 mg/kg. For a 30 gram mouse inhaling 0.039 m^3 of air per day, and assuming equal absorption efficiencies by the oral and inhalation routes, the NOEL is equivalent to 77 mg/m^3. This value was used to derive the AAC as follows:

$$AAC = \frac{77\frac{mg}{m^3}}{1000} = .077\frac{mg}{m^3} = 77\frac{\mu g}{m^3}$$

The National Toxicology Program is currently evaluating 2,4—dichlorophenol in their carcinogenicity bioassay program. The animal testing has been completed, and the results are being evaluated. A draft report should be available by the end of this year at which time the AAC derived in this memo should be re—evaluated.

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CAS :mh