MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for 4,6-Dinitro-*o*-cresol (CAS # 534-52-1)

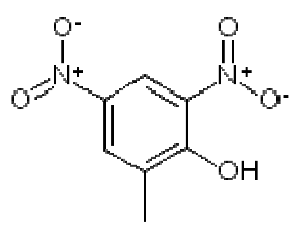
FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: June 23, 2011

SUBJECT: Screening Level for 4,6-Dinitro-*o*-cresol (CAS # 534-52-1)

The initial threshold screening level (ITSL) for 4,6-dinitro-*o*-cresol (CAS # 534-52-1) is 2 µg/m^3 based on an 8-hour averaging time.

4,6-Dinitro-*o*-cresol (CAS #534-52-1) also known as dinitro-*o*-cresol, DNOC, 2-methyl-4,6-dinitrophenol, and 3,5-dinitro-2-hydroxytoluene is an odorless yellow, crystalline solid with a molecular weight of 198.13. 4,6-Dinitro-*o*-cresol was used in the 1920s and 1930s as a treatment for obesity and was used in the dye industry; as a selective herbicide to control broad-leaved weeds in cereal, maize, legume, flax, tree fruit, bush fruit, hops, and grass seed crops; on apple and peach trees to thin fruit; as a desiccant for leguminous seed crops; for destruction of potato haulms; for chemical stripping of hops; as an insecticide, fungicide, and defoliant; as a wood preservative; and in the plastic industry as an inhibitor of polymerization in styrene and vinyl products. DNOC is not currently registered for use in the United States. DNOC may also form in the atmosphere during the combustion of fossil fuels or as a result of photochemical reactions between precursor compounds (e.g., benzene, toluene) and hydroxyl radicals and nitrogen oxides (Tremp et al., 1993)



A literature review was conducted to determine an initial threshold screening level (ITSL) for 4,6-dinitro-*o*-cresol. The following references and databases were searched to derive the above screening level: EPBCCD, United States Environmental Protection Agency (US EPA) Integrated Risk Information System (IRIS), National Institute for Occupational Safety and Health (NIOSH), American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values and Biological Exposure Indices (TLV/BEI) 2010 guide, National Toxicology Program (NTP) Study Database, International Agency for Research on Cancer (IARC), Acute Database, Chemical Abstract Service (CAS) Online (searched 5/4/11), National Library of Medicine (NLM)-online, EPA Aggregated Computational Toxicology Resource (ACToR) Database, US EPA TSCATS database, and Hazardous Substances Data Bank (HSDB).

RfC or RfD values were unavailable. No inhalation toxicity studies were identified from the literature search. There is an occupational exposure limit of 0.2 mg/m^3 Threshold Limit Value – Time-Weighted Average (TLV-TWA) from ACGIH. This TLV-TWA is recommended for airborne occupational exposure to dinitro-*o*-cresol to minimize the potential for disruption of metabolic processes and rate that can lead to elevated body temperature (hyperpyrexia), headache and malaise (ACGIH, 2001).

Agency for Toxic Substances and Disease Registry (ATSDR) has listed an oral Minimal Risk Level (MRL) of 0.004 mg/kg/day for acute-duration oral exposure (14 days or less) and for intermediate-duration oral exposure (15-364 days) for DNOC based on a study by Plotz, 1936, where 4 patients and the researcher were administered levels of DNOC ranging from 0.35 mg/kg/day to 1.0 mg/kg/day. ATSDR based the MRL on a Lowest Observed Adverse Effect Level (LOAEL) of 0.35 mg/kg/day for neurological effects in a human who took DNOC for the purpose of weight reduction. Even though this study was performed on humans and according to King and Harvey (1953b), humans are more sensitive to the effects of DNOC than animals, the Plotz study only had one patient taking the lowest dose and therefore, it would be inappropriate to base an ITSL on the effects seen in one person.

Primary effects of DNOC exposure are due to DNOC's ability to uncouple oxidative phosphorylation. This causes a mitochondrial change that is evidenced by an increased basal metabolic rate, increased body temperatures and resulting increased perspiration. Environmental temperatures influenced the mortality rate among rats orally dosed with DNOC (King and Harvey 1953a). Six of 12 rats died after receiving 20 mg/kg at 37-40°C, while only 2 of 12 rats died after receiving twice the dose (40 mg/kg) at almost half the temperature (20-22°C). Because DNOC uncouples oxidative phosphorylation, an increase in heat production and body temperature occurs. Toxicokinetic studies indicate that humans tend to accumulate DNOC to a greater extent and eliminate DNOC more slowly than animals do (King and Harvey, 1953b). DNOC has been found to cause reproductive effects; Takahashi et al. (2004) showed that exposure of sexually mature male rats to DNOC resulted in reduced sperm motility and increased incidence of tailless sperm. Male rats were given daily doses of 0, 10, or 15 mg/kg DNOC for 5 days. Sperm were examined on days 1, 7, and 14 after the last dosing. On day 1, post-dosing peeled (loss of mitochondrial sheath at the proximal end of the mid shaft) sperm were observed in the caput epididymides. On day 7, the highest incidence of peeled sperm was found in the corpus epididymides. On day 14, the highest incidence of abnormal sperm was in the cauda epididymides, where the primary abnormality was taillessness.

The studies reported above support the information provided by ACGIH in their TLV recommendation and indicates the OEL of 0.2 mg/m^3 is sufficiently health protective and appropriate for use in developing an ITSL for DNOC. Based on Rule 232(1)(c) an ITSL can be determined from an occupational exposure level (OEL) if one exists for the toxic air contaminant, then the ITSL is determined as follows:

$$ITSL = \frac{OEL}{100}$$

The OEL from the ACGIH TLV of 0.2 mg/m^3 = 200 ug/m^3. Using the equation above:

$$ITSL = \frac{200\,{}^{\mu g}\!/_{m^3}}{100} = 2\,{}^{\mu g}\!/_{m^3}$$

According to Rule 232(2)(a), an 8-hour averaging time period is used for the ITSL.

The initial threshold screening level (ITSL) for 4,6-dinitro-*o*-cresol (CAS # 534-52-1) is 2 µg/m^3 based on an 8-hour averaging time.

References:

ACGIH. 2010. TLVs and BEIs Based on the Documentation of the Threshold Limit Values for Chemical Substances and Physical Agents & Biological Exposure Indices. ACGIH Worldwide Signature Publications.

Act 451 of 1994, Natural Resources and Environmental Protection Act and Air Pollution Control Rules, Michigan Department of Environmental Quality.

ATSDR. 1995. Toxicological Profile for Dinitrocresols. U.S. Department of Health and Human Services. Public Health Service. Atlanta, GA. Agency for Toxic Substances and Disease Registry.

ATSDR. 2009. Addendum to the Toxicological Profile for Dinitrocresols. Agency for Toxic Substances and Disease Registry. Division of Toxicology and Environmental Medicine. Atlanta, GA.

King E, Harvey DG. 1953a. Some observations on the absorption and excretion of 4,6-dinitro-*o*-cresol (DNOC). 1. Blood dinitro-o-cresol levels in the rat and the rabbit following different methods of absorption. Biochem J 53:185-195.

King E, Harvey DG. 1953b. Some observations on the absorption and excretion of 4,6-dinitro-o-cresol. 2. The elimination of 4,6-dinitro-o-cresol by man and animals. Biochem J 53:196-200.

Plotz M. 1936. Dinitro-ortho-cresol. A metabolic stimulator and its toxic side-actions. N Y State J Med 41:266-268.

Takahashi KL, Hojo H, Aoyama H, Teramoto S. 2004. Comparative studies on the spermatotoxic effects of dinoseb and its structurally related chemicals. Reprod Toxicol 18(4):581-588.

Tremp J, Mattrell P, Fingler S, Giger W. 1993. Phenols and nitrophenols as tropospheric pollutants: emissions from automobile exhausts and phase transfer in the atmosphere. Water Air Soil Pollut 68:113-123.

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