MICHIGAN DEPARTMENT OF ENVIRONMENT, GREAT LAKES, AND ENERGY

INTEROFFICE COMMUNICATION

TO: File for Sodium Dimethyl Dithiocarbamate (CAS Number 128-04-1)

FROM: Brian Hughes, Air Quality Division, Toxics Unit

DATE: August 27, 2024

SUBJECT: Screening Level for Sodium Dimethyl Dithiocarbamate

This memorandum describes the screening level update for Sodium dimethyl dithiocarbamate (SDDC) (CAS number 128-04-1).

The former initial threshold screening level for Sodium dimethyl dithiocarbamate (SDDC) was established on September 1, 1999, as a default level of 0.1 µg/m^3. This screening level evaluation is updated based on currently available information and is set at 20 µg/m^3 (24-hour averaging time).

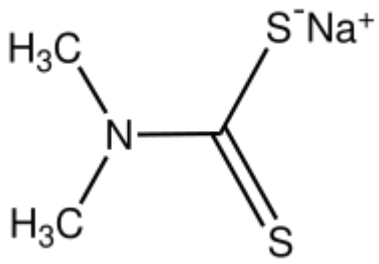
A literature review was conducted to determine an ITSL for SDDC on July 30, 2024. The following references and databases were searched to derive the screening level: United States Environmental Protection Agency (USEPA) Integrated Risk Information System (IRIS), National Institute for Occupational Safety and Health (NIOSH), American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values and Biological Exposure Indices (TLV/BEI) 2022 guide, National Toxicology Program (NTP) Study Database, International Agency for Research on Cancer (IARC), Chemical Abstract Service (CAS) SciFinder, PubMed, USEPA Computational Toxicology (CompTox) Database, National Technical Information Service (NTIS), and California Office of Environmental Health Hazard Assessment (OEHHA).

Uses and Physical Chemical Properties:

SDDC in the sodium salt of dimethyl dithiocarbamic acid. It is an antimicrobial agent which belongs to the class of dithiocarbamate disinfectants, corrosion inhibitors, coagulants, vulcanizing agents, chelating agents, fungicides, and biocides[i]. Other commonly used salts of the acid are potassium dimethyl dithiocarbamate (KDDC), copper dimethyl dithiocarbamate (CuDDC), ferric dimethyl dithiocarbamate (aka Ferbam), and zinc dimethyl dithiocarbamate (aka Ziram). The following is a list of physical/chemical properties for SDDC.

As mentioned above, SDDC also exists in many ionic forms such as zinc and potassium. These salts dissociate into the cation and the dimethyl dithiocarbamic acid components.

Table 1: Physical Chemical Properties of Sodium Dimethyl Dithiocarbamate (ECHA 2024[a,b]).

Structure: Sodium dimethyl dithiocarbamate (CAS Number: 128-04-1)	
Molecular Weight	143.21 g/mol
Molecular Formula	$C_3H_6NNaS_2$
Physical State	Solid/liquid
Melting Point	110°C
Boiling Point	253°C
Vapor Pressure	0 Pa at 25°C
Water Solubility	374 g/L
Henry's Law constant	$5.0X10^{-8}$ atm-cu m/mole

Pharmacokinetics:

The gastrointestinal absorption of SDDC is estimated to be in the range of 58% to 69% based on pharmacokinetic studies on ziram. Ziram dissociates into zinc cation and dimethyl dithiocarbamate, which is excreted as a S-glucuronide conjugate. Other metabolites include carbon disulfide, sulfate and dimethylamine. The main elimination routes are expired air and urine followed by the feces.

Sensitization:

An OECD 406 guideline study (Guinea Pig Maximization Test) was conducted for SDDC (ECHA 2024a). The induction period consisted of three injections of SDDC in water with Freund's Complete Adjuvant: Day 1: 5% in water with FCA, Day 3: 5% in water with FCA and Day 7: 50% in water with FCA. The challenge exposures occurred on Day 21 with concentrations of 50% and 75%. Evaluations occurred at 24 and 48 hours. Results indicated that only 2 out of 9 guinea pigs had visible reactions after 48 hours (22%) and thus SDDC was not classifiable as a sensitizer. A similar result occurred when KDDC was evaluated in an OECD (406) Guideline study (ECHA 2024b).

Genotoxicity:

***In Vitro* Testing**

SCCD was positive in the OECD guideline (471) bacterial reverse mutation assay using TA 1535, TA 1537, TA 98 and TA 100 with or without metabolic activation using S9 fractions from rat livers treated with Aroclor 1254 up to 1000 µg/plate. Positive results were found in TA 100 and TA1535 with and without metabolic activation. Similar results were obtained when SDDC was co-incubated with E. coli up to 1000 µg/plate without metabolic activation.

SCCD was negative when tested in the OECD Guideline (473) *in vitro* mammalian chromosome aberration test using human lymphocytes with and without microsomal activation and using Chinese Hamster ovary cells.

***In Vivo* Testing:**

Negative results were reported in an OECE guideline (474) Mammalian Erythrocyte Micronucleus test and in the OECD guideline Unscheduled DNA synthesis test with mammalian liver cells.

SDDC is not classified as a genotoxic agent.

Mechanism of Action:

The mechanism of action for the toxicity of dithiocarbamates is thought to occur via metabolism by the liver to form carbon disulfide and therefore mimic its effects on the nervous system. Dithiocarbamates are also chelating agents and therefore remove metal ions from biological activity[ii].

Repeat dose studies:

A 90-day subchronic study similar to OECD 408 guidelines was conducted in Sprague-Dawley rats via oral gavage (ECHA 2024 study report 2003). Rats (10/sex/dose) were administered SDDC (purity 41%) and corrected to doses of 0, 10, 50, and 250 mg/kg/day (mkd) of the active agent. Examinations included: clinical observations, food/water intake, body weight, ophthalmic examination, hematology, clinical chemistry, neurobehavioral examination, gross and histopathology. A NOAEL was identified at 10 mkd based on treatment related responses in the 50 mkd group of hemosiderosis in spleen and kidney, hematology, and behavioral changes.

Reproduction/Developmental Effects:

No reproductive studies were found for SDDC. A study similar to an OECD (414) guideline Prenatal Developmental Toxicity study was conducted in Sprague-Dawley rats (ECHA 2024a study report 1987). Rats were given SDDC via gavage in water at doses of 5, 50 and 500 mkd from Day 6 through Day 15 of gestation. Actual doses of SDDC based on formulation analysis and body weight gain of maternal animals were 3.95, 56.9, and 540 mkd (actual dose). The NOAEL for systemic maternal toxicity was 3.95 mkd due to decreased body weight and weight gain, clinical signs (chromodacryorrhea and excess salivation), and food consumption. There was no treatment related developmental effects at the highest dose.

In a rat developmental study toxicity study by Weir (1987a as reported by OEHHA 2005), a formulation of SDDC was administered at doses of 0, 1.6, 23, or 240 mkd SDDC via gavage to Sprague-Dawley rats from gestation Days 6 through 15. For developmental toxicity, the LOEL was 1.6 mkd based on a statistically significant higher incidence of distended renal pelvis/ureter in the low- and mid-dose groups at 23 mkd.

In a second developmental study by Weir (1987b as reported by OEHHA 2005), a formulation of SDDC was administered at doses of 0, 0.4, 4, and 40 mkd SDDC by gavage to New Zealand white rabbits from gestation Days 6 through 18. The NOEL was 0.4 mkd. The lowest-observed-adverse-effect-level (LOAEL) of 4 mkd was based on the increased incidence of 13th thoracic ribs, “rudimentary or short.” OEHAA (2005) used this as the critical study from which to derive a 23 µg/day maximum allowable dose level for SDDC.

Carcinogenicity:

No evidence exists for the carcinogenic activity of SDDC.

Discussion:

SDDC is a developmental toxicant based on a developmental study by Weir (1987b as reported by OEHHA 2005). In this study, an antimicrobial formulation of SDDC was administered at doses of 0, 0.4, 4, and 40 mkd as SDDC by gavage to New Zealand white rabbits from gestation Days 6 through 18. A developmental NOEL of 0.4 mkd was identified. The developmental LOAEL of 4 mkd was observed based on the increased incidence of 13th thoracic ribs, "rudimentary or short." Although the subchronic oral gavage study in Sprague-Dawley rats was a well-designed and reported study, the free-standing NOAEL of 10 mkd was higher than the LOAEL of 4 mkd identified in the developmental study (Weir, 1987b as reported by OEHHA 2005). Therefore, the subchronic study (ECHA 2024 study report 2003) is not appropriate to identify the key species or effect deemed the critical effect of SDDC, namely teratogenic effects in rabbits.

Derivation of Screening Level:

The ITSL was derived pursuant to Rule 229(2)(b). A developmental Reference Dose (RfD_{DEV}) was derived, which was subsequently used to derive the ITSL pursuant to Rule 232(1)(b). Using the developmental study of Exxon Biomedical (Weir 1987b as cited in OEHHA 2005), the ITSL was derived the NOAEL was identified as 0.4 mg/kg/day based on skeletal variations. Therefore, the administered dose is equal to the adjusted dose (e.g., NOAEL = $NOAEL_{ADJ}$). The NOAEL human equivalent dose ($NOAEL_{HED}$) is calculated pursuant to USEPA (2011) where using the default weight of the Female New Zealand Rabbit of 3.93 kg. (USEPA 1988), the dosimetric adjustment factor (DAF) is derived as follows:

$DAF = [(\text{animal body weight})/(\text{human body weight})]^{1/4}$
$DAF = (3.93\ kg)^{0.25}/(70\ kg)^{0.25}$
$DAF = 1.3569 / 2.8926$
$DAF = 0.47$

The HED is derived as:

$NOAEL_{HED} = NOAEL_{ADJ} \times DAF$
$NOAEL_{HED} = 0.4\ mkg \times 0.47$
$NOAEL_{HED} = 0.1876\ mkd$

The RfD is calculated where the Point of Departure (POD) is the $NOAEL_{HED}$ of 0.1876 mkd:

$RfD = POD/(UF1 \times UF2) \times \text{unit conversion}$

The uncertainty factors (UFs) are

- 10 for sensitive subpopulations (intraspecies) and
- 3 for toxicodynamic differences between animals and humans,

The RfD is:

RfD = 0.1876 mkd/(10 × 3)
RfD = 0.00625 mkd

The ITSL is derived pursuant to Rule 232(1)(b):

ITSL = RfD × (default human body weight/default human inhalation rate) × unit conversion
ITSL = 0.00625 mkd × 70 kg/20 m^3 × 1000 µg/mg
ITSL = 21.875 µg/m^3, rounded to 1 significant figure is 20 µg/m^3

The ITSL is assigned a 24-hour averaging time because the duration of the animal study was short-term and the developmental effects of exposure during human gestation are thought to occur over short periods most closely approximated by daily exposure.

The ITSL for SDDC is 20 µg/m^3 with a 24-hour averaging time.

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[ii] Adeyemi, J.O. and Onwudiwe, D.C. 2020. The mechanisms of action involving dithiocarbamate complexes in Biological Systems. Inorganica Chimica Acta 511:119809. https://doi.org/10.1016/j.ica.2020.119809.