MICHIGAN DEPARTMENT OF ENVIRONMENT, GREAT LAKES, AND ENERGY

INTEROFFICE COMMUNICATION

TO: File for Dazomet (CAS No. 533-74-4)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

SUBJECT: Screening Level Evaluation for Dazomet (CAS No. 533-74-4)

DATE: November 4, 2021

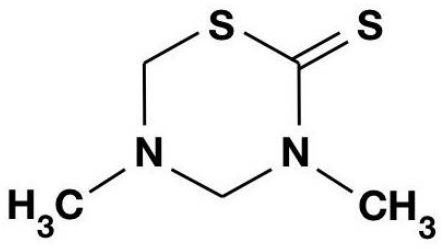
Summary

The initial threshold screening level (ITSL) for dazomet is 19 µg/m³, with an annual averaging time.

Uses and Physical Chemical Properties

Dazomet is a fungicide, herbicide, nematicide, algaecide, bacteriostat, microbiocide, and mildewcide, and it is used: as a soil fumigant for use on golf greens or tees, turf sites, ornamental sites, field nurseries, compost piles, potting soils, and in agriculture in nonbearing crops prior to sowing or planting to kill soil fungi, nematodes, bacteria, and weeds; as a fumigant in agriculture for poultry litter and eggs to control Salmonella; as a treatment during the production of pulp and paper; as a material preservative treatment for coatings, adhesives, epoxy flooring compounds, slurries, and high viscous suspensions; as a biocide treatment used during petroleum operations; as a biocide treatment to recirculating cooling water systems; and as a biocide in wood preservation for prevention of internal decay for treated wood (e.g., utility poles) (EPA, 2008).

Table 1. Physical/Chemical Properties of Dazomet

Structure	

CAS Number	533-74-4
Synonyms	Basamid; 3,5-Dimethyl-1,3,5-thiadiazinane-2-thione; Thiazone; OsmoFume; Buscan 1059
Appearance/Odor	White crystals or off-white powder with a pungent, acrid odor
Molecular Weight	162.28 g/mol
Melting Point	106.0°C
Flash Point	93°C
Density	1.3 at 20°C
Vapor Pressure	2.8 x 10-6 mm Hg at 20°C
Log Kow	0.63 at pH 7
Henry's Law Constant	2.66X10-10 atm-cu m/mole at 25°C
pKa	20
Molar enthalpy of dissolution	27kJ/mol

EPA (2008) states that when dazomet is applied, it is quickly broken down into several degradates; the major degradate being methylisothiocyanate (MITC). Other dazomet degradation products include formaldehyde, monomethylamine, hydrogen sulfide, and carbon disulfide (when applied to acidic soils). The fumigant activity is not from the dazomet, but from MITC; therefore, EPA evaluated human health risk based on exposure to MITC for inhalation. EPA (2008) has stated that for field fumigation that workers are prohibited from entering untarped fields for 5 days (120 hours) after dazomet application. EPA (2008) also states that monitoring must take place to ensure that MITC concentrations stay below 100 ppb (300 µg/m^3). The European Food Safety Authority (EFSA, 2010) evaluated several studies on dazomet. Dazomet breakdown into MITC depends on the moisture content of the soil and how much organic material (i.e., soil microbes) are present. In field samples, loamy sand dazomet degraded to MITC with a DT50 (the time required for 50% disappearance) value of 1.4 days. For loamy silt the DT50 value is 7.4 days. Dazomet is rapidly degraded in moist soil with a DT50 of less than 2 days. In biologically active soils, dazomet is degraded to MITC with a DT50 of 12 hours. Dazomet can undergo photolytic degradation to MITC with a DT50 of 3.6 hours in daylight and a DT50 of 6.4 hours at night. In laboratory studies, dazomet can undergo aerobic degradation to MITC with a DT50 of 1.3 days at 10°C. Under anaerobic conditions the DT50 was 15 minutes at 20°C. Looking at the acid dissociation constant (pKa) and molar enthalpy of dissolution shows that dazomet is a weak acid that can generate some heat when it breaks down.

Literature Search

The literature was searched to find relevant data to assess the toxicity of dazomet. The following references or databases were searched: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Levels (RELs), International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS)

SciFinder (searched 4/8/2021), U.S. EPA ChemView, California Office of Environmental Health Hazard Assessment (OEHHA), the U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry (ATSDR), European Chemical Agency (ECHA), and the U.S. National Toxicology Program (NTP).

Studies

In a 24-month oral rat study by Kunbroth B, (EPA, 1991), groups of 20 male and 20 female Wistar rats were fed dazomet in the diet for 104 weeks at doses of 0, 5 ppm (0.23 mg/kg/day males; 0.29 mg/kg/day females), 20 ppm (0.94 mg/kg/day males; 1.19 mg/kg/day females), 80 ppm (3.81 mg/kg/day males; 5.09 mg/kg/day females), or 320 ppm (16.36 mg/kg/day males; 21.54 mg/kg/day females). Male and female rats at the 320-ppm dose level showed reduced group mean body weight in males (12% by the end of the study) and decreased group mean body weight in females (8% by the end of the study) when compared to controls. Female rats at the 80 and 320 ppm dose level had significant decreases in hematologic parameters (red blood cell, hemoglobin, hematocrit); significant decreases in serum albumin, total, protein, and globulins; and a significant increase in platelets. "Male rats showed slight increases in platelets at the 320-ppm dose level and a significant increase in serum cholesterol at the 80 and 320-ppm dose levels (EPA, 1991)." Male rats at the 320-ppm dose showed increased relative liver:body weight ratios, but no significant organ weight increases were observed in female rats. The no observed effect level (NOEL) of 20 ppm. The lowest observed effect level (LEL) of 80 ppm due to the following critical effects: "decrease in serum albumin, globulins, total protein, hemoglobin, hematocrit, and red blood cells in female rats; and increased serum cholesterol in male rats (EPA,1991)." This study is listed to corroborate that body weight reduction and liver effects are common critical effects found upon exposure to dazomet. Also, the dose levels where effects are seen according to this study support the dose levels effects seen in the 2-generation reproduction/developmental study listed below.

In a 2-generation reproduction/developmental study by Hellwig (EPA, 1991), groups of 24 males and 24 females Wistar rats were fed dazomet over two generations at doses of 0, 5 ppm (0.46 mg/kg/day males; 0.54 mg/kg/day females), 30 ppm (2.78 mg/kg/day males; 3.19 mg/kg/day females), and 180 ppm (16.98 mg/kg/day males; 19.0 mg/kg/day females). The F_0 generation of rats were 36 days old at study initiation. They were fed for 70 days prior to mating, 21 days maximum mating period, 21 days female gestation and 21 days to raise pups (F1a litter). Then were mated for a second litter (21 days mating, 21 days gestation, and 21 days to raise second litter of pups – F1b litter) for a total dazomet treatment time of 190 days. Groups of 24 male and 24 female rats were selected from the F1a litter and administered dazomet in the diet post-weaning at either 0, 5, 30, or 180 ppm for 98 days prior to mating, then 21 days maximum mating period, 21 days gestation, and 21 days to raise pups (F2 litter) for a total dazomet treatment time of 159 days.

The F0 female parental rats showed decreased body weight gain (7%) in the first 10 weeks of study at the 180-ppm dose level (112 g weight gain vs. 120 g weight gain in

controls). F0 male rat body weight and body weight gain were not significantly different than control. In F1 parental rats, male rats had decreased body weight in the 180-ppm dose group at the start of dazomet administration when compared to controls (111 g vs 119 g in controls). At week 10, F1 male rats in the 30 and 180 ppm test group had significantly decreased body weight when compared to controls "(decreases of 5% and 8% respectively, $p < 0.05$)" (EPA, 1991). F1 female rats had decreased absolute body weight at the start of dazomet dosing when compared to controls (99 g vs 109 g in controls). "However, body weight gain and food consumption in female F1 rats was unaffected from weeks 1-10" (EPA, 1991). "Increased liver:body weight ratios were observed in F0 male rats and F1 males and females (EPA, 1991)." Reduction of "alanine aminotransferase activity in male and female F0 rats at the 180-ppm dose level was observed, as was significantly decreased serum albumin in F0 female rats at the 180-ppm dose level, and significant decreases in serum globulins in F0 and F1 male rats at the 180-ppm dose level. An increase in the incidence and severity of intracellular hepatic neutral lipids was observed in the F0 and F1 male rats. No significant effects of test article administration were observed on reproductive performance or viability and survival in pups of the F1a, F1b, and F2 generations" (EPA, 1991). The no observed effect level (NOEL) for parental toxicity was 5 ppm. The lowest observed effect level (LEL) for parental toxicity of 30 ppm was due to the following critical effects: "increased incidence and severity of hepatic intracellular neutral lipids in male rats; decreased body weight in F1 male rats" (EPA, 1991).

ITSL Derivation

The EPA Benchmark dose software [BMDS] (version 3.1.2) was used with continuous endpoints. The statistically significant changes due to exposure to dazomet were entered into the BMDS program. The statistically significant critical effects are listed in Table 2. The calculated model predictions for significant changes in adult rats are listed in Table 3.

Table 2. Significant Changes in Wistar Rats Dosed with Dazomet in the Feed (Hellwig study, EPA, 1991)

		Dosage (mg/kg/day)	**Dosage (mg/kg/day)**	
		F0 Males		
Critical Effect	**0**	**0.46**	**2.78**	**16.98**
Liver:Body weight ratio (%)	2.98±0.2	2.87±0.17	2.93±0.19	3.15±0.18
		F1 Males		
Critical Effect	**0**	**0.46**	**2.71**	**17.06**
Mean body weight (g) week 10	420.8±29.3	416.1±33.4	401.1±25.7	390.7±34.1

F0 Females – Litter A				
Critical Effect	**0**	**0.54**	**3.19**	**19.0**
Mean body weight (g) day 21 of lactation	304.6±19.6	306.2±18.2	300.4±24.3	287.0±20.4
F1 Females				
Critical Effect	**0**	**0.51**	**3.11**	**18.92**
Mean body weight (g) week 0	109.6±10.3	110.9±10.9	113.4±12.9	99.4±8.2
Mean body weight (g) day 20 of gestation	393.6±26.9	387.4±30.9	404.5±32.2	368.2±36.9
Mean body weight (g) day 21 of lactation	324.2±18.9	325.0±26.3	328.8±18.6	301.0±23.6
Liver:Body weight ratio (%)	3.74±0.37	3.70±0.44	3.91±0.29	4.38±0.48

Table 3. Model Predictions for Significant Changes in Wistar Rats Dosed with Dazomet in Feed (Hellwig study, EPA, 1991)

Critical Effect	Model	p-Value	AIC	Scaled Residual	BMDL
F0 Male Liver:body weight ratio (%)	Polynomial	0.1150	-44.9545	0.0015	10.6361
F1 Male mean body weight (g) week 10	Polynomial	0.8989	934.5200	-0.0065	2.4337
F0 Female – Litter A mean body weight (g) day 21 of lactation	Exponential	0.5787	858.8965	0.0507	3.3430
F1 Female mean body weight (g) week 0	Hill	0.2036	733.1769	0.9724	3.6784
F1 Female mean body weight (g) day 20 gestation	Polynomial	0.3128	942.3412	-0.0066	18.3925
F1 Female mean body weight (g) day 21 lactation	Polynomial	0.7225	869.2620	-0.0029	13.2006
F1 Female Liver:body weight ratio (%)	Linear	0.5652	100.3110	-0.1121	9.0164

Discussion

The most critical effects seen in the Hellwig two-generation reproductive/developmental rat study (EPA, 1991) were the decreased body weight in F1 generation male rats at week 10 of the study and an increased incidence and severity of hepatic intracellular neutral lipids in male rats. Body weight is not biologically relevant until 10% or greater change when compared to controls are seen for an adult and 5% for fetal weights in developmental studies. The increased incidence and severity of hepatic intracellular neutral lipids are frank effects and unfortunately these hepatic effects were not amenable to benchmark dose modeling. The lowest BMDL of 2.4337 mg/kg/day may not be health protective for hepatic effects, as the BMDL is very close to the LEL of 2.71 mg/kg/day. The benchmark dose exercise does help to support the study NOEL of 0.46 mg/kg/day.

Potential ITSL Using the Benchmark Dose Software Results

If the screening level was derived from the BMDS results above, EPA (2012) states the p-value must be greater than 0.1, such that the greater the p-value, the better the model fits the data. Also, the lower the Akaike Information Criterion (AIC), the better the model fits the available data. The AIC is used to compare different possible models to determine which model is the best fit for the data. The scaled residual must be less than 2 decimals away from 0, in either a positive or negative direction and is used to verify that the p-value is acceptable. The lower-bound confidence limit on the benchmark dose (BMDL) is the point of departure value determined by the model. If the available BMDLs are within 3-fold range, then the model with the lowest AIC is selected. If the BMDLs are not within 3-fold range, then the model with the lowest BMDL is selected.

Following the EPA (2012) criteria, the most critical effect would be the F1 male mean body weight at week 10 with the corresponding BMDL of 2.4337 mg/kg/day. EPA (2011) recommends use of a factor of ¾ body weight as the default method in the derivation of an oral reference dose (RfD). This methodology is used for calculating the dosimetric adjustment factor (DAF) to determine the human equivalent dose for both cancer and noncancer endpoints.

$$DAF = \left(\frac{W_H}{W_A}\right)^{1/4}$$

Where W_H= Average weight of an adult human (assumed to be 70 kg).

W_A= Body weight of the F1 male Wistar rat (control group at week 10).

$$DAF = \left(\frac{70\ kg}{0.4208\ kg}\right)^{1/4} = 166.3498^{1/4} = 3.5913\ kg$$

The BMDL of 2.4337 mg/kg/day for rats needs to be converted to a human equivalent dose (HED) by multiplying the DAF factor above.

$$BMDL \times DAF = BMDL_{HED}$$
$$2.4337\ {}^{mg}/_{kg/day} \times 3.5913\ kg = 8.7402\ {}^{mg}/_{kg/day}$$

The $BMDL_{HED}$ can be used to determine an oral reference dose (RfD) using the following equation:

$$RfD = \frac{BMDL_{HED}}{(UF_H \times UF_A \times UF_S)}$$

Where UF = The uncertainty factor used to account for differences between the available data and the possible effects in the human population, usually expressed as factors of 10.

UF_H= Uncertainty factor used to account for the variation in sensitivity among individuals of the human population.

UF_A= Uncertainty factor used to account for the extrapolation from animal data to humans. When using a DAF, the reduction of uncertainty allows for a value of 3.

UF_S= Uncertainty factor used to account for the extrapolation from less than chronic point-of-departures to chronic point-of-departures.

$$RfD = \frac{8.7402\ {}^{mg}/_{kg/day}}{10\ \times 3\ \times 10} = 0.02913\ {}^{mg}/_{kg/day}$$

Rule 232(1)(b) uses an oral RfD to determine an ITSL using the following equation:

$$ITSL = Oral\ RfD\ \times \frac{70\ kg}{20\ m^3}$$

According to Rule 232(1)(b), 70 kg is the default body weight for an average human and 20 m^3 is used to define the minute volume (default ventilation rate) for an average human. Taking the oral RfD, which was determined to be 0.02913 mg/kg/day above, this leads to the following equation:

$$ITSL = 0.02913\ {}^{mg}/_{kg/day} \times \frac{70\ kg}{20\ m^3} = 0.102\ {}^{mg}/_{m^3} = 100\ {}^{\mu g}/_{m^3}$$

ITSL Using the NOEL from the 2 Generation Reproductive/Developmental Study

The screening level will be based on the statistically significant critical effects of increased incidence and severity of hepatic intracellular neutral lipids in male rats and decreased body weight in F1 male rats. Using the NOEL of 0.46 mg/kg/day as stated above and using the EPA (2011) body weight ¾ power provides the default method in the derivation of an oral reference dose (RfD). This methodology is used for calculating the DAF to determine the human equivalent dose for both cancer and noncancer endpoints. Using the same equation as for the DAF for the BMDL above:

$$DAF = \left(\frac{W_H}{W_A}\right)^{1/4}$$

$$DAF = \left(\frac{70\ kg}{0.4208\ kg}\right)^{1/4} = 166.3498^{1/4} = 3.5913\ kg$$

Converting the NOEL to a human equivalent dose (HED) by multiplying the DAF factor above uses the following equation:

$$NOEL \times DAF = NOEL_{HED}$$

$$0.46\ {}^{mg}/_{kg/day} \times 3.5913\ kg = 1.6520\ {}^{mg}/_{kg/day}$$

The $NOEL_{HED}$ can be used to determine an RfD using the following equation:

$$RfD = \frac{NOEL_{HED}}{(UF_H \times UF_A \times UF_S)}$$

$$RfD = \frac{1.6520\ {}^{mg}/_{kg/day}}{10\ \times 3\ \times 10} = 0.005507\ {}^{mg}/_{kg/day}$$

Rule 232(1)(b) uses an oral RfD to determine an ITSL using the following equation:

$$ITSL = Oral\ RfD\ \times \frac{70\ kg}{20\ m^3}$$

$$ITSL = 0.005507\ {}^{mg}/_{kg/day} \times \frac{70\ kg}{20\ m^3} = 0.01927\ {}^{mg}/_{m^3} = 19\ {}^{\mu g}/_{m^3}$$

Based on Rule 232(2)(b) the averaging time is annual. Therefore, the ITSL for dazomet is 19 µg/m³, with an annual averaging time.

References

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