MIXED DIETHYLBENZENES

Document History
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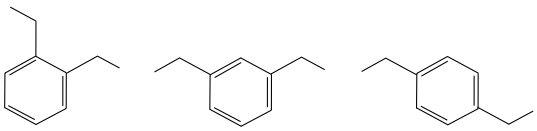
I. IDENTIFICATION

Chemical Name: Diethylbenzene mixtures containing no more than 25% 1,2-diethylbenzene
Synonyms: DEB, Dowtherm J
CAS Number: 25340–17–4
Molecular formula: $C_{10}H_{14}$
Structural formula:



Mixture of 1,2-, 1,3-, and 1,4-isomers

II. CHEMICAL AND PHYSICAL PROPERTIES

Physical state: Liquid, colorless to yellowish
Odor description: Unpleasant, aromatic odor; the odor threshold = 12 ppm.[1]
Molecular weight: 134.2
Conversion factors: 1 ppm = 5.5 mg/m^3
1 mg/m^3 = 0.18 ppm
Boiling point: 181°C (358°F)
Vapor pressure: 1–15 mmHg at 25°C (77°F)
Saturated vapor concentration: 1300–2000 ppm
Vapor density: No data located
Specific gravity: 0.86 at 25°C
Flash point (closed cup): 145°F
Flammability limits: LEL = 0.8%, UEL = 5%
Autoignition temperature: 430°C
Solubility in water: Insoluble; soluble in acetone, xylene, and kerosene
Stability and reactivity: Heat stable to 575°F, reacts with oxidizing materials

III. USES

Diethylbenzenes are used as a heat transfer solvent; in manufacturing divinylbenzene polymer, ethylbenzene, solvents, and pharmaceutical products; and in making magnesium printing plates.[2]

IV. ANIMAL TOXICITY DATA

Diethylbenzenes are manufactured as mixtures of the 1,2-, 1-3-, and 1-4-isomers. 1,2-DEB is more toxic than the other two. It causes neurotoxicity, a blue to blue-green discoloration of tissues and organs, and developmental toxicity at much lower levels than the other isomers. Manufacturers usually maintain the content of 1,2-DEB to less than 25% of the mixture. Only a few studies have utilized one specific isomer or a defined mixture of two isomers. In the remainder of studies, the 1,2-DEB content ranges from 1–25%, although sometimes the content is not reported.

A. Acute Toxicity

1. Oral Toxicity

The oral LD_{50} of Dowtherm J in female rats is between 2520 and 5000 mg/kg when administered as a neat material.[3]

In rats, Dowtherm J turned tissues blue, and urine green. In a follow-up study of a 1,2- and 1,4-mixture, 10 of 12 rats died at 2000 mg/kg and 1 of 12, at 1000 mg/kg.[4] Rats appeared nervous and shaky, and their urine was bluish green.

The 1,3-isomer produced no evidence of toxicity at single oral doses of 1000 or 2000 mg/kg to rats.[5]

The oral LD_{50} in rats for diethylbenzene mixtures ranged between 2050 and 6900 mg/kg.[6,7]

The oral LD_{50} for 1,4-diethylbenzene was greater than 2000 mg/kg in Sprague-Dawley rats.[8]

2. Eye Irritation

In rabbits, eye contact with Dowtherm J resulted in slight discomfort and transient moderate conjunctival redness. This irritation resolved within 48 hours.[3]

In an inhalation study in rats, irritation occurred after 3 minutes at approximately 100 ppm of Dowtherm J.[9]

In another study of a diethylbenzene mixture, 3 male and 3 female NZW rabbits were exposed for 24 hours to 0.1 mL. In the unwashed right eye, mild reversible irritation was found, which was entirely gone in 3–7 days.[10] The irritation consisted of conjunctival redness, chemosis, discharge, and iridial changes. No corneal effects were detected.

A diethylbenzene mixture caused slight to moderate conjunctival irritation (Draize score of 2.7 of a possible 110).[11,12]

3. Dermal toxicity

a. Irritation

Prolonged (4-hour) or repeated skin contact with Dowtherm J resulted in moderate redness, slight swelling, and slight burns with exfoliation when tested on a rabbit.[3]

In 3 female rabbits exposed to Dowtherm J by skin contact for 4 hours,[13] slight eschar or severe erythema with slight edema was noted. It was scored as a skin irritant.

In a study of diethylbenzenes, a 4-hour semi-occlusive application resulted in very slight to slight erythema, with moderate to severe edema, which was gone by Day 10 in 5 of the 6 rabbits. Very slight irritation was present in one animal on the final day of the study.[14] In the same study, 24-hour occlusive exposure caused slight erythema with slight to moderate edema following exposure. This produced superficial necrosis in 2 of 6 rabbits and further progressed to subepidermal necrosis on Days 10–14 in one animal.

Diethylbenzenes caused reversible moderate skin irritation (average scores at 24, 48, and 72 hours were 3.1 for erythema and 0.4 for edema following a 4-hour occluded application.[12,15]

b. Skin Absorption

In one study, 5 male and 5 female NZW rabbits survived a single 24-hour dermal dose of 5000 mg/kg. The only effect observed was slight body weight loss and decrease in food consumption during Days 1 through 7 of the 2-week observation period.[16] Thus, the dermal LD_{50} is greater than 5000 mg/kg.

In two studies in rats, the dermal LD_{50} for diethylbenzenes was reported to be greater than 2000 mg/kg.[17]

c. Sensitization

In the Beuhler test in guinea pigs, diethylbenzenes were negative for skin sensitization potential.[18]

4. Inhalation

Groups of 3 rats were exposed for 7 hours to a nominal saturated vapor concentration of Dowtherm J generated at room temperature (1400 ppm) or heated to 100°C (2100 ppm). All rats survived. Drowsiness occurred toward the end of exposure, indicating mild central nervous system (CNS) effects. Slight liver and kidney effects (no details given) were also noted.[19]

Groups of 10 rats, 2 guinea pigs, and 1 rabbit were exposed to 600 ppm of Dowtherm J for four 7-hour exposures.[9] There were no deaths, and the rats were affected (depressed body weight gain and general health) more severely than guinea pigs or the rabbit.

Groups of ten rats were exposed to 200 ppm of Dowtherm J for three 7-hour exposures.[9] Both sexes showed depressed body weight gain.

B. Subacute Toxicity

No data located.

C. Subchronic Toxicity

1. Oral Toxicity

In a repeated oral gavage study, groups of 10 or 12 rats were given doses of 0, 500, or 750 mg/kg/day of DEB mixed isomers (containing approximately 7% 1,2-DEB) for 10 weeks. Treatment-related effects included: blue skin and urine, severe hind limb weakness, and gait disturbances starting in the fourth week, with complete paralysis in some rats.[20] Mortality was increased at both doses. Neurological measurements showed significant deficits at both dose levels, as well.

The guinea pig was insensitive to 1,2-DEB diethylbenzene, in that no signs of neurotoxicity were noted among 10 guinea pigs given 100 or 500 mg/kg for 10 weeks.[21]

Rats were dosed orally with 1,4-diethylbenzene at 0, 30, 150 or 750 mg/kg/day for 28 days in the combined repeat dose and reproductive/developmental toxicity screening

test.[8] At 150 and 750 mg/kg, effects were noted in the livers (increased weights, brown color, and swollen cells) and kidneys (increased weights), with corresponding effects noted in the blood chemistry; however, there were no corresponding histopathologic findings. The no-observed-adverse-effect-level (NOAEL) was 30 mg/kg/day.

In an unverifiable study, groups of rats and rabbits were fed 2.5 mg/kg/day 1,2-DEB. Effects on the liver, spleen, intestine and kidney were reported. The number of animals and duration of feeding were not specified. No effects were noted at 0.25 mg/kg/day.[22]

2. *Inhalation Toxicity*

In a 183-day inhalation study, groups of 40 rats, 6 rabbits, and 2 monkeys were exposed to 0, 100, 200, or 600 ppm of Dowtherm J, 7 hours/day, 5 days/week for 127 exposures. None of the animals showed any adverse effects, other than fatty degeneration of the liver and cloudy swelling, with interstitial nephritis of the kidneys in female rats exposed to 600 ppm.[9] These effects were reversed 30 days after exposure. Inhalation of diethylbenzene in concentrations over 100 ppm caused tissues of test animals to turn blue, and urine to turn green.[9] The NOAEL for discoloration is 100 ppm and the NOAEL for liver and kidneys effects is 200 ppm.

Groups of 12 or 15 rats were exposed to 0, 500, 700, or 900 ppm of a diethylbenzene mixture for 6 hours/day, 5 days/week for 18 weeks, with a 6-week recovery period (young rats) or to 0, 600, or 800 ppm (~6% 1,2-DEB), for 6 hours/day, 5 days/week, for 18 weeks (old rats). The older rats (19-weeks old versus 9-weeks) showed moderate clinical signs of neurotoxicity while the younger rats showed lesser effects.[23] However, deficits were detected in parameters of peripheral and central nervous functions in all exposed groups. The lowest-observed-adverse-effect-level (LOAEL) for neurotoxicity was 500 ppm.

Rats were exposed by inhalation to mixed diethylbenzenes (~7% 1,2-DEB) at 0, 190, 610, and 1400 mg/m^3 (0, 35, 111, or 225 ppm) for 6 hours/day, 5 days/week for 10 weeks.[24] Mean body weights were decreased throughout the study in animals exposed to 225 ppm. There were no treatment-related abnormal clinical observations or ocular abnormalities. Treatment-related changes in hematological parameters included moderate decreases in total white cell and lymphocyte counts in males exposed to 111 or 225 ppm. Abnormal sera color (blue or blue-gray) was observed in males and females exposed to 225 ppm. Treatment-related changes in serum chemistry parameters included decreases in alanine aminotransferase, aspartate aminotransferase and creatinine phosphokinase in females exposed to 225 ppm; increases in potassium in males exposed to 225 ppm; and phosphorus in males exposed to 225 ppm and females exposed to 111 or 225 ppm. An abnormal blue-gray color was observed in most tissues from all but one animal exposed to 225 ppm. At 111 ppm, the same color was observed in brains, and in the urinary bladders of some animals. This abnormal color probably resulted from the presence of the parent chemical or a metabolite in these tissues. There were no other gross or microscopic changes attributed to the test material, including effects on the reproductive organs of either sex. The no-observed-adverse-effects-level (NOAEL) for hematological effects and blue discoloration of tissues was 35 ppm, with a LOAEL of 111 ppm. No evidence of neurotoxicity was noted at any exposure level.

3. *Other*

In a repeated dose study, groups of 10 or 12 rats were given i.p. doses of 10 mg/kg, 4 days/week for 11 weeks or 20 mg/kg (approximately equivalent to a 6-hour exposure to 100 ppm), 5 days/week for 6 weeks. 1,2-DEB produced the same signs of neurotoxicity as the mixture, while 500 mg/kg/day of the 1,3- or 1,4- isomers produced no signs of systemic toxicity, including neurological effects. The 1,2-diacetylbenzene metabolite is believed to contribute to the neurotoxicity of 1,2-DEB.[25]

Groups of 15 rats were given 75 or 100 mg/kg 1,2-DEB via gavage or 10 or 15 mg/kg 1,2-diacetylbenzene i.p., 4 days/week for 8 weeks.[26] Increases in peak latencies and decreases in peak amplitude were noted in brainstem auditory evoked potentials.

D. Chronic Effects/Carcinogenicity

In a dermal carcinogenicity study, application of 25 µl of 10% Dowtherm J diluted in acetone was applied to the backs of groups of 40 male C3H/HeJ mice 3 times per week until the deaths of the

animals.[2] An additional 40 mice received 25 µl of acetone only, as controls. In the group receiving 10% Dowtherm J, squamous cell carcinoma was found at the application site of one mouse. Two nodules found in the acetone-treated control group were diagnosed as a fibrosarcoma and a lymphosarcoma. Dowtherm J treatment was associated with increases in hyperkeratosis, epidermal hyperplasia, surface crusting, dermatitis, and dermal fibrosis. No significant difference in mortality rates was observed between the treated and control group. Although the carcinoma in one mouse was judged to be treatment-induced (due to a low incidence of this type of tumor in C3H/HeJ mice), this borderline response suggests a weak oncogenic potential, particularly in comparison with other materials that have been shown to produce skin tumors in mice.

E. Reproductive/Developmental Toxicity

Groups of 25 female SD rats were dosed with 0, 20, 100, or 200 mg/kg/day of mixed diethylbenzenes in corn oil from Days 6–15 of gestation. Maternal weight gain and food consumption were decreased at 100 and 200 mg/kg/day levels during the first part of the study. Greenish-blue discoloration of the amniotic sac was observed at both 100 and 200 mg/kg/day levels. There was a decrease in fetal body weights, indicating a slight degree of developmental toxicity at 200 mg/kg, but no evidence of teratogenicity was found. The NOAEL for maternal toxicity was 20 mg/kg/day and the NOAEL for developmental toxicity was 100 mg/kg/day in this study.[27]

1,2-Diethylbenzene was administered orally to groups of 28–29 pregnant Sprague-Dawley rats at 0 (corn oil vehicle), 5, 15, 25, or 35 mg/kg on gestation days 5–20.[28] Maternal weight gain and food consumption were decreased in the rats that received 15, 25, or 35 mg/kg. There was no effect on the number of live fetuses, implantations, nonsurviving implantations per litter, or fetal sex ratios. Fetal body weights were reduced in a dose-related fashion in the groups receiving 15, 25, and 35 mg/kg. The NOAEL for both maternal and developmental toxicity was 5 mg/kg. There was no treatment-related effect on external visceral and skeletal malformations. 1,2-Diethylbenzene was not teratogenic in this study.

In a subchronic inhalation study in rats, exposure at 0, 35, 111, or 225 ppm of mixed diethylbenzenes, 6 hours/day, 5 days/week for 10 weeks produced no effects on the reproductive organs of either sex.[24]

Sprague-Dawley rats were dosed orally with 1,4-diethylbenzene at 0, 30, 150 or 750 mg/kg/day in the combined repeat dose and reproductive/developmental toxicity screen level.[8] Males were dosed for 44 days, including 14 days before mating, and females were dosed from 14 days before mating until Day 3 of lactation. There were no effects on mating, fertility, estrus cycle, pup body weight, or gross abnormalities at any dose. A slight increase in the duration of gestation, and a slight decrease in viability index at Day 4 in male pups in the 750 mg/kg/day group were noted.

F. Genotoxicity/Mutagenicity

The test material was not mutagenic in the Ames test.[29]

Diethylbenzenes were negative for the reverse mutation assay with *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA 1537 with and without S-9 activation,[30,31] and with *E. coli WP2 uvrA* with and without S-9 activation.[30]

Diethylbenzenes were also negative in an *in vivo* micronucleus study, in which mice were dosed intraperitoneally with 1000, 2000, or 4000 mg/kg.[32]

In a chromosomal aberration study using Chinese hamster ovary cells, mixed diethylbenzenes were negative with and without S-9 activation.[33]

1,4-Diethylbenzene was negative in a bacterial reverse mutation assay (*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538, and *E. coli uvrA* with and without metabolic activation).[34] It was also negative in a CHO cytogenetics assay with and without metabolic activation.[34]

G. Pharmacokinetics/Metabolism

In male Sprague-Dawley rats administered [14C] 1,2-diethylbenzene intravenously (1 mg/kg) or oral (1 or 100 mg/kg), radioactivity was rapidly absorbed, and mainly excreted in the urine (65–76% of the dose), to a lesser extent in the feces (15–23% of the dose), or via exhaled air (3–5% of the dose).[35] Biliary metabolites were extensively reabsorbed from the gut, and ultimately excreted in urine. The two main metabolites were two glucuronide conjugates, probably of the two enantiomers of 1-(2'-ethylphenyl) ethanol, suggesting that the initial conversion step of the primary metabolic pathway appears to be the hydroxylation of the alpha-carbon of the side chain. In this study, insignificant amounts of the neurotoxic metabolite 1,2-diacetylbenzene were detected in urine, bile, and feces.

Of the dose given, 65–76% was excreted in the urine.[35] More than 50% of the absorbed material was initially excreted in bile, subsequently reabsorbed from the GI tract, and ultimately excreted in urine after several enterohepatic circulations.

Repeated oral gavage doses (4–5 days/week, for 8 weeks) of each of the three isomers to rats showed 100 mg/kg/day of 1,2-DEB to produce the same signs of neurotoxicity as the mixture. The metabolite, 1,2-diacetylbenzene (DAB), was identified in the urine, and is believed to contribute to the neurotoxicity of 1,2-DEB.[25]

In groups of 4 pregnant Sprague-Dawley rats given a single oral dose of 25 mg/kg, [14C] 1,2-diethylbenzene concentrations in the fetus measured at 28–60% of the levels in maternal plasma within the first 48 hours after dosing, and were consistently lower than levels in the placenta.[28] Placental and fetal tissues accounted for < 0.35% of the administered dose.

The two major metabolites of 1,2-diethylbenzenes in the urine of treated rats are the glucuronide conjugates of two enantiomers of 1-(2'-ethylphenyl)ethanol.[36] The metabolic steps which lead to the conjugates are under stereoselective control.

H. Other Effects

No data located.

V. HUMAN USE AND EXPERIENCE

A. Odor Data

The odor is described as an unpleasant, aromatic odor.[1]

B. Human toxicity

No effects were noted in workers exposed to Dowtherm J concentrations ranging between non-detected (ND) [detection limit of 1 ppm] and 5 ppm in an air monitoring study performed prior to 1990.[3]

C. Epidemiology Data

No data located.

VI. RATIONALE

Dowtherm J and other diethylbenzene mixtures show relatively low volatility at room temperature, with low acute oral toxicity. The oral LD_{50} in female rats is between 2500 and 5000 mg/kg. It is moderately irritating to the skin and eye of rabbits. It is not readily absorbed across the skin. All rats exposed for 7 hours to 1400 ppm showed evidence of CNS depression, as well as liver and kidney effects. It is not genotoxic.

In subchronic studies, slight liver and kidney effects were noted in female rats exposed to 100 ppm (LOAEL), but no effects were noted in guinea pigs, rabbits, and monkeys. At 500 ppm, depressed weight gain and decline in general health were noted in rats and guinea pigs. Signs of neurotoxicity were noted in rats exposed to 500 ppm, but not in guinea pigs at this level. The NOAEL for maternal toxicity was 20 mg/kg for mixed diethylbenzenes (approximately equivalent to a 6-hr exposure to 100 ppm) compared to 5 ppm for 1,2-DEB. No epidemiology studies were located.

An OEL of 5 ppm as an 8-hr TWA should be protective against maternal and developmental toxicity, as well as neurotoxic effects, liver or kidney effects, and green or blue discoloration.

VII. RECOMMENDED OEL GUIDE

5 ppm as a 8-hr TWA

VIII. REFERENCES

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