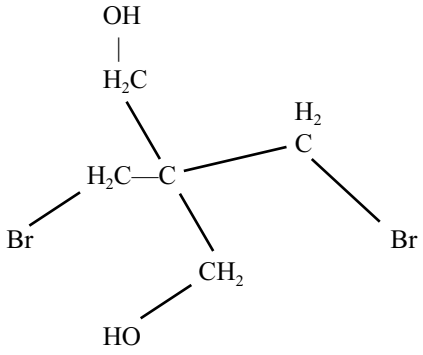
Dibromoneopentyl Glycol

I. IDENTIFICATION

Chemical Name: Dibromoneopentyl glycol
Synonyms: 2,2-bis(bromomethyl)- 1,3-propanediol; dibromopentaerythritol; pentaerythritol dibromide; pentaerythritol dibromohydrin; FR-1138; FR-522; Dynol; BBMP
CAS Number: 3296-90-0
Molecular Formula: $C_4H_{10}Br_2O_2$
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[1–7]

Physical State: white or brown crystalline powder
Odor Description and Threshold: Mild musty odor, no information found for threshold
Molecular Weight: 261.97
Conversion Factors: 1 ppm = 10.7 mg/m³; 1 mg/m³ = 0.09 ppm (v/v) at 25°C (77°F)
Boiling Point: decomposes at 235°C (455°F) and 760 mm Hg
Melting Point: 109–111°C (228–232°F)
Vapor Pressure (estimated): 1.3×10^{-5} mm Hg at 25°C (77°F)
Saturated Vapor Concentration: 0.02 ppm
Vapor Density: No information found
Flash Point: Not flammable
Specific Gravity: 2.2 @ 25°C (77°F)
Solubility: 20 g/L in water
Log Pow: 2.29
Stability: stable
Reactivity and Incompatibilities: Avoid strong oxidizing agents. Decomposes at 235°C (455°F) producing carbon monoxide, carbon dioxide, hydrogen bromide and bromine fumes.

III. USES

Flame retardant in unsaturated polyester resins, for molded products, and in the production of rigid polyurethane foam. It is used as a chemical intermediate for pentaerythritol ethers and other derivatives used as flame retardants.[5]

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity and Irritancy

1. *Oral Toxicity*

LD_{50} (Sprague-Dawley male rats): 3458 mg/kg (2810–4257)[8]

LD_{50} (Charles River CD strain male and female rat, not GLP study): 1880 mg/kg (1691–2120)[9]

2. *Eye Irritation*

Results of two separate trials using New Zealand White albino rabbits (sex not specified) and one trial with an unspecified strain of rabbit indicate that Dynol is a reversible irritant to the eye.[10–12]

3. *Skin Absorption*

Authors conclude there is no indication that this material is absorbed through the skin in acutely toxic amounts based on repeated unspecified doses of 2,2-bis(bromomethyl)-1,3-propanediol (BBMP) in skin irritation tests.[3]

4. *Skin Irritation*

Groups of six outbred New Zealand White albino rabbits (sex not specified) were

administered 0.5 grams BBMP. Results indicate the test material is mildly irritating to the skin.[6]

In a group of three rabbits (strain and sex not specified) test material was essentially non-irritating to intact skin (10 rabbits) and slightly irritating to freshly abraded skin.[10]

5. Skin Sensitization

Skin sensitization was not observed in six to eight week old Hartley strain male albino guinea pigs by two methods.[12]

6. Inhalation Toxicity

No adverse effects other than slight nasal irritation and slight labored breathing were observed in a group of rats exposed for 7 hours to an atmosphere saturated with vapours generated on heating BBMP to 100°C. The nominal concentration was calculated to be 2.49 mg BBMP/L of air (2490 mg FR-1138/m^3 of air).[8]

B. Subacute Toxicity

In a 30-day dietary study groups of 5/sex/dose male and female Sprague Dawley, Spartan strain, SPF-derived rats were fed diets containing 0, 10, 30, 100, and 300 mg/kg-day BBMP. The only indication of a treatment related effect was an increase in the liver to body weight ratio observed in male rats administered diets of 300 mg/kg-day of test material. The no observed effect level (NOEL) was determined to be greater than 300 mg/kg-day for female rats and between 100 and 300 mg/kg-day for male rats.[13]

C. Subchronic Toxicity

Groups of 10 male and 10 female F344/N rats were exposed to technical grade BBMP (78.6% pure) doses of 0, 50, 100, 200, 400 or 800 mg/kg by gavage five days/week for 13 weeks. Two of the high dose males died. A dose-related decrease in body weight occurred in both males and females at 800 mg/kg. Renal papillary degeneration was present in the 400 and 800 mg/kg males. Transitional cell hyperplasia of the urinary bladder was present in males at the 800 mg/kg dose. Dose-related clinical signs of toxicity included inactivity or lethargy after dosing at 400 or 800 mg/kg in male and female rats. NOEL in this study was 200 mg/kg for male and female rats.[14]

Groups of 10 male and 10 female F344/N rats were exposed to technical grade BBMP (78.6% pure) in feed for 13 weeks. Dietary levels of 0, 1250, 2500, 5000, 10,000 and 20,000 ppm delivered average daily doses of 0, 100, 200, 400, 800, or 1700 mg/kg to males and 0, 100, 200, 400, 800, or 1630 mg/kg to females. No dose-related mortality occurred in this study. The final mean body weights and weight gains at doses above 2500 ppm were significantly lower than those of the controls for both males and females. No treatment-related toxicity was observed. Renal papillary degeneration was present in 5000 and 10,000 ppm males, and in 20,000 ppm males and females. Transitional cell hyperplasia of the urinary bladder was present in males and females at the 20,000 ppm dose. The NOEL was reported as 100 mg/kg-day and the LOEL was reported as 200 mg/kg-day in male and female rats.[15]

Groups of 10 male and 10 female $B6C3F_1$ mice were exposed to technical grade BBMP (78.6% pure) by gavage. Animals received doses of 0, 25, 50, 100, 200, and 400 mg/kg 5 days/week for 13 weeks. Three of the high dose males died. A dose-related decrease in body weight occurred in males at 200 and 400 mg/kg and females at 400 mg/kg. Renal tubular cell regeneration was present in the 200 and 400 mg/kg males and 400 mg/kg females. Transitional cell hyperplasia of the urinary bladder was present in males and females at the two high doses. Dose-related clinical signs of toxicity included inactivity or lethargy after dosing at 400 mg/kg in male and female mice. NOEL in this study was 100 mg/kg for male and 200 mg/kg for female mice.[14]

Groups of 10 male and 10 female $B6C3F_1$ mice were exposed to technical grade BBMP (78.6% pure) in feed for 13 weeks. Dietary levels of 0, 625, 1250, 2500, 5000 and 10,000 ppm delivered and average of 0, 100, 200, 500, 1300, or 3000 mg/kg-day to males and 0, 140, 300, 600, 1200, or 2900 mg/kg-day to females. Deaths of five males and five females were not considered to be related to administered BBMP. The final mean body weights and body weight gains of males receiving more than 625 ppm and of females at all dose levels were significantly lower than those of the controls. Feed consumption by exposed mice was generally higher than that by controls throughout the study. Clinical findings included abnormal posture and hypoactivity in 10,000 ppm male and female mice. The NOEL (mice) for this study was reported as 100 mg/kg-day (males) and not achieved for females while the LOEL (mice) was reported as 200 mg/kg-day (males) and 100 mg/kg-day (females).[15]

D. Chronic Toxicity and Carcinogenicity

Groups of 60 male and 60 female F344/N rats received average daily doses of 100, 200, or 430 mg/kg of BBMP for males and 115, 230, or 460

mg/kg of BBMP for females in feed for 104 to 105 weeks. Control groups of 70 males and 60 females received 0 ppm BBMP in feed for 104 to 105 weeks. A stop-exposure (recovery) group of 70 male rats received an average daily dose of 800 mg/kg BBMP in feed for 3 months, after which animals received undosed feed for the remainder of the 2-year study.

Survival of 5000 and 10,000 ppm continuous-exposure study males and females and 20,000 ppm stop-exposure males was significantly lower than that of the controls. Mean body weights of exposed male and female rats receiving 10,000 ppm and stop-exposure males receiving 20,000 ppm were lower than those of the controls throughout most of the study. In the continuous-exposure study, feed consumption by exposed rats was generally similar to that by controls throughout the study. In 20,000 ppm stop-exposure males, the feed consumption was lower than that by controls. Clinical findings included skin and/or subcutaneous masses on the face, tail, and the ventral and dorsal surfaces of exposed rats.

In addition to a wide variety of tissues and organs exhibiting proliferative changes in male rats in the continuous-feeding portion of the study, the presence of a high incidence of neoplasms in animals in the stop-exposure portion of the study is noteworthy. Male rats receiving BBMP at 20,000 ppm for only 13 weeks and then fed standard diet for the remainder of the study generally exhibited essentially the same pattern and magnitude of proliferative changes as male rats in the continuous-feeding study. BBMP administered in the stop-exposure group caused the early deaths of all treated male rats attributable primarily to the carcinogenic effects of the chemical.

Under the conditions of these 2-year feed studies there was clear evidence of carcinogenic activity of BBMP (FR-1138) in male and female F344/N rats.

The LOAEL for F344/N male rats was 100 mg/kg/day and 115 mg/kg/day for female F344/N rats.[1,16]

Groups of 60/sex B6C3F_1 mice received average doses of 0, 35, 70, or 140 mg/kg-day BBMP for males and 0, 40, 80, or 170 mg/kg-day BBMP for females. BBMP in feed for 104 to 105 weeks.

Survival of 1250 ppm males and females was significantly lower than that of the controls. Mean and final body weights of exposed male and female mice were similar to controls throughout the study. Feed consumption by exposed male and female mice was similar to that by controls. Clinical findings included tissue masses involving the eye in exposed mice.[15]

There was clear evidence of carcinogenic activity of BBMP in B6C3F_1 mice based on increased incidences of neoplasms of the harderian gland, lung and kidney in males and of neoplasms of the harderian gland, lung and subcutaneous tissue in females.

The LOAEL was 35 mg/kg/day for male and 40 mg/kg/day for female mice.[1,15,16]

Groups consisting of 50 Spartan sub-strain Sprague Dawley rats of each sex, plus 5/sex/group for the one-year interim kill, 10/sex/group for tissue analysis, and 5/sex/group for cytogenics were maintained on diets supplying 0, 5, or 100 mg FR-1138 /kg/day for up to two years.

The high dose level, 100 mg/kg/day, was associated with some degree of toxicity, with pathological observations occurring in the liver, lenses of the eyes, and possibly the thyroid.

The low dose level of 5 mg/kg/day showed no effects which could be attributed to treatment with the test material. Statistical analysis of the incidence of tumors found at necropsy showed there were no significant differences between control and treatment groups.

The results of this study revealed no oncogenic response even when administered at sufficiently high dosage to induce discernable toxicity.[17]

The NOAEL is reported to be 5 mg/kg/day and the LOAEL is reported to be 100 mg/kg/day for this study.[1]

E. Developmental and Reproductive Toxicity[18,19]

The effect of BBMP on reproduction in Swiss CD-1 mice was evaluated by use of a continuous breeding protocol. BBMP was administered in the feed at 0, 0.1, 0.2, and 0.4% concentrations. Based on body weights and food consumption, the estimated daily doses were 0, 141, 274, and 589 mg/kg. Both male and female F_0 mice, 20 pairs per treatment group and 40 pairs of control animals were dosed 7 days prior to and during a 98-day cohabitation period. Although the fertility index was unchanged in the high-dose group BBMP exposure significantly decreased the numbers of litters per pair, pups born alive per litter, and pup weight when adjusted for litter size. Crossover mating between treated and control F_0 animals indicated a specific effect only on female reproductive capacity. At the highest dose BBMP caused a body weight decrease in the F_0 animals of both sexes with no effect on relative organ weights. Sperm concentration, motility, morpholo-

gy, and estrual cyclicity were unaffected by BBMP exposure. Histopathology in the F_0 animals revealed specific kidney lesions in both sexes. Males were more sensitive than females.

The last litter born in the 98-day breeding phase was reared to age 74 days and then mated to non-siblings of the same treatment group. The effect of high-dose BBMP exposure on F_1 fertility, body and organ weights, sperm parameters, and estrual cyclicity was the same as that for the F_0 animals with the exception of the lack of renal lesions seen in the F_1 females. These data show that BBMP impaired fertility in female mice in both generations in the absence of an effect on reproductive organ weights and estrual cyclicity.

BBMP is not a reproductive or developmental toxicant as these effects were seen concomitant with the general toxicity.

The NOEL is about 141 mg/kg/day for adults and offspring in both F_0 and F_1 generations.[1]

F. Genotoxicity and Mutagenicity

Results of mutagenicity tests in *Salmonella typhimurium* and *Saccharomyces cerevisiae*, strain D4, were negative or not reproducible with or without activation.[20–24] In one study *S. typhimurium* TA 100 was judged positive only in the presence of 30% liver S9 from Aroclor-induced male Syrian hamster liver. There was no significant increase in sister chromatid exchanges with or without activation.[24]

Cultured Chinese hamster ovary cells were treated with doses of BBMP ranging from 16.7 to 500 µg/mL in absence of liver S9 activation and 800 to 1200 µg/mL in presence of liver S9 activation. Small increases in sister chromatid exchange frequency were seen in the presence of S9 but these results were judged equivocal.[25]

A concentration-related increase in chromosomal aberrations was observed in Chinese hamster ovary cells treated with BBMP at concentrations ranging from 400 to 700 µg/mL in the presence of rat liver S9 metabolic activation. The aberrations observed were considered unusual by the researchers because the majority of the breaks were preferentially located in the heterochromatic region of the long arm of the X chromosome. No increase in chromosomal aberrations was observed without metabolic activation.[25]

In vivo, BBMP induced significant increases in frequency of micronucleated erythrocytes in male and female mice fed 625, 2250, 2500, 5000, and 10,000 ppm for 13 weeks. Significant increases in micronucleated normochromatic erythrocytes were observed in peripheral blood samples at the two highest doses in male mice and three highest doses in female mice. Results of a bone marrow micronucleus test in male mice, where BBMP was administered by gavage, were considered to be equivocal due to inconsistent results obtained in two trials.[15]

An additional bone marrow micronucleus test was performed with male and female mice. BBMP was administered as a single intraperitoneal injection of 150, 300, or 600 mg/kg. Results of this test were positive in females and negative in males.[15]

The weight of evidence suggests that BBMP is not genotoxic.

G. Metabolism and Pharmacokinetics

BBMP was not detected in tissues of rats orally administered 5 or 100 mg/kg/day BBMP in a lifetime oncogenicity study. Rats ingesting the high dose level of 100 mg/kg/day of BBMP had statistically increased level of bromide in liver, kidney, fat and serum. However, these increased bromide levels, less than 10-fold increase over controls, were achieved relatively early and appeared to plateau during the remainder of the study, with the possible exception of the kidney in both sexes and fat in females, in which there was a slight upward trend which appeared to continue to some degree through the duration of the study. The concentration of bromide in the liver and fat never exceeded that in the serum any time during the study at either dose level or in either sex. The concentration in the kidney exceeded that of serum only in the rats killed at one and two years. The highest kidney to serum ratio, 2.3, was seen only in the 100 mg/kg/day males at the termination of the study. In the group of rats ingesting 5 mg/kg/day of BBMP, there was only marginal increase in bromide content of some of the tissues measured, with most values in the same range as controls. Overall, these data are interpreted to indicate that the compound BBMP does not have significant potential to bioaccumulate in mammalian tissues.[17]

Male F344 rats received single doses of BBMP at 150, 300, or 600 mg/kg by gavage or 15 mg/kg by intravenous (i.v.) injection into the caudal vein. Doses were prepared by diluting [^{14}C]-BBMP (uniformly labeled) with unlabeled BBMP in ethanol, emulphor, and water at a ratio of 1:1:3 by volume, to administer 25 to 50 µCi/kg-body weight. BBMP was rapidly, and nearly completely, absorbed from the gastrointestinal tract of the rats. BBMP was rapidly excreted in the urine of the rats as the glucuronide conjugate, with < 10% of the total dose being excreted in feces and none being detected as exhaled volatiles or CO_2. The ^{14}C

in bile consisted of > 99% of the same glucuronide conjugate. The amount of excreted BBMP was determined by analysis for ^{14}C in urine, feces, and tissue. The relative amounts of BBMP and radiolabeled metabolites in rat urine, plasma, and bile were analyzed via high-performance liquid chromatography. The major metabolite derived from BBMP in rat urine was identified as a glucuronide conjugate of BBMP.[5]

The absorption, tissue distribution, metabolism, and excretion of BBMP in $B6C3F_1$ mice have been studied. Mice received BBMP at either 150 mg/kg by gavage or 15 mg/kg by i.v. injection (N = 4/group). Doses were prepared by diluting [^{14}C]-BBMP (uniformly labeled) with unlabeled BBMP in ethanol, emulphor, and water at a ratio of 1:1:3 by volume, to administer 25 to 50 µCi/kg-body weight. BBMP was rapidly, and nearly completely, absorbed from the gastrointestinal tract of the mice and rapidly excreted in the urine as the glucuronide conjugate, with <10% of the total dose being excreted in feces and none being detected as exhaled volatiles or CO_2. The ^{14}C in bile consisted of >99% of the same glucuronide conjugate. The amount of excreted BBMP was determined by analysis for ^{14}C in urine, feces, and tissue. The relative amounts of BBMP and radiolabeled metabolites in mouse urine were analyzed via high- performance liquid chromatography.[5]

BBMP undergoes rapid conjugation and excretion following absorption from the gut in rats and mice. BBMP did not form reactive metabolites or accumulate in the tissues of either species. However, BBMP significantly increased bromide concentrations in the liver, kidney, fat, and serum of exposed rats.[5]

V. HUMAN USE AND EXPERIENCE

The primary routes of human exposure are inhalation and dermal contact. Occupational exposure may occur in industries where it is used as a flame retardant in unsaturated polyester resins, in molded products, and in rigid polyurethane foam. Consumer exposure may occur as a result of releases from products containing BBMP.[5]

There were no case reports or epidemiological studies on the occurrence of human cancer and exposure to BBMP.[5]

VI. RATIONALE

BBMP is an eye irritant and moderately irritating to skin. It does not appear to be absorbed in significant amounts through skin and is not a skin sensitizer. It is not a selective reproductive toxicant as these effects were seen concomitant with general toxicity.

A battery of genotoxicity tests was mostly negative *in vitro* and equivocal *in vivo*. The weight of evidence suggests that BBMP is not genotoxic.

BBMP does not appear to bioaccumulate in tissues.

There is clear evidence of carcinogenicity in male and female F344/N rats and $B6C3F_1$ mice in two-year feeding studies at high dose levels. The NOEL for a two year feeding study using Sprague Dawley rats was 5 mg/kg/day.

A reasonable margin of safety against possible adverse effects in humans may be derived by extrapolation to a "benchmark dose," according to standard methodology adopted by the USEPA.[26] Benchmark doses for the most sensitive sites ranged from 4.8 mg/kg-day for mammary tumors in female rats to 80 mg/kg-day for subcutaneous skin tumors in male rats.

Based on these data, a WEEL™ of 0.2 mg/m^3 would result in a dose of 0.03 mg/kg/day and is expected to provide a reasonable margin of safety against possible adverse effects in humans.

VII. RECOMMENDED OEL

0.2 mg/m^3 (0.02 ppm) as an 8-hour TWA

VIII. REFERENCES

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