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Technical Information

Summaries of Toxicity Studies on Dazomet

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DESCRIPTION OF THE TEST COMPOUND

Dazomet is a chemical synthesized by Dr. Delepine for the first time in 1890s. Through a number of trials on its biological activity, it has been confirmed that Dazomet is an effective soil sterilant having a wide range of activity; soil borne diseases, nematodes, soil insects and weeds before germination. Dazomet has been registered for the first time in Belgium in 1968 as a soil sterilant in case of the one from BASF Aktiengesellschaft, and is being marketed in a number of countries these days.

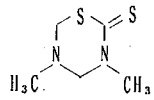
This article provides a toxicological feature of Dazomet obtained from numerous toxicological studies with Dazomet technical grade (hereafter as DAZOMET), and some toxicological features obtained with its main metabolite; methylisothiocyanate (hereafter as MITC). Dazomet technical grade and its commercial products; Basamid MG and Gasturd MG, containing over 98% Dazomet in Japan are identical in terms of the composition.

The chemical structure and physical properties of Dazomet are given below:

Common name: Dazomet

Chemical name: Tetrahydro-3,5-dimethyl-2H-1,3,5-thiadiazine-2-thione

Structural formula:



Molecular formula: $C_5H_{10}N_2S_2$

Molecular weight: 162.3

Appearance: White crystals

Melting point: 104–105°C

Vapor pressure: 4.35×10^{-6} mmHg or 5.8×10^{-6} mbar (20°C)

Solubility (g/100 g solvent at 20°C): Water 0.36, chloroform 39.1, dichloromethane 36.5, acetone 17.3, benzene 5.1, methyl alcohol 2.8, ethyl alcohol 1.5, diethyl ether 0.6, cyclohexane 0.04.

Partition coefficient (*n*-octanol/water): Log P_{ow} 1.14 (mean value of measurements at different pH of 5, 7 and 9 obtained with MITC because of quite quick degradation of Dazomet)

Stability: No decomposition at 50°C for 2 years in an unopened original package. Half life of 0.62 hours in 0.1 HCl and immediately hydrolyzed in 0.1 N NaOH. Half life longer than 24 hours during exposure of light at wave length of 238–579 nm (15 cm distance, 15–20°C).

ACUTE TOXICITY

Table 1 shows results of acute toxicity studies with DAZOMET.

The toxicity symptoms with Dazomet were numerous and non specific, showing systemic toxicity; dyspnea, apathy, staggering, poor general state, *etc.*, and no abnormalities were observed in pathological examination. In the inhalation toxicity, numerous toxic symptoms were also observed, such as trembling gait, reddish nasal discharge, piloerection, squatting posture and reddish urine as well as paresis of the hind limbs. However, most of the symptoms were reversible within the observation period of 14 days.

The oral administration of MITC caused slight intraabdominal adhesions of the forestomach as well as thickening of the wall with distinct intraabdominal adhesions in rats, whereas intraperitoneal adhesions with the

Table 1

Test substance	Animal species, strain	Administration route	LD_{50} (mg/kg) Male	Female	Testing facility, reporting year
DAZOMET	Rat, Wistar	Oral	550	710	Showa University, 1977
	Mouse, dd		455	430	Showa University, 1977
	Rat, Wistar	Dermal	2260	2600	Showa University, 1977
	Mouse, dd		2400	2530	Showa University, 1977
	Rat, Wistar	Intraperi-	91	94	Showa University, 1977
	Mouse, dd	toneal	98	113	Showa University, 1977
	Rat, Wistar	Subcutaneous	470	550	Showa University, 1980
	Mouse, ICR		248		Showa University, 1980
	Rat, Wistar	Inhalation[a)]	>8.40	7.29	Department of Toxicology, BASF, 1986
MITC	Rat, Wistar	Oral	*ca.* 147.0		Department of Toxicology, BASF, 1986
	Mouse, NMRI		*ca.* 114		Department of Toxicology, BASF, 1987

[a)] Values are shown in mg/*l*.

gastrointestinal tract, spleen and peritoneum in mice were observed after administration of MITC *via* gavage.

LOCAL IRRITATION AND SENSITIZATION

The instillation of 0.1 ml DAZOMET (about 39 mg/eye) into the conjunctival sac of the right eyelid of rabbits induced a well defined redness and slight swelling of the conjunctivae together with a contraction of the pupils. All symptoms were fully reversible within 72 hr after application.

(Department of Toxicology, BASF, 1985)

The skin irritation of DAZOMET was tested by application of 0.5 g DAZOMET in a 50% aqueous formulation to the intact dorsal skin of rabbits under a semi-occlusive dressing for 4 hr. No signs of irritation or systemic toxicity were observed.

(Department of Toxicology, BASF, 1985)

The sensitizing potential of DAZOMET on the skin of guinea pigs was tested in a maximization test.

The test substance did not induce any skin reaction, showing no skin sensitizing potential of Dazomet.

(Department of Toxicology, BASF, 1985)

SUBACUTE TOXICITY STUDIES

A four-week range-finding study was performed with Wistar rats, administering DAZOMET to 5 animals/sex and dose, at dose levels of 0, 20, 60, 180 and 540 ppm.

At 540 ppm, a marked reduction in body weight gain and food consumption in the females, which were less pronounced in the males, were observed. After 2 weeks of the administration, clinical signs such as hind limb paresis, strutting and waddling gait and non-physiological posture of the forelimbs were observed in the females at the high dose group. A decrease in GOT, GPT and plasma cholinesterase in females as well as a decrease in creatinine values of both sexes were observed. Absolute and relative liver weights increased in males, whereas an increase in relative liver weights was observed in females. At 180 ppm, reduced food consumption and reduction in body weight gain of the females during the first 2 test weeks were observed. Female animals showed a decrease in GPT activity, whereas male animals showed an increase in relative liver weights. No test substance-related effects were seen at 20 and 60 ppm with the exception of a decrease in GPT activities in females at 60 ppm. The NOEL was 60 ppm (=5.7 mg/kg b.w.) for males and

20 ppm (=1.9 mg/kg b.w.) for females.

(Department of Toxicology, BASF, 1989)

In another four-week range-finding study, B6C3F1 mice, 5 animals/sex and dose, were administered DAZOMET *via* the diet at dose levels of 0, 20, 60, 180, 360 and 540 ppm. In the absence of any signs of toxicity at these dose levels, the study was extended to 3-month.

The administration of 540 ppm caused a temporary reduction of food consumption in males. Furthermore, reduced hemoglobin and erythrocyte values in both sexes, and reduced hematocrit values in males were observed. The administration of the test substance caused an increase in mean cell volume, reticulocytes and in polychromasia and reduced MCHC values in both sexes. Further findings were an increased anisocytosis in both sexes, increased macrocytes in males, suggesting substance-induced hemolytic anemia. Increased absolute and relative liver weights and slightly increased hemosiderin deposits in the spleen in both sexes were noted. These findings were also observed at 360 ppm, while at 180 ppm, absolute liver weights in males were increased. No substance-related changes were noted at 60 and 20 ppm. The NOEL was 180 ppm (=54.7 mg/kg b.w.) for females and 60 ppm (=13.2 mg/kg b.w.) for males.

(Department of Toxicology, BASF, 1989)

The commercial product containing over 98% DAZOMET was tested for subacute dermal toxicity in New Zealand White rabbits, 5 animals/sex and dose. A 0.5 and 5% aqueous sodium carboxymethyl cellulose suspension of the test substance was applied to the abraded skin of the animals 7 days a week for 3 consecutive weeks, during which the animals were exposed to a constant volume of 2 ml/kg. The occlusive dressing was removed from the treated area after 6 hr of exposure and the skin was washed. This procedure was repeated during the test period.

There were neither signs of systemic toxicity nor changes in clinicochemical and hematological parameters. The body weight and food consumption were comparable to the untreated animals. The only findings were restricted to the abraded skin showing various degrees of epidermal and dermal necrosis, minimal epidermal hyperplasia and inflammatory reaction. As for the application, the skin was destructed by incisions. It is possible that this procedure also contributed to the damage.

(Huntingdon Research Centre, 1976)

Subacute inhalation was also tested with the commercial product containing over 98% DAZOMET to evaluate the possible risk of dust generated from the product. Wistar rats, 10 animals/sex and dose, were exposed (whole body exposure) for 3 weeks (6 hr/day and 5 days/week) to dust particles generated by mechanical agitation of the test substance. Five animals/sex and group were sacrificed after the exposure period, and the remaining ones after a 14-day observation period. The same procedures were used for the animals exposed to test substance free air.

The concentration of the test substance in the air was approximately 33 $\mu g/m^3$ and all particle sizes were below 5 μm which is respirable. There were neither signs of clinical intoxication, nor changes in body weight, food consumption, clinicochemical or hematological parameters. No differences in organ weights or gross-pathological changes were observed.

(Huntingdon Research Centre, 1976)

SUBCHRONIC TOXICITY STUDIES

In a three-month study with Wistar rats, 10 animals/sex and dose, DAZOMET was administered *via* the diet at dose levels of 0, 20, 60, 180 and 360 ppm.

At 360 ppm, reduced food efficiency, a decrease in the hemoglobin concentration and the total protein concentration, an increased liver weight and a fatty degeneration of liver cells were observed in both sexes. Females showed a decrease of creatinine, potassium and albumin levels, whereas the triglyceride levels decreased in male animals. The body weight of the males was about 7%, and of the females about 10–13% lower than the untreated control. At 180 ppm, clinicochemical examination revealed a decrease of total protein concentration in male animals. Increased liver weights and a fatty degeneration of liver cells were observed in both sexes. At 60 ppm, the liver weights of the males were increased, and the liver cells were fatty degenerated. The NOEL in this study was 20 ppm (=1.5 mg/kg

b.w.) for males and 60 ppm (=5.4 mg/kg b.w.) for females.

(Department of Toxicology, BASF, 1987)

Beagle dogs, 4 animals/sex and dose, were administered DAZOMET *via* the diet at dose levels of 0, 25, 100 and 400/200 ppm for a period of three months.

As DAZOMET showed clear toxic effects at 400 ppm, the dose was reduced to 200 ppm after 21 days of test substance administration. At the highest dose level, a marked reduction of body weight, food consumption, and food efficiency were observed. Hemoglobin, erythrocyte, hematocrit values and GPT activity were decreased in both sexes. Females showed increased platelet values, and a decrease in total protein, albumin and cholesterol concentrations. At 100 ppm, an increase in relative liver weights without a morphological correlation was noticed in males. One female showed a reduced food consumption. Therefore, the NOEL was 25 ppm (=0.9 mg/kg b.w.) for males and females.

(Department of Toxicology, BASF, 1987)

CHRONIC TOXICITY AND ONCOGENICITY

In a chronic toxicity study, 20 Wistar rats/sex and dose received 0, 5, 20, 80 and 320 ppm DAZOMET *via* the diet over a period of 104 weeks.

At the highest dose, the body weights and the body weight gain were reduced in both sexes. Clinical chemistry revealed a decrease in total protein, albumin, globulines, triglycerides and serum-cholinesterase in females. Erythrocytes, hemoglobin and hematocrit were also decreased in females. Total bilirubin was increased in females, whereas an increase in platelets was noted in both sexes. The relative liver weight was increased in males. In females, a slightly increased incidence and severity of hepatocellular fat deposition which was associated with hepatocellular vacuolation in 5 rats was noted. At 80 ppm, toxicity was only observed in females (decreased total protein, albumin, globulines, triglyceride, serum cholinesterase and erythrocytes, and increased numbers of platelets). At 20 and 5 ppm, no substance-related effects were observed. The NOEL was established at 80 ppm (=3.8 mg/kg b.w.) for males and 20 ppm (=1.3 mg/kg b.w.) for females.

(Department of Toxicology, BASF, 1989)

In a twelve-month feeding study in Beagle dogs, 6 animals/sex and dose were administered 0, 15, 50 and 150 ppm DAZOMET *via* the diet.

At the highest dose (150 ppm), clinical findings such as marginally impaired food consumption and body weight gain as well as emaciation in one female dog were observed, and one male animal revealed reduced body weight gain. These findings and some changes in clinicochemical parameters (increased alanine and aspartate aminotransferase and alkaline phosphatase) were found in some females, but not in all animals at 150 ppm level. In females, a decreased albumin concentration was measured. Males showed increased relative liver weights. Gross-pathological and histopathological examinations revealed signs of hepatotoxicity which were mainly indicated by a chronic hepatitis in 2 females, a cirrhosis of one male and an increased deposition of iron-positive pigments in the liver of both sexes. At 50 ppm, an increased deposition of iron-positive pigment in the liver of the females was observed. The NOEL in dogs was 50 ppm (=1.5 mg/kg b.w.) for males and 15 ppm (=0.5 mg/kg b.w.) for females.

(Department of Toxicology, BASF, 1989)

In a carcinogenicity study, 50 Wistar rats/sex and dose were administered DAZOMET *via* the diet at dose levels of 0, 5, 20 and 80 ppm over a period of 104 weeks.

No substance-related clinical and hematological alterations were observed. At 80 ppm, male rats showed a slightly increased incidence and severity of diffuse hepatocellular fat deposition and hepatocellular vacuolization, whereas in females, a slightly increased incidence of mixed cell and basophilic cell foci was diagnosed. No treatment-related oncogenic effects were observed. The NOEL in this study was 20 ppm for both sexes (0.9 mg/kg b.w. in males and 1.3 mg/kg b.w. in females).

(Department of Toxicology, BASF, 1989)

Another carcinogenicity study was performed with B6C3F1 mice for a period of 78 weeks. DAZOMET was administered to 60 animals/sex and dose at dose levels of 0, 20, 80

and 320 ppm.

No substance-related findings concerning clinical or hematological parameters were observed. At 320 ppm, absolute and relative liver weights of both sexes were increased. An increased number of animals showed focal discoloration and masses of the liver in both sexes. An increased centrilobular lipid deposition in the liver and hemosiderin deposition and extramedullary hemopoiesis in the spleen in both sexes were observed. The incidence of animals with basophilic foci was increased in females. Furthermore, an increased lipofuscin deposition in the transitional epithelium of the urinary bladder in females was noted at this dose level and at 80 ppm. At 80 ppm, the number of male mice showing focal discoloration or bearing masses was greater than in the controls. An increased centrilobular lipid deposition in the liver, and hemosiderin deposition in the spleen was also observed in males, and in females increased lipofuscin in the transitional epithelium of the urinary bladder was noted. The NOEL was 20 ppm for both males and females (=4 mg/kg b.w. in males and 6 mg/kg b.w. in females). Dazomet has no carcinogenic potential up to the highest dose tested in this study.

(Department of Toxicology, BASF, 1989)

TERATOGENICITY AND REPRODUCTION STUDY

DAZOMET was tested for the effect on reproduction activity in Wistar rats. The test substance was administered *via* the diet to groups of 24 males and 24 immature females (F_0 parental generation) at dose levels of 0, 5, 30 and 180 ppm. At least 70 days after the beginning of treatment, F_0 animals were mated to produce a first litter (F_{1a}) and subsequently remated to produce a second (F_{1b} retained only until weaning) litter. Groups of 24 males and 24 females selected from F_{1a} pups as F_1 parental generation were offered the food containing 0, 5, 30 and 180 ppm of the test substance post weaning, and the breeding program was repeated to produce F_2 litter. The study was terminated with F_2 weanings. The food containing DAZOMET was continuously administered throughout the study.

The highest dose was clearly toxic in terms of decreased body weight and/or body weight gain for F_1 generation males and F_0 and F_1 generation females. At the same dose levels, effects on clinicochemical parameters as described in subchronic/chronic studies were observed. At 30 ppm, male animals of the F_1 generation showed slightly reduced body weight and body weight gain. At 5 ppm, no test substance-related findings were noted. The test substance administration was tolerated by all litters without any substance-induced adverse effects and by the parental animals of all generations without any impairment of mating or reproduction performance and without any adverse effects on reproductive organs. The NOEL for reproductive function is 180 ppm, and the NOEL for systemic toxicity is 5 ppm for the F_0 and F_1 generations. The NOEL for the off-spring is 180 ppm. No teratogenic effects were observed in this study.

(Department of Toxicology, BASF, 1989)

DAZOMET was tested for its prenatal toxicity in Wistar rats. The test substance was administered to 25 females/group by stomach tube in doses of 0, 3, 10 and 30 mg/kg b. w. on day 6 through day 15 post coitum. On day 20 post coitum, all females were sacrificed. The fetuses were removed by cesarean section and investigated.

The highest dose level revealed reduced food consumption and body weight gain of the dams during and post administration periods. A slight reduction of uterus weight and fetal weight was observed. The number of fetuses weighing less than 75% of the mean fetal weight per litter group was increased, which was also observed in the intermediate dose groups. All other parameters regarding fetotoxic or embryotoxic effects were comparable with the control group. Animals of the 10 mg/kg dose level showed a trend to reduced food consumption at the beginning of the administration and slight decrease in corrected body weight gain (body weight at sacrifice minus uterus weight). The uterus weights were also slightly decreased. No test substance-related findings were observed at the 3 mg/kg dose level. The NOEL in this prenatal toxicity study is 3 mg/kg for maternal and embryo-/fetotoxicity. No teratogenic effects were observed even at the highest dose level.

(Department of Toxicology, BASF, 1987)

DAZOMET was further tested for its prenatal toxicity in rabbits. Himalayan rabbits were administered the test substance by gavage in doses of 25.0, 50.0 and 75.0 mg/kg b. w. from day 6 to day 18 post insemination. On day 30 post insemination, the animals were sacrificed. The fetuses were delivered by cesarean section and investigated.

The administration of 75.0 mg/kg b. w. led to the death of 2 animals and this dose caused reduced food consumption and body weight gain, which must be related to the high embryolethality. Similar findings were obtained at 50.0 mg/kg b.w. but to a lesser extent. The administration of 25.0 mg/kg b. w. was tolerated by the animals without any symptoms and any adverse effect on body weight gain and food consumption. However, a slight increase embryolethality was observed which may be related to the test substance administration. No teratogenic effect was observed, and the NOEL for dams is expected to be between 50.0 and 75.0 mg/kg b. w., and it is expected to lie below 25.0 mg/kg b. w. for fetuses.

(Department of Toxicology, BASF, 1980)

In addition to the above mentioned study, DAZOMET was tested for its prenatal toxicity in rabbits at lower doses. The test substance was administered by gavage at dose levels of 6.25, 12.50 and 25.00 mg/kg b. w. from day 6 to day 18 post insemination. On day 29 post insemination, the animals were sacrificed. The fetuses were delivered by cesarean section and assessed.

No impairment of body weight gain, food consumption or other signs of maternal toxicity was observed. The postimplantation loss was increased at 25.00 mg/kg b. w. At 12.50 mg/kg b. w., the post implantation loss was slightly but not significantly increased and was regarded as incidental. No other test substance-related embryo-/fetotoxic effects were observed. There was no indication that the test substance is a teratogen in rabbits under the test conditions described. The NOEL for maternal toxicity is 25 mg/kg b. w., and 12.5 mg/kg for embryo-/fetotoxicity.

(Department of Toxicology, BASF, 1980)

MUTAGENICITY STUDIES

A rec-assay was performed with *Bacillus subtilis*, strains H 17 (Rec^+) and M 45 (Rec^-). DAZOMET, dissolved in DMSO, was tested at doses of 10 to 200 μg/disk.

At all dose levels, no DNA-damaging activity was observed.

(The Institute of Environmental Toxicology, 1977)

A further rec-assay was performed using doses from 1 to 10,000 μg/plate without and with metabolic activation derived from SD rats.

No difference was observed in the inhibition zone of rec^+ and rec^- strains, thus indicating that Dazomet has no DNA-damaging activity.

(Hazleton Biotechnologies, 1989)

Genetic damage resulting from gene mutation was investigated in the Ames test using *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538, and *Escherichia coli* strain WP2 hcr^- with and without metabolic activation (liver homogenate from SD rats). The dose range was between 1 and 200 μg/plate.

Cytotoxicity was observed at 100 μg/plate and higher. Under the test conditions chosen, Dazomet did not induce point mutation.

(The Institute of Environmental Toxicology, 1977)

Genetic damage through chromosomal aberration was investigated *in vitro* with human lymphocytes. DAZOMET was tested in a dose range of 2.5, 12 and 25 μg/ml with metabolic activation (S-9 mix from SD rats) and 0.002, 0.01 and 0.05 μg/ml without metabolic activation.

DAZOMET did not induce an increase in the number of aberrant metaphases either without S-9 mix or with metabolizing system. Thus, the compound has no chromosome-damaging abilities *in vitro* in human lymphocytes.

(Department of Toxicology, BASF, 1989)

In vivo chromosome aberration was investigated in somatic cells (micronucleus test) with NMRI mice. Five animals/sex and dose were administered DAZOMET at dose levels of 45, 90 and 180 mg/kg b. w. by gavage. After the animals' sacrifice, the bone marrow of the femur was prepared. One thousand polychro-

matic erythrocytes were evaluated and investigated for micronuclei. Also the normocytes with and without micronuclei occurring per 1000 polychromatic erythrocytes were recorded.

In general, the state of the test animals was poor. Some of the clinical signs which were observed at the highest dose level were still observed two days after the administration. No gross-pathological changes were observed. No increase in the number of polychromatic erythrocytes containing micronuclei were observed compared to the control. No inhibition of erythropoiesis was detected from the ratio of polychromatic to normochromatic erythrocytes. Thus, Dazomet has no chromosome-damaging (clastogenic) effect. There was no indication of any impairment of chromosome distriubtion in the course of mitosis.

(Department of Toxicology, BASF, 1985)

In the host-mediated assay, ICR mice, 6 males/dose, received 100 and 200 mg/kg b. w. DAZOMET in two equal doses over a period of 24 hr by gastric intubation. After the 2nd administration, a 2 ml suspension of *Salmonella typhimurium* G 46 (his^-) was given intraperitoneally. The animals were sacrificed 3 hr after treatment. The peritoneal fluid was transferred to an agar plate for the detection of revertant bacterial cells.

No mutagenic activity was observed.

(The Institute of Environmental Toxicology, 1977)

MITC was tested in the Ames test using *Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 with and without metabolic activation (liver homogenate from SD rats). The test substance was dissolved in DMSO. The dose range was between 20 and 5000 μg/plate for the first test and 30 to 500 μg/plate for the second test.

A bacteriotoxic effect was observed depending on the strain and experimental doses at 500 μg/plate. No increase in the numbers of his^+ revertants was observed either with and without metabolic activation. Thus, no mutagenic activity was observed under the test conditions chosen.

(Department of Toxicology, BASF, 1986)

MITC was tested for its ability to induce chromosome aberration in human lymphocytes. Concentrations of 0.05, 0.1 and 0.5 μg/ml without metabolic activation, and 0.1, 0.5 and 1.0 μg/ml with metabolic activation (liver homogenate from SD rats) were selected for metaphase scoring.

MITC was assessed not to be a clastogenic agent as no biologically significant increase in the number of aberrant metaphases was observed.

(Department of Toxicology, BASF, 1987)

A rec-assay was performed with MITC using *Bacillus subtilis* strains H 17 (Rec^+) and M 45 (Rec^-). MITC, dissolved in DMSO, was tested in concentrations of 1.0 to 10,008 μg/plate with and without metabolic activation (rat liver homogenate).

No indication of DNA damage and repair either with or without metabolic activation was observed.

(Hazleton Laboratories America, 1989)

GENERAL PHARMACOLOGY

1. Effect on Central Nervous System

1.1 General observation on native behavior

NMRI mice, 3 males/dose, were administered DAZOMET at dose levels of 0, 100 and 200 mg/kg b. w. by oral gavage.

The test substance caused passivity, sedation, lacrimation and eye closure. The symptoms appeared 10–25 min after the administration, and continued for 5–40 min at the low dose, and for 5–110 min at the high dose.

1.2 Prolongation of sleeping time induced by hexobarbitone

NMRI mice, 6 males/dose, were administered DAZOMET at dose levels of 0, 100 and 200 mg/kg b. w. by oral gavage. After 45 min, 70 mg/kg b. w. hexobarbitone were intraperitoneally injected. The duration of sleeping time was measured by the disappearance and reappearance of the lighting reflex.

DAZOMET prolonged the sleeping time to 206% at 100 mg/kg b. w. and to 101% at 200 mg/kg b. w.

1.3 Effects on convulsion induced by pentetrazole or strychnine

NMRI mice, 6 males/dose, were administered DAZOMET at dose levels of 0, 100 and 200 mg/kg b. w. by oral gavage. After 45 min, 150 mg/kg b. w. pentetrazole or 2 mg/kg b. w. strychnine were intraperitoneally injected. The

time until the convulsions appeared was measured and the mortality was recorded.

DAZOMET had a slight anticonvulsive effect on pentetrazole-induced convulsion. The administration of 100 mg/kg b. w. increased the time of convulsion onset 27.5%, whereas 200 mg/kg b. w. increased convulsion onset 17.6% when compared to the control. No effect was observed on convulsion onset and mortality induced by strychnine.

1.4 Effects on body temperature

DAZOMET was administered orally to Wistar rats, 6 males/dose, at dose levels of 0, 100 and 200 mg/kg b. w. and to New Zealand White rabbits, 5 males/dose, at a dose level of 100 mg/kg b. w. The rectal temperature was recorded every hour.

In rats 2 hr after the administration, the test substance lowered the body temperature by about 1.5°C when compared to the normal body temperature. After 5 hr, the body temperature was in the physiological range. DAZOMET had no effect on body temperature in rabbits.

1.5 Effects on locomotor activity

NMRI mice, 4 males/dose, were administered DAZOMET at dose levels of 0, 100 and 200 mg/kg b. w. by oral gavage, and locomotor activity was recorded at a certain time interval; 30–45 min and 90–105 min after the administration. The administration of DAZOMET had a strong inhibitory effect on the locomotor activity. The strongest inhibition was after 30–45 min. The acitvity increased with time over the testing period, however, it did not reach control values.

1.6 Effects on electroencephalogram (EEG)

Wistar rats, 6 males/dose, were administered DAZOMET at 200 mg/kg b. w. by oral gavage. The EEG was recorded at a certain time interval.

DAZOMET induced seizure discharges (bursts of spikes, spike and wave complexes) in the cortical EEG, that occurred rapidly after the administration and was of short duration. This was followed by long-lasting depression of the electrical activity of the brain, and a normalization was seen 1.5–3 hr after the administration. Some animals showed brief clonic convulsion behavior, and all animals showed prolonged and marked reduction of motor activity but they did not sleep during that period.

2. Effects on Autonomic Nervous System and Smooth Muscle

2.1 Effects on isolated ileum

Specimens of the ileum of one guinea pig were prepared and suspended in organ bath solution. DAZOMET was injected to the bath in concentrations of 10^{-3}, 10^{-4} and 10^{-5} g/ml as well as histamine (10^{-7} g/ml) and acetylcholine (10^{-7} g/ml).

The test substance had no effect on the acetylcholine-induced contraction of the ileum at 10^{-4} and 10^{-5} g/ml, but inhibited to 10.7% at 10^{-3} g/ml. Concentration of 10^{-3} g/ml of DAZOMET reduced the histamine-induced contractile response to 28.2% of the control value, whereas 10^{-4} and 10^{-5} g/ml had no effect on the contraction of the ileum.

2.2 Effects on isolated vas deferens

Vas deferentia were prepared from 4 male guinea pigs and then suspended in organ bath.

DAZOMET at concentrations of 10^{-3}, 10^{-4} and 10^{-5} g/ml had no effect on acetylcholine- or epinephrine-induced contraction of the vas deferens.

2.3 Effects on isolated trachea

Trachea segments were prepared from 6 male guinea pigs and suspended in organ bath.

There was a strong DAZOMET-related relaxation of the trachea noted. At 10^{-4} g/ml, a relaxing effect of 13.9%, and at 10^{-3} g/ml a relaxing effect of 64.9% was recorded. The epinephrine-induced relaxation decreased accordingly as the DAZOMET-related relaxation increased so that the total effect was in the same range as the control. The acetylcholine-induced contraction was increased up to 139.0 %, 178.7% and 146.0%. The histamine-induced contraction was increased at 10^{-5} g/ml up to 117.2% at 10^{-4} g/ml to 121.5% and at 10^{-3} g/ml to 60.2% when compared to the control.

3. Effects on Blood Pressure, Heart Rate and Respiration

Three male New Zealand White rabbits were used for the test. DAZOMET was intraperitoneally injected at a dose level of 50 mg/kg b. w.

DAZOMET had no effects on blood pressure, heart rate and respiratory rate. The standardized blood pressure responses to acetylcholine and histamine were not influenced, whereas the one to norepinephrine was reduced to 58%

(30–45 min after the administration).

4. Effects on Digestive System

4.1 Effects on intestinal motility-charcoal propulsion

NMRI mice, 10 males/dose, were subcutaneously injected 100 mg/kg b. w. DAZOMET. After the injection, a charcoal powder suspension in arabic gum solution was administered orally. After the animals were sacrificed, the gastrointestinal tract was investigated.

The test substance inhibited the intestinal mobility in 5 out of 10 mice, and the charcoal propulsion was inhibited.

4.2 Effects on gastric secretion

Wistar rats, 5 males/dose, were administered DAZOMET at dose levels of 100 and 200 mg/kg b. w. by oral gavage. Six hours later, the cardiac orifice was clamped and the stomach was removed. Gastric juice was collected to measure the volume and pH.

The test substance inhibited the gastric secretion 55% and 47% at the low and the high dose respectively, and the pH values were 2.00 at 100 mg/kg b. w. and 2.26 at 200 mg/kg b. w. which was due to reduced acidity.

5. Effects on Skeletal Muscle

Wistar rats, 4 males/dose, were intraperitoneally administered 50 mg/kg b. w. of DAZOMET. The ischiatic nerve was electrically stimulated and the contractile responses were recorded as well as blood pressure.

A time-related increase in the contractile response was measured.

6. Effects on Blood

6.1 Effects on blood coagulation

Wistar rats, 7 males/dose, were administered DAZOMET at dose levels of 0, 100 and 200 mg/kg b. w. by oral gavage. After 3 hr, blood was drawn from the retro-orbital plexus and coagulation tests such as PT, PTT and TT were performed.

The test substance had no effects on blood coagulation parameters.

6.2 Effect on hemolysis

Two male New Zealand White rabbits were used for the test. The effect was tested by adding an erythrocyte suspension to 0.1, 1 and 10% DAZOMET solutions.

A 0.1% DAZOMET solution had a slight to moderate hemolyzing effect, whereas a 1% had a moderate to severe hemolyzing effect and 10% DAZOMET solution caused a severe to complete hemolyzing effect on a 10% *in vitro* erythrocyte suspension.

(Research & Consulting Company AG, and Knoll AG, 1986)

The results obtained in pharmacological studies revealed that Dazomet has effects on the central nervous system, slight effects on the autonomic nervous system, the digestive system, the skeletal muscle, and on hemolysis. No effects were observed on blood pressure, heart rate and respiratory rate as well as the circulatory system and the respiratory tract were not affected.

SUMMARY

In order to investigate toxicological properties of Dazomet, a number of toxicological studies were carried out with DAZOMET. In addition, the toxicological features of MITC, a major metabolite of Dazomet, were also tested. The studies show that the acute toxicity, subacute toxicity, and long-term toxicity are rather low. DAZOMET is neither irritating nor sensitizing to the skin. Inhalation risk can be excluded under practical conditions. No influence on reproduction parameters was observed, and no signs of teratogenic effects were noted. DAZOMET is neither mutagenic nor carcinogenic.

Withholding values have been set for the registration; 0.2 ppm for vegetables and for potatoes, and 0.1 ppm for fruits and for sugar crops. Dazomet products named BASAMID MG and GASTURD MG were registered to JMAFF on November 7, 1991 as a soil sterilant for a number of edible crops as well as for ornamentals and tobacco.

A safety risk for Dazomet is not to be expected as far as it is used in accordance with the established safe use standard.

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問合せ

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