FOREWORD INTRODUCTION

Disodium disulphite

CAS N°: 7681-57-4

SIDS Initial Assessment Report for 13th SIAM

(Bern, 6-9 November 2001)

Chemical Name: Disodium disulphite

CAS No: 7681-57-4

Sponsor Country: Republic of Korea/ ICCA(BASF)

National SIDS Contact Point in Sponsor Country:

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History:

This HPV chemical was assigned to Korea in 1999. In 2000, ICCA (BASF) proposed to be co-sponsor and prepared the draft documents (Dossier, SIAR, SIAP). It was submitted to the SIDS Contact Point of Korea on Nov. 2000. The draft documents were revised by Korea after discussion with BASF. Robust Study Summaries were prepared according to the new RSS templates by Korea. The revised draft was sent to BASF for a detailed discussion on Aug 2001. In the meantime, Korea performed an acute toxicity test with fish. After agreement, the documents were finalized and the checklist was developed by Korea.

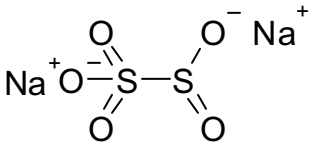
Testing: No testing ( )
Testing (x) Acute toxicity to Fish

Comments :

Deadline for circulation:
Date of Circulation:

Revised : September 2001

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7681-57-4
Chemical Name	Disodium disulphite
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Disodium disulphite is rapidly eliminated as sulphate in humans and dogs. When sulphite is present in the tissues in sufficiently high concentrations, it may be metabolized to inorganic thiosulphate that is then excreted in the urine. The acute toxicity of oral LD_{50} in rats is 1,540 mg/kg bw. In decedents, toxicity was observed to the stomach and liver, and the gastro-intestinal tract was filled with blood. For repeated dose toxicity, disodium disulphite was given to rats through diet for 30 to 104 weeks. The predominant effect was the induction of stomach lesions due to local irritation and was characterized as forestomach and glandular stomach hyperplasias and inflammation. There were no signs of local toxicity (stomach irritation) at ca. 217 mg/kg bw/day, and the lowest dose where this effect occurred was ca. 454 mg/kg bw/day as actual intake dose [NOAEL for local (stomach irritation), rats, oral feed : ca. 217 mg/kg bw/day]. From the same dietary study in rats, the NOAEL for systemic effects was the highest dose tested (942 mg/kg bw/day).

The results of genotoxic tests *in vitro* are equivocal but there is no evidence that disodium disulphite is genotoxic *in vivo*. It was not carcinogenic in rats that received disodium disulphite via feed for 104 weeks. No reproduction toxicity of disodium disulphite was observed for a period of up to 2 years and over three generations (NOAEL, fertility, oral feed: ca. 942 mg/kg bw/day). No developmental toxicity and teratogenic effects appeared in rats or rabbits at the highest dose tested (NOAEL 110 and 123 mg/kg bw/day, respectively).

This chemical is not irritating to the skin, but irritating to the eyes. In humans, urticaria and asthma with itching, edema, rhinitis, and nasal congestion were reported. An immunological pathogenesis of these reactions is still not clear. In a non-guideline study, no indication of skin sensitization for guinea pig was observed. In a few cases allergic contact dermatitis as well as positive patch-testing was observed. With respect to wide spread use, it is not considered as a skin sensitizer. Disodium disulphite is unlikely to induce respiratory sensitization but may enhance symptoms of asthma in sensitive individuals. Given the wide-spread use, the number of cases is considered to be low.

Environment

Boiling point, melting point and vapour pressure are not relevant for disodium disulphite. Also, testing for the endpoint of biodegradability, is not appropriate due the chemical not being an organic chemical. Bioaccumulation is not expected. For the boiling point, decomposition occurred at 150 ^{o}C to form sulfur dioxide. This chemical will be mainly transported to the water compartment when released to environmental compartments since it is highly water soluble (470 g/L at 20?). The low K_{OC} (2.447) indicates that disodium disulphite is so mobile in soil that it may not stay in the terrestrial compartment. Instead it has a potential to leach into the groundwater.

The chemical has been tested in a limited number of aquatic species. In an acute toxicity test with fish, the 96 hr-LC_{50} was >100 mg/L. For algae, the 72 hr-EC_{50} was 48.1 mg/L. For daphnids, the acute 48 hr-EC_{50} was 88.76 mg/L,

and the chronic 21day-NOEC was >10 mg/L. Therefore, a PNEC of 0.1 mg/L for aquatic organisms was obtained from the chronic NOEC for daphnids using an assessment factor of 100.

Exposure

In 1999, estimates for the world market of sodium salts of sulphites, without China and the Russian Federation, amounted to approx. 330,000 tonnes/ year. These are distributed as follows : 20,000 tonnes in Germany, 60,000 tonnes in the rest of Europe and 250,000 tonnes in the rest of the world. Disodium disulphite is a basic chemical and used in chemical synthesis. Exposure to consumer may occur, but the extent of this exposure is unknown. There is a potential for exposure to the respiratory tract, skin and eyes during manufacture or formulation of the chemical into products.

In Korea, the total production of disodium disulphite was about 3,200 tonnes/year in 1998. The chemical is used in tanning agents, food additives, bleaching agents, photography and reducing agents but the amount for each use pattern is not available. There is no exposure data for the environment and humans at the present time.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

FULL SIDS SUMMARY

CAS NO : 7681-57-4		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point		NA	150 °C (decomposes to form sulfur dioxide)
2.2	Boiling Point		-	Decomposed
2.3	Density		NA	1480 kg/m^3
2.4	Vapour Pressure		-	Not relevant
2.5	Partition Coefficient (Log P_{OW})		NA	-3.7 at 25 °C
2.6 A	Water Solubility		NA	470 g/L at 20 °C
B	pH		NA	pH 3.5~5.0 (50 g/L) at 20 °C
	pKa		-	No data
2.12	Oxidation: Reduction Potential		-	-
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation		-	Not relevant
3.1.2	Stability in Water		-	Not relevant (Dissociates in water to sodium cations, disulfite anions and sulfur dioxide)
3.2	Monitoring Data		-	No data
3.3	Transport and Distribution		-	Not relevant
3.5	Biodegradation		-	Not relevant (inorganic compounds)
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	*Oryzias latipes*	OECD TG 203	LC_{50} (96 hr) >100 mg/L
		Salmo gairdneri	Other (DIN38412)	LC_{50} (96 hr) >147 mg/L and < 215 mg/L
4.2	Acute Toxicity to Aquatic Invertebrates	*Daphnia magna*	Other (79 / 831 / EWG)	EC_{50} (48 hr) = 88.76 mg/L
4.3	Toxicity to Aquatic Plants e.g. Algae	*Scenedesmus subspicatus*	OECD TG 201	EC_{50} (72 hr) =48.1mg/L
4.5.2	Chronic Toxicity to Aquatic Invertebrates	*Daphnia magna*	OECD TG 211	LC_0 (21 d) > 10 mg/L NOEC (21 d) > 10 mg/L
4.6.1	Toxicity to Soil Dwelling Organisms			No data
4.6.2	Toxicity to Terrestrial plants			No relevant data available
(4.6.3)	Toxicity to Other Non- Mammalian Terrestrial Species (Including Birds)			No data
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	OECD TG 401	LD_{50} = 1540 mg/kg
5.1.2	Acute Inhalation Toxicity			No data
5.1.3	Acute Dermal Toxicity			No data
5.2.1	Skin irritation	Rabbit	OECD TG 404	Not irritating
5.2.2	Eye irritation	Rabbit	OECD TG 405	Irritating
5.3	Skin sensitization	Guinea pig	Other (Standardized skin sensitization test)	Not sensitizing

CAS NO : 7681-57-4		SPECIES	PROTOCOL	RESULTS
5.4	Repeated Dose Toxicity	Rat	Other (multigeneration study)	NOAEL= 217 mg $Na_2S_2O_5$/kg bw/day (0.5 % in the diet) for local toxicity NOAEL = 942 mg $Na_2S_2O_5$ /kg bw/day (2 % in the diet) for systemic toxicity
5.5	Genetic Toxicity In Vitro			
A	Bacterial Test (Gene mutation)	*S. typhimurium* *E. coli* *S. typhimurium*	OECD 471 Other Other(Ames assay)	Negative (With&without metabolic activation) Negative(With & without metabolic activation) positive(Without metabolic activation)
B	Non-Bacterial In Vitro Test (Chromosomal aberrations)	CHL	Other (cytogenetic)	negative(Without metabolic activation)
5.6	Genetic Toxicity In Vivo	Rat	Other(cytogenetic)	negative
5.7	Carcinogenicity	Rat	Other	No tumorigenesis
5.8	Toxicity to Reproduction	Rat	Other (multigeneration study)	NOAEL = 942 mg of $Na_2S_2O_5$/kg bw/day (2 % in the diet)
5.9	Developmental Toxicity/ Teratogenicity	Rat Rabbit	Other Other	NOAEL = 110 $Na_2S_2O_5$ mg/kg bw/day NOAEL = 123 $Na_2S_2O_5$ mg/kg bw/day
5.11	Experience with Human Exposure	human	Patch test (dermatitis) Patch-tests (ocular hypersensitivity) Inhalation, ingestion	Positive negative Asthma, anaphylaxis

SIDS INITIAL ASSESSMENT REPORT

1. IDENTITY

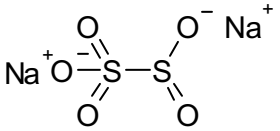
- **OECD Name :** Disodium disulphite

- **Synonym :** Dinatriumdisulfit
  Disodium disulphite
  Disodium metabisulfite
  Disodium pyrosulfite
  Disulfurous acid, disodium salt (9CI)
  Natriumdisulfit
  Pyrosulfurous acid, disodium salt (8CI)
  Sodium disulfite
  Sodium metabisulfite
  Sodium pyrosulfite

- **CAS Number :** 7681-57-4

- **Molecular Formula :** $Na_2S_2O_5$

- **Structural Formula :**



- **Degree of Purity :** > 98 % w/w

- **Physical-chemical properties**
  - **Melting Point :** 150 ? (decomposition)
  - **Boiling Point :** -
  - **Vapour Pressure :** -
  - **Water Solubility :** 470 g/L at 20?
  - **Log Pow :** -3.7 at 25?

- **Classification in member countries**
  Not classified as a toxic chemical in the Toxic Chemicals Control Act, Republic of Korea

2. GENERAL INFORMATION ON EXPOSURE

In 1999, the estimates of the world market for sodium salts of sulfites without China and Russian Federation amounted to approx. 330,000 tonnes/year. These are distributed as follows: 20,000 tonnes in Germany, 60,000 tonnes in the rest Europe and 250,000 tonnes in the rest of the world. Disodium disulphite is a basic chemical and used in synthesis. It is also used in tanning agents, food/foodstuff additives, bleaching agents, photography, etc. Total production of disodium disulphite in Korea was about 3,200 tonnes/year in 1998 (MOE , Korea, 1998). There is no exposure data for the environment and humans at the present time.

2.1 Environmental Fate

Testing for the endpoint of biodegradability is not appropriate due the chemical not being an organic chemical. Also, bioaccumulation is not expected. The product may lead chemical consumption of oxygen in biological sewage treatment plants or in natural water. Inhibition of degradation activities in sewage treatment plants is not to be expected from the introduction of low concentrations. The substance can release sulphur dioxide under acid conditions, but this is not likely to occur under normal natural environmental conditions.

Disodium disulphite dissolves in water and forms sodium cations, disulfite anions, and sulfur dioxide. Depending on the pH-value, sulfur dioxide, sodium hydrogen sulfite or sodium sulfite are present in the aqueous solution.

Photodegradation of disodium disulphite in water is not relevant because it is quickly ionized in water.

The evaluation of the fugacity model for disodium disulphite is not relevant because it is an inorganic chemical, very soluble in water (470 g/L)

2.2 Human Exposure

Exposure to consumers may occur but the extent of this exposure is unknown. Several occupational and consumer exposure cases have been reported. An occupational asthma in laundry workers (Le-Stradic-Reygagne, 1991), dermatitis and asthma in a photographic technician (Jacobs et al, 1992), occupational bronchospasm (Vallon et al., 1995), a case of asthma after ingesting a disodium disulphite containing salad (Baker et al, 1981) and a case of intermittent urticaria (Wuethrich et al., 1993) indicate that this chemical could have an impact on sensitive individuals. No data is available regarding human exposure in Korea.

3. HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics & Metabolism

It was stated that a rapid and quantitative elimination of disodium disulphite as sulfate was observed in man and dog (Rost, 1993). When sulphite is present in the tissues in sufficiently high concentrations, it may be metabolized to inorganic thiosulphate excreted in the urine. Sulphite may damage DNA chains, presumably by a reaction involving free radicals. However, mammalian tissues are largely protected against hazards from sulphite by its oxidation to the relatively non-toxic sulphate (Renner, 1983).

3.1.2 Acute Toxicity

Acute toxicity data are reported in literature for rats and other species. Oral LD_{50s} of 1540 and 2480 mg/kg bw in rats have been reported (Hoechst AG, 1987; NTIS, 1972). The acute LD_{50} by oral exposure in rat is 1540 mg/kg bw and deaths were observed at 1250 mg/kg and above. In the dead animals, the following gross observations were seen; the gastro-intestinal tract was filled with blood, reddened mucosa of the stomach and the dark colored liver, but unusual gross abnormalities were not found in surviving rats (Hoechst AG, 1987).

Conclusion :

The acute oral LD_{50} in rats is 1540 mg/kg bw. In decedents, toxicity was observed to the stomach, liver and the gastro-intestinal tract was filled with blood.

3.1.3 Repeated Dose Toxicity

An assessment of repeated dose toxicity was performed using a multigeneration study with Wistar rats (Til *et al.,* 1972). Rats were exposed to disodium disulphite in a supplemented diet with thiamine (ca. 2 mg/kg bw) since sulfites are known to break down thiamine. Twenty animals/dose/sex received a diet containing 0, 0.125, 0.25, 0.5, 1.0 or 2.0 % of disodium disulphite (i.e. actual doses of ca. 48, 106, 217, 454, and 942 mg/kg/day) for 104 weeks (F0- and F1-generations) or for 30 weeks (F2-generation).
The general condition of the animals was good during the first 72 weeks of the F0-generation, as was the case in the next generation. Overall, survival in the sulphite groups was generally higher than in the controls, except in the case of males of the F1-generation given 2 % sulphite. However, no deaths occurred in the females of the same dose group. The body weights of the F0-generation were comparable in all groups irrespective of treatment. There was a marginal reduction in body weight gain in both sexes of F1-and F2-generation rats given 2 % disodium disulphite.
A marginally reduced hemoglobin content, hematocrit and erythrocyte count occurred in F0-generation males at the 2 % dose at week 52, 78 and 100, and the F1-generation males at 2 % showed an increase in leukocyte count at week 102. All rats in the highest dose group showed indications of occult blood in the feces of all generations; this also occurred at other doses, however, only sporadically.
Pathological changes attributable to feeding sulfites were only observed in the stomach. A raised and thickened limiting ridge and small amounts of a reddish brown flocky material in the mucous layer of the glandular stomach were seen grossly in the two highest doses. Lesions were microscopically characterized as forestomach and glandular stomach hyperplasia or inflammation, and were seen mostly in the 1 and 2 % dose groups (seen mainly at 2 years in the F0- and F1-

generation, and at 30 weeks in the F2-generation). At the 0.5 % dose, a few forestomach lesions were seen in the F2-generation rats. Other non-neoplastic lesions observed in treated groups were comparable to controls. In section 3.1.5 information on neoplastic changes are reported. No histologic changes were noted in the gonads. Section 3.1.6 of this SIAR describes the reproductive effects seen in this experiment.

In summary, no signs of systemic toxicity were observed. Therefore, the NOAEL for systemic toxicity was the highest dose tested. The only major finding in this study was local irritation in the stomach. The repeated dose where no stomach irritation occurred in the F0-generation was 0.5 % in the diet. Taking the loss of sulphite into account, the actual dose was 0.44 % $Na_2S_2O_5$ that is equivalent to an intake of 217 mg $Na_2S_2O_5$ /kg bw/day. The lowest dose where local effects occurred in the F0-generation was 1.0 % in the diet that is equivalent to an intake of 454 mg $Na_2S_2O_5$/kg bw/day.

Conclusion :

Disodium disulphite primarily caused stomach lesions due to local irritation under the conditions of the present study. There were no signs of local toxicity at ca. 217 mg/kg bw/day, and the lowest dose where this effect occurred was ca. 454 mg/kg bw/day as actual intake dose (NOAEL & LOAEL for local toxicity, rats, oral feed: ca. 217 mg/kg bw/day & 454 mg/kg bw/day). From the same dietary study in rats, the NOAEL for systemic toxicity was the highest dose tested (NOAEL for systemic toxicity, rats, oral feed: ca. 942 mg/kg bw/day).

3.1.4 Genetic Toxicity

Genetic Toxicity in vitro

Disodium disulphite was not mutagenic in the Ames assay performed with and without S-9 mix, using both standard plate and preincubation test conditions (NTIS, 1978; BASF AG, 1989). Nor did it induce chromosomal aberrations in a Chinese hamster fibroblast cell line (Ishidate *et al.,* 1984). However, there were other *in vitro* bacterial assays with positive results (Pagano and Zeiger, 1987; Pagano *et al.,* 1990; De Giovanni-Donelly, 1985). Sensitivity to mutation by bisulfite was shown in strains which carried cytosines in the appropriate context in the putative target region of DNA, since bisulfite has been suggested to cause cytosine deamination in single stranded DNA. In summary they mentioned that bisulfite was a weak mutagen in bacteria when cytosines were found as CCC and CCCCCC runs, but not in CCCC or GC runs (De Giovanni-Donelly 1985, Pagano and Zeiger, 1987). These positive results also suggest that the SO_3^- radical is responsible for the mutagenic activity (Pagano et al., 1990) and clearly depends on the specific test condition such as pH value. The proper pH range (pH 4.4 to 5.6) for mutagenicity was also determined (Pagano and Zeiger, 1987). However, their doses were not clearly presented. If very high doses were used, the positive effects could be attributed to an impurity. No data on purity was given. These positive *in vitro* studies referred above could not support that the substance is clearly genotoxic since the free radical-mediated mutagenic effects are generally very transient. Moreover, such mutagenic mechanism does not seem to be relevant to *in vivo* condition where the autooxidation of disodium disulphite occurred (Renner 1983).

Genetic Toxicity in vivo

No adverse effect on bone marrow chromosomes was observed in rats as a result of disodium disulphite treatment by gavage (NTIS, 1972 and Maxwell *et al.*, 1974). Likewise, an evaluation for mutagenicity in a dominant lethal assay showed no substance-related effect attributable to disodium disulphite given by feed (NTIS, 1979).

Conclusion :

The genetic toxicity of this chemical is equivocal *in vitro* but the substance is not genotoxic under *in vivo* condition.

3.1.5. Carcinogenicity

The study described in section 3.1.3 (disodium disulphite given in the diet with 0.125, 0.25, 0.5, 1.0, 2.0 %, i.e. ca. 48, 106, 217, 454, and 942 mg/kg/day as actual dose and supplemented with thiamine due to its breakdown by sulphite) using rats by Til *et al.* (1972) is not a conventional carcinogenicity study as the animals were mated to determine reproductive performance. Nevertheless, this data is sufficient to assess the carcinogenic potential of disodium disulphite since animals were maintained for 104 weeks, the usual time frame for a carcinogenicity bioassay, and suitable histologic examinations were performed. In this regard, the number of lymphoreticular pulmonary tumors in males decreased with increasing levels of sulphite. The incidence of thyroid and pituitary tumors in control males was exceptionally low, whereas those noted in the various test groups represented numbers normally found in the strain of Wistar rats used. All other neoplasms occurred in a sporadic manner with no apparent relationship between number, location or type of tumors and the treatment.

Conclusion :
Disodium disulphite was not carcinogenic to rats.

3.1.6. Reproduction Toxicity

As described in section 3.1.3, rats were treated with 0, 0.125, 0.25, 0.5, 1.0, and 2.0 % of disodium disulphite (ca. 0, 48, 106, 217, 454, and 942 mg/kg bw/day actual doses) in a supplemented diet with thiamine, since sulphites are known to break down thiamine (Til *et al.*, 1972). The F0-generation was mated at week 21 of treatment. Half of the animals were mated again at week 34. Animals from the 1st litter were selected at weaning to become the F1a-generation. The F1a-generation was mated at weeks 12 and 30 to produce F2a- and F2b-generations. Animals from the F2a litters were mated to produce F3a- and F3b-generations by pairing on weeks 14 and 22.
Body weight was not reduced in any treatment group in the F0-generation. There was a marginal reduction in body weight in both sexes of the 2% group in the F1- and the F2-generations.
Results in successive generations showed no substantial treatment-related effects in terms of fertility, the number of animals/litter or the birth weight or mortality of the young. During lactation the body weight of the young in the 2% group was generally lower than the controls and the lower-dosed groups. In the F1a- and the F1b-generation offspring (F2a and F2b pups) dietary levels of 1 and 2 % disodium disulphite were associated with decreased body weight on days 8 and 21. This effect was primarily transient for the F2a pups, since animals of the 1% group recovered their body weight after weaning and the 2 % group nearly recovered their body weight as compared to the control. The F2b pups were discarded after weaning. This reduced body weight was probably not a true substance-related effect since it could be due to a higher initial body weight in the control groups. Furthermore, these body weight changes were within or were not dramatically different from the control values of the F1 pups. A reduction in the number of F2a-generation offspring (F3a pups) was observed in the 0.5, 1.0, and 2.0 % dose groups, but it was not dose-dependent and did not occur in the F2b-generation offspring (F3b pups).
No pronounced effects were observed on reproductive performance in any generation and no effects on gonads were seen histologically ; thus, the NOAEL for reproduction toxicity was the highest dose 2 % in the diet that is equivalent to 942 mg/kg bw/day as actual dose.

Conclusion :

There is no suggestive evidence of reproductive toxicity in rats that received orally 942 mg/kg bw/day of disodium disulphite as actual dose (2 % in the diet). The NOAEL (rat, fertility, F0, F1, F2, F3, oral feed) was 942 mg/kg bw/day.

3.1.7. Developmental Toxicity

When pregnant Wistar rats were exposed to 0, 1, 5, 24, 110 mg/kg bw/day by gavage for 6-15 days of gestation (NTIS, 1972), disodium disulphite had no effect on nidation, on maternal and fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the numbers occurring in the sham-treated controls. Thus, the NOAELs for maternal toxicity and teratogenicity as well as embryo/fetotoxicity were the highest dose tested.

NOAEL, rats, maternal toxicity, oral:	110 mg/kg bw/day
NOAEL, rats, teratogenicity, oral:	110 mg/kg bw/day
NOAEL, rats, embryo/fetotoxicity, oral:	110 mg/kg bw/day

Pregnant rabbits (Dutch-belted) were treated by gavage on days 6-18 of gestation with 0, 1.23, 5.71, 26.5 or 123 mg/kg bw /day of disodium disulphite, and were sacrificed on day 29 (NTIS, 1974). Again, the test substance had no clear effect on nidation, or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls. The NOAELs for maternal toxicity, teratogenicity and embryo/fetotoxicity were the highest dose tested.

NOAEL, rabbits, maternal toxicity, oral:	123 mg/kg bw/day
NOAEL, rabbits, teratogenicity, oral:	123 mg/kg bw/day
NOAEL, rabbits, embryo/fetotoxicity, oral:	123 mg/kg bw/day

Conclusion :

Disodium disulphite showed no evidence of developmental toxicity or teratogenicity. The NOAELs were established at 110 mg/kg bw/day in rats and 123 mg/kg bw/day in rabbits, respectively.

3.1.8. Other: *Irritation (Human data); Sensitisation; Corrosivity*

There are only a few animal studies relating to irritation of disodium disulphite. These two studies show disodium disulphite is not irritating to the skin but irritating to the eyes of rabbits (Hoechst AG, 1987). Regarding skin sensitization in animals, no guideline studies were available for an assessment, however, in one study with guinea pigs which was not well-documented, no indication of sensitization was observed. In humans urticaria and asthma with itching, edema, rhinitis, and nasal congestion are reported (Le-Stradic-Reygagne, 1991; Baker, 1981; Vallon, 1995; Valero, 1993; Sanz, 1992; Wüthrich et al., 1993). An immunological pathogenesis of these are not still clear. In a few cases allergic contact dermatitis, as well as positive patch-testing was observed (Jacobs, 1992; Apetato, 1986; Sokol, 1990; Petersen, 1990; Larame, 1989; Vestergaard and Andesen, 1995).

Conclusion :

Disodium disulphite is not irritating to the skin but irritating to the eyes. It is not considered as skin sensitizer and also unlikely to induce respiratory sensitization but may enhance symptoms of asthma in sensitive individuals.

3.2 Initial Assessment for Human Health

Acute toxicity of disodium disulphite is likely to be low since the LD_{50} by oral exposure in rat is 1540 mg/kg bw. This chemical is not irritating to the skin, but irritating to the eyes with risk of serious damage.

For repeated dose toxicity, in long term dietary studies (30 to 104 weeks) in rats, the predominant effect was the induction of stomach lesions due to local irritation and was characterized as

forestomach and glandular stomach hyperplasias and inflammation. There were no signs of local toxicity at ca. 217 mg/kg bw/day, and the lowest dose where this effect occurred was ca. 454 mg/kg bw/day as actual intake dose (NOAEL for local toxicity: ca. 217 mg/kg bw/day). From the same dietary study in rats, the NOAEL for systemic toxicity was the highest dose tested (NOAEL, rats, oral feed: ca. 942 mg/kg bw/day).

The results of genotoxic tests *in vitro* are equivocal but there is no evidence demonstrating that disodium disulphite is genotoxic *in vivo*.

Reproduction toxicity of disodium disulphite was not observed (NOAEL, rats, fertility, oral feed: ca. 942 mg/kg bw). No developmental toxicity and teratogenic effects were observed in rats or rabbits (NOAEL, rats, maternal toxicity/teratogenicity/embryo/fetotoxicity, oral : 110 mg/kg bw; NOAEL, rabbits, maternal toxicity/teratogenicity/embryo/fetotoxicity, oral: 123 mg/kg bw).

It was not carcinogenic in rats that received disodium disulphite via feed.

In humans, urticaria and asthma with itching, edema, rhinitis and nasal congestion were reported. An immunological pathogenesis of these reactions is not still clear. In a non-guideline study, no indication of skin sensitization with guinea pigs was observed. In a few cases allergic contact dermatitis as well as positive patch-testing was observed. With respect to wide spread use, it is not considered as a skin sensitizer. Disodium disulphite is unlikely to induce respiratory sensitization but may enhance symptoms of asthma in sensitive individuals. Given the wide-spread use, the number of cases is considered to be low.

4. HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

The following acute toxicity tests with aquatic organisms were available:
Medaka *(Oryzias latipes)* : LC_{50} (96 h) >100 mg/L, nominal concentration (MOE, Korea ,2001)
Rainbow trout *(Salmo gairdneri)* : LC_{50} (96 hr) >147 mg/L and <215mg/L, nominal concentration (BASF, 1981)
Water flea *(Daphnia magna)* : EC_{50} (48 h) = 88. 76 mg/L, nominal concentration (BASF, 1989)
Algae *(Scenedesmus subspicatus)* : EC_{50} (72 h) = 48.1 mg/L, nominal concentration (BASF, 1989)
Bacteria *(Pseudomonas putida)* : EC_{50} (17 h) = 56.1 mg/L, nominal concentration (BASF, 1988)
The following chronic toxicity test with aquatic organisms was available:
Water flea *(Daphnia magna)* : 21d-NOEC > 10 mg/L (BASF, 1993). The test concentrations were 1, 5, and 10 mg/L.

4.2 Terrestrial Effects

There is almost no data available on the terrestrial organisms. A study showed that treatment of tomato leaves with different concentrations of disodium disulphite induced degradation of green pigments and protein. The author suggested that SO_2 might be responsible for the decreased protein content of treated leaves. However, the value of K_{OC} (2.477) is low implying that it is very mobile in soil. Therefore given the low potential for exposure in terrestrial compartment, significant toxicity in terrestrial organism is unlikely.

4.3 Other Environmental Effects

There is no available information.

4.4 Initial Assessment for the Environment

Testing for the endpoint of biodegradability is not appropriate due the chemical not being an organic chemical. Also, bioaccumulation is not expected. As mentioned above, the low Koc (2.447) indicates that disodium disulphite is so mobile in soil that it may not stay in the terrestrial compartment. Instead it has a potential to leach into the groundwater.
From the experimental acute toxicity result of the most sensitive organism, 48.1 mg/L (72 hr-EC_{50} for algae; *Scenedesmus subspicatus*), an assessment factor 100 was applied to determine PNEC of 0.481 mg/L. From a chronic toxicity value of > 10 mg/L (21days-NOEC for *Daphnia magna*), a PNEC of 0.1 mg/L was derived by applying an assessment factor of 100. Therefore the lowest PNEC was determined to be 0.1 mg/L.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

Physical/Chemical property, production, use and distribution

In 1999, estimates for the world market of sodium salts of sulphites, without China and the Russian federation, amounted to approx. 330,000 tonnes/year. Total production of disodium disulphite in Korea was about 3,200 tonnes/year. Disodium disulphite is a basic chemical and used in synthesis. The substance is also used in tanning agents, food/foodstuff additives, bleaching agents, photography, etc.

Environment

The estimated distribution shows water is the main target compartment for disodium disulphite. The substance has no considerable potential for bio- and geoaccumulation ($logP_{OW}$-3.7, measured). Biodegradation or elimination tests may not be appropriate since disodium disulphite is an inorganic substance. Disodium disulphite dissolves in water and forms sodium cations, disulfite anions, and sulfur dioxide. Photodegradation is not relevant under environmental conditions.

The following acute toxicity tests with aquatic organisms were available:

Medaka *(Oryzias latipes)* : LC_{50} (96 h) >100 mg/L, nominal concentration (MOE, Korea ,2001)

Rainbow trout *(Salmo gairdneri)* : LC_{50} (96 hr) >147 mg/L and <215mg/L, nominal concentration (BASF, 1981)

Water flea *(Daphnia magna)* : EC_{50} (48 h) = 88. 76 mg/L, nominal concentration (BASF, 1989)

Algae *(Scenedesmus subspicatus)* : EC_{50} (72 h) = 48.1 mg/L nominal concentration (BASF, 1989)

Bacteria *(Pseudomonas putida)* : EC_{50} (17 h) = 56.1 mg/L nominal concentration (BASF, 1988)

The following chronic toxicity test with aquatic organisms was available:

Water flea (*Daphnia magna*) : 21d-NOEC > 10 mg/L (BASF, 1993). The test concentrations were 1, 5, and 10 mg/L.

From a chronic toxicity value of 10 mg/L (21days-NOEC of *Daphnia magna*), a PNEC of 0.1 mg/L was derived by applying an assessment factor of 100.

Human Health

Acute toxicity of disodium disulphite is likely to be low since the LD_{50} for oral exposure in rats is 1540 mg/kg bw. This chemical is not irritating to the skin, but irritating to the eyes with risk of serious damage.

In long term dietary studies (30 to 104 weeks) in rats, the predominant effect was the induction of stomach lesions due to local irritation and was characterized as forestomach and glandular stomach hyperplasias and inflammation. There were no signs of local toxicity at ca. 217 mg/kg bw/day, and the lowest dose where this effect occurred was ca. 454 mg/kg bw/day as actual intake dose (NOAEL for local toxicity: ca. 106 mg/kg bw/day) in the F0 generation. From the same dietary study in rats, the NOAEL for systemic toxicity was the highest dose tested (NOAEL, rats, oral feed: ca. 942 mg/kg bw/day).

The results of genotoxic tests *in vitro* are equivocal but there is no evidence that disodium disulphite is genotoxic *in vivo*.

Reproductive toxicity of disodium disulphite was not observed (NOAEL, rats, fertility, oral feed: ca. 942 mg/kg bw). No developmental toxicity or teratogenic effects appeared in rats or rabbits (NOAEL, rats, maternal toxicity/teratogenicity/embryo/fetotoxicity, oral: 110 mg/kg bw; NOAEL, rabbits, maternal toxicity/teratogenicity/embryo/fetotoxicity, oral: 123 mg/kg bw). It was not carcinogenic in rats that received disodium disulphite via feed.

In humans, urticaria and asthma with itching, edema, rhinitis, and nasal congestion have been reported. An immunological pathogenesis of these reactions is still unclear. In a few cases allergic contact dermatitis as well as positive patch-testing was observed. Given the wide-spread use, the

number of cases is considered to be low.

5.2 Recommendations

The chemical is currently of low priority for further work.

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SIDS DOSSIER

Disodium Disulphite

CAS No. 7681-57-4

Sponsor Country : Republic of Korea/ICCA(BASF)

DATE : September 2001

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Note: Data elements in the SIDS

SIDS PROFILE

1.01 A.	CAS No.	7681-57-4
1.01 C.	CHEMICAL NAME (OECD Name)	Disodium disulphite(EINECS)
1.01 D.	CAS DESCRIPTOR	Not applicable
1.01 G.	STRUCTURAL FORMULA	Na2S2O5
1.2	OTHER CHEMICAL IDENTITY INFORMATION	Dinatriumdisulfit Disodium disulphite Disodium metabisulfite Disodium pyrosulfite Disulfurous acid, disodium salt (9CI) Natriumdisulfit Pyrosulfurous acid, disodium salt (8CI) Sodium disulfite Sodium metabisulfite Sodium pyrosulfite
1.5	QUANTITY	100 000 - 500 000 tonnes per annum (World) 1,000-5,000 tonnes per annum (Korea)
1.7	USE PATTERN	Wide -dispersive use (tanning agents, food/foodstuff additives, bleaching agents, photography, etc.)
1.9	SOURCES AND LEVELS OF EXPOSURE	
ISSUES FOR DISCUSSION (IDENTIFY, IF ANY)		

SIDS SUMMARY

CAS NO: 7681-57-4		Information	OECD Study	GLP	Other Study	Estimation Method	Acceptable	SIDS Testing Required
STUDY		Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL DATA								
2.1	Melting Point	Y	N		Y	N	Y	N
2.2	Boiling Point							
2.3	Density	Y	N		Y	N	Y	N
2.4	Vapour Pressure							
2.5	Partition Coefficient	Y	N		Y	N	Y	N
2.6	Water Solubility	Y	N		Y	N	Y	N
	pH and pKa values	Y	N		Y	N	Y	N
2.12	Oxidation: Reduction potential							
OTHER P/C STUDIES RECEIVED								
ENVIRONMENTAL FATE and PATHWAY								
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3.3	Transport and Distribution							
3.5	Biodegradation							
OTHER ENV FATE STUDIES RECEIVED								
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4.1	Acute toxicity to Fish	Y	Y	Y	N	N	Y	N
4.2	Acute toxicity to Daphnia	Y	N	N	Y	N	Y	N
4.3	Toxicity to Algae	Y	Y	N	N	N	Y	N
4.5.2	Chronic toxicity to Daphnia	Y	Y	Y	N	N	Y	N
4.6.1	Toxicity to Soil dwelling organisms	N						N
4.6.2	Toxicity to Terrestrial plants	Y					N	N
4.6.3	Toxicity to Birds	N						N
OTHER ECOTOXICITY STUDIES RECEIVED								
TOXICITY								
5.1.1	Acute Oral	Y	Y	Y	N	N	Y	N
5.1.2	Acute Inhalation	N						N
5.1.3	Acute Dermal	N						N
5.4	Repeated Dose	Y	N		Y	N	Y	N
5.5	Genetic Toxicity in vitro							
	. Gene mutation	Y	Y	N	N	N	Y	N
	. Chromosomal aberration	Y	N		Y	N	Y	N
5.6	Genetic Toxicity in vivo	Y	N		Y	N	Y	N
5.8	Reproduction Toxicity	Y	N		Y	N	Y	N
5.9	Development / Teratogenicity	Y	N		Y	N	Y	N
5.11	Human experience	Y	N	N	Y	N	Y	N
OTHER TOXICITY STUDIES RECEIVED								

1. GENERAL INFORMATION

1.01 SUBSTANCE INFORMATION

A. CAS number 7681-57-4

B. Name (IUPAC name) Disodium disulphite

C. Name (OECD name) Disodium disulphite (EINECS)

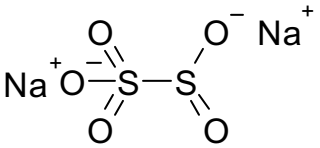
D. CAS Descriptor

Not Applicable since disodium disulphite is not a complex chemical.

E. EINECS-Number 231-673-0

F. Molecular Formula $Na_2S_2O_5$

G. Structural Formula



Smiles Code : [Na]OS[=O][=O]S[=O]O[Na]

H. Substance Group
Not applicable

I. Substance Remark (Indicate the substance remark as prescribed in the EINECS Inventory, if possible)
Not applicable since no prescription in the EINECS Inventory.

J. Molecular Weight 190.10

1.02 OECD INFORMATION

A. Sponsor Country: Republic of Korea/ICCA (BASF)

B. Lead Organisation:
Name of Lead Organisation: National Institute of Environmental Research
Contact person: Dr. Moon-Soon LEE
Address:
Street: Gyeongseo-dong, Seo-gu
Postal code 404-170
Town: Incheon
Country: Republic of Korea
Tel: 82-32-560-7113
Fax: 82-32-568-2037
E-mail : mslee416@me.go.kr

C. Name of responder (Information on a responder should be provided when companies respond to Lead Organisation or SIDS Contact Points.)

Name : same as above
Address : same as above

1.1 GENERAL SUBSTANCE INFORMATION

A. Type of Substance

element [ ]; inorganic [x]; natural substance [ ]; organic [ ];
organometallic [ ]; petroleum product [ ]

B. Physical State (at 20 °C and 1.013 hPa)

gaseous [ ]; liquid [ ]; solid [x]

C. Purity

> 98 % w/w

1.2 SYNONYMS

Dinatriumdisulfit
Disodium disulphite
Disodium metabisulfite
Disodium pyrosulfite
Disulfurous acid, disodium salt (9CI)
Natriumdisulfit
Pyrosulfurous acid, disodium salt (8CI)
Sodium disulfite
Sodium metabisulfite
Sodium pyrosulfite

1.3 IMPURITIES

[Indicate CAS No., chemical name (IUPAC name is preferable), percentage, if possible EINECS number.]

CAS No:
EINECS No:
Name: Cl^-
Value: Less than 0.05 %
Remarks:

CAS No:
EINECS No:
Name: $S_2O_3^{2-}$
Value: Less than 0.05 %
Remarks:

CAS No:
EINECS No:
Name: heavy metals
Value: Less than 0.001 %
Remarks:

CAS No:
EINECS No:
Name: Fe
Value: Less than 0.002 %
Remarks:

CAS No:
EINECS No:
Name: Insolubles
Value: Less than 0.005 %
Remarks:

1.4 ADDITIVES (e.g. stabilising agents, inhibitors etc. Indicate CAS No., chemical name (IUPAC name is preferable), percentage, if possible EINECS number), the component of the UVCB (substance with no defined composition) should be indicated here.)

CAS No:
EINECS No:
Name:
Value:
Remarks:

1.5 QUANTITY [Information on production or import levels should be provided in figures or ranges (e.g. 1,000-5,000, 5,000-10,000 tonnes, etc.) per responder or country and the date for which those ranges apply should be given. For EU Member states, only indicate the EU import figure. Give an estimation of the global production quantity in the remarks field. Information on the number of producers in the country and the source of information should also be given in the remarks field.]

Estimated production
- World wide : 100,000 – 500,000 tonnes per annum (1999)
- Korea : 3,200 tonnes per annum (MOE, 1998)

Remarks: (If possible, indicate if the substance was produced and/or imported during the 12 months following adoption of the EU regulation on existing chemicals.)

Reference : Ministry of Environment (MOE), Korea(1998), Survey on Circulation Volume of Chemicals in Korea.

1.6 LABELLING AND CLASSIFICATION [If possible, enter information on labelling and classification, such as labelling and classification system, existence of specific limit, symbols, nota, R-Phrases and S-Phrases of EC Directive 67/548/EEC. See HEDSET Explanatory Note.]

Labelling
Type:
Specific limits:
Symbols:
Nota:
R-phrases:
S-phrases:
Text of S-phrases:
Remarks:

Classification
Type:
Category of danger:
R-phrases:
Remarks:

*Disodium disulphite is not classified as toxic chemicals in Korea

1.7 USE PATTERN

A. General [Data on use pattern have to be given by assigning main types according to their exposure relevance (i.e. non-dispersive use, use in closed systems, use resulting in inclusion into or onto matrix and wide dispersive use), industrial categories (e.g. basic chemical industry, chemical industry, agricultural industry, personal and domestic use) and use categories such as colouring agents, intermediates, solvents, adhesives, cleaning/washing agents, fertilizers, impregnation agents, surface-active, etc. If available, give an estimation of different uses in percentage terms.]

	Type of Use:	**Category:**
(a)	main	Wide dispersive use
	industrial	Chemical Industry

	use	Tanning agents
(b)	main industrial use	Non dispersive use Personal and domestic use Food/foodstuff additives
(c)	main industrial use	Non dispersive use Personal and domestic use Bleaching agents
(d)	main industrial use	Non dispersive use Personal and domestic use Photography

Remarks: General use of Disodium disulphite in the world are shown above. Among 3,200 tonnes consumed in Korea, most of them are used for Tanning agents, Food/foodstuff additives. Information of other use is not available

Reference: Ministry of Environment (MOE), Korea (1998), Survey on Circulation Volume of Chemicals in Korea.

B. Uses in Consumer Products (If the chemical is present in consumer products as marketed give details of form of products function (e.g. detergent etc.), and percent in product and physical state of product as marketed (e.g. aerosol, powder or liquid))

	Function	Amount present	Physical state
Remarks:	Information of other use is not available.		
Reference:			

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUE (Indicate the type of occupational exposure limit value including short-term exposure limit value. If a value does not exist, give the hygiene standard of the producer company if available. See also 5.11.)

Exposure limit value
Type: TLV (KO)
Value: 5 mg/m^3 (8 hr TWA)

Short term exposure limit value
Value: Length of exposure period
Frequency:
Remarks:
Reference: Industrial safety and health act in Korea (1998)

Exposure limit value
Type: TLV (US)
Value: 5 mg/m^3

Short term exposure limit value
Value: Length of exposure period
Frequency:
Remarks:
Reference: ACGIH Documentation of the TLV and Biological Exposure Indices (1991)

Exposure limit value
Type: REL (US)
Value: 5 mg/m^3 (10 hr TWA)

Short term exposure limit value
Value:
Length of exposure period
Frequency:
Remarks:
Reference: NIOSH pocket guide to chemical hazards (1994)

1.9 SOURCES OF EXPOSURE

Describe sources of potential human [other than concentration of chemicals in the workplace and indoor environment (see 5.11)], or environmental exposure, including emission data (e.g. quantities per media with information such as time dimensions of release, indication of type of release (e.g. point source or diffuse), type of estimating (e.g. average or worst case), uncertainties in estimation), for all phases of the life cycle of the chemical, if available, including manufacturing and user areas.
For environmental exposure, indicate the production process briefly, number of sites of manufacture and, the basis for concluding that the process is "closed" if applicable.
Also an indication of measured exposure levels (expressed in an appropriate form, e.g. geometric mean and standard deviation) can be mentioned here. Any information that will help to focus the assessment of exposure (either quantitative or quantitative in nature) can be mentioned, if available.)

Source:

Remarks: the most probable human exposure would be occupational exposure, which may occur through dermal contact at workplaces.
Reference: NIOSH National Occupational Exposure Survey 1983

1.10 ADDITIONAL REMARKS

A. Options for disposal [Mode of disposal (e.g. incineration, release to sewage system, etc.) for each category and type of use, if appropriate; recycling possibility]

Remarks:
Reference:

B. Other remarks

Remarks:
Reference:

2. PHYSICAL-CHEMICAL DATA

2.1 MELTING POINT (If more than one, identify the recommended value.)

Value:
Decomposition: Yes [x] No [ ] Ambiguous [ ]
Sublimation: Yes [ ] No [ ] Ambiguous [ ]
Method:
GLP: Yes [ ] No [ ] ? [x]
Remarks: Solid temperature 150 °C (decompose to form sulfur dioxide)
Reference: BASF AG safety data sheet sodium metabisulfite, 06. January. 1999

2.2 BOILING POINT (If more than one, identify the recommended value.)

Value:
Pressure:
Decomposition: Yes [x] No[ ] Ambiguous [ ]
Method:
GLP: Yes [ ] No [ ] ? [x]
Remarks: not relevant (decomposition)
Reference:

2.3 DENSITY (relative density) (Where applicable, indicate the relative density of the substance.)

Type: Relative Density
Value: 1.48 g/cm^3
Temperature: 15 °C
Method:
GLP: Yes [ ] No [ ] ? [x]
Remarks:
Reference: BASF AG safety data sheet sodium metabisulfite, 06. January. 1999

2.4 VAPOUR PRESSURE (if more than one, identify the recommended value)

Value:
Temperature: °C
Method:
GLP: Yes [ ] No [ ] ?[ ]
Remarks: not relevant
Reference:

2.5 PARTITION COEFFICIENT log POW (if more than one, identify the recommended value)

Log POW : -3.7
Temperature: 25 °C
Method: calculated [ ]; measured [x]
GLP: Yes [ ] No [ ] ?[x]
Remarks: log POW strongly depend on pH value
Reference : BASF AG Physical/chemical, unpublished investigation, report BRU 88. 221, 02. November. 1988

2.6 WATER SOLUBILITY (if more than one, identify the recommended value)

A. Solubility

a) Preferred result
Value: 470 g/l

Temperature: 0 °C
Description: Miscible[ ]; Of very high solubility [ ]; Of high solubility [x]; Soluble [ ]; Slightly soluble [ ]; Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method
GLP: Yes [ ] No [ ] ?[x]
Remarks :
Reference: BASF AG, Sicherheitsdatenblatt Natriumdisulfit, 30.October. 2000

b)
Value: 640 g/l
Temperature: 25 °C
Description: Miscible[ ]; Of very high solubility [ ]; Of high solubility [x]; Soluble [ ]; Slightly soluble [ ]; Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:
GLP: Yes [ ] No [ ] ?[x]
Remarks:
Reference: Sorbe, Sicherheitstechnische Kenndaten chemischer Stoffe, p.97, 28. Erg. Lfg. 12/92

c)
Value: 540 g/l
Temperature: 25 °C
Description: Miscible[ ]; Of very high solubility [ ]; Of high solubility [x]; Soluble [ ]; Slightly soluble [ ]; Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:
GLP: Yes [ ] No [ ] ?[x]
Remarks:
Reference: Richardson, M.L. and S. Gangolli. The Dictionary of Substances and their Effects. Royal Society of Chemistry. p. 19, 1995

B. pH Value, pKa value

pH Value: 3.5-5.0
Concentration: 50 g/l
Temperature: 20 °C
Method:
GLP: Yes [ ] No [ ] ?[x]
pKa value:
Remarks:
Reference: BASF AG, Sicherheitsdatenblatt Natriumdisulfit, 30. October. 2000

2.10 EXPLOSIVE PROPERTIES

Results: Explosive under influence of a flame[ ];
More sensitive to friction than m -dinitrobenzene [ ];
More sensitive to shock than m-dinitrobenzene [ ]; Not explosive [x]; Other [ ]
Method:
GLP: Yes [ ] No [ ] ?[x]
Remarks: because of chemical structure
Reference: BASF AG, Sicherheitstechnik, interne Mitteilung, 29.October.1999

2.11 OXIDIZING PROPERTIES

Results: Maximum burning rate equal or higher than reference mixture [ ];
Vigorous reaction in preliminary test [ ]; No oxidising properties [x]; Other [ ]
Method:
GLP: Yes [ ] No [ ] ?[x]
Remarks: because of chemical structure

Reference: BASF AG, Sicherheitstechnik, interne Mitteilung, 29. October. 1999

2.12 OXIDATION: REDUCTION POTENTIAL

(Where applicable, indicate the redox potential and the conditions under which it was measured.)

Value: No data available
Method:
GLP: Yes [ ] No [ ] ?[x]
Remarks:

2.13 ADDITIONAL DATA

A. Partition co-efficient between soil/sediment and water (Kd)

Value:
KOC : 2.447
Method: calculated by PCKOCWIN V. 1.63
GLP: Yes [ ] No [ ] ?[x]
Remarks: very high mobility in soil.
Reference: BASF AG, department of ecology, unpublished calculation, 18, December.1998

B. Other data

(e.g. Henry's Law constant, fat solubility, surface tension (of aqueous solution), adsorption/desorption on soil, particle size distribution, etc.)

3. ENVIRONMENTAL FATE AND PATHWAYS

[Reporting of studies should give the test method, test conditions (laboratory versus field studies), test results (e.g. % degradation in specified time period) and reference. Information on breakdown products (transient and stable) should be provided when available.]

3.1 STABILITY

3.1.1 PHOTODEGRADATION

(a)
Type: Air [ ]; Water [ ]; Soil [ ]; Other [ ]
Light source: Sun light [ ]; Xenon lamp [ ]; Other [ ]
Light spectrum: .nm
Relative intensity: (based on intensity of sunlight)
Spectrum of substance: (e.g. lambda (max.)[> 295 nm] and epsilon[max] or epsilon [295 nm])nm
Concentration of Substance:
Temperature: °C
Direct photolysis:
Half life:
Degradation: % (weight/weight) after . . . .(exposure time)
Quantum yield: Indirect Photolysis:
Type of sensitizer:
Concentration of sensitizer
Rate constant (radical): cm^3/molecule*sec
Degradation:
Method: calculated [ ]; measured[ ]
(e.g. OECD, other (with the year of publication or updated of the method used))
GLP: Yes [ ] No [ ] ? [ ]
Test substance: .
Remarks: Molecules with an adsorbance maximum of light with wavelength range of 290-600 nm electrons may get promoted from bonding orbitals to antibonding orbitals (eg. $\pi \rightarrow \pi^*$ transitions). The molecule is then in a so-called exited state. But molecules with the basic structure RS-SR has an adsorption maximum near by 300 nm and a single bound. Additionally the molecule needs a chromophore group like a conjugated double bonds. Heteroatoms like oxygen makes so-called $n \rightarrow n^*$ transition are principle also possibly but commonly at longer wavelength. Due to these chemical features probably it does not seem that disodium disulphite undergoes photochemical reactions neither in air (totally soluble in water) nor in water depending on its chemical structure.
Reference:

3.1.2 STABILITY IN WATER

Type: Abiotic (hydrolysis)[ ] ; biotic (sediment)[ ]
Half life: (T 1/2 :)
Degradation: at pH at °C after (exposure time)
Method:
GLP: Yes [ ] No [ ] ? [ ]
Test substance: purity:
Remarks: Disodium disulphite dissolves in water forming sodium cations, disulfite anions, and sulfur dioxide. Depending on the pH-value, sulfur dioxide, sodium hydrogen sulfite or sodium sulfite is present in aqueous solution.
Reference:

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS

3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

a) Preferred result

Media:	Air-biota[ ]; Air-biota-sediment-soil-water[ ]; Soil-biota[ ]; Water-air[ ]; Water-biota[ ]; Water-soil[ ]; Other[ ];
Method:	Fugacity level I[ ]; Fugacity level? [ ]; Fugacity level III[ ]; Fugacity level IV [ ]; Other (calculation) [ ]; Other(measurement)[ ]
Results:	In air %
	In water %
	In soil %
	In sediment %
Remarks:	Not relevant
Reference:	

3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE

Results:	
Remarks:	No data available
Reference:	

3.5 BIODEGRADATION

Type:	aerobic [ ]; anaerobic [ ]
Inoculum:	adapted [ ]; non-adapted [ ];
Concentration of the chemical:	related to COD [ ]; DOC [ ]; test substance [ ]
Medium:	water [ ]; water-sediment [ ]; soil [ ]; sewage treatment [ ]
Degradation:	% after (time)
Results:	readily biodeg. [ ]; inherently biodeg. [ ]; under test condition no biodegradation observed [ ], other [ ]
Kinetic (e.g. Zahn-Wellens-Test)	% in (time)
Method:	
GLP:	Yes [ ] No [ ] ? [ ]
Test substance:	purity:
Remarks:	Not relevant (inorganic compounds). Elimination test can not be carried out cause it is an inorganic substance. The product may lead chemical consumption of oxygen in biological sewage works or natural water. Inhibition of degradation activity in activated sludge is not to be anticipated during correct introduction of low concentrations. The substance develops sulphurdioxide in acid milieu.
Reference:	

3.6 BOD5,COD OR RATIO BOD5/COD

BOD5

Method:	
Concentration:	mg/L related to COD [ ]; DOC [ ]; Test substance [ ];
Value:	= mg O2/L
GLP:	Yes [ ] No [ ] ? [x]

COD

Method:	
Value:	= mg O2/g
GLP:	Yes [ ] No [ ] ? [ ]
Ratio BOD5/COD:	
Remarks:	Not relevant (inorganic compounds)
Reference:	

3.7 BIOACCUMULATION

Species:	
Exposure period:	
Temperature:	
Concentration:	mg/L
BCF:	
Elimination:	Yes [ ] No [ ] ? [ ]
Method:	(e.g. OECD, other (with the year of publication or updated of the method used))
Type of test:	calculated [ ] ; measured [ ] static [ ]; semi-static [ ]; flow -through [ ]; other (e.g. field test) [ ]
GLP:	Yes [ ] No [ ] ? [ ]
Test substance:	
Remarks:	Not expected
Reference:	

3.8 ADDITIONAL REMARKS

A. Sewage treatment (information on treatability of the substance)

Results:	
Remarks:	No data available
Reference:	

B. Other information (information that will help to focus the exposure assessment (either qualitative or quantitative)

Results:	
Remarks:	No data available
Reference:	

4. ECOTOXICITY

4.1 ACUTE/PROLONGED TOXICITY TO FISH

(a)

Type of test:	static [x]; semistatic [ ]; flow-through [ ]; other[ ]; open-system[ ]; closed system[ ]
Species:	*Oryzias latipes*
Exposure period:	96 hr
Results:	LC50 (96 hr) > 100 mg/L
Analytical monitoring:	Yes[ ] No[x] ? [ ]
Method:	OECD TG 203
GLP:	Yes[x] No[ ] ? [ ]
Test substance:	98.3 %
Remarks:	
Reference :	Ministry of Environment (MOE), Korea (2001), The Toxicity of disodium disulphite to Fish (tested by KRICT)

(b)

Type of test:	static [x]; semistatic [ ]; flow-through [ ]; other[ ]; open-system[ ]; closed system[ ]
Species:	*Salmo gairdneri* (Fish, estuary, fresh water)
Exposure period:	96 hr
Results:	LC50(96 hr) > 147 and < 215 mg/L
Analytical monitoring:	Yes[ ] No[x] ? [ ]
Method:	other : German Industrial Standard Guideline Number, DIN 38412 Group L, Part 1 and 15; 1979
GLP:	Yes[ ] No[x] ? [ ]
Test substance:	approx.98 %, BASF AG No 80/339
Remarks:	
Reference :	BASF AG, Dept. of Toxicology, unpublished result (80/339) 06. January. 1981

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

A. Daphnia

Type of test:	static [x]; semistatic [ ]; flow-through [ ]; other[ ]; open-system[ ]; closed-system[ ]
Species:	*Daphnia magna*
Exposure period:	48 hr
Results:	EC0 (48 hr) = 62.5 mg/L EC50 (48 hr) = 88.76 mg/L EC100 (48 hr) = 125.0 mg/L
Analytical monitoring:	Yes[ ] No[ ] ? [x]
Method:	Other: EEG guideline 79/831/EWG, appendix V, part of C "Acute toxicity for Daphnia"
GLP:	Yes[ ] No[x] ? [ ]
Test substance:	purity > 98 % (w/w), BASF Sulphite-factory RCA B 306
Remarks:	
Reference :	BASF AG, Dept. of Ecology ; unpublished result (0897/88), 10. May. 1989

B. Other aquatic organisms

No data available.

4.3 TOXICITY TO AQUATIC PLANTS (e.g. algae)

Species:	*Scenedesmus subspicatus* (Algae)
End point:	Biomass [x]; Growth rate [ ]; Other [ ]
Exposure period:	72 hr , 96 hr

Results: Biomass : EC20 (72 hr) = 39.2 mg/mL
EC50 (72 hr) = 48.1 mg/mL
EC90 (72 hr) = 60.0 mg/mL
EC20 (96 hr) = 20.0 mg/mL
EC50 (96 hr) = 39.8 mg/mL
EC90 (96 hr) = 58.0 mg/mL
Analytical monitoring: Yes[ ] No[ ] ? [x]
Method: other: OECD Guide-line 201 " Algae, Growth Inhibition Test"
open-system[ ]; closed-system[ ]
GLP: Yes[ ] No[x] ? [ ]
Test substance: purity > 98 % (w/w)
Remarks:
Reference : BASF AG , Dept. of Ecology, unpublished result (0897/88), 21. July. 1989

4.4 TOXICITY TO BACTERIA

(a) Preferred result
Type of test: Aquatic [x]; Field [ ]; Soil [ ]; Other [ ]
Species: *Pseudomonas putida* (Bacteria)
Exposure period: 17 hr
Results: EC10 (17 hr) = 30.8 mg/L
EC50 (17 hr) = 56.1 mg/L
EC90 (17 hr) =115.1 mg/L
Analytical monitoring: Yes[ ] No[ ] ? [x]
Method: other: DIN 38412, part 8, Determination of inhibitory effect on the cell multiplication
GLP: Yes[ ] No[x] ? [ ]
Test substance: purity > 98 % (w/w)
Remarks:
Reference: BASF AG, Dept. of Ecology, unpublished result (0897/88), 29. July. 1989

(b)
Type of test: Aquatic [ ]; Field [ ]; Soil [ ]; Other [ ]
Species: *Salmonella typhimurium, Escherichia coli*, and *Pseudomonas aeruginosa*
Exposure period: hr
Results: EC (h) = mg/L
Analytical monitoring: Yes[ ] No[ ]
Method:
GLP: Yes[ ] No[ ] ? [x]
Test substance:
Remarks: *Salmonella typhimurium* 59143, *Escherichia coli* ES-1, and *Pseudomonas aeruginosa* 8602 were not viable to disodium disulphite concentration of 800, 1000, and 2000 ppm, respectively, in gelatin medium. In rehydrated bone meal, *Salmonella typhimurium* showed no viability in 2 out of 4 cases at 4000 ppm.
Reference: Abalaka, J.A., R.H. Deibel. A comparative study of the lethal effect of metabisulphite on the viability of three bacterial species in bone meal and gelatin. Microbios. 27 (108), 79-88, 1980

4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

4.5.1 CHRONIC TOXICITY TO FISH

No data available.

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Type of test: static [ ]; semistatic [x]; flow-through [ ]; other[ ]; open-system[ ]; closed-system[ ]
Species: *Daphnia magna*
Endpoint: Mortality [ ];Reproduction rate[x]; other[ ]
Exposure period: 21 days
Unit: mg/L

Results:	NOEC > 10.0 mg/L LC0 > 10.0 mg/L
Analytical monitoring:	Yes[ ] No[x] ? [ ]
Method:	other: OECD Guideline 202, part 2: "Daphnia sp., Reproduction test".
GLP:	Yes[x] No[ ] ? [ ]
Test substance:	purity > 98 % (w/w)
Remarks:	
Reference:	BASF AG, Dept. of Ecology, unpublished result (2057/93), 15. December. 1993

4.6 TERRESTRIAL ORGANISMS

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

No data available.

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

Species:	Tomato leaves
End-point:	Emergence [ ]; Growth [ ]; Other [x]
Exposure period:	5 hr
Results:	
Method:	
GLP:	Yes [ ] No [ ] ? [x]
Test Substances:	purity
Remarks:	Treatment of tomato leaves with different concentration of disodium disulphite induced degradation of green pigments and protein. Chlorophyll content was reduced by 71.15 % and protein by 42.85 % in treated leaves at a concentration of 660 µg/mL as compared with controls.
Reference:	Singh, S.N., M. Yumus, N.Singh. Effect of Sodium Metabisulphite on Chlorophyll, Protein and Nitrate Reductase Activity of Tomato Leaves. Sci. Total Environ. 91, 269-74,1990

4.6.3 TOXICITY TO OTHER NON-MAMMALIAN TERRESTRIAL SPECIES

No data available.

4.7 BIOLOGICAL EFFECTS MONITORING

No data available.

4.8 BIOTRANSFORMATION AND KINETICS

No data available.

4.9 ADDITIONAL REMARKS

No data available.

5. TOXICITY

5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

(a) Preferred Result

Type:	LD0[ ]; LD50[x] LD100[ ]; LDLo[ ]; Other [ ]
Species/strain	Rat
Value:	LD50= 1,540 mg/kg Discriminating dose : 0, 800, 1250, 1600, 2000 mg/kg bw
Method:	OECD TG 401
GLP:	Yes[x] No[ ] ? [ ]
Test substance:	Disodium disulphite-powder, purity min. 96 %, other TS
Remark:	
Reference:	Hoechst AG (1987); unpublished studies (87.1374), 04. September. 1987

(b)

Type:	LD0[ ]; LD50[x] LD100[ ]; LDLo[ ]; Other [ ]
Species/strain	Rat
Value:	LD50= 2,480 mg/kg Discriminating dose : unknown
Method:	Not specified
GLP:	Yes[ ] No[ ] ? [x]
Test substance:	Disodium disulphite purity : unknown
Remark:	
Reference:	National Technical Information Service U.S. Department of Commerce (NTIS), FDA 71-22, PB 221 825 (1972)

(c)

Type:	LD0[ ]; LD50[x]; LD100[ ]; LDLo[ ]; Other [ ]
Species/strain	Sheep
Value:	2,515 mg/kg Discriminating dose : N/A
Method:	
GLP:	Yes[ ] No[ ] ? [x]
Test substance:	
Remark:	
Reference:	Nikolaev, K. and Dzhidzheva, V. Vet-Med Nauki 10 (4), 61-5, 1973

5.1.2 ACUTE INHALATION TOXICITY

No data available

5.1.3 ACUTE DERMAL TOXICITY

No data available

5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

(a)

Type:	LC0[ ]; LC50[ ]; LC100[ ]; LCLo [ ]; Other [ ] LD0[ ]; LD50[x]; LD100[ ]; LDLo [ ]; Other [ ]
Species/strain	Rat/Sherman
Route of Administration:	i.m.[ ]; i.p [ ]; i.v. [x]; infusion [ ]; s.c. [ ]; Other [ ]
Exposure time:	
Value:	approximately 115 mg/kg bw
Method:	
GLP:	Yes[ ] No[x] ?[ ]
Test substance:	Disodium disulphite
Remarks:	
Reference:	Hoppe, J. O., F. C. Goble. The intravenous toxicity of sodium bisulfite. J. Pharmacol. Exp. Therap. 101, 101-6, 1951

(b)
Type: LC0[ ]; LC50[ ]; LC100[ ]; LCLo [ ]; Other [ ]
LD0[ ]; LD50[x]; LD100[ ]; LDLo [ ]; Other [ ]
Species/strain Mouse/Albino Webstar
Route of Administration: i.m.[ ]; i.p [ ]; i.v. [x]; infusion [ ]; s.c. [ ]; Other [ ]
Exposure time:
Value: approximately 130 mg/kg bw
Method:
GLP: Yes[ ] No[x] ?[ ]
Test substance: Disodium disulphite
Remarks:
Reference: Hoppe, J. O., F. C. Goble. The intravenous toxicity of sodium bisulfite. J. Pharmacol. Exp. Therap. 101, 101-6, 1951

(c)
Type: LC0[ ]; LC50[ ]; LC100[ ]; LCLo [ ]; Other [ ]
LD0[ ]; LD50[x]; LD100[ ]; LDLo [ ]; Other [ ]
Species/strain Rabbit
Route of Administration: i.m.[ ]; i.p [ ]; i.v. [x]; infusion [ ]; s.c. [ ]; Other [ ]
Exposure time:
Value: approximately 65 mg/kg bw
Method:
GLP: Yes[ ] No[x] ?[ ]
Test substance: Disodium disulphite
Remarks:
Reference: Hoppe, J. O., F. C. Goble. The intravenous toxicity of sodium bisulfite. J. Pharmacol. Exp. Therap. 101, 101-6, 1951

(d)
Type: LC0[ ]; LC50[ ]; LC100[ ]; LCLo [ ]; Other [ ]
LD0[ ]; LD50[x]; LD100[ ]; LDLo [ ]; Other [ ]
Species/strain Hamster/Golden Syrian
Route of Administration: i.m.[ ]; i.p [ ]; i.v. [x]; infusion [ ]; s.c. [ ]; Other [ ]
Exposure time:
Value: approximately 95 mg/kg bw
Method:
GLP: Yes[ ] No[x] ?[ ]
Test substance: Disodium disulphite
Remarks:
Reference: Hoppe, J. O., F. C. Goble. The intravenous toxicity of sodium bisulfite. J. Pharmacol. Exp. Therap. 101, 101-6, 1951

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION

(a)
Species/strain Rabbit/Albino New Zealand
Results: Highly corrosive [ ] ; corrosive [ ]; Highly irritating [ ]; Irritating [ ]; Moderate irritating [ ]; Slightly irritating [ ]; Not irritating [x]
Classification: Highly corrosive (cause severe burns) [ ]; Corrosive (caused burns) [ ]; Irritating [ ]; Not irritating [x]
Method: OECD Guideline 404 "Acute Dermal Irritation/Corrosion" 19981
GLP: Yes[x] No[ ] ?[ ]
Test substance: Disodium disulphite-powder, min. purity 96 %, Other TS
Remarks: 500 mg of the chemical was prepared into a paste with a saline solution (NaCl 0.9 %) and applied to the animal semiocclusively over a 2.5 x 2.5 cm2 area. The skin was evaluated after 30-60 min, as well as 24, 48 and 72 h after the patch was removed.
Reference: Hoechst AG (1987); unpublished studies (87.1241)

5.2.2 EYE IRRITATION/CORROSION

(a) Preferred result

Species/strain	Rabbit
Results:	Highly corrosive [ ] ; corrosive [ ]; Highly irritating [ ]; Irritating [x]; Moderate irritating [ ]; Slightly irritating [ ]; Not irritating [ ]
Classification:	Irritating [x]; Not irritating [ ]; Risk of serious damage to eyes [ ]
Method:	OECD TG 405 (1987)
GLP:	Yes[x] No[ ] ?[ ]
Test substance:	Disodium disulphite-powder, min. purity 96 %, other TS
Remarks:	
Reference:	Hoechst AG (1987); unpublished result (87.1293).

5.3 SKIN SENSITIZATION

(a)

Type:	
Species/strain:	Guinea pig
Results:	Sensitizing [ ]; Not sensitizing [x]; ambiguous [ ]
Classification:	(If possible, according to EC Directive 67/548/EEC) Sensitizing [ ]; Not sensitizing [ ]
Method:	Standardized skin sensitization test
GLP:	Yes [ ] No [ ] ? [x]
Test substance:	
Remarks:	0/10 guinea pigs responded positively
Reference:	Eastman Kodak Co., U.S. Toxic Substance Control Act Submission, Microfiche No. OTS 0557795, Old Doc ID:86940000099, 1980

5.4 REPEATED DOSE TOXICITY

(a) Preferred Result

Species/strains:	Rat / Wistar
Sex:	Female [ ]; Male [ ]; Male/Female [x]; No data [ ]
Route of administration:	Feeding(p.o)
Exposure period:	104 weeks (F0 and F1 generations), 30 weeks (F2 generations)
Frequency of treatment:	Daily
Post exposure observation period:	
Dose:	0, 0.125, 0.25, 0.5, 1.0, 2.0 % in feed
Control group:	Yes [x]; No [ ]; No data [ ] Concurrent no treatment [x]; Concurrent vehicle [ ]; Historical [ ]
NOAEL:	local toxicity : 0.44 % (as actual dose) or 0.5 % (in the diet) system toxicity : 1.91 % (as actual dose) or 2 % (in the diet)
LOAEL:	0.92 % (actual dose) or 1.0 % (in the diet)
Results:	The most sensitive criteria of sulphite damage in the present studies turned out to be the presence of occult blood in the faeces and changes in gastric morphology. At 0.5 % of this chemical, neither these nor any of the other criteria were affected. Taking the loss of sulphite into account, the NOAEL was 0.44 % $Na_2S_2O_5$ which corresponds to an intake of 217 mg $Na_2S_2O_5$ /kg b.w./day.
Method:	Other (multigeneration study)
GLP:	Yes [ ]; No [x]; ? [ ]
Test substance:	source : Amsterdamsche Chinine Fabriek, purity : 95-99 % (as calculated from SO_2 determination)
Remark:	The actual doses were 0, 0.098, 0.215, 0.44, 0.92, 1.91 % (sulphit loss occurred)
Reference:	Til, H.P., V.J. Feron, A.P. De Groot. The toxicity of sulfite. I. Long-term feeding and multigeneration studies in rats. Fd. Cosmet. Toxicol. 10, 291-310, 1972

(b)

Species/strains:	Rat / Wistar
Sex:	Female [ ]; Male [ ]; Male/Female [x]; No data [ ]
Route of administration:	Feeding (p.o)
Exposure period:	8 or 12 weeks

Frequency of treatment: Daily
Post exposure observation period:
Dose: 4, 6 % in feed
Control group: Yes [x]; No [ ]; No data [ ]
Concurrent no treatment [x]; Concurrent vehicle [ ]; Historical [ ]
NOEL:
LOEL:
Results: Feeding sulfite induce hyperplastic fundic glands and dilated glands.
Method: Subchronic study
GLP: Yes [ ]; No [ ]; ? [x]
Test substance:
Remark: The animals were fed on thiamine-supplemented feed, which was mixed with 4 or 6 % test substance
Reference: Beems, R.B., B.J. Spit, H.B.W.M. Koeter, V.J. Feron. Nature and Histogenesis of sulfite-induced gastric lesions in rats. Exp. Mol. Pathol. 36 (3), 316-25, 1982

(c)
Species/strains: Rabbit
Sex: Female [ ]; Male [x]; Male/Female [ ]; No data [ ]
Route of administration: i.v.
Exposure period: 3 weeks
Frequency of treatment: 3 times/day and 5 d/weeks
Post exposure observation period:
Dose: 10, 20, 40 mg/kg
Control group: Yes [x]; No [ ]; No data [ ]
Concurrent no treatment [x]; Concurrent vehicle [ ]; Historical [ ]
NOEL: > 40 mg/kg in feed
LOEL:
Results: The test was performed using 3 animals/dose (2 animals in control). During the experimental period (21 days), no dead animals were observed. Neither macroscopic nor microscopic changes were observed in the heart, lung, liver, spleen and kidney. Intravenous injection caused the formation of 2-3 cm long thrombus. The addition of 6 % parenamin (protein hydrolysate) could hinder this thrombus formation.
Method:
GLP: Yes [ ]; No [x]; ? [ ]
Test substance:
Remark:
Reference: Hoppe, J. O., F. C. Goble. The intravenous toxicity of sodium bisulfite. J. Pharmacol. Exp. Therap. 101, 101-6, 1951

(d)
Species/strains: Pig / other: Hollaendische Landrasse
Sex: Female [ ]; Male [ ]; Male/Female [x]; No data [ ]
Route of administration: Oral feed
Exposure period: 15-19 or 48-51 weeks
Frequency of treatment: Daily
Post exposure observation period:
Dose: 0.06, 0.16, 0.35, 0.83, 1.72 % in feed
Control group: Yes [x]; No [ ]; No data [ ]
Concurrent no treatment [x]; Concurrent vehicle [ ]; Historical [ ]
NOEL: 0.35 % in feed
LOEL:
Results:
Method: The testing was performed using 20 each of male and female animals for dose groups. The animals were given thiamine-supplemented feed. At 1.72 % dose, the feed intake and body weight were reduced. The mortality was not affected. The thiamine content in urine and liver was reduced dose-dependently and it was lower than control animals at 1.72-% dose. In another study 15 each of male and female animals with 1.72 % sodium metasulfite (paired feeding study), no effect on feed intake and weight gain was observed. Hematological examination showed no change in comparison with control. Besides these, no indication of blood in feces was observed. Each 14 animals of male and female were sacrificed after 15-19

weeks and the remaining animals were sacrificed after 48-51 weeks. Relative organ weight was increased in heart, kidney and spleen at 0.83 % and 1.72 % doses and in liver at 1.72 % dose. Alteration of stomach and darkening of cecum were formed at 0.83 % and 1.72 % doses. At three doses, hyperplastic in stomach mucosa was observed. Epithelial hyperplasia and neutrophilic leucocyte in the gullet was also observed. In the mucosa of blind gut at 0.83 and 1.72 % dosing, pigmented macrophage often appeared. In the highest dose, lipid-containing Kupffer's cells were frequently observed in the liver.

GLP: Yes [ ]; No [x]; ? [ ]
Test substance: source : Amsterdamsche Chinine Fabriek, purity : 95-99 %
Remark:
Reference: Til, H.P., V.J. Feron, A.P. De Groot. The toxicity of sulfite. II. Short and long-term feeding studies in pigs. Fd. Cosmet. Toxicol. 10, 463-472, 1972

5. 5 GENETIC TOXICITY *IN VITRO*

A. BACTERIAL TEST

(a) Preferred Result
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* TA98, TA100, 1537 & 1538
Concentration: 20 - 5000 µg /plate
Metabolic activation: With [ ]; Without [ ]; With and Without [x]; No data [ ]
Results:
Cytotoxicity conc: With metabolic activation : not observed
Without metabolic activation : not observed
Precipitation conc:
Genotoxic effects: + ? -
With metabolic activation : [ ] [ ] [x]
Without metabolic activation : [ ] [ ] [x]
Method: OECD TG 471 (1983)
GLP: Yes [ ]; No [x]; ? [ ]
Test substance: Source : BASF Aktiengesellschaft Purity : 98 %
Remarks: Standard Plate Test; Preincubations test
Reference: BASF AG, Dept. Toxicology, unpublished result (89/380), 09.October.1989

(b)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* TA98, TA100, 1535, 1537 & 1538
Escherichia coli WP 2 (uvrA)
Concentration: 0.3 – 10000.0 µg/plate
Metabolic activation: With [ ]; Without [ ]; With and Without [x]; No data [ ]
Results:
Cytotoxicity conc: With metabolic activation : 333.3 µg/plate
Without metabolic activation : 10000 µg/plate
Precipitation conc:
Genotoxic effects: + ? -
With metabolic activation : [ ] [ ] [x]
Without metabolic activation : [ ] [ ] [x]
Method: Other
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: Source : Baker Chemical Co., Phillipsburg
Remarks:
Reference: 1. National Technical Information Service U.S. Department of Commerce (NTIS), Microbial Mutagenesis Testing of Substances : Compound Report F76-004 Sodium Meta-Bisulfite, PB 89-193684 (1978)

2. Prival, M.J., Simmon,V.F. , Mortelmans, K.E. Bacterial mutagenicity testing of 49 food ingredients gives very few positive results. Mutat. Res. 260 (4), 321-329, 1991

(c)
Type: Bacterial reverse mutation as say
System of testing: *Salmonella typhimurium* TA1530
Concentration: Not specified
Metabolic activation: With [ ]; Without [x]; With and Without [ ]; No data [ ]
Results:
Cytotoxicity conc: With metabolic activation : mg/plate
Without metabolic activation : no data
Precipitation conc:
Genotoxic effects: + ? -
With metabolic activation : [ ] [ ] [ ]
Without metabolic activation : [ ] [ ] [x]
Method: Other(Ames1975)
GLP: Yes [ ]; No [ ]; ? [x]
Test substance:
Remarks:
Reference: Green, S., J. Present and future uses of mutagenicity tests for assessment of the safety of food additives. Environ. Pathol. Toxicol., 1, 49-54, 1977

(d)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* TA 92, 94, 98, 100, 1535 &1537
Concentration: maximum dose 50 mg/plate
Metabolic activation: With [ ]; Without [ ]; With and Without [x]; No data [ ]
Results:
Cytotoxicity conc: With metabolic activation : not observed
Without metabolic activation : not observed
Precipitation conc:
Genotoxic effects: + ? -
With metabolic activation : [ ] [ ] [x]
Without metabolic activation : [ ] [ ] [x]
Method: Other (Ames 1975)
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: Provided by Japan Food Additive Association, Purity : 95 %
Remarks:
Reference: Ishidate, M., T. Sofuni, K. Yoshikawa, M. Hayashi, T. Nohmi, M. Sawada, A. Mastuoka. Primary mutagenicity screening of food additives currently used in Japan. Fd. Chem. Toxic. 22, 623-636, 1984

(e)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* TA 1530
Concentration: no details
Metabolic activation: With [ ]; Without [ ]; With and Without [ ]; No data [x]
Results: Positive
Cytotoxicity conc: With metabolic activation : mg/plate
Without metabolic activation : mg/plate
Precipitation conc:
Genotoxic effects: + ? -
With metabolic activation : [ ] [ ] [ ]
Without metabolic activation : [ ] [ ] [ ]
Method:
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: disodium disulphite
Remarks: The article is not to explain, by which system was found the positive reaction.
Reference: Maxwell, W. A. and Newell, G. W. Mol. Environ. Aspects Mutagenesis, Proc. Publ. Rochester Int. Conf. Environ. Toxic. 6th , 223-252,1973

(f)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* TA 97
Concentration:
Metabolic activation: With [ ]; Without [x]; With and Without [ ]; No data [ ]
Results:
Cytotoxicity conc: With metabolic activation : mg/plate
Without metabolic activation : no data
Precipitation conc:
Genotoxic effects: + ? -
With metabolic activation : [ ] [ ] [ ]
Without metabolic activation : [x] [ ] [ ]
Method:
GLP: Yes [ ]; No [ ]; ? [x]
Test substance:
Remarks: The study indicates that the mutagenic action of sodium metabisulfite depends on incubation conditions (temperature, pH, content of mannitol, ethanol etc.)
Reference: Pagano, D., A. E. Zeiger, A. Stack. Autoxidation and mutagenicity of sodium bisulfite. Mutation Res. 228, 89-96, 1990

(g)
Type: Bacterial reverse mutation assay
System of testing: *Escherichia coli* AP 16, AP 18
Concentration:
Metabolic activation: With [ ]; Without [x]; With and Without [ ]; No data [ ]
Results:
Cytotoxicity conc: With metabolic activation : mg/plate
Without metabolic activation : no data
Precipitation conc:
Genotoxic effects: + ? -
With metabolic activation : [ ] [ ] [ ]
Without metabolic activation : [x] [ ] [ ]
Method:
GLP: Yes [ ]; No [x]; ? [ ]
Test substance:
Remarks:
Reference: Pekhov, A.P, V.N. Reshetnikova. Test strains of *E. coli* for the detection of chemical mutagens. Bull. Exp. Biol. Med. (USSR) 84, 1043-5, 1977

(h)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* G 46, C 207, 3076, TA 98, 100, 1535, 1537
Concentration:
Metabolic activation: With [ ]; Without [ ]; With and Without [x]; No data [ ]
Results:
Cytotoxicity conc: With metabolic activation : no data
Without metabolic activation : no data
Precipitation conc:
Genotoxic effects: + ? -
With metabolic activation : [x] [ ] [ ]
Without metabolic activation : [ ] [ ] [x]
Method:
GLP: Yes [ ]; No [x]; ? [ ]
Test substance: Source : E.Merck, Darmstadt
Remarks: Spot test
Reference: Subba Rao, V. and A.S .Aiyar. Mutagenicity evaluation studies with food additives and radiolytic products of sugars. Proc. Symp. Mutagen. Carcinogen Teratogen Chem. 88, 104-14, 1975

(i)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* G 46 : TA 92, 1535, 100, SB 2802, 2061(his G46)
TR 3243 : TA88, 110, 90, 97(his D6610)

D 3052 : TA 1538, 98(his D3052)
C3076 : TA1537, 1977(his C3076)

Concentration: 0.01-0.64 M/plate
Metabolic activation: With [ ]; Without [x]; With and Without [ ]; No data [ ]
Results:
Cytotoxicity conc: With metabolic activation : mg/plate
Without metabolic activation : 0. 32 M
Precipitation conc:
Genotoxic effects:

	+	?	-
With metabolic activation :	[ ]	[ ]	[ ]
Without metabolic activation :	[x]	[ ]	[ ]

Method:
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: Source : Sigma Chemical Co.
Remarks: Sodium metabisulfite showed a weak m utagenicity in the above system. These systems are characterized by mutation in his G46 or D6610. No mutagenicity was observed in other systems.
Reference: Pagano, D. G. and E. Zeiger. Condition affecting the mutagenicity of sodium bisulfite in *S. typhimurium* . Mutation Res. 179, 159-66, 1987

(j)
Type: Bacterial reverse mutation assay
System of testing: *Salmonella typhimurium* G 46 : TA 92, 1950, 2410, GW 19, TS 24
Concentration: 0, 0.1, 0.5, 1.0, 1.5, 2.0 M
Metabolic activation: With [ ]; Without [x]; With and Without [ ]; No data [ ]
Results:
Cytotoxicity conc: With metabolic activation : mg/plate
Without metabolic activation : not specified
Precipitation conc:
Genotoxic effects:

	+	?	-
With metabolic activation :	[ ]	[ ]	[ ]
Without metabolic activation :	[x]	[ ]	[ ]

Method:
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: source : Fisher Scientific Co. mixture of disodium disulphite and sodium metabisulfite
Remarks:
Reference: De Giovanni-Donnelly, R. The mutagenicity of sodium busulfite on based-substitution strains of *S. typhimurium*. Teratogen. Carcinogen. Mutagen. 5, 195-203, 1985

(k)
Type: Host mediated assay
System of testing: *Salmonella typhimurium* G 46, TA 1530/ Mouse
Concentration: 5 %(w/v)
Metabolic activation: With [ ]; Without [ ]; With and Without [ ]; No data [ ]
Results:
Cytotoxicity conc: With metabolic activation : mg/plate
Without metabolic activation : mg/plate
Precipitation conc:
Genotoxic effects:

	+	?	-
With metabolic activation :	[ ]	[ ]	[x]
Without metabolic activation :	[ ]	[ ]	[ ]

Method:
GLP: Yes [ ]; No [ ]; ? [x]
Test substance:
Remarks:
Reference: 1. National Technical Information Service U.S. Department of Commerce (NTIS), Study of the Mutagenic Effect of Sodium Meta- Bisulfite (71-22), PB -221 825 (1972)
2. Maxwell, W. A. and G. W. Newell. Mol. Environ. Aspects Mutagenesis, Proc. Publ. Rochester Int. Conf. Environ. Toxic. 6th (1973), 223-252 ,1974

B. NON-BACTERIAL TEST

(a) Preferred Results

Type: Cytogenetic assay
System of testing: CHL-cell
Concentration: up to 0.125 mg/mL
Metabolic activation: With [ ]; Without [x]; With and Without [ ]; No data [ ]
Results:
Cytotoxicity conc: With metabolic activation : mg/plate
Without metabolic activation : not observed
Precipitation conc:
Genotoxic effects: + ? -
With metabolic activation : [ ] [ ] [ ]
Without metabolic activation : [ ] [ ] [x]
Method:
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: Source : Japan Food Additive Association, Purity : 95 %
Remarks:
Reference: Ishidate, M., T. Sofuni, K. Yoshikawa, M. Hayashi, T. Nohmi, M. Sawada, A. Matsuoka. Primary mutagenicity screening of food additives currently used in Japan, Fd. Chem. Toxic. 22, 623-636, 1984

(b)

Type: Cytogenetic assay
System of testing: Embryonic lung cell WI-38
Concentration: 2.5, 25, 250 µg/mL
Metabolic activation: With [ ]; Without [x]; With and Without [ ]; No data [ ]
Results:
Cytotoxicity conc: With metabolic activation : mg/plate
Without metabolic activation : mg/plate
Precipitation conc:
Genotoxic effects: + ? -
With metabolic activation : [ ] [ ] [ ]
Without metabolic activation : [x] [ ] [ ]
Method:
GLP: Yes [ ]; No [ ]; ? [x]
Test substance:
Remarks: Test substance indicates the inhibition of cell division and remarkable damage (aberration) in anaphase cells.
Reference: 1. National Technical Information Service U.S. Department of Commerce (NTIS), Study of the Mutagenic Effect of Sodium Meta- Bisulfite (71-22), PB-221 825 (1972)
2. Maxwell, W. A. and G. W. Newell. Mol. Environ. Aspects Mutagenesis, Proc. Publ. Rochester Int. Conf. Environ. Toxic. 6th (1973), 223-252 (1974)

(c)

Type: Cytogenetic assay
System of testing: Human embryonic lung cell WI-38
Concentration: mg/plate
Metabolic activation: With [ ]; Without [x]; With and Without [ ]; No data [ ]
Results:
Cytotoxicity conc: With metabolic activation : mg/plate
Without metabolic activation : mg/plate
Precipitation conc:
Genotoxic effects: + ? -
With metabolic activation : [ ] [ ] [ ]
Without metabolic activation : [x] [ ] [ ]
Method:
GLP: Yes [ ]; No [ ]; ? [x]
Test substance:
Remarks: The result showed non-correlation with other testing systems. No detailed experimental information.

Reference: Green, S., J. Present and future uses of mutagenicity tests for assessment of the safety of food additives. Environ. Pathol. Toxicol. 1, 49-54, 1977

(d)
Type: Recombination assay
System of testing: *Saccharomyces cerevisiae* D 3
Concentration: mg/plate
Metabolic activation: With [ ]; Without [x]; With and Without [ ]; No data [ ]
Results: Negative
Cytotoxicity conc: With metabolic activation : mg/plate
Without metabolic activation : mg/plate
Precipitation conc:
Genotoxic effects: + ? -
With metabolic activation : [ ] [ ] [ ]
Without metabolic activation : [ ] [ ] [x]
Method:
GLP: Yes [ ]; No [ ]; ? [x]
Test substance:
Remarks:
Reference: Green, S., J. Present and future uses of mutagenicity tests for assessment of the safety of food additives. Environ. Pathol. Toxicol. 1, 49-54, 1977

(e)
Type: Recombination assay
System of testing: *Saccharomyces cerevisiae* D 3
Concentration: 0.1 %(w/v)
Metabolic activation: With [ ]; Without [ ]; With and Without [ ]; No data [ ]
Results: Negative
Cytotoxicity conc: With metabolic activation : mg/plate
Without metabolic activation : mg/plate
Precipitation conc:
Genotoxic effects: + ? -
With metabolic activation : [ ] [ ] [ ]
Without metabolic activation : [ ] [ ] [ ]
Method:
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: Provided by FDA U.S, no detail information
Remarks:
Reference: 1. National Technical Information Service U.S. Department of Commerce (NTIS), Study of the Mutagenic Effect of Sodium Meta- Bisulfite (71-22), PB -221 825 (1972)
2. Maxwell, W. A. and G. W. Newell. Mol. Environ. Aspects Mutagenesis, Proc. Publ. Rochester Int. Conf. Environ. Toxic. 6th (1973), 223-252 (1974)

5. 6 GENETIC TOXICITY IN VIVO

(a) Preferred Result
Type: Cytogenetic assay
Species/Strains: Rat/Albino
Sex: Female [ ]; Male [x]; Male/Female [ ]; No data [ ]
Route of Administration: Oral
Exposure period: Max. 5 days
Doses: 0, 30, 700, 1200 mg/kg
Results: Negative
Method: chromosome aberration test
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: Provided by FDA US, no detail information
Remarks: No adverse effect on bone marrow cells.
Reference: 1. National Technical Information Service U.S. Department of Commerce (NTIS), Study of the Mutagenic Effect of Sodium Meta- Bisulfite (71-22), PB -221 825 (1972)

2. Maxwell, W. A. and G. W. Newell. Mol. Environ. Aspects Mutagenesis, Proc. Publ. Rochester Int. Conf. Environ. Toxic. 6th (1973), 223-252 (1974)

(b)

Type: Cytogenetic assay
Species/Strains: Chinese Hamster, Mouse
Sex: Female [ ]; Male [ ]; Male/Female [x]; No data [ ]
Route of Administration: Gavage
Exposure period: 2 times applications
Doses: Equivalent to 660 mg/ kg (normal animal), 330 mg/kg (deficient animal) SO2
Results: Negative
Method: Other
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: Disodium disulphite
Remarks: The study was performed using sulfite-oxidase deficient and normal animals. Sulfite-oxidase deficiency was obtained by molybdenum -deficient diet and tungsten supply. As a protein control, animals treated with cyclophosphamid were used.
Reference: Renner, H. W. and J .Wever. Attempts to induce cytogenetic effects with sulphite in sulphite oxidase-deficient Chinese Hamsters and mice. Food Chem. Toxicol. 21, 123-7,1983

(c)

Type: Rodent dominant lethal assay
Species/Strains: Rat/Sprague-Dawley
Sex: Female [ ]; Male [x]; Male/Female [ ]; No data [ ]
Route of Administration: Oral feed
Exposure period: 10 weeks
Doses: 0,125, 417, 1250 mg/kg daily
Results: Negative
Method: The positive control was triethylenemelamine given in the drinking water at a dose of 0.6 mg/L. The diet was supplemented with 50 mg/kg in corn oil. The controls (+ and-) were fed a diet with the corn oil alone. After the 10 wk treatment, 40 male rats from the vehicle control group and 20 from each TS and positive control group were individually housed and paired with 2 virgin females for 7 days. Each female was sacrificed 15-19 d after the 1st d of cohabitation. To investigate the dominant lethal effect the following were investigated : total implants, total dead implants, total live implants, preimplantation loss. Total corpora lutea were also recorded.
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: source : J.T. Baker Chemical Co.
Remarks:
Reference: National Technical Information Service U.S. Department of Commerce (NTIS), Study of the Mutagenic Effect of Sodium Meta-Bisulfite (76-73) by Dominant Lethal Test in Rats, PB -299 836 (1979)

(d)

Type: Dominant lethal assay
Species/Strains: Rat
Sex: Female [ ]; Male [x]; Male/Female [ ]; No data [ ]
Route of Administration: Oral
Exposure period: single dose
Doses: 30, 700, 1200 mg/kg (single dose)
Results: Negative
Method: other
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: Disodium disulphite
Remarks: No adverse effect
Reference: 1. National Technical Information Service U.S. Department of Commerce (NTIS), Study of the Mutagenic Effect of Sodium Meta- Bisulfite (71-22), PB -221 825 (1972)
2. Maxwell, W. A. and G. W. Newell. Mol. Environ. Aspects Mutagenesis, Proc. Publ. Rochester Int. Conf. Environ. Toxic. 6th (1973), 223-252 (1974)

(e)

Type:	Micronucleus assay
Species/Strains:	Hamster, Mouse
Sex:	Female [ ]; Male [ ]; Male/Female [x]; No data [ ]
Route of Administration:	Gavage
Exposure period:	flushing out of bone marrow cell 30 and 6 hour after 2 times application
Doses:	Equivalent to 660 mg/kg (normal animal), 330 mg/kg (deficient animal) SO2
Results:	Negative
Method:	Other (Schimd 1973)
GLP:	Yes [ ]; No [ ]; ? [x]
Test substance:	Disodium disulphite
Remarks:	The study was undertaken using sulfite-oxidized deficient and normal animals. Sulfite-oxidase deficiency was obtained by molybdenum -deficient diet and tungsten supply. As a protein control, animals treated with cyclophosphamid were used.
Reference:	Renner, H. W. and J .Wever. Attempts to induce cytogenetic effects with sulphite in sulphite oxidase-deficient Chinese Hamsters and mice. Food Chem. Toxicol. 21, 123-7 ,1983

(f)

Type:	Sister chromatid exchange assay
Species/Strains:	Hamster, Mouse
Sex:	Female [ ]; Male [ ]; Male/Female [x]; No data [ ]
Route of Administration	s.c.
Exposure period:	animals killed 30 and 6 hour after 2 equal dose
Doses:	Equivalent to 50 mg/kg, 660 mg/kg (normal animal), 165 mg SO2/kg (enzyme deficient animal) calculated as SO2
Results:	Negative
Method:	other (Schwarzacher & Wolf, 1974)
GLP:	Yes [ ]; No [ ]; ? [x]
Test substance:	Disodium disulphite
Remarks:	The study was undertaken using sulfite-oxidase deficient and normal animals. Sulfite-oxidase deficiency was obtained by molybdenum -deficient diet and tungsten supply. As a protein control, animals treated with cyclophosphamid were used.
Reference:	Renner, H. W. and J. Wever. Attempts to induce cytogenetic effects with sulphite in sulphite oxidase-deficient Chinese Hamsters and mice. Food Chem. Toxicol. 21, 123-7,1983

5. 7 CARCINOGENECITY

(a) Preferred Result

Species/Strains:	Rat / Wistar
Sex:	Female [ ]; Male [ ]; Male/Female [x]; No data [ ]
Route of Administration:	p.o.
Exposure period:	104 weeks
Frequency of treatment:	
Postexposure observation period:	
Doses:	0; 0.125; 0.25; 0.5; 1; 2 % in diet
Control group:	Yes [x]; No [ ]; No data [ ]; Concurrent no treatment [x]; Concurrent vehicle [ ]; Historical [ ]
Results:	Negative
Method:	
GLP:	Yes [ ]; No [x]; ? [ ]
Test substance:	source : Amsterdamsche Chinine Fabriek, purity : 95-99 %
Remarks:	multiple generation study referred 5.4, 5.8 Regarding neoplatic findings, the number of lymphoreticular pulmonary tumors in males decreased with increasing levels of sulphite. The incidence of thyroid and pituitary tumors in control males was exceptionally low, whereas those noted in the various test groups represented numbers normally found in the strain of rats used. All other neoplasms occurred in a random manner.
Reference:	Til, H.P., V.J. Feron, A.P. De Groot. The toxicity of sulfite. I. Long-term feeding and multigeneration studies in rats. Fd. Cosmet. Toxicol. 10, 291-310, 1972

b)
Species/Strains: Rat
Sex: Female [ ]; Male [ ]; Male/Female [ ]; No data [x]
Route of Administration: Drinking water
Exposure period: about 3 years
Frequency of treatment: Daily
Postexposure observation period:
Doses: Equivalent to 350, 750 ppm as SO2
Control group: Yes [x]; No [ ] ; No data [ ];
Concurrent no treatment [x]; Concurrent vehicle [ ]; Historical [ ]
Results: The study was undertaken for 2.5 years and 3 generations per dose group were used 13-19 animals. Effect of feed and water intake on the feces excretion, reproduction, lactation or incidence of tumor was not observed (NOEL > 750 ppm).
Method: 3 generation study
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: Disodium disulphite
Remarks:
Reference: Lockett, M. F. and I. L. Natoff. A study of toxicity of sulphite. J. Pharm. Pharmacol. 12, 488-96 (1960), cited in: Toxicological Evaluation of Certain Food Additives and Contaminants, WHO Food Additives Series 21, 30th Meeting of the Joint FAO/WHO Expert Committee on Food Additives,1986

5. 8 TOXICITY TO REPRODUCTION

(a) Preferred Result
Type: Fertility [ ]; One generation study [ ]; Two generation study [x]; Other [ ]
Species/Strains: Rat / Wistar
Sex: Female [ ]; Male [ ]; Male/Female [x]; No data [ ]
Route of Administration: Oral feed
Exposure period: 104 weeks (F0, F1-generation), 30 weeks (F2-generation)
Frequency of treatment: Once a day
Postexposure observation period:
Premating exposure period: Male: 21 weeks Female: 21 weeks
Duration of test: until the weaning of the F3 animals
Doses: 0.125, 0.25, 0.5, 1.0, 2.0 % in feed
Control group: Yes [x]; No [ ]; No data [ ];
Concurrent no treatment [x]; Concurrent vehicle [ ]; Historical [ ]
NOAEL parental : = 1.91 % (actual dose), 2 % (in the diet)
NOAEL F1 Offspring: = 1.91 % (actual dose), 2 % (in the diet)
NOAEL F2 Offspring: = 1.91 % (actual dose), 2 % (in the diet)
Results: No pronounced effects were observed on reproductive performance in any generation and no effects on gonads were seen histologically
Method: continuous breeding
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: source : Amsterdamsche Chinine Fabriek, Holland, purity : 95-99 %
Remarks:
Reference: Til, H.P., V.J. Feron, A.P. De Groot. The toxicity of sulfite. I. Long-term feeding and multigeneration studies in rats. Fd. Cosmet. Toxicol. 10, 291-310, 1972

(b)
Type: Fertility [x]; One generation study [ ]; Two generation study [ ]; Other [x]
Species/Strains: Rat
Sex: Female [ ]; Male [ ]; Male/Female [ ]; No data [x]
Route of Administration: Drinking water
Exposure period: Lifetime
Frequency of treatment: Daily
Postexposure observation period:
Premating exposure period: Male: Female:
Duration of test:
Doses: Equivalent to 350, 750 ppm SO2
Control group: Yes [x]; No [ ]; No data [ ];

Concurrent no treatment [x]; Concurrent vehicle [ ]; Historical [ ]
NOEL parental : = 750 ppm
NOEL F1 Offspring: = 750 ppm
NOEL F2 Offspring: = 750 ppm
Results: The study was undertaken for 2.5 years and 3 generations. Per dose group 13-19 animals were used. Effect of feed and water intake on the feces excretion, reproduction, lactation or incidence of tumor were not observed. Detailed description was not given (NOEL > 750 ppm).
Method:
GLP: Yes [ ]; No [ ]; ? [x]
Test substance: Disodium disulphite
Remarks:
Reference: Lockett, M. F. and I. L. Natoff. A study of toxicity of sulphite. J. Pharm. Pharmacol. 12, 488-96 (1960), cited in: Toxicological Evaluation of Certain Food Additives and Contaminants, WHO Food Additives Series 21, 30th Meeting of the Joint FAO/WHO Expert Committee on Food Additives, 1986

5. 9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

(a) Preferred Result
Species/strain: Rat / Wistar
Sex: Female [x]; male [ ]; Male/Female [ ]; No data [ ]
Route of administration: Gavage
Duration of the test: day 20 of gestation
Exposure period: day of 6-15 of gestation
Frequency of treatment: Daily
Doses: 0, 1, 5, 24, 110 mg/kg bw
Control group: Yes [x]; No [ ]; No data [ ];
Concurrent no treatment [x]; Concurrent vehicle [ ]; Historical [ ]
NOAEL Maternal Toxicity :110 mg/kg bw/day
NOAEL Teratogenicity : 110 mg/kg bw/day
Results: Test substance did not cause any effect in implantation or survival rate in maternal and fetus. In comparison with control, no significant change was observed in the number of anomaly in soft and skeletal tissues.
GLP: Yes [ ]; No [ ]; ?[x]
Test substance: disodium disulphite (FDA 71-22)
Remarks:
Reference: National Technical Information Service U.S. Department of Commerce (NTIS), Teratologic Evaluation of FDA 71-22 (Sodium Meta-Bisulfite), PB-221 795 (1972)

(b)
Species/strain: Rabbit/Dutch
Sex: Female [x]; male [ ]; Male/Female [ ]; No data [ ]
Route of administration: Gavage
Duration of the test: day 29 of gestation
Exposure period: 6th –18th pregnated days
Frequency of treatment: Daily
Doses: 0, 1.23, 5.71, 26.5, 123 mg/kg bw
Control group: Yes [x]; No [ ]; No data [ ];
Concurrent no treatment [ ]; Concurrent vehicle [x]; Historical [ ]
NOAEL Maternal Toxicity:= 123 mg/kg bw/day
NOAEL Teratogenicity: = 123 mg/kg bw/day
Results: No clear effect on nidation, or on maternal or fetal survival. In comparison with control, no change was observed in the number of anomaly in soft and skeletal tissues.
GLP: Yes [ ]; No [ ]; ?[x]
Test substance: Disodium disulphite (FDA 71-22)
Remarks:
Reference: National Technical Information Service U.S. Department of Commerce (NTIS), Teratologic Evaluation of Compound FDA 71-22. Sodium Meta-Bisulfite in Rabbit, PB-267 194 (1974)

(c)

Species/strain:	Hamster
Sex:	Female [x]; male [ ]; Male/Female [ ]; No data [ ]
Route of administration:	Gavage
Duration of the test:	no details
Exposure period:	6th –10th pregnated days
Frequency of treatment:	Daily
Doses:	0, 1, 6, 26, 120 mg/kg
Control group:	Yes [ ]; No [ ]; No data [ ]; Concurrent no treatment [ ]; Concurrent vehicle [x]; Historical [ ]
NOEL Maternal Toxicity:	120 mg/kg bw/day
NOEL Teratogenicity:	120 mg/kg bw/day
Results:	Test substance did not cause any effect in implantation or survival rate in maternal and fetus. In comparison with control, no change was observed in the number of anomaly in soft and skeletal tissues.
GLP:	Yes [ ]; No [ ]; ?[x]
Test substance:	Disodium disulphite
Remarks:	
Reference:	National Technical Information Service U.S. Department of Commerce (NTIS), Teratologic Evaluation of Compound FDA 71-22. Sodium Meta-Bisulfite in Rabbit, PB-267 194 (1974)

(d)

Species/strain:	Rat / Wistar
Sex:	Female [x]; male [ ]; Male/Female [ ]; No data [ ]
Route of administration:	Drinking water
Duration of the test:	
Exposure period:	3 weeks before mating to 20th pregnated day
Frequency of treatment:	Daily
Doses:	4750, 9500 mg/L (25, 50 mM)
Control group:	Yes [x]; No [ ]; No data [ ]; Concurrent no treatment [x]; Concurrent vehicle [ ]; Historical [ ]
NOEL Maternal Toxicity:	
NOEL Teratogenicity	
Results:	Tested with normal and tungsten - treated animals. The tungsten brought about sulfite-oxidized deficiency. It could not identify any adverse effect induced by disodium disulphite in reproduction or teratogenicity.
GLP:	Yes [ ]; No [ ]; ?[x]
Test substance:	
Remarks:	
Reference:	Dulak, L., G.Chiang, A.F. Gunnison. A sulphite oxidase-deficient rat model: Reproductive toxicology of sulphite in the female. Food Chem. Toxicol. 22, 599-607, 1984

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

Type:	Sensory irritation
Results:	Sodium metabisulfite aerosol actively evoked sensory irritation to upper respiratory tract in mice, due to presence of bisulfite anion formed in slightly alkaline pH of nasal mucosa.
Remarks:	
Reference:	Alarie, Y., Wakisaka I., Oka S. Sensory irritation by sulfite aerosol. Environ. Physiol. Biochem. 3 (4), 182-4, 1973.

B. Toxicodynamics, toxicokinetics

(a)

Type:	Metabolism
Results:	
Remarks:	The literature states that a rapid and quantitative elimination of disodium disulphite

as sulfate was observed in man and dog.

Reference: Rost. E., Handbuch der Lebensmittelchemie, Band 1, S.993, Springer- Verlag (1933) cited in : Toxicological Evaluation of Certain Food additives and Contaminants, WHO Food Additives Series 21 (1986)

(b)

Type: Metabolism

Results:

Remarks: The study describes comparative metabolic examinations of injected sulfite in rats, rabbits and monkeys for the purpose of estimating the in vivo function of sulfite oxidase. The excretion rate was 1: 0.34: 0.2 in rats, rabbits and monkeys, respectively. If it is assumed that man clears sulfite similarly to the rhesus monkey, it would appear that the rat is not a good model for prediction of human toxicity.

Reference: Gunnison, A. F. et al., Toxicol. Appl. Pharmacol. 42, 99-109 (1977)

5.11 EXPERIENCE WITH HUMAN EXPOSURE

(a)

Type: Respiratory disease

Results: Four cases of respiratory diseases probably due to the exposure or handling of sulfur derivates were presented. The responsibility of theses compounds stands on the clinical history, biological cellular tests and for one of them on the evolution under a metabisulfite-free diet and a positive oral provocation test at 5 mg.

Remarks:

Reference: Vallon C, J. Sainte-Laudy, M. Nasr. Allergie et exposition professionnelle aux composes soufres:questions posees. Allerg Immunol (Paris), 27, 83-87, 1995

(b)

Type: Asthma

Results: 6 or 20 presented a positive reaction, confirmed in 4 of 20 by double-blind challenge.

Remarks: Oral challenge tests were carried out with sodium metabisulfite solution doses of 5, 10, 25, 50 and 100 mg in 20 children aged 7-14 years with steroid-dependent brochial asthma.

Reference: Sanz J, A. Martorell, I Torro, J.C. Cerda, V Alvarez. Intolerance to sodium metabisulfite in children with steroid-dependent asthma. J Investig Allergol Clin Immunol. 2, 36-38, 1992

(c)

Type: Life-threatening asthma

Results: Sodium metabisulfite in food and drugs provoked life-threatening asthma. In one case, a 67-yr-old woman developed severe asthma almost immediately after ingesting a salad with a vinegar based dressing (the vinegar contained sodium metabisulfite). During oral challenge studies 2 weeks later, she developed severe bronchospasm within 30 min of ingesting sodium metabisulfite. In another case, a 23- yr-old woman developed rapid deterioration of moderately severe asthma following administration of an infusion of dexamethasone (24 mg) and an injection of metaclopromide (metoclopramide) (10 mg); both drugs contained sidium metabisulfite. Challenge reactions to sodium metabisulfite were positive. Orally administered dexamethasome which did not contain sodium metabisulfite induced no bronchospasm. The patient improved significantly during 6 months on a sodium metabisulfite free diet. It was suggested that the use of sodium metabisulfite as a preservative and anti-oxidant may need re-evaluation.

Remarks:

Reference: Baker G.J., P. Collett, D.H. Allen. Bronchospasm induced by metabisulfite-containing foods and drugs. Med J Aust. 2, 614-617, 1981

(d)

Type: Dermal disease

Results: acute urticaria attack.

Remarks: Case report of a 47-year-old man with severe acute intermittent urticaria. A placebo-controlled oral challenge test with 50 mg sodium disulfite
Reference: Wüthrich B, M.K. Kagi, J. Hafner. Disulfite-induced acute intermittent urticaria with vasculitis, Dermatology. 187, 290-292, 1993

(e)
Type: Patch-test
Results: positive
Remarks: Case report of contact dermatitis and asthma from sodium metabisulfite in a photographic technician. Patch-test with sodium metabisulfite 5 % pet.
Reference: Jacobs M C, R.J.G. Rycroft. Contact dermatitis and asthma from sodium metabisulfite in a photographic technician. Contact Dermatitis. 33, 65-66, 1992

(f)
Type: Patch-test
Results: positive
Remarks: Case report of a 39-year old man with dermatitis. Patch-test with sodium metabisulfite 2, 5, and 10 % in water. Control tests at 10 % in 5 subjects were all negative.
Reference: Apetato, M., Marques, M., S., J.; Contact Dermatitis 14, 194, (1986)

(g)
Type: Occupational asthma
Results: Two cases of occupational asthma in laundry workers exposed to sodium metabisulfite have been reported.
Remarks:
Reference: Le-Stradic-Reygagne A, in: Sodium metabisulfite, Documentation of threshold limit values. ACGIH, Cincinnati, 1991

(h)
Type: Patch-test
Results: negative
Remarks: Patch-tests in five patients with ocular hypersensitivity to eyes-drops also among other compounds.
Reference: Petersen P.E, R.B.Evans, M.A.Johnstone, W.R Handerson. Evaluation of ocular hypersensitivity to dipovalyl epinephrine by component eye-drop testing. J Allergy Clin Immunol. 85, 954-958, 1990

(i)
Type: Patch-test
Results: positive
Remarks: A thirty-year old male with erythematous vesiculapular skin eruptions with extreme pruritus on both hands showed positive patch-test reaction to DSD (10, 20, and 50 mg in pet.). Three controls were negative. Single oral provocation test with DS (5, 30, 50, and 100 mg in citric acid) gave neither skin nor pulmonary manifestations.
Reference: Larame B, P.M. Bedard, J. Hebert. Contact dermatitis to sulfating agents. J Allergy Clin Immunol. 28, 197, 1989

(j)
Type: Patch-test
Results: positive
Remarks: A 31-year-old woman with psoriasis developed acute allergic contact dermatitis during topical drug trial. Patch testing with ingredients showed a positive reaction to DSD (1 and 0.2 % in pet.).
Reference: Vestergaard LL., K. E Andersen. Am. J. Contact Dermatitis. 6, 174-175, 1995

(k)
Type: Anaphylaxis
Results: A case of metabisulfite induced anaphylaxis is presented in which convincing evidence of an IgE-mediated mechanism of action was found. The patient demonstrated urticaria, angioedema, nasal congestion, and apparent nasal polyp swelling following provocative challenge with sodium metabisulfite. Skin test to metabisulfite was positive as was a basophil histamine release test when the

patient's cells were incubated with metabisulfite. A review of metabisulfite induced allergic reactions in which an IgE-mediated mechanism demonstrated is presented

Remarks:

Reference: Sokol W.N, I.B. Hydick. Nasal congestion, urticaria, and angioedema, caused by IgE-mediated reaction to sodium metabisulfite. J. Allerg Clin Immunol. 65, 233-238, 1990

(l)

Type: Bronchospasm

Results: A case is reported of a patient with episodes of bronchospasm requiring hospital admission after handling disodium disulphite on the job. Skin tests for sodium metasulfite at a concn 10 mg/mL were negative. A simple blind oral provocation test of sodium metasulfite (1, 5, 20, and 50 mg) in acid medium was positive at the 50-mg dose, eliciting bronchial and nasal symptoms, and a decrease in CVF, FEVI, and PEF of more than 20 % over baseline values. The episode of bronchospasm has not recurred in the workplace since exposure to disodium disulphite was eliminated. Oral provocation with metasulfite in acid medium is considered as a good technique for confirming the diagnosis of these cases.

Remarks:

Reference: Valero, A.L., M. Bescos, P. Amat, and A. Malet. Bronchial asthma caused by occupational sulfite exposure. Allergol. Immunopathol. (Madr). 21(6), 221-4, 1993

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ROBUST STUDY SUMMARIES

Disodium disulphite (CAS No. 7681-57-4)

PHYSICAL/CHEMICAL ELEMENTS

1) MELTING POINT

TEST SUBSTANCE

- Identity : Disodium Disulphite (CAS NO. 7681-57-4)

⇒ Remarks : Source : BASF corporation, NR 80/339
Purity : 95 %

METHOD

- Method/guideline followed : Not stated
- GLP : No details
- Year : 1999

⇒ Remarks

RESULTS

- Melting point value in ºC: Not stated
- Decomposition : Yes --- 150ºC
- Sublimation (yes/no/ambiguous) : Not stated

⇒ Remarks : solid temperature 150ºC (decompose to form sulfur dioxide)

CONCLUSIONS

Decomposition starts at 150ºC

DATA QUALITY

- Reliabilities : Reliable with restrictions.

⇒ Remarks

REFERENCES (Free Text)

BASF AG safety data sheet sodium metadisulfite, 06. January. 1999

OTHER

- Last changed : September, 2001
- Order number for sorting

⇒ Remarks

4) PARTITION COEFFICIENT

TEST SUBSTANCE

- Identity : Disodium Disulphite(CAS NO. 7681-57-4)

⇒ Remarks : Source : BASF corporation, NR 80/339
Purity : Natriumpyrosulfit 95 %
1-Octano : > 99 %, Merck, Water : demineralizes

METHOD

- Method/guideline followed : Not stated
- GLP : No details
- Year : 1998

⇒ Remarks :
Test condition was not stated and Test chemical was analyzed by atomic absorption-spectrometric regulation.

RESULTS

- Log Pow : -3.7
- Temperature : 25ºC

⇒ Remarks :

- Measured result

substance name	substance content		balanced distribution(Pow)**a)**	Log Pow
	C(octanol) X 10^{-3}: g/L	**C**(water) : g/L		
Disodium disulphite	2.58	15.1	$1.7E10^{-4}$	-3.77
	6.71	60.3	$1.1E10^{-4}$	-3.95
	16.0	30.1	$5.3E10^{-4}$	-3.27
Mean value			$2.2E10^{-4}$	-3.7 ±0.3

a) Pow = C (octanol) / C (water)
C : concentration of the substance in 1-octanol or water

CONCLUSIONS

- Log Pow : –3.7.

⇒ Remarks

DATA QUALITY

- Reliabilities : Reliable with restrictions.

⇒ Remarks :

REFERENCES (Free Text)

BASF AG Physical/chemical, unpublished investigation, report BRU 88.221, 02. November. 1988.

OTHER

- Last changed : September, 2001
- Order number for sorting

⇒ Remarks

5) WATER SOLUBILITY

TEST SUBSTANCE

- Identity : Disodium Disulphite (CAS NO. 7681-57-4)

⇒ Remarks

METHOD

- Method/guideline followed : Not stated
- GLP : No details
- Year : 1999

⇒ Remarks :

RESULTS

- Value(g/L) at Temperature : 470 g/L at 20ºC
- Description of solubility : high soluble
- pH value and concentration at Temperature : Not stated
- *pKa value at 25ºC : Not stated.

⇒ Remarks :

CONCLUSIONS

- Solubility in water : 470 g/L at 20ºC

⇒ Remarks : This chemical is high soluble in water with 20ºC .

DATA QUALITY

- Reliabilities : Reliable with restrictions.

⇒ Remarks :

REFERENCES (Free Text)

. BASF AG, Sicherheitsdatenblatt Natriumdisulfit, 30.October. 2000

OTHER

- Last changed : September. 2001
- Order number for sorting

⇒ Remarks

10-1) ACUTE TOXICITY TO FISH

TEST SUBSTANCE

- Identity: Disodium Disulphite (CAS NO. 7681-57-4)

⇒ Remarks: Source : disodium disulphite, 98.3 %

METHOD

- Method / guideline followed : OECD TG 203
- Type (test type) : static
- GLP : Yes
- Year : 2001(study performed)
- Species / Strain / Supplier : *Oryzias latipes* (Medaka)
- Analytical monitoring : No
- Exposure period : 96 hours
- Statistical methods : Not relevant(limit test)

⇒ Remarks

– Test fish
  ·Age : 9 months
  ·Body length : 3.2 ±0.1 cm
  ·Body weight : 0.25 ±0.02 g

– Test condition:
  · Details of test: static
  · Dilution water source: underground water by passing through activated carbon and the membrane filter (1μm)
  · Dilution water chemistry : not stated
  · Stock and test solution and how they are prepared: dilution water was used to prepare the stock solution
  · Concentrations dosing rate, flow -through rate, in what medium : control, 100 mg/L
  · Vehicle/solvent and concentrations : not used
  · Stability of the test chemicals solutions : not stated
  · Exposure vessel type : 5 L glass aquarium non-sealed (25 x 14 x 25 cm), light/dark=16/8 hr
  · Number of replicates, fish per replicate: no replicates, 7 fish per concentration
  · Water chemistry in test (O2, pH) in the control and one concentration where effects were observed :DO 4.8 - 8.6 ; pH : 6.25 - 7.39

– Test temperature range : 23.9 - 24.5ºC
– Methods of calculating mean measured concentration: not relevant (limit test)

RESULTS

- Nominal concentration (as mg/L) : 100.0
- Measured concentration (as mg/L) : not stated
- Unit (results expressed in what unit) : mg/L
- Statistical results as appropriate : not relevant
- Element value:
  96 hr - LC50 > 100 mg/L

⇒ Remarks
- Biological observations :
  ·Observable symptoms of intoxication : All normal
- Table showing cumulative mortality: no death was observed

Nominal conc. (mg/L)	Number of fish at the beginning	Cumulative number of dead fish			
		24 hr	48 hr	72 hr	96 hr
0.0	7	0	0	0	0
100.0	7	0	0	0	0

Nominal conc. (mg/L)	Number of fish at the beginning	Cumulative number of dead fish			
		24 hr	48 hr	72 hr	96 hr
0.0	7	0	0	0	0
100.0	7	0	0	0	0

Nominal conc. (mg/L)	Number of fish at the beginning	Cumulative number of dead fish			
		24 hr	48 hr	72 hr	96 hr
0.0	7	0	0	0	0
100.0	7	0	0	0	0

10-2) ACUTE TOXICITY TO FISH

TEST SUBSTANCE

- Identity : Disodium Disulphite (CAS NO. 7681-57-4)

⇒ Remarks : Source : disodium disulphite, approx. 98 %, (BASF AG No 80/339)

METHOD

- Method / guideline followed : (other) German Industrial Standard Guideline Number DIN 38412 Group L, part 1 and part 15
- Type (test type) : static
- GLP: No
- Year : 1979
- Species / Strain / Supplier: rainbow trout (*Salmo gairdneri*), Obtained from Forellenhof fredelsloh 3413 morin towards 1, FRG.
- Analytical monitoring : No
- Exposure period : 96 hours
- Statistical methods : Probit Analysis

⇒ Remarks

– Test fish
  · Body length : 7.6 cm (avg.)
  · Body weight : 5.4 g (avg)
  ·Duration of adaptation : 3 days

– Test condition:
  · Details of test : static
  · Dilution water source : tap water
  · Dilution water chemistry : reconstituted freshwater was prepared from demineralized tap water that was resalted by the addition of 344 mg/L $CaSO_4.2H_2O$, 124 mg/L $MgSO_4.7H_2O$, 70 mg/L $NaHCO_3$ and 3 mg/L KCl, Oxygen content : > 6 mg/L, pH : 7 - 8
  · Stock and test solution and how they are prepared : not stated
  · Concentrations dosing rate, flow-through rate, in what medium : 0, 68.1, 100.0, 147.0, 215.0, 316.0 mg/L were tested
  · Vehicle/solvent and concentrations : not stated
  · Stability of the test chemicals solutions: not stated
  · Exposure vessel type : All-glass aquarium non-sealed (30 x 22 x 24 cm)
  · Number of replicates, fish per replicate : 10 fish per concentration
  · Water chemistry in test (O_2, pH) in the control and one concentration where effects were observed: Oxygen content : > 6 mg/L, pH : 7 - 8

pH values during the test

Conc. mg/L	Starting pH	Ending pH
0.0	7.6	7.4
68.1	6.5	7.1
100.0	6.1	6.8
147.0	6.0	5.0
215.0	5.6	4.3
316.0	5.0	2.7

Conc. mg/L	Starting DO	Ending DO
0.0	8.8	8.5
68.1	7.7	8.6
100.0	7.1	8.4
147.0	6.1	8.9
215.0	5.9	9.2
316.0	2.8	9.9

Conc. mg/L	Starting pH	Ending pH
0.0	7.6	7.4
68.1	6.5	7.1
100.0	6.1	6.8
147.0	6.0	5.0
215.0	5.6	4.3
316.0	5.0	2.7

Conc. mg/L	Starting pH	Ending pH
0.0	7.6	7.4
68.1	6.5	7.1
100.0	6.1	6.8
147.0	6.0	5.0
215.0	5.6	4.3
316.0	5.0	2.7

11) TOXICITY TO AQUATIC PLANTS (ALGAE)

TEST SUBSTANCE

- Identity : Disodium Disulphite (CAS No. 7681-57-4)

⇒ Remarks : Source : disodium disulphite, > 98 %(w/w)

METHOD

- Method : OECD Guideline 201 "Algae, Growth Inhibition Test".
- Test type : static
- Element basis : area under the curve
- Exposure period : 72 hr, 96 hr
- GLP : No
- Year : 1989
- Species/Strain/Supplier : *Scenedesmus subspicatus* 86.81 SAG
- Analytical monitoring : No details
- Statistical methods : Not stated

⇒ Remarks:

– Test organism:
· Laboratory culture : OECD- medium
· Method of cultivation : Not stated
· Controls:

– Test condition:
· Test temperature range : 20 ºC
· Growth/test medium chemistry :
· Dilution water source :
Exposure vessel type : 100 mL-medium in a 250 mL -Erlenmeyer flaks
·Water chemistry in test (pH) in at least one replicate of each concentration :

pH

Conc.(mg/L)	0 hr	96 hr
0.0	8.20	7.90
7.8	7.50	8.00
15.6	7.27	7.90
31.3	6.97	7.70
62.5	6.60	4.80
125.0	6.00	3.30
250.0	5.40	2.90
500.0	4.38	2.80

·Stock solutions preparation :
·Light levels and quality during exposure :

– Test design:
· Concentration : 7.8 – 500.0 mg/L
· Initial cell number in cells/mL : 1 x 10^4

– Methods of calculating mean measured concentration : Not stated

RESULTS

- Nominal Concentration in mg/L : 7.8, 15.6, 31.3, 62.5, 125.0, 250.0, 500.0 (mg/L)

(1) 72 hr
EC20 : 39.2 mg/L
EC50 : 48.1 mg/L
EC90 : 60.0 mg/L

(2) 96 hr
EC20 : 20.0 mg/L
EC50 : 39.8 mg/L
EC90 : 58.0 mg/L

- Was control response satisfactory? Yes (cell density increased 54 times after 72 hr)
- Statistical results, as appropriate

⇒ Remarks:

– Biological observations
· cell density of each flask at each measuring point

Duration of the test : 72 hr

Nominal Conc. (mg/L)	% of control
0.0	100.00
7.8	121.41
15.6	113.19
31.3	106.86
62.5	1.55
125.0	0.10
250.0	0.10
500.0	0.00

The EC - values are given in nominal concentration.

EC20 : 39.2 mg/L
EC50 : 48.1 mg/L
EC90 : 60.0 mg/L

Duration of the test: 96 hr

The EC - values are given in nominal concentration.

EC20 : 20 mg/L
EC50 : 39.8 mg/L
EC90 : 58 mg/L
·Growth curves

Nominal Conc.(mg/L)	% of control
0.0	100.00
7.8	109.47
15.6	84.31
31.3	68.83
62.5	0.22
125.0	0.00
250.0	0.00
500.0	0.00

CONCLUSIONS

12) ACUTE TOXICITY TO INVERTEBRATES (DAPHNIA)

TEST SUBSTANCE

• Identity : Disodium disulphite (CAS NO. 7681-57-4)
⇒ Remarks : Source : disodium disulphite, > 98 %(w/w), (BASF sulfite - factory RCA B 306)

METHOD

• Method : EEC guideline 79/831/EWG, appendix V, part of C
• Test type : 48 hr, immobilization test
• GLP : No
• Year : 1989
• Analytical monitoring : No details
• Species/Strain/Supplier : *Daphnia magna*
• Test details : static
• Statistical methods : Probit Analysis
⇒ Remarks:

– Test organism :
·Source, Supplier, any pretreatment, breeding method : The clone of *Daphnia straus* used was supplied by Institut National de Recherche Climique Appliquee, France, in 1978. The Daphnids are cultured under standard conditions in the laboratory for environmental analytics and ecology of the BASF AG Ludwigshafen bred.
· Age at study initiation : 2 - 24 hrs

– Test condition:
·Stock solution preparation : not stated
· Test temperature range : 19 – 21 °C
· Exposure vessel type : not stated
· Dilution water source : not stated
· Dilution water chemistry : hardness= 2. 88 [m mol/L];
Ca: Mg = approx. 4:1; alkalinity = 0.97 [m mol/L]
· Lighting: Day : Night rhythm 16:8 hours
Density of light: approx. 5 Microstone/(m*m*s) in the Wavelength coverage of 400 - 750 nm
· Water chemistry in test : Oxygen content : > 2 mg/L; pH=8.0
– Element (unit) basis : immobilization
– Test design (volume/animals : 2 mL, number of animals/vessel: 5, total number of animals/concentration: 20, replicates : 4)
– Method of calculating mean measured concentrations : Not stated
– Exposure period : 48 hr
– Analytical monitoring : No

RESULTS

• Nominal concentration (as mg/L) : 7.8, 15.6, 31.3, 62.5, 125.0, 250.0, 500.0
• Measured concentration (as mg/L) : not stated
• Units (results expressed in what unit) : mg/L
• EC50 (48 hrs)=88.76 mg/L, NOEC=62.5 mg/L
• Statistical results, as appropriate : not stated
⇒ Remarks :

- Biological observations
·Number immobilized as compared to the number exposed: none
·Concentration response with 95 % confidence limit

Duration of the test : 3 hr
EC50 = 148.99 mg/L
CI 95% = 82.6 - 215.38 mg/L
EC0 = 62.5 mg/L
EC100 = 250 mg/L

Duration of the test : 24 hr
EC50 = 88.76 mg/L
CI 95% = 88.76 - 88.76 mg/L
EC0 = 62.5 mg/L
EC100 = 125 mg/L

Duration of the test : 48hr
EC50 = 88.76 mg/L
CI 95 % = 88.76 - 88.76 mg/L
EC0 = 62.5 mg/L
EC100 = 125 mg/L

Cumulative immobilization

Immobility numbers

Conc. [mg/L]	Immobility numbers				
	0 h	3 h	6 h	24 h	48 h
7.8	0	0	0	0	0
15.6	0	0	0	0	0
31.3	0	0	0	0	0
62.5	0	0	0	0	0
125.0	0	6	20	20	20
250.0	0	20	20	20	20
500.0	0	20	20	20	20
0.0	0	0	0	0	0

·Was control response satisfactory : Yes

CONCLUSIONS

For Disodium disulphite, 24 hr-EC50 value was 88.76 mg/L. Experimental designs and results were well documented and prescribed conditions in the guideline were well satisfied.

⇒ Remarks :

DATA QUALITY

- Reliabilities : Reliable with restrictions.

⇒ Remarks :

REFERENCES (Free Text)

BASF AG, Dept. of Ecology, unpublished data (0897/88) 10, May, 1989.

OTHER

- Last changed : September 2001
- Order number for sorting

⇒ Remarks :

HEALTH ELEMENTS

13) ACUTE TOXICITY

TEST SUBSTANCE

- Identity : Disodium disulphite -powder(CAS No. 7681-57-4)

⇒ Remarks : Source : Hoechst AG, Purity : 96 % (2 % Na_2SO_3, 2 % Na_2SO_4)

METHOD

- **Method/guideline followed** : OECD TG 401
- **Type** : Acute oral toxicity test
- **GLP** : yes
- **Year** (study performed) : 1987
- **Species/Strain** : Rat / Wistar
- **Sex** : male and female
- **No. of animals per sex per dose** : 5 animals/sex/dose
- **Vehicle** : water
- **Route of administration** : oral (gavage)

REMARKS FIELD FOR TEST CONDITIONS

- ***Age*** : 7 weeks(male) and 8 weeks(female)
- ***Doses*** : 800, 1250, 1600 mg/kg(female), 1250, 1600, 2000 mg/kg (male)
- ***Volume administered*** : 10 mL/kg bw
- ***Concentration*** : 8, 12.5, 16, 20 % (w/v)
- ***Post dose observation period*** : 14 days

RESULTS

- **LD_{50} with confidence limits:** 1540 (1290 - 1960, p=0.05) mg/kg bw (male/female)
  - Male : 1630 (1210 - 2260, p= 0.05) mg/kg bw
  - Female : 1420(1040– 2110, p=0.05) mg/kg bw
- **Number of deaths at each dose level**:

  Males : 1/5, 2/5 and 4/5 in the 1250, 1600 and 2000 mg/kg dose groups respectively

  Females : 0/5, 1/5 and 4/5 in the 800, 1250 and 1600 mg/kg dose groups respectively

REMARKS FIELD FOR RESULTS

- Time of death

Dead animals were observed at day 1 after dosing for male and female.

	Lethality		Time of death	
Dose(mg/kg)	male	female	male	female
800	-	0/5	-	0/5
1250	1/5	1/5	1hr	1hr
1600	2/5	4/5	1hr and 4 hr	all at 4 hr
2000	4/5	-	all at 4 hr	-

– ***Description, severity, time of onset and duration of clinical signs a each dose level*** : The symptoms observed in male and female animals were the reduction of activity, crouching, retracted flanks, ruffled fur, irregular breathing and a stiff-legged gait. Additionally, males in the 2 high dose groups displayed prone-position, contracted eyelids, and apathy. After the first day the symptoms were reversed in the surviving animals.

– ***Necropsy findings, included doses affected*** : The g.i. tract was filled with blood, the mucosa of the stomach was lightly reddened and the liver was dark in color. At the end of the experiment the surviving animals were sacrificed and were found to be free of any unusual gross abnormalities. Body weight gain was not influenced by treatment.

CONCLUSIONS

LD_{50} was calculated to be 1540 mg/kg with a 95 % confidence interval of 1290 - 1960 mg/kg bw

DATA QUALITY

- Reliabilities : Reliable without restriction

REFERENCES (Free Text)

Hoechst AG, Unpublished studies (87.1374), 04.Sept.1987

OTHER

- Last changed (administrative field for updating) : September 2001
- Order number for sorting (administrative field)

GENETIC TOXICITY ELEMENTS

14) GENETIC TOXICITY IN VIVO (CHROMOSOMAL ABERRATIONS)

TEST SUBSTANCE

- Identity : Disodium disulphite (CAS No. 7681-57-4)

⇒ Remarks : Provided by Food and Drug Administration, US

METHOD

- **Method/guideline followed** : other
- **Type (test type)** : Cytogenetic *in vivo* assay
- **GLP** : No details
- **Year (study performed)** : 1972
- **Species** : Rat
- **Strain** : Albino
- **Sex :** male
- **Route of administration** : oral
- **Doses/concentration levels** : 0, 30, 700, 1200 mg/kg
- **Exposure period** : Animals were treated either one time and then sacrificed in 6, 24 or 48 h, or they were treated once/day for 5 d, and then were sacrificed in 6 h after the last treatment.
- **Statistical methods** : Chi-square test

REMARKS FIELD FOR TEST CONDITIONS

- ***Age at study initiation*** : Unknown
- ***No. of animals per dose*** : 5 animals/dose/time point (3 rats used in negative control)
- ***Vehicle*** : Unknown
- ***Duration of test*** : 1 to 5 days
- ***Frequency of treatment :*** single & multiple (once a day for 5 day)
- ***Sampling times and number of samples*** : 6, 24, 48 hr subsequent to intubation or 6 hr after last intubation (subacute), 50 bone marrow cells per animal were evaluated.
- ***Control groups*** *(e.g. vehicle, positive, negative)* : The positive control was triethylenemelamine injected i.p. at a dose of 0.4 mg/kg.
- ***Clinical observations performed*** : not stated
- ***Organs examined at necropsy*** : not stated
- ***Criteria for evaluating results*** : Number and type of chromosomal aberrations (except gabs), mitotic index
- ***Criteria for selection of M.T.D.*** : LD50

RESULTS

- **Effect on mitotic index**
- The mitotic index was reduced in the high dose groups after all single administration time points which indicates that the test substance reached the bone marrow to a sufficient level
- **Genotoxic effects** : negative
- **Statistical results, as appropriate**

Dosage mg/kg)	time	Mitoic Index(%)	No.of Animal	No.of cell	Cell with Breaks(%)	Cell with Rearrangemnet(%)	Cell with more than one type of aberr.(%)	Cell with Aberr.(%)
TEM(0.4)	24	2.05	5	250	36.0	7.2	5.6	37.6
(-)	6	1.95	3	150	1.3	0	0	1.3
30	6	2.20	5	250	0.4	0	0	0.4
700	6	2.25	5	250	0.8	0	0	0.8
1200	6	1.90	5	250	1.2	0	0	1.2
(-)	24	2.10	3	150	1.3	0	0	1.3
30	24	2.05	4	200	0	0	0	0
700	24	2.20	5	250	0.8	0	0	0.8
1200	24	1.65	5	250	0	0	0	0
(-)	48	2.20	3	150	0.7	0	0	0.7
30	48	1.70	5	250	1.6	0	0	1.6
700	48	1.60	5	250	1.2	0	0	1.2
1200	48	1.80	5	250	0.4	0	0	0.4
(-)	SA	1.75	3	150	2.6	0	0	2.6
30	SA	2.35	5	250	0.8	0.4	0	1.2
700	SA	2.15	5	250	0.8	0	0	0.8
1200	SA	2.10	3	150	0.7	0	0	0.7

* SA : Sub acute (5 days treatments)

REMARKS FIELD FOR RESULTS

- ***Mortality at each dose level by sex :*** not stated
- ***Description, severity, time of onset and duration of clinical signs at each dose level :*** not stated
- ***Body weight changes by dose and sex :*** not stated
- ***Food/water consumption changes by dose and sex*** : not stated

CONCLUSIONS

No adverse effect on bone marrow chromosomes was observed as a result of disodium disulphite treatment.

DATA QUALITY

• Reliability **:** Reliable with restriction

REFERENCES (Free Text)

1. National Technical Information Service U.S. Department of Commerce(NTIS), Study of the Mutagenic Effect of Sodium Meta-Bisulfite (71-22), PB-221 825, July 1972
2. Maxwell, W.A. and Newell, G.W., Mol. Environ. Aspects Mutagenesis Proc. Publ., Rochester Int. Conf. Environ. Toxic. 6th, 1973, 223-252, 1974

OTHER

- Last changed (administrative field for updating) : September 2001
- Order number for sorting (administrative field)

15-1) GENETIC TOXICITY IN VITRO (GENE MUTATIONS)

TEST SUBSTANCE

- Identity : Disodium disulphite (CAS No. 7681-57-4)

⇒ Remarks : Source : BASF Aktiengesellschaft, Purity : 98 %

METHOD

- **Method/guideline followed** : OECD TG 471
- **Type** : Reverse mutation assay (standard plate test & preincubation test)
- **System of testing** : bacterial
- **GLP** (Y/N) : No
- **Year** (study performed) : 1983
- **Species/Strain** : *Salmonella typhimurium* TA 1535, 1537, 98, 100
- **Metabolic activation**
  - ***Species and cell type :*** sprague-Dawley rats
  - ***Induced or not induced*** : Aroclor-1254-induced
- **Concentrations tested** : 0, 20, 100, 500, 2500, 5000 ? /plate
- **Statistical Methods** : Not mentioned

REMARKS FIELD FOR TEST CONDITIONS

- **Test Design**
  - ***Number of replicates*** : 2
  - ***Number of plate*** : 3 plate/dose (and /control)
  - ***Positive and negative control groups and treatment :***

    negative control ; solvent control, sterility control

    positive control ; -S9 mix : 10 ? 2-aminoantharcene(dissolved in DMSO) for all strains

    +S9 mix : 5 ? N-methyl-N'-nitro-N-nitrosoguanidine for TA 100, 1535

    10 ? 4-nitro-o-phenylendiamine for TA 98

    100 ? 9-aminoacridine chloride monohydrate for TA 1537
- **Solvent** : DMSO (dimethylsulfoxide)
- **Description of follow up repeat study**

  1st experiment : standard plate test with and without S-9 mix

  2nd experiment : preincubation test with and without S-9 mix
- **Criteria for evaluating results** : doubling of the spontaneous mutation rate (control), dose-response relationship, reproducibility of the results

RESULTS

- **Cytotoxic concentration** : No bacteriotoxic effect
- **Genotoxic effects**
  - ***With metabolic activation*** : negative
  - ***Without metabolic activation*** : negative
- **Statistical results** : Not mentioned

REMARKS FIELD FOR RESULTS

CONCLUSIONS

An increase in the number of his+ revertants was not observed both in the standard plate test and in the preincubation test either without or with S-9 mix.

DATA QUALITY

- Reliabilities : Reliable without restrictions

Remarks fields of reliability

Well conducted, followed GLP-like requirement.

REFERENCES

BASF AG, Dept. of Toxicology, Unpublished study (89/380), 09.Oct.1989

OTHER

- Last changed : September 2001
- Order number for sorting (administrative field)

15-2) GENETIC TOXICITY IN VITRO (GENE MUTATIONS)

TEST SUBSTANCE

- Identity : disodium disulphite (CAS No. 7681-57-4)

⇒ Remarks : Source : Sigma Chemical Co., St. Louis, MO.

METHOD

- **Method/guideline followed** : Other
- **Type** : reverse mutation assay (preincubation)
- **System of testing** : bacterial
- **GLP** (Y/N) : Not details
- **Year** (Paper received) : 1986
- **Species/Strain :** *Salmonella typhimurium* TA 92, 1535, 100, 88, 110, 90, 97, 1538, 98, SB 2802, 2061
- **Metabolic activation** : Not applied
- **Concentrations tested** : 0.01-0.64 M
- **Statistical Methods** : No stated

REMARKS FIELD FOR TEST CONDITIONS

– **Test Design**
  · ***Number of replicates*** : 3-4
  · ***Positive and negative control groups and treatment*** : Only negative control used
  · ***Number of metaphases analysed*** : Not applicable

– **Solvent** : 0.1 M sodium phosphate buffer
– **Criteria for evaluating results** : The level of toxicity seen on the nutrient plates after 24 h incubation was compared to toxicity seen in the background lawns of the mutation plates scored after 48 h incubation at 37ºC

RESULTS

- **Cytotoxic concentration :**
  No significant effects on mutagenicity of any strains at concentration up to 0.32 M
- **Genotoxic effects** : slightly positive
- **Statistical results** : Not mentioned

REMARKS FIELD FOR RESULTS

– **Mutagenic response strains** : G 46, TR 3243 (only the strain carrying the *his* D6610 or *his* G46)
– **Condition affecting mutagenicity** : bisulfit-induced mutation appear to be the result of two different mechanisms which may be a function of the repair capacity of the strains. It suggests that the deamination of cytosine may be responsible for base pair substitution mutagenesis and the deamination of cytosine may be the result of oxidative damage rather than through the direct formation of a cytosine-bisulfite adduct because the rate of bisulfite autooxidation appears to play a role in the mutagenic process.

  · ***Plasmid***: pKM101 slightly enhanced the level of base-pair substitutions
  · ***Genotype*** : *his* O1242 mutation, *uvrB* and *rfa* mutations affected the mutagencity
  · ***pH range*** : In the pH range of 4.4 - 5.6, the mutagenic response was maximized for TA97. The pH of the bisulfite solution has an effect on bisulfite mutagenesis and autooxidation. If a lower pH slows the rate of autooxidation allowing more unoxidized product to be taken up by the cell, then the enhanced

mutagenicity seen after increasing the exposure length suggests that alterations in the rate of bisulfite autooxidation should have effects on the level of mutagenicity.

· ***Preincubation time*** : 60 - 120 min of Preincubation time increased the No. of revertants

– **Statistical results** : Not mentioned

CONCLUSIONS

This chemical is a weak mutagen at pH 5 and 6 in *S. typhimurium* strains carrying the *his* G46 and *his* D6610 mutations.

DATA QUALITY

- Reliabilities : Reliable with restrictions

REFERENCES

Pagano DG und Zeiger E, Conducting affecting the mutagenicity of sodium bisulfite in *Salmonella typhimurium* , Mutation Research, 179, 159-166 (1987)

GENRERAL REMARKS

The dose levels in this study are not clear. This could make it difficult to compare to other studies.

OTHER

- Last changed : May 2001
- Order number for sorting (administrative field)

16) REPEATED DOSE TOXICITY

TEST SUBSTANCE

- Identity : Disodium disulphite (CAS No. 7681-57-4)

⇒Remarks : Source : Amsterdamsche Chinine Fabriek (ACF) - purity 95~99 % (as calculated from SO2 determinations)

METHOD

- **Method/guideline followed** : Other
- **Test type** : Long-term feeding study
- **GLP** : No
- **Year** : 1971
- **Species** : Rat
- **Strain** : Wistar
- **Route of administration** : oral (feed)
- **Duration of test** : about 2 year
- **Doses/concentration levels** : 0, 0.125, 0.25, 0.5, 1.0, 2.0 %
- **Sex** : male & female
- **Exposure period** : 104 weeks(F0 and F1 generations), 30 weeks(F2 generations)
- **Frequency of treatment** : 7 d/ week
- **Control group and treatment** : basal diet containing 0 % $Na_2S_2O_5$
- **Post exposure observation period** : None
- **Statistical methods** : Student's *t* test and chi-square test

REMARKS FIELD FOR TEST CONDITIONS

– **Test Subjects**
  · ***Age at study initiation*** : Newly weaned rats
  · ***No. of animals per sex per dose*** : 20 animals/dose/sex

– **Study Design**
  · ***Vehicle***: none (stock diet containing the test substance)
  · ***Satellite groups and reasons they were added*** : none
  · ***Clinical observations performed and frequency :*** Changes of body weight were recorded weekly for the 1st 12wk and once every 4 wk thereafter. The food consumption of each diet group was measured at intervals during 1 wk periods. Hematological investigations were performed from control, 1, and 2 % dose groups of F0 at wk 52, 78, 100, at 52, 102 wk in the F1a generation and at wk 20 of F2 generation. At week 32, 64, and 100 all rats of the F0 and F1a generation and at wk 28 those of the F2a generations were examined for occult blood in feaces. Serum activities of glutamic-oxalacetic and glutamic-pyruvic transaminases were estimated at wk 52, 104 in the F0 generation rats. Kidney function was examined in the urine from controls, 1, and 2 % dose groups, at wk 13, 28, 52, 78 and 101 in F0, at wk 28, 52, 100 in the F1 and wk 28 in the F2. Concurrently pooled urine analysis was performed for appearance, pH, glucose, albumin, occult blood, ketones and microscopy of the sediment.

  · ***Organs examined at necropsy (macroscopic and microscopic)***
    Interim observation on organ weight and pathological changes.
    Mircoscopic: heart, kidneys, liver, spleen, brain, testes, ovaries, pituitary, thyroid, parathyroids, adrenals, thymus, lungs, trachea, salivary glands, gastro-intestinal tract, pancreas, urinary bladder,

skeletal muscle, spinal cord, femoral nerve, skin, bone marrow(sternum), axillary and mesenteric lymph nodes, exorbital lachrymal gland, aorta, mammary glands, uterus, prostate, seminal vesicle and coagulating gland.

RESULTS

- **NOAEL(NOEL)**
  - local toxicity (presence of occult blood and changes in gastric morphology) : 0.215 % $Na_2S_2O_5$ as actual dose(72 mg SO_2/kg b.w. day or 106 mg $Na_2S_2O_5$ /kg b.w/day) or 0.25 % (in the diet)
  - system toxicity : 1.91 % as actual dose (942 $Na_2S_2O_5$ mg /kg b.w./day) or
- **Actual dose received by dose level**: The SO2 determinations on the diets showed considerable losses of sulphite. Proportionally the losses of sulphite decreased with increasing dietary levels of sulphite as table shown below

Level of $Na_2S_2O_5$ added to diet (%)	Loss of $Na_2S_2O_5$ after storage for 1 week at –18ºC(%)	Actual dose level of $Na_2S_2O_5$ (%)
0.125	22	0.098
0.25	14	0.215
0.5	12	0.44
1.0	8	0.92
2.0	5	1.91

- **Toxic response/effects by dose level**
  Occult blood was present in the faeces in groups given 1 % sulphite or more. Relative weights of the kidneys were increased by the 2 % sulphite level in the F2-generation females only, but this increase was accompanied by neither functional nor histological changes. Pathological examination revealed hyperplastic changes in both the fore- and glandular stomach with level of 1 and 2 % sulphite in each of the three generation. Some slight alterations were found also with 0.5 % in the stomach of the F2-generation rats. No carcinogenic effect was shown.

REMARKS FIELD FOR RESULTS

- ***Body weight***: There was a marginal reduction in body-weight gain in both sexes of the F1 and F2-generation given 2 % sulphite, also in females F1 given 0.125, 0.25, 0.5 % sulphite and those given 0.25, 0.5 % in the F2 generation. But there was no dose-relationship and the differences could partly be explained by the higher initial body weights of controls.
- ***Food consumption*** : There was no distinct differences in food consumption.
- ***Thiamine content of urine and liver*** *:* The group given 2 % sulphite showed no distinct changes in the thiamine status when compared with control rats on the stock diet without extra thiamine. This indicates that thiamine added to the sulphited diets prevented thiamine deficiency even at a dietary level of 2 % sulphite
- ***General condition, mortality and growth*** : The general condition of the rats remained good during the first 72 week in the F0-generation as well as in the two descendant generations. After this, aging symptoms developed in many rats and mortality increased rapidly in nearly all group. The survival in the sulphite groups was generally higher than in the controls, except in the case of males of the F1-generation given 2 % sulphite. No deaths occurred in the females of the same group.
- ***Hematological findings incidence and severity***: A marginally reduced haemoglobin content, haematocrit value and erythrocyte count occurred in the F0-generation females fed on 2 % sulphite at week 52, 78 and 100, while the F1 generation males at 2 % showed an increase in leucocyte count at week 102. All haematological values for test and control animals in all successive generations were within normal ranges at all stages.
- ***Description, severity and duration of clinical signs***
  All rats in the highest dose group showed indications of occult blood in the faeces of all generations, while this effect occurred in only 13 - 60 % of the animals on diets containing 1 % sulphite. In 10 % of the females given 0.25 % and in 10 % of the males given 0.5 % sulphite slight indications of intestinal blood loss were observed in the F0-generation rats at week 32 only.

  · Occult blood in the faeces

17) TOXICITY TO REPRODUCTION

TEST SUBSTANCE

- Identity: Disodium disulphite (CAS No. 7681-57-4)

⇒ Remarks : Source : Amsterdamsche Chinine Fabriek (ACF) - purity 95~99 %(as calculated from SO_2 determinations)

METHOD

- **Method/guideline followed** : Other
- **Type** : multigeneration study
- **GLP** (Y/N) : No details
- **Year** : 1971
- **Species** : Rat
- **Strain** : Wistar
- **Route of administration** : oral (feed)
- **Doses/concentration levels** : 0, 0.125, 0.25, 0.5, 1.0, 2.0 %
- **Sex** : male/female
- **Control group and treatment :** basal diet containing 0 % $Na_2S_2O_5$
- **Frequency of treatment** : 7 d/ week
- **Duration of test** : 2 yr
- **Premating exposure period for males and female (P and F1) as appropriate** : F0 : 21 weeks
- **Statistical methods** : Student's *t* test and chi-square test

REMARKS FIELD FOR TEST CONDITIONS

– **Test animals**

· ***Number, age, sex per dose for P*** : Newly weaned rats, 20 animals/dose/sex

· ***Number, age, sex per dose for F1a, F2a*** : 10 animals/dose/sex selected at weaning (F1-gen.) for produce F2a, F2b and 10 males, 15 females of the F2a litters were selected for producing the next generation.

– **Test design**

· ***Vehicle*** : none (stock diet containing the substance)

· ***Dosing schedules and pre and post dosing observations periods for P, F1 and F2***,: All rats of the F0-generation were mated within their diet group at about week 21 and half of them also at week 34. 10 animals/dose/sex from the first litters were selected at weaning for rearing further generations. The F0-generation rats as well as the selected F1a-generation rats were maintained on their diet for a period of 104 weeks. Rats of the F1a-generation were mated at week 12 and 30 to produce the F2a and the F2b generations. 10 males and 15 females form the F2a litters were mated to produce an F3a-, F3b-generation by pairing them on week 14 and 22. These litters were discarded after weaning, and the parents were kept on their diets for about 30 weeks.

· ***Mating procedures***

Group mating was used throughout and lasted for a period of 2 week. At day 20 after the beginning of the mating period, the females were individually housed until the litters had been weaned. Records were made of the number of pups in each litter, and of the total weight of the litter at days 1, 8 and 21. On the 1st day, the litters containing more than 8 pups were reduced to that number to equalize the stress of lactation on the dams.

· ***Clinical observations performed and frequency***

All changes of body weight were recorded weekly for the 1st 12 wk and once every 4 wk thereafter. The food consumption of each diet group was measured weekly. Hematological investigations were performed with control, 1, 2 % dose groups of F0 at wk 52, 78, 100 in F1a at 52, 102 wk and at week 20 in the F2 generation. F0-, F1a- and F2-generation were examined for occult blood in feaces at week 32, 64 and 100. Serum activities of glutamic-oxalacetic and glutamic-pyruvic transaminases were estimated at week 52, 104 in F0. Kidney function was examined for the controls, 1 and 2 % dose groups, at week 13, 28, 52, 78 and 101 in F0, at week 28, 52, 100 in the F1 and week 28 in the F2. Concurrently urine analysis was performed.

· ***Organs examined at necropsy (macroscopic and microscopic)***

Interim observation on organ weight and pathological changes .

Mircoscopic : heart, kidneys, liver, spleen, brain, testes, ovaries, pituitary, thyroid, parathyroids, adrenals, thymus, lungs, trachea, salivary glands, gastro-intestinal tract, pancreas, urinary bladder, skeletal muscle, spinal cord, femoral nerve, skin, bone marrow (sternum), axillary and mesenteric lymph nodes, exorbital lachrymal gland, aorta, mammary glands, uterus, prostate, seminal vesicle and coagulating gland.

– **Parameters assessed during study**

Female fertility, the number of young per litter, the birth weight, mortality of the young.

RESULTS

- **NOAEL (NOEL) and LOAEL (LOEL) for P, F1, F2 and F3**

NOAEL : 2 % in the diet (actual dose 1.91 %) which is equivalent to 942 mg of $Na_2S_2O_5$ /kg b.w/day

- **Actual dose received by dose level :** 0, 0.098, 0.213, 0.440, 0.920, 1.91 % doses result from stock diet loss.

- **Parental data and F1 as appropriate :** No consistent differences between groups in female fertility, the number of young per litter

- **Offspring toxicity:** No consistent differences between groups in birth weight or mortality of the young. Body weight changes were seen in the offspring (F1, F2, F3). A signification reduction in the number of F2a-generation young was observed with 0.5, 1, and 2 % sulphite. During the lactation period the body weights of the young in the 2 % group were generally lower than those of the controls and significantly decreased body weights at day 8 and 21, but there was no distinct dose-related response.

REMARKS FIELD FOR RESULTS

– ***Fertility and offspring toxi city :*** During lactation the body weight of the young in the 2 % group was generally lower than the controls and the lower-dosed groups. In the F1a- and the F1b-generation offspring (F2a and F2b pups) dietary levels of 1 and 2 % disodium disulfite were associated with decreased body weight on days 8 and 21. This effect was primarily transient for the F2a pups, since animals of the 1 % group recovered their body weight after weaning and the 2% group nearly recovered their body weight as compared to the control. This reduced body weight was probably not a true substance-related effect since it could be due to a higher initial body weight in the control groups. Furthermore, these body weight changes were within or were not dramatically different from the control values of the F1 pubs. A reduction in the number of F2a-generation offspring (F3a pups) was observed in the 0.5, 1.0 and 2.0 % dose groups, but it was not dose-dependent and did not occur in the F2b-generation offspring (F3b pups).

Dose (%)	No. of females with litters	Mean no. of rats/litters at birth	Mean b.w. of young at day 1	8	21	Mortality (%) At birth	At weaning
			F_0-generation- 1st mating				
0	90	8.7	5.9	15.7	44.5	9	13
0.125	90	9.1	5.9	15.0	42.5	1	23
0.25	75	9.8	5.9	14.3	40.0	9	25
0.5	85	9.5	6.1	15.1	42.3	1	1
1.0	90	10.6	6.1	15.6	43.2	5	9
2.0	85	9.8	5.9	13.8	3801	8	14
			F_0-generation- 2nd mating				
0	80	9.5	6.0	14.6	38.9	8	0
0.125	90	8.6	6.8	14.4	39.4	26	0
0.25	80	9.3	6.2	17.5	44.7	8	17
0.5	100	10.7	6.4	15.7	40.2	0	5
1.0	90	7.8	6.4	15.8	41.3	0	4
2.0	90	8.9	5.9	14.4	37.6	13	8
			F_1-generation- 1st mating				
0	90	10.4	6.2	17.9	45.6	0	16
0.125	90	10.7	5.9	14.8	40.6	1	11
0.25	80	10.0	5.7	16.2	40.9	0	5
0.5	90	8.8	6.0	15.6	43.2	1	15
1.0	70	9.1	6.0	15.0	38.6	0	15
2.0	90	9.7	6.2	14.7	37.7	2	10
			F_1-generation- 2nd mating				
0	100	10.4	6.7	18.3	49.4	0	11
0.125	80	11.0	6.2	16.0	45.9	1	8
0.25	80	10.9	5.9	16.9	44.8	3	3
0.5	100	8.7	6.1	19.4	51.9	3	4
1.0	100	9.4	6.5	15.9	45.1	5	7
2.0	90	10.8	6.2	15.9	42.9	4	3
			F_2-generation- 1st mating				
0	100	11.7	6.2	17.3	47.1	5	2
0.125	100	10.5	5.6	15.8	42.2	1	14
0.25	100	11.2	5.5	14.6	40.2	0	0
0.5	87	8.9	6.1	16.8	41.9	3	10
1.0	100	8.9	6.0	15.5	41.1	0	1
2.0	100	8.8	5.9	15.2	38.8	3	2
			F_2-generation- 2nd mating				
0	100	10.2	6.4	17.2	44.3	3	8
0.125	100	11.4	6.0	16.8	45.9	2	13
0.25	100	11.3	5.8	15.3	40.4	0	4
0.5	93	9.9	6.2	16.4	44.4	1	7
1.0	100	9.8	6.3	14.3	44.0	2	21
2.0	100	10.5	6.2	15.5	41.2	0	7

- ***Body weight*** : There was a marginal reduction in both sexes of the F1 and F2-generation given 2 % sulphite, 0.125, 0.25, 0.5 % sulphite in the female F1 and 0.25, 0.5% in the F2 generation. But there was no dose- relationship.
- ***Food consumption*** : There was no distinct differences in food consumption.
- ***General condition, mortality and growth*** : The general condition of the rats remained good during the first 72 week in the two descendant generations. After this, aging symptoms developed in many rats and mortality increased rapidly in nearly all group. The survival in the sulphite groups was generally higher than in the controls, except in the case of males of the F1-generation given 2 % sulphite. No deaths occurred in the females of the same group.
- ***Precoital interval*** : not stated
- ***Duration of gestation*** : not stated
- ***Gestation index (live litters/pregnancies)*** : no details
- ***Changes in lactation*** : not stated
- ***Changes in estrus cycles*** : not stated
- ***Effects on sperm*** : unknown
- ***Hematological findings incidence and severity***: A marginally reduced haemoglobin content, haematocrit value and erythrocyte count occurred in the F0-generation females fed on 2 % sulphite at week 57, 78 and 100, while the F1 generation males at 2 % showed an increase in leucocyte count at week 102. All haematological values for test and control animals in all successive generations were within normal ranges at all stages.
- ***Kidney function and enzyme activity*** : Phenol-red excretion, specific gravity and glutamic-oxalacetic-transaminase activity in the urine were not adversely affected by the feeding of sulphite. Urine analysis values were essentially normal. Significant ($p < 0.05$) decreases in serum glutamic-pyruvic- transaminase values occurred at week 104 in male rats of the F0-generation receiving 0.125 % sulphite. There were no differences in transaminase between the test and control animals of this generation activities either at week 52 or at week 104.
- ***Number of implantations***: not stated

18-1) DEVELOPMENTAL TOXICITY/TERATOGENICITY

TEST SUBSTANCE

- Identity : Disodium disulphite

⇒ Remarks : White crystalline material (FDA 71-22)

METHOD

- **Method/guideline followed :** Other
- **GLP :** No details
- **Year :** 1972
- **Species :** Rat
- **Strain :** Wistar
- **Route of administration :** oral (gavage)
- **Doses/concentration levels :** 0, 1, 5, 24, 110 mg/kg bw
- **Sex :** Female
- **Exposure period :** day of 6-15 of gestation
- **Frequency of treatment :** daily
- **Control group and treatment :** Negative control : sham treated controls
  Positive control : Asprin 250 mg/kg bw
- **Duration of test :** day of 20 gestation
- **Statistical methods :** Not described
- **Statistical methods :** Not described
  - **Age at study initiation :** Not stated
  - **Number of animals per dose per sex :** Not stated
  - **Vehicle :** water
  - **Clinical observations performed and frequency:**
    Body weights : on days 0, 6, 11, 15 and 20 of gestation
    Appearance, behaviour and food consumption : daily
  - **Mating procedures :** Not stated
  - **Parameters assessed during study(maternal and fetal) :** Average body weight, pregnancy data, skeletal abnormality, soft tissue abnormality
  - **Organs examined at necropsy :** The numbers of implantation site, resorptions and live/dead fetuses were recorded. Fetuses were examined for the presence of external congenital abnormality, visceral examination(1/3 of fetuses) and skeletal defect(remaining 2/3 of the fetuses)

RESULTS

- **NOAEL maternal toxicity :** 110 mg/kg bw/day
- **NOAEL teratgenicity :** 110 mg/kg bw/day
- **Maternal data with dose level :** No clear effect on maternal toxicity
- **Fetal data with dose level :** No clear effect on fetal survival

REMARKS FIELD FOR RESULTS

- ***Reproduction data***
  The administration of the disodium disulphite to pregnant rats had no clear effect on nidation, or on maternal or fetal survival.

Dose (mg/kg)	Sham	Positive	1.0	5.0	24.0	110.0
Pregnancies						
Total No.	21	23	24	23	24	24
Died or Aborted(before day 20)	0	0	0	0	0	0
To term(on day 20)	21	23	24	23	24	24
Corpora Lutea						
Total No.	236	266	274	266	282	270
Average/dam mated	9.83	11.1	11.4	11.1	11.8	11.3
Live Litters						
Total No.	21	23	24	23	24	24
Implant sites						
Total No.	232	265	266	265	274	266
Average/dam	11.0	11.5	11.4	11.5	11.4	11.1
Resorptions						
Total No.	4	9	4	8	10	8
Dams with 1 or more sites resorbed	3	7	4	6	6	6
Dams with all sites resorptions	0	0	0	0	0	0
% partial resorptions	14.3	30.4	16.7	26.1	25.0	25.0
% comlete resorptions	-	-	-	-	-	-
Live Fetuses						
Total No.	227	256	261	257	264	258
Average/dam	10.8	11.1	10.9	11.2	11.0	10.8
Sex ratio(M/F)	0.86	0.91	0.63	0.67	0.87	0.73
Dead Fetuses						
Total No.	1	0	1	0	0	0
Dams with 1 or more dead	1	-	1	-	-	-
Dams with all dead	0	-	0	-	-	-
% partial dead	4.76	-	4.17	-	-	-
% all dead	-	-	-	-	-	-
Average Fetuses Weight g	3.67	2.53	3.80	3.81	3.87	3.86

– ***Body weight***

No significant differences were found between treatment and negative control group.

Average body weight of pregnant dams

Dose	Average Body wt(g)				
(mg/kg)	day 0	day 6	day 11	day 15	day 20
0	209	227	252	276	346
positive control	216	237	257	279	342
1.0	209	232	253	278	343
5.0	209	229	250	272	337
24.0	211	231	253	277	348
110.0	213	233	253	274	345

– **Food/water consumption**

No significant difference is found in comparison with to control.

– **Description, severity, time of onset and duration of clinical signs :** Not described

– **Gross pathology incidence and severity :**

No clear effect on nidation, or on maternal or fetal survival

– **Fetal data**·

. ***Grossly visible abnormalities***

The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.

Summary of skeletal findings

	Dose (mg/kg)					
findings	**0**	**1.0**	**5.0**	**24.0**	**110.0**	**Positive**
Sternebrae						
Incompletd oss.	31/14	12/7	14/11	13/10	16/12	163/23
Bipartite			1/1			2/1
Missing	3/1	1/1		1/1	1/1	105/22
Ribs						
Wavy	6/5	8/7	4/4	9/7	3/3	84/21
Less than 12			1/1			3/3
Vertebrae						
Incompletd oss.	2/1	1/1	1/1	2/2	1/1	127/23
Skull						
Incompletd oss.	16/10	11/8	16/11	35/13	23/9	149/23
Miscellaneous						
Hyoid;missing	19/11	8/6	6/5	18/8	17/7	120-23
Hyoid;reduced		2/2		1/1	4/3	

Numerator=Number of fetuses affected; Denominator= Number of litters affected

CONCLUSIONS

No teratological or other developmental effects were indicated in fetues at any dose level.

DATA QUALITY

- Reliabilities **:** Reliable with restriction

REFERENCES (Free Text)

National Technical Information Service (NTIS) U.S. Department of Commerce, Teratologic Evaluation of Compound FDA 71-22 (Sodium Meta-Bisulfite), Prepared for the FDA, PB-221 795, Sept. 1972

OTHER

- Last changed : September 2001
- Order number for sorting (administrative field)

18-2) DEVELOPMENTAL TOXICITY/TERATOGENICITY

TEST SUBSTANCE

- Identity : Disodium disulphite

⇒ Remarks : White crystalline material (FDA 71-22)

METHOD

- **Method/guideline followed** : Other
- **GLP :** No details
- **Year :** 1972
- **Species :** Rabbit
- **Strain :** Dutch
- **Route of administration :** oral (gavage)
- **Doses/concentration levels :** 1.23, 5.71, 26.5, 123 mg/kg bw
- **Sex :** Female
- **Exposure period :** day 6 - 18 of gestation
- **Frequency of treatment :** daily
- **Control group and treatment :** Negative control : sham treated controls

  Positive control : 2.5 mg/kg of 6-aminonicotinamide dosed on day 9
- **Duration of test :** 29 days of gestation
- **Statistical methods :** Not described
- **Statistical methods :** Not described
  - **Age at study initiation :** Not stated
  - **Number of animals per dose per sex :** 20 - 14 animals/dose
  - **Vehicle :** water
  - **Clinical observations performed and frequency :** Body weights were recorded on days 0, 6, 12, 18 and 29 of gestation, and were observed daily for appearance, behavior and food consumption.
  - **Mating procedures :** Not specified
  - **Parameters assessed during study(maternal and fetal) :** Average body weight, survival data, pregnancy data, skeletal abnormality, soft tissue abnormality
  - **Organs examined at necropsy :** The numbers of corpora lutea, implantation site, resorptions and live/dead fetuses were recorded. Fetuses were examined for the visceral abnormalities by dissection. All fetuses were processed for staining with Alizarin Red S dye and examined for skeletal defects.

RESULTS

- **NOAEL maternal toxicity :** 123 mg/kg bw/day
- **NOAEL teratogenicity :** 123 mg/kg bw/day
- **Maternal data with dose level :** No clear effect on maternal toxicity
- **Fetal data with dose level :** No clear effect on fetal survival

REMARKS FIELD FOR RESULTS

- ***Reproduction data***

  The administration of the disodium disulphite to pregnant rats had no clearly discernible effect on nidation, or on maternal or fetal survival.
- ***Body weight***

No significant differences were found between treatment and negative control group.

– **Food/water consumption**
No significant difference is found in comparison with to control.

– **Description, severity, time of onset and duration of clinical signs:** Not described

– **Fetal data**·
. ***Grossly visible abnormalities***
The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.

CONCLUSIONS

No teratological or other developmental effects were indicated in fetues at any dose level.

DATA QUALITY

- Reliabilities **:** Valid with restriction

REFERENCES (Free Text)

National Technical Information Service (NTIS) U.S. Department of Commerce, Teratologic Evaluation of Compound FDA 71-22. Sodium Metabisulfite in Rabbit, PB -267 194, July 1974

OTHER

- Last changed : September 2001
- Order number for sorting (administrative field)

BEYOND S IDS ELEMENTS

1) CHRONIC TOXICITY TO AQUATIC INVERTEBRATES (DAPHNIA)

TEST SUBSTANCE

- Identity : Disodium disulphite (CAS NO. 7681-57-4)

⇒ Remarks : Source : disodium disulphite, > 98 % (w/w), (BASF sulfite - factory RCA B 306)

METHOD

- Method : OECD TG202
- Test type : 21 days reproduction test
- GLP : YES
- Year : 1993
- Analytical monitoring : not stated
- Species/Strain/Supplier : *Daphnia magna*
- Test details : semi-static
- Statistical methods : Duncan's multiple range test

⇒ Remarks:

– Test organism :
·Source, Supplier, any pretreatment, breeding method : The clone of *Daphnia straus* used was supplied by Institut National de Recherche Climique Appliquee, France, in 1978. The Daphnids are cultured under standard conditions in the laboratory
· Age at study initiation : 2 - 24 hrs

– Test condition :
· Stock solution preparation : a defined amount of the test substance was weighed out and suspended directly in the test medium by stirring. The nominal concentration of the stock solutions were 100 mg/L
· Test temperature range : 20 ±2?
· Exposure vessel type : numbered glass beakers nominal volume 100 mL, covered with numbered caps
· Dilution water source : the synthetic medium M4
· Dilution water chemistry : hardness = 2.20-3.20 [m mol/L];
Ca: Mg = approx. 4:1; alkalinity up to pH 4.3 = 0.80-1.00 [m mol/L]
· Lighting- Day : Night rhythm 16:8 hours
Density of light : 5-6 µE/(m*m*s) in the range of 400-700 nm
· Water chemistry in test : Oxygen content : 8.0 - 15.5 mg/L; pH=7.5 - 8.0
· Feeding : Green algae (*Scenedesmus subspicatus*)

– Element (unit) basis : reproduction
– Test design : number of animals/vessel : 1, total number of animals/concentration : 10
– **Method of calculating mean measured concentrations : Not stated**
– Exposure period : 21 days
– Analytical monitoring : Not stated

RESULTS

- Nominal concentration (as mg/L) : 1.0, 5.0, 10.0
- Measured concentration (as mg/L) : not determined
- Units (results expressed in what unit) : mg/L
- Reproduction LC0 (21days) > 10.0 mg/L, NOEC (21days) > 10.0 mg/L
- Statistical results, as appropriate : by Duncan's multiple range test , NOEC is >10.0 mg/L

⇒ Remarks:

- Biological observations
· summary of the effect of the test substance on the reproduction of *Daphnia magna*. The values given are the mean, cumulative values for parent animals which survived the exposure for 21 days

Conc. (mg/L)	Survival of parent animals	Live young per live parental animal		Dead young per live parental animal		Aborted eggs per live parent animal	
	%	n	±1 SD*	n	±1 SD*	n	±1 SD*
0.0	100	108.3	21.2	0.0	0.0	0.0	0.0
1.0	100	105.0	17.9	0.0	0.0	0.0	0.0
5.0	100	119.2	19.1	0.0	0.0	0.0	0.0
10.0	90	107.7	9.1	0.0	0.0	0.0	0.0

1SD*: 1 standard deviation

·Was control response satisfactory? : Yes

CONCLUSIONS

For Disodium disulphite, LC0 is 10.0 mg/L and NOEC is >10.0 mg/L. Experimental designs and results were well documented and prescribed conditions in the guideline were well satisfied.

⇒ Remarks :

DATA QUALITY

- Reliabilities : Reliable without restrictions.

⇒ Remarks :

REFERENCES (Free Text)

BASF AG, Dept. of ecology, unpublished data (2057/93) 10, December, 1993.

OTHER

- Last changed : September 2001
- Order number for sorting

⇒ Remarks :

2) SKIN IRRITATION

TEST SUBSTANCE

- **Identity** : Disodium disulphite –powder (CAS No. 7681-57-4)
- **pH** : 4.4 – 4.9 in a 20 % solution of water

⇒ Remarks : Source : Hoechst AG purity : > 96 %

METHOD

- **Method/guideline followed** : OECD TG 404
- **Type** : *in vivo* semiocclusive study
- **GLP** : yes
- **Year** (study performed) : 1981
- **Species/Strain** : Rabbit / Albino New zealand
- **Sex** : not specified
- **No. of animals**: 3
- **Total dose** : 500 mg of disodium disulphite
- **Vehicle** : 0.1 mL saline solution (NaCl 0.9 %)
- **Exposure time** : 4 hours
- **Grading scale** : Draize

REMARKS FIELD FOR TEST CONDITIONS

_ ***Controls*** : none
_ **Area of exposure** : about 24 h before treatment the dorsal surface (ca. 25 cm^2) was shaved with electronic clippers. Only animals with intact skin were used.

RESULTS

Not irritating

- **Cumulative total and percent responders :** all 3 animals responded with slight erythema with an average score of 0.4. No edema was observed.

REMARKS FIELD FOR RESULTS

- ***Numerical skin grades at 1, 24, 48 and 72 hours*** :

Individual Animal Grades for erythema and eschar
1 h after patch removal (animal No. 1,2,3)
0, 0, 0
24 h after patch removal (animal No. 1,2,3)
1, 1, 1
48 h after patch removal (animal No. 1,2,3)
0, 0, 1
72 h after patch removal (animal No. 1,2,3)
0, 0, 0

No edema was observed.

- ***Delayed grading scores at 7 to 14 days*** : not necessary to perform
  – ***Reversible effects*** **:** all effects were reversible by 72 hours.
  – ***Erythema/edema findings*** : only erythema was observed

– ***Other dermal lesion including systemic effects*** **:** none

CONCLUSIONS

The disodium disulphite was not irritating to the skin of the rabbit.

DATA QUALITY

- Reliabilities : Reliable without restriction

REFERENCES (Free Text)

Hoechst AG, Unpublished studies (87.1241), 11.Aug.1987

OTHER

- Last changed (administrative field for updating) : September 2001
- Order number for sorting (administrative field)

3) EYE IRRITATION

TEST SUBSTANCE

- **Identity** : Disodium disulphite –fine crystal powder (CAS No. 7681-57-4)
- **pH** : 4.4 – 4.9 in a 20 % solution of water

⇒Remarks : Source : Hoechst AG, Purity : > 96 %, impurities : Na_2SO_3 (2 %), Na_2SO_4(2 %)

METHOD

- **Method/guideline followed** : OECD TG 405
- **Type** : *in vivo* study
- **GLP** : yes
- **Year** (study performed) : 1987
- **Species/Strain** : Rabbit / Albino New zealand
- **Sex** : not specified
- **No. of animals per dose** : 3
- **Dose :** 100 mg/eye
- **Observation period** (list the time points at which grading/scoring took place) : 1, 24, 48, and 72 hours after application of the test substance, as well as 7 days after application.
- **Exposure time** : 24 hours
- **Scoring method used** : Draize

REMARKS FIELD FOR TEST CONDITIONS

_ ***Anesthetics*** :
_ ***Vehicles*** :
_ ***Eye washed*** **:** rinsed after 24 hr exposure

RESULTS

- **Corrosive** (yes or no) : no
- **Individual scores :** 1 h, 24 h, 48 h, 72 h, and 7 d for animals 1, 2, 3

  - ***Conjunctiva chemosis*** 1 h : 3, 3, 3; 24 h : 2, 2, 3; 48 h : 1, 1, 2; 72 h : 1, 2, 2; 7 d : 1, 1, 3
  - ***Conjunctiva redness*** : 1 h : 2, 3, 3; 24 h : 3, 3, 3; 48 h : 3, 2, 3; 72 h : 3, 3, 3; 7 d : 2, 3, 3
  - ***Iris*** : 1 h : 1, 0, 1; 24 h : 1, 1, 1; 48 h : 1, 1, 1; 72 h : 1, 1, 1; 7 d : 1, 1, 1
  - ***Corneal opacity*** : 1 h : 1, 1, 1; 24 h : 2, 2, 2; 48 h : 2, 2, 2; 72 h : 1, 2, 2; 7 d : 2, 3, 3
  - ***Corneal opacity fluor***: 24 h : 3, 1, 2; 72 h : 2, 4, 4; 7 d : 2, 3, 2

In addition, on day 7 corneal vascularization was slightly noticeable in two animals and clearly noticeable in one animal.

- **Overall irritation score** : not specified
- **Tool used to assess score**: additional evaluation of corneal opacity under UV light after fluorescein installation at the 24 and 72 hour time points, as well as after 7 days.
- **Description of lesions** : corneal opacity and vascularization of the cornea

REMARKS FIELD FOR RESULTS

- ***Number of affected*** : all animals
- ***Score reduced time*** (up to 21 days) **:**
- ***Reversible effect*** **:** based on the effects seen after 7 days (corneal opacity and vascularization of the

cornea) the effects were probably not reversible.

CONCLUSIONS

The disodium disulphite was irritating to the eye in rabbit.

DATA QUALITY

- Reliabilities : Reliable without restriction

REFERENCES (Free Text)

Hoechst AG, Unpublished studies (87.1293), 21.Aug. 1987

OTHER

- Last changed (administrative field for updating) : September 2001
- Order number for sorting (administrative field)

4) CARCINOGENICITY

TEST SUBSTANCE

- **Identity** : Disodium disulphite (CAS No 7681-57-4)

⇒ **Remarks** : Source : Amsterdamsche Chinine Fabriek (ACF) - purity 95 ~ 99 % (as calculated from SO_2 determinations)

METHOD

- **Method/guideline followed** : Other
- **Test type** : Long-term feeding study
- **GLP** : No
- **Year** : 1971
- **Species** : Rat
- **Strain** : Wistar
- **Route of administration** : oral (feed)
- **Duration of test** : about 2 year
- **Doses/concentration levels** : 0, 0.125, 0.25, 0.5, 1.0, 2.0 %
- **Sex** : male & female
- **Exposure period** : 104 weeks(F0 and F1 generations), 30 weeks(F2 generations)
- **Frequency of treatment** : 7 days/ week
- **Control group and treatment** : basal diet containing 0 % $Na_2S_2O_5$
- **Post exposure observation period** : None
- **Statistical methods** : Student's *t* test and chi-square test

REMARKS FIELD FOR TEST CONDITIONS

– **Test Subjects**
  · ***Age at study initiation*** : Newly weaned rats
  · ***No. of animals per sex per dose*** : 20 animals/dose/sex

– **Study Design**

6 experimental groups were maintained on a diet containing 0, 0.125, 0.25, 0.5, 1.0 and 2.0 % of disodium disulfite. 20 animals/dose/sex were used. All rats (F0-generation) were mated at wk 21 of treatment within their dose group. Half of them were mated again at wk 34. 10 males and 10 females were selected at weaning from the 1st litters of each group to become the F1a-generation. The F0-generation rats, as well as selected F1a-generation rats were maintained on their diets for a period of 104 wk. Rats of the F1a-generation were mated at wk 12 and 30 to produce the F2a and F2b generations. 10 males and 15 females from the F2a litters were mated to produce an F3a- and F3b-generation by pairing them on wk 14 and 22. The resulting litters were discarded after weaning, and the parents were kept on their diets for about 30 wk. The number of animals used for histological examinations after 1 year was 4-5 from the F0 animals; after 104 weeks of treatment was 19-24/dose/sex from the F0-gen. and the F1-gen. together; and after 30 wk of treatment, 10-15/dose/sex were used from the F2-generation. An extensive set of tissues from each rat of the F0-, F1a- and F2a-gen. were examined microscopically. Several special stains were also employed. For more details of the method used see section 16.

· ***Vehicle***: none(stock diet containing the test substance)
· ***Satellite groups and reasons they were added*** : none
· ***Organs examined at necropsy (macroscopic and microscopic)***

Interim observation on organ weight and pathological changes.

Mircoscopic : heart, kidneys, liver, spleen, brain, testes, ovaries, pituitary, thyroid, parathyroids, adrenals, thymus, lungs, trachea, salivary glands, gastro-intestinal tract, pancreas, urinary bladder, skeletal muscle, spinal cord, femoral nerve, skin, bone marrow(sternum), axillary and mesenteric lymph nodes, exorbital lachrymal gland, aorta, mammary glands, uterus, prostate, seminal vesicle and

coagulating gland.

RESULTS

- **NOAEL(NOEL)**
  1.91 % as actual dose (942 $Na_2S_2O_5$ mg /kg bw/day)

- **Actual dose received by dose level** : The SO_2 determinations on the diets showed considerable losses of sulphite. Proportionally the losses of sulphite decreased with increasing dietary levels of sulphite as shown below table.

Level of $Na_2S_2O_5$ added to diet(%)	Loss of $Na_2S_2O_5$ after storage for 1 week at –18 °C (%)	Actual dose level of $Na_2S_2O_5$ (%)
0.125	22	0.098
0.25	14	0.215
0.5	12	0.44
1.0	8	0.92
2.0	5	1.91

REMARKS FIELD FOR RESULTS

– ***General condition, mortality and growth*** : The general condition of the rats remained good during the first 72 week in the F0-generation as well as in the two descendant generations. After this, aging symptoms developed in many rats and mortality increased rapidly in nearly all group. The survival in the sulphite groups was generally higher than in the controls, except in the case of males of the F1-generation given 2 % sulphite. No deaths occurred in the females of the same group.

– ***Type and incidence of tumours***
The number of lymphoreticular pulmonary tumours in males decreased with increasing levels of sulphite in the diet. The incidence of thyroid and pituitary tumours in the control group of the male rats was exceptionally low, whereas those noted in the various test groups represented numbers normally found in the strain of rats used. All other neoplasms occurred in a random manner with no apparent relationship between number, location or type of tumours and the treatment.

	Males						Females					
Dietary level (%)	0	0.125	0.25	0.5	1	2	0	0.125	0.25	0.5	1	2
No.of rats examined	24	24	25	25	25	25	25	25	25	25	25	25
Total no. of rats with tumors	17	22	21	18	17	18	20	12	16	15	17	14
Lung:												
Malignant lymphoreticular tumor	10	10	8	6	6	3	2	5	4	5	2	4
Thyroid:												
Light-cell tumor: adenoma	1	8	6	4	8	5	4	5	5	4	3	7
Pituitary												
Adenoma	0	5	5	1	4	4	8	2	4	3	4	0
Carcinoma	0	2	1	2	2	2	0	1	1	1	0	0
Adrenal												
Phaeochromocytoma												
Benign :	6	4	8	5	1	7	1	0	4	1	2	2
Malignant :	1	2	1	4	1	0	0	0	0	0	0	0
Cortical adenoma	0	0	0	1	0	0	0	0	0	0	0	0
Cortical carcinoma	0	1	0	0	0	0	0	0	0	0	0	0
Ovary granulose cell tumor							1	0	0	0	0	1
Uterus Polyp							3	3	4	3	3	3
Leukemia	3	1	2	0	0	0	2	0	1	0	2	0

CONCLUSIONS

Non-neoplastic observations were found in this study.

DATA QUALITY

- Reliabilities : Reliable with restrictions

REFERENCES (Free Text)