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# Initial Risk Assessment of Disodium Disulphite in OECD High Production Volume Chemical Program

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***ABSTRACT*** *: Disodium disulphite, the HPV chemical, was assigned to Korea in order to implement OECD SIDS program in 1999. It was produced about 3,200 ton/year in 1998. This report evaluates the toxic potency of disodium disuphite based on the environmental and mammalian effects as well as human exposure. Oral $LD_{50}$ in rats is 1,540 mg/kg b.w. and effects was observed to the stomach, liver, and the GI track that was filled with blood. For repeated dose toxicity, the predominant effect was the induction of stomach lesions due to local irritation. The no observed adverse effect level for local (stomach irritation) was about 217 mg/kg bw/day . There is no evidence that disodium disulphite is genotoxic in vivo. No reproductive or developmental toxicity of disodium disulphite was observed for the period up to 2 yr and over three generations. In humans, urticaria and asthma with itching, edema, rhinitis, and nasal congestion were reported. Disodium disulphite is unlikely to induce respiratory sensitization but may enhance symptoms of asthma in sensitive individuals. This chemical would be mainly transported to water compartment when released to environmental compartments since it is highly water soluble (470 g/l at 20). Low $K_{OC}$ (2.447) indicates disodium disulphite is so mobile in soil that it may not stay in the terrestrial compartment. The chemical has been tested in a limited number of aquatic species. From acute toxicity test to fish, 96 hr-$LC_{50}$ was > 100 mg/l. For algae, 72 hr-$EC_{50}$ was 48.1 mg/l. For daphnid, the acute toxicity value of 48 hr-$EC_{50}$ was 88.76 mg/l, and chronic value of 21day-NOEC was > 10 mg/l. Therefore, PNEC of 0.1 mg/l for the aquatic organisms was obtained from the chronic value of daphnid using the assessment factor of 100. Based on these data the disodium disulphite was recommended as low priority for further post-SIDS work in OECD.*

***Key Words*** *: Disodium disulphite, Hazard assessment, SIDS (Screening Information Data Set), SIAM (SIDS Initial Assessment Meeting)*

## I. INTRODUCTION

Disodium disulphite is used as additives in foods or basic chemical in industrial purpose synthesis. Total production of disodium disulphite in Korea was about 3,200 tonnes/year as of 1998 survey (MOE[a], Korea, 1998) and produced mostly in one chemical industry. In 1999, the estimates for sodium salts of sulfites for the world market without China and Russian Federation amounted to approx. 330,000 tonnes/year. 20,000 tonnes in Germany, 60,000 tonnes in the rest Europe and 250,000 tonnes in the rest of the world are distributed for tanning agents, food/foodstuff additives, bleaching agents, photography, etc. This high productive volume (HPV) chemical was assigned in 1999 to Korea for OECD co-operative HPV chemical programme in which OECD developed the Screening Information Data Set (SIDS), the minimum data elements essential for determining whether or not a chemical requires further investigation. In this paper we provide a minimum set of hazard information on disodium disulphite, to draw conclusions on the potential risk of disodium disulphite thorough undertaking initial assessment of the information and to make recommendation related to the need for further work.

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## II. INITIAL RISK ASSESSMENT OF DISODIUM DISULPHITE

### 1. General information on exposure

Disodium disulphite is made by the reaction of sulfur dioxide with sodium carbonate or soda ash at a chemical industry in Korea. The production is a solid inorganic substance and a reactive chemical that may exist in different forms depending on pH or concentration. The solubility in water is relatively high and the partition coefficient log $P_{OW}$ is low but strongly depend on pH value (Table 1).

Environmental fate. The substance can release sulphur dioxide under acid conditions, but this is not likely to occur under normal natural environmental conditions. It 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 aqueous solution. It is not relevant to the evaluation of the fugacity model for assessing distribution in environment because disodium disulphite is an inorganic chemical soluble in water to 100%. The product of disodium disulphite 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. Photodegradation of disodium disulphite in water is not relevant because it is quickly ionized in water. Bioaccumulation of the substance is also not expected.

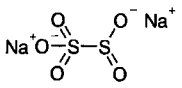
Human exposure. Exposure to consumer may occur but the extent of this exposure is unknown. Several occupational and consumer exposure cases have been reported. An occupational asthma in laundry workers (Le-Stradic-Reygagne, 1991), dermatitis and asthma in a photographic technician (Jacobs *et al.*, 1992), 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 impact on sensitive individuals. No data is available regarding human exposure in Korea.

### 2. Human health hazards

1) Experimental Animal Data

Toxicokinetics & metabolism. It was stated that a

**Table 1.** Properties of disodium disulphite

| Elements | | Summary |
|---|---|---|
| OECD Name | | Disodium disulphite |
| Synonym | | Dinatriumdisulfit<br>Disodium disulphite<br>Disodium metabisulfite<br>Disodium pyrosulfite<br>Disulfurous acid, disodium salt (9CI)<br>Natriumdisulfit<br>Pyrosulfurous acid, disodium salt (8CI)<br>Sodium disulfite<br>Sodium metabisulfite<br>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<br>Water Solubility<br>Log Pow<br>Vapour Pressure<br>Boiling Point | 150°C (decomposition)<br>470 g/l at 20°C<br>–3.7 at 25°C |
| Classification in Korea | | Not classified as toxic chemicals in the Toxic Chemicals Control Act, Republic of Korea |

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 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).

Acute toxicity. Acute toxicity data are reported in some literatures for rats and other species. The oral $LD_{50}$ of 1540 and 2480 mg/kg b.w. in rat have been reported (Hoechst AG, 1987; NTIS 1972). The acute toxicity $LD_{50}$ of 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 g.i. tract was filled with blood, reddened mucosa of the stomach and the dark colored liver, but unusual gross abnormalities were not found in survival rats (Hoechst AG, 1987).

Repeated dose toxicity. An assessment of repeated dose toxicity was performed using a multigeneration study of Wistar rats (Til *et al.,* 1972). Rats were exposed to disodium disulphite in a supplemented diet with thiamine (ca. 2 mg/kg b.w.) 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 for 104 weeks ($F_0$- and $F_1$-generations) or for 30 weeks ($F_2$-generation). The general condition of the animals was good during the first 72 weeks of the F-generation, as was the case in the next generation. Overall, survival rate in the sulphite groups was generally higher than in the controls, except in the case of males of the $F_1$-generation given 2% sulphite. However, no deaths occurred in the females of the same dose group. The body weights of the $F_0$-generation were comparable in all groups irrespective of treatment. There was a marginal reduction in body weight gain in both sexes of $F_1$-and $F_2$-generation rats given 2% disodium disulphite. A marginally reduced hemoglobin content, hematocrit and erythrocyte count occurred in F-generation males at the 2% dose at week 52, 78 and 100, and the $F_1$-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 $F_0$- and $F_1$-generation, and at 30 weeks in the $F_2$-generation). At the 0.5% dose, a few forestomach lesions were seen in the $F_2$-generation rats. Other non-neoplastic lesions observed in treated groups were comparable to controls. No histologic changes were noted in the gonads.

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

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 $SO_3^-$ 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; 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).

Carcinogenicity. The study described in above repeated dose toxicity section(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 in that 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.

Reproduction toxicity. As described in repeated dose toxicity section, 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 on actual dose) in a supplemented diet with thiamine, since sulphites are known to break down thiamine (Til *et al.*, 1972). The F-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 $F_{1a}$-generation. The $F_{1a}$-generation was mated at weeks 12 and 30 to produce $F_{2a}$- and $F_{2b}$-generations. Animals from the $F_{2a}$ litters were mated to produce $F_{3a}$- and $F_{3b}$-generation by pairing on weeks 14 and 22.

Body weight was not reduced in any treatment group in the F-generation. There was a marginal reduction in body weight in both sexes of the 2% group in the $F_1$- and the $F_2$-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 $F_{1a}$- and the $F_{1b}$-generation offspring ($F_{2a}$ and $F_{2b}$ 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 $F_{2a}$ 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 $F_{2b}$ 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 $F_1$ pups. A reduction in the number of $F_{2a}$-generation offspring ($F_{3a}$ 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 $F_{2b}$-generation offspring ($F_{3b}$ pups). No pronounced effects were observed on reproductive performance in any generation and no effects on gonads were seen histologically; thus, the no observed adversed effect level (NOAEL) for reproduction toxicity was the highest dose 2% in the diet that is equivalent to 942 mg/kg bw/day as actual dose.

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.

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.

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 of 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; W thrich *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).

2) Initial assessment for human health

Acute toxicity of disodium disulphite is likely low since the $LD_{50}$ of 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: 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 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.

### 3. Hazards to the environment

1) Experimental animal data

Aquatic effects. The toxicity tests with aquatic organisms are indicated in Table 2.

Terrestrial effects. There is almost no data available on the terrestrial organisms. A study showed treatment of tomato leaves with different concentration 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.

2) Initial assessment for the environment

Testing for the endpoint of biodegradability is not

**Table 2.** Ecotoxicity tests of disodium disulphite using aquatic organism

| Species | Results | Reference |
|---|---|---|
| acute toxicity | | |
| Medaka (*Oryzias latipes*) | $LC_{50}$ (96 h) > 100 mg/*l* | MOE[b], Korea (2001) |
| Rainbow trout (*Salmo gairdneri*) | $LC_{50}$ (96 hr) > 147 mg/*l* and < 215 mg/*l* | BASF (1981) |
| Water flea (*Daphnia magna*) | $EC_{50}$ (48 h) = 88.76 mg/*l* | BASF (1989) |
| Algae (*Scenedesmus subspicatus*) | $EC_{50}$ (72 h) = 48.1 mg/*l* | BASF (1989) |
| Bacteria (*Pseudomonas putida*) | $EC_{50}$ (17 h) = 56.1 mg/*l* | BASF (1988) |
| chronic toxicity | | |
| Water flea (*Daphnia magna*) | NOEC > 10 mg/*l** | BASF (1993) |

* The ranges of test concentration were 1, 5, and 10 mg/*l*.

appropriate due the chemical not being an organic chemical. Also, bioaccumulation is not expected. As mentioned above, low $K_{OC}$ (2.447) indicates 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 data of most sensitive organism, 48.1 mg/l (72 hr- $EC_{50}$ of algae; *Scenedesmus subspicatus)*, assessment factor 100 was applied to determine prediced no effect concentration (PNEC) of 0.481 mg/*l*. From a chronic toxicity value of > 10 mg/*l* (21 days-NOEC (no observed effect concentration) of *Daphnia magna*), the value of PNEC, 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*.

## III. CONCLUSIONS

Careful consideration was made of the quality of the studies, the methods, the reporting of the results, the conclusions drawn and the results. The SIDS initial assessment drew conclusions on the potential hazards of disodium disulphite. No significant hazard on ecology and human was found. Exposure to environment and human may has little potential risk since the quantity of chemical production is rather small. Based on these conclusions it is recommended that disodium disulphite is currently low priority for further work including post-SIDS exposure assessment or further testing.

Most OECD member countries are encouraged to collaborate with chemical industries that are responsible for collating and generating data in order to make the most efficient way to assess risk of their chemicals. The SIDS of disodium disulphite is lack of solid information on exposure profiles because it is carried out by only government initiative along. In this context the readily available data was rough information for use pattern or quantity of chemical produced. To produce a sound scientific basis for national risk assessment, the voluntary participation of domestic chemical industries should be encouraged. Disodium disulphite was recommended as low priority for further work due to its weak toxicity and relatively low production volume despite of lack of its detailed exposure data. The recommendation on the chemical was agreed at the 13th SIDS Initial Assessment Meeting (SIAM). It is expected that these conclusion and recommendation will be applied by OECD member countries for national and regional priority setting.

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