SUBSTANCE EVALUATION REPORT

Public Name: Disodium disulphite

EC Number(s): 231-673-0

CAS Number(s): 7681-57-4

Submitting Member State Competent Authority:

National Institute of Chemical Safety, Hungary

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Year of evaluation (as given in the CoRAP): 2014

VERSION NUMBER: 1 DATE: 30.10.2015

Conclusions of the most recent evaluation step*	Tick relevant box(es)
Concern not clarified; Need to request further information from the Registrant(s) with the draft decision	
Concern clarified; No need of further risk management measures	
Concern clarified; Need for risk management measures; RMO analysis to be performed	
Other: Concern clarified; need for risk management measure (proposal for harmonized C&L), but no need for RMOA	X

**Include details in the executive summary.*

DISCLAIMER

Executive summary

Grounds for concern

Disodium disulphite is produced in high volumes, and has a wide dispersive use (worker, professional).

Further to this, various international literature and also self-classifications available from the C&L Inventory suggested that there are grounds to the following initial concerns.

Concern 1: Exposure to the environment

Taking into consideration certain hazard classes given as self-classification in the C&L Inventory, certain ways of exposure may raise a concern. In particular classification as toxic to the aquatic environment together with some of the uses raised the concern of environmental exposure and the possible exposure of sensitive population.

Concern 2: Mutagenicity

Although the majority of the mutagenicity studies are negative, also positive results were found, which raised concern. There is a study available on the substance that suggests mutagenic property. In the *in vitro* study the substance induced chromosome aberration and sister chromatid exchange in human lymphocytes dose-dependently.

Concern 3: Sensitisation

The self-classification in the C&L inventory suggests that the substance also has sensitising properties. A few notifiers classified the substance as respiratory and skin sensitiser. Also, human data is available showing many cases of contact allergies and patch test reactions to disodium disulphite, which triggered detailed evaluation of this endpoint.

The evaluating Member State evaluated all relevant endpoints along with the following additional identified concerns.

<u>Additional concerns:</u>

Concern 4: Acute toxicity

Self-classification notified in the C&L Inventory indicates that the current harmonized classification of the substance as Acute tox. 4 is not correct, but more severe classification may be justified.

Concern 5: Irritation

Again, self-classification notified in the C&L Inventory indicated that more detailed evaluation of the possible irritating properties is necessary.

Concern 6: Repeated dose toxicity

The hazard class of STOT RE 1; H372: Causes damage to organs has been notified among the aggregated self-classifications in the C&L Inventory, and the evaluating Member State considered that this raised some concern about this endpoint.

Concern 7: Carcinogenicity

Considering the above specified concern on mutagenicity, the evaluating Member State decided to have a prudent approach and examine in more detail also the carcinogenicity of disodium disulphite.

Concern 8: Toxicity for reproduction

-Fertility

The issue of reproductive toxicity was also raised as an additional concern for disodium disulphite. Several fertility studies are available, and some indications were present that suggested some potential effects of the test material and warranted a thorough inspection of the submitted data.

-Developmental toxicity

Developmental toxicity studies have also been evaluated in detail to identify any further potential effects of disodium disulphite.

Procedure

Disodium disulphite has been selected for substance evaluation according to Article 44 of REACH Regulation for 2014, based upon the Justification Document prepared by the Hungarian REACH Competent Authority. The Justification Document identified the above mentioned concerns which warranted the substance evaluation of disodium disulphite. The evaluation was executed by the Hungarian REACH Competent Authority.

In the course of the evaluation, the evaluating Member State concentrated on the above mentioned initial concerns and additional issues identified during the evaluation process, and in this way, the evaluating Member State considers that all relevant endpoints have been addressed.

The core documents used for the evaluation were the registration dossier, including the chemical safety reports and the exposure scenarios prepared by the Registrants, as well as further reports referenced by the registration dossier. Further to this, the evaluating Member State identified several relevant scientific studies and articles that were also considered in the course of the evaluation. Information on and studies with structurally similar substances were also used, as read-across with several substances was considered as acceptable.

Most of the relevant studies are from the years 2000's, with some further publications also from the 70's and 80's.

Conclusions

Conclusion 1: Exposure to the environment

Based on the fate and toxicity properties of the substance it appears that the substance is not a concern for the environment and therefore it is not considered necessary to further investigate the releases and exposure to the environment.

Conclusion 2: Mutagenicity

In relation to the initial concern on mutagenicity of disodium disulphite the evaluating Member State is of the opinion that the available information is sufficient and reliable to conclude on this concern and there is no need of further studies on this aspect. The conclusion of the evaluating Member State is that there is no consistent evidence of induction of genetic toxicity, and the negative results are robust enough, and thus the initial concern can be disregarded. Based on the available information and the weight of evidence, the evaluating Member State concludes that the concern for mutagenicity is not substantiated. Thus no classification or other risk management seems warranted.

Conclusion 3: Sensitisation

Based on the evaluated literature data, which was sufficient and reliable to assess this endpoint, it is unlikely that disodium disulphite is a skin sensitiser or induces respiratory sensitisation, but may enhance symptoms of asthma in sensitive individuals. Consequently, the initial concern can be dropped without the need for further studies.

Conclusion 4: Acute toxicity

The information related to the acute oral toxicity of the disodium disulphite presented by the Registrant is relevant and acceptable, therefore the evaluating Member State agrees to the conclusion made by the Registrant and concludes that harmonized classification in category Acute Tox. 4 can be confirmed. The study also revealed that application of STOT SE category based on acute oral toxicity is not relevant.

However, considering the results of the acute inhalation toxicity studies in Guinea pigs, Beagle dogs and Sprague-Dawley rats at relatively low concentration levels of sodium sulphite and ammonium sulphite, as well as the human observations reported in section *5.3.3. Respiratory tract* in relation to the irritation effect of disodium disulphite (itching, rhinitis, nasal congestion) the application of category STOT SE 3 for respiratory tract irritation seems to be justified.

Conclusion 5: Irritation

Based on the outcome of the read-across studies, it can be concluded, that disodium disulphite is not irritating to the skin.

Conclusion 6: Repeated dose toxicity

Based on the evaluated literature data on repeated dose toxicity of disodium disulphite the evaluating Member State is of the opinion that the available information is sufficient and reliable to establish that disodium disulphite does not need to be classified for repeated dose toxicity.

Conclusion 7: Carcinogenicity

In relation to the concern on carcinogenicity the evaluating Member State is of opinion that the available and reliable studies on this endpoint are sufficient to conclude that there is no concern for carcinogenicity.

Conclusion 8: Toxicity for reproduction

-Fertility

Based on the weight of evidence of available data the evaluating Member State concluded that there is no concern regarding the endpoint of fertility.

-Developmental toxicity

Developmental toxicity study results do not indicate any clear fetotoxic or teratogenic effects of disodium disulphite either. Based on the submitted data there is no concern for developmental toxicity and further information is not required.

Statement of reasons

Concern 1 may be rejected due to the following reasons:

Concern 1: Exposure to the environment

The evaluating Member State carefully assessed the information submitted by the Registrant with regard to various environmental endpoints and also several other available and relevant publications. The following was concluded:

Disodium disulphite has low bioaccumulation potential, further to this, under environmental conditions sulphate rapidly forms from sulphite. The evaluating Member State agrees with the Registrant that the secondary poisoning is an unlikely exposure pathway.

Data on short-term and long-term toxicity to the aquatic environment was available with either disodium disulphite or structurally related substances, with a key study on disodium disulphite on *Daphnia magna*, which was considered by the evaluating Member State as the most sensitive species. None of the data in the relevant studies warranted classification of disodium disulphite as toxic to the aquatic environment.

Due to the salt-character and physico-chemical properties (negligible vapour pressure, very high solubility and dissociation in water), the Henry constant is near to zero, and therefore disodium disulphite as well as its dissociation products are not volatile from aqueous solutions. Relevant adsorption onto soils, sediments or suspended matter is not to be expected.

In water and in other aqueous media disodium disulphite is present in dissociated forms. Although these have a strong anionic nature, sulphite substances in the presence of water do not show any quantitatively relevant adsorption to the soil, sediment or suspended material.

Consequently, the basis of the initial concern on environmental exposure could not be substantiated.

Concern 2 may be rejected due to the following reasons:

Concern 2: Mutagenicity

There are both positive and negative results of *in vivo* and *in vitro* mutagenicity tests on sulphites which raised concern. Detailed analysis revealed that some publications are not reliable because of methodological and reporting deficiencies. Reliable *in vivo* mutagenicity tests with per os and

subcutaneous administration gave negative results except one micronucleus assay on bone marrow cells of mice. Two *in vivo* micronucleus and two chromosome aberration assays with sulphite on bone marrow cells were negative. Two dominant lethal tests on rats and mice also gave negative results.

The evaluating Member State is of the opinion that there is very vague and inconsistent evidence of induction of genetic toxicity with relevance to humans for sulphites. The studies with negative results were reliable and sufficient; therefore based on the weight of evidence the concern can be rejected without the need for further studies.

Concern 3 may be rejected due to the following reasons:

Concern 3: Sensitisation

Based on the evaluated literature data it is unlikely that disodium disulphite is a skin sensitiser or induce respiratory sensitization but may enhance symptoms of asthma in sensitive individuals. The information related to the skin and respiratory sensitizing properties of the disodium disulphite presented by the Registrant is relevant and acceptable, therefore the evaluating Member State concludes that sensitization by disodium disulphite is not a concern. With regard to skin sensitization the conclusion is also supported by the review of the available study performed by the German MAK Commission in 2014, who also concluded that in view of the widespread use of disodium disulphite, and therefore the numerous possibilities for contact in everyday life and the occupational field, the number of persons dermally sensitised is, however, very small.

Concern 4 may be accepted due to the following reasons:

Concern 4: Acute toxicity

The results of two inhalation toxicity studies performed by Chen at al. in 1987 and Last et al. in 1980 support the existence of local cytotoxic effect of a structurally closely related substance, sodium sulphite. According to the Guidance on CLP, respiratory tract irritation (RTI) covers two different effects: “sensory irritation” and “local cytotoxic effects”, and classification as STOT SE 3 is generally limited to this latter effect. Consequently, the evaluating Member State considers that the classification of disodium disulphite into STOT SE Category 3 for RTI may be warranted.

Concern 5 may be rejected due to the following reasons:

Concern 5: Irritation

Several reliable and relevant studies with structurally similar substances indicated no skin irritation when applied as aqueous solution (substance as such does not exist in dry form). Erythema and edema scores were zero after 24, 48 and 72h for all test substances. The evaluating Member State considered these studies as sufficient to establish that there is no concern for skin irritation.

Concern 6 may be rejected due to the following reasons:

Concern 6: Repeated dose toxicity

Based upon the physico-chemical properties of disodium disulphite, and especially the particulate size of it (the median particle size of the disodium disulphite is 66.8 µm, so the particles are most likely to deposit in the upper respiratory tract and they are excreted with mucus), and considering also the above mentioned respiratory tract irritation, as well as the fact that disodium disulphite is not used in sprays, the evaluating Member State considers that the concern about the inhalation toxicity of disodium disulphite after repeated exposure can be disregarded.

Concern 7 may be rejected due to the following reasons:

Concern 7: Carcinogenicity

No reliable study suggested that disodium disulphite has any carcinogenic activity *in vitro*, and in the cohort study due to the lack of exposure informations the contribution of disodium disulphite in the increase of brain tumour incidencies was not verified.

Concern 8 may be rejected due to the following reasons:

Concern 8: Toxicity for reproduction

-Fertility

In the key study on disodium disulphite (Til et al., 1972) no effects were seen on fertility or reproduction, thus the NOAEL for these effects was above the highest treatment dose of 2.0% (955 mg/kg bw/day) for all generations. Another study also did not reveal any reproductive effects of disodium disulphite.

Two other submitted studies on disodium disulphite were not considered relevant or reliable for the evaluation.

The available studies did not follow any guidelines and several parameters were not examined (e.g. sperm parameters, estrous cyclicity, offspring pathology, etc.), nevertheless the weight of evidence approach to the available data showed no concern for the endpoint of fertility.

-Developmental toxicity

No effects suggesting any teratogenic potential were seen in the submitted studies. The available tests were considered on the basis of a read-across concept for sulphites, metabisulphites, hydrogensulphites and thiosulphates. In a study performed on rats (Ema et al., 1985) fetotoxicity (reduced fetal body weight) was observed only at maternally toxic doses, suggesting a secondary effect that may have been caused by maternal malnutrition. In the study of Itami et al. (1989) slight reduced fetal body weight was observed at all treatment doses, even below the maternal NOAEL, however these effects were not dose-dependent and were not present in the live-birth part of the study. Other studies did not reveal any fetotoxic or teratogenic effects. As a conclusion, based on the available information the evaluating Member State concluded that the concern for developmental toxicity was not substantiated.

CONTENTS

TABLES

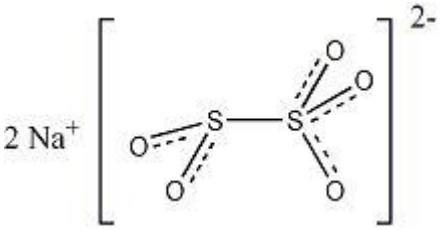
1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Table 1: Substance identity

Public Name:	Disodium disulphite
EC number:	231-673-0
EC name:	Disodium disulphite
CAS number (in the EC inventory):	7681-57-4
CAS number:	7681-57-4
CAS name:	Disodium disulphite
IUPAC name:	Disodium disulphite
Index number in Annex VI of the CLP Regulation	016-063-00-2
Molecular formula:	H2O5S2.2Na
Molecular weight range:	190.1
Synonyms:	*Sodium metabisulphite,* *Natrium disulfit,* *Sodium pyrosulfite,* *Disulfurous acid, disodium salt (9Cl).*

Structural formula:



1.2 Composition of the substance

Name: disodium disulphite

Details on the composition of the substance can be found in the Annex of the Report (confidential information).

1.3 Physico-chemical properties

The registrant gathered enough available experimental data (literature data) to support the submitted physical and chemical properties of disodium disulphite.

Table 2: Physico-chemical properties

Property	**Result**
Physical state at 20°C and 1013 hPa	Disodium disulphite has the appearance of a white crystalline or powder with SO2 odour.
Melting / freezing point	Decomposition temperature of disodium disulphite: > 150 °C
Relative density	Density of disodium disulphite = 2.36 g/cm³ at 20°C
Surface tension	This study only needs to be conducted if – based on structure surface activity – it is expected or can be predicted that the substance is surface active (cf. Annex VII section 7.6 Column 2 of regulation 1907/2006/EC): according to EU Directive 648/2004/EEC. Surfactant means any organic substance and/or preparation used in detergents, which has surface-active properties and which consists of one or more hydrophilic and one or more hydrophobic groups of such a nature and size that it is capable of reducing the surface tension of water, and of forming spreading or adsorption monolayers at the water-air interface, and of forming emulsions and/or microemulsions and/or micelles, and of adsorption at water-solid interfaces. Therefore, the substance disodium disulphite should be regarded as a nonsurface active substance.
Water solubility	Disodium disulphite is highly soluble in water.
Flammability	Flammability of disodium disulphite (experimental results, according to the guideline

Property	**Result**
	in Official Journal L 283 A.10.): not flammable
Explosive properties	Explosive properties of disodium disulphite (experimental results, according to the guideline in Official Journal L 283 A.14.): Disodium disulphite does not exhibit explosive properties.
Granulometry	The particle size of a representative disodium disulphite sample was determined: D50 = 66.8 µm D10 = 9.4 µm D90 = 238.5 µm Dustiness and MMAD (GSD) of airborne material: Dustiness: 18.55 mg/g, MMAD (GSD): 23.11 µm (2.15)

2 MANUFACTURE AND USES

2.1 Quantities

According to the information on the dissemination site of ECHA, the aggregated tonnage per year is 100,000-1,000,000 tonnes.

2.2 Identified uses

2.2.1 Uses by workers in industrial settings

- Manufacture of disodium disulphite and industrial use of disodium disulphite in the chemical industry
- Photographic industry
- Textile/Leather industry
- Rubber/Plastic industry
- Paper and pulpindustry/Bleaching
- Industrial use of disodium disulphite in the wood and furniture industry
- Food industry (processing aid for fructose and sugar production, starch industry)
- Water treatment/Mining/Offshore/Metalindustry/Surface treatment)
- Fibre industry
- Additive for cement
- Agriculture and fertiliser industry
- Industrial use of disodium disulphite in cosmetic industry

2.2.2 Use by professional workers

- Photographic sector
- Textile/Leather sector

- Paper and pulp/Bleaching sector
- Professional use of wood products or furniture containing disodium disulphite
- Use in food
- Water treatment/Mining/Offshore/Metal sector/Surface treatment
- Use in cement
- Agriculture and fertiliser sector

2.2.3 Uses by consumers

- Consumer use of disodium disulphite in photographic applications

2.3 Uses advised against

This section is not applicable for disodium disulphite since no uses were identified which need to be advised against.

2.3.1 Uses by workers in industrial settings advised against

Not relevant.

2.3.2 Use by professional workers advised against

Not relevant.

2.3.3 Uses by consumers advised against

Not relevant.

3 CLASSIFICATION AND LABELLING

3.1 Harmonised Classification in Annex VI of the CLP Regulation

Table 3: CLP classification (as in Annex VI, Part 3, Table 3.1):

	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
	Hazard Class and Category Code(s)	Hazard state-ment Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Disodium disulphite Index No.: 016-063-00-2	Acute tox. 4 (*)	H302	 GHS05  GHS07 Danger	H302 H318	EUH031		
	Eye Dam. 1	H318					

Table 4: DSD classification (as in Annex VI, Part 3, Table 3.2):

	Classification	**Labelling**	**Concentration Limits**	**Notes**
Disodium disulphite Index No.: 016-063-00-2	Xn; R22 Xi; R41 R31	Xn R: 22-31-41 S: (2-)26-39-46		

3.2 Self classification

Table 5: Self classification

In the registration		Precautionary statements	Aggregated self classifications in the C&L Inventory		Additional labelling requirements
Acute tox. 4	H302	P264	Acute Tox. 3	H301	EUH031
Eye Damage 1	H318	P280	Aquatic Chronic 3	H412	
		P330	Skin Sens. 1	H317	
		P305+P351+P338	Resp. Sens. 1	H334	
		P310	STOT SE 3	H335	
			STOT RE 1	H372	

4 ENVIRONMENTAL FATE PROPERTIES

4.1 Degradation

4.1.1 Abiotic degradation

4.1.1.1 Hydrolysis

According to the Registrant hydrolysis is not to be expected due to the chemical properties of sulphite compounds. The evaluating Member State agrees and accepts this argument.

4.1.1.2 Phototransformation/photolysis

4.1.1.2.1 Phototransformation in air

No photodegradation can be expected in air, based on the physico-chemical properties and the chemical structure of the substance.

4.1.1.2.2 Phototransformation in water

Photodegradation in water is not relevant because disodium disulphite is rapidly ionised in water.

4.1.1.2.3 Phototransformation in soil

Not relevant.

4.1.2 Biodegradation

Inorganic substances cannot be tested for being readily biodegradable. However, according to the Registrant sulphite substances can be transformed via oxidation by microbial activity under certain circumstances.

4.1.2.1 Biodegradation in water

Not relevant.

4.1.2.2 Biodegradation in soil

Not relevant.

4.1.3 Summary and discussion on degradation

The evaluating Member State agrees with the Registrant that hydrolysis and photolysis are not expected due to the chemical properties of sulphite compounds.
The substance is an inorganic compound, therefore biodegradation is not relevant.

4.2 Environmental distribution

4.2.1 Adsorption/desorption

No study measuring the adsorption and desorption has been conducted.
In water and in other aqueous media disodium disulphite is present in dissociated forms. Although these have a strong anionic nature, sulphite substances in the presence of water do not show any quantitatively relevant adsorption to the soil, sediment or suspended material.

4.2.2 Volatilisation

Due to the very low Henry’s Law constant of the substance a release into air from water is not to be expected.

4.2.3 Distribution modelling

Not relevant.

4.2.4 Summary and discussion of environmental distribution

Due to the salt-character and physico-chemical properties (negligible vapour pressure, very high solubility and dissociation in water), the Henry constant is near to zero, and therefore disodium disulphite and its dissociation products are not volatile in aqueous solutions. Relevant adsorption onto soils, sediments or suspended matter is not to be expected.

4.3 Bioaccumulation

The octanol/water partition coefficient of disodium disulphite is very low (according to OECD 2001 the logPow is -3.7), for this reason it is considered that the substance has no potential for bioaccumulation.

References:

OECD (2001). SIDS Initial Assessment Report for SIAM 13 (Bern, 6 - 9 November 2001) - Disodium disulfite, CAS: 7681-57-4. UNEP Publications.

4.3.1 Aquatic bioaccumulation

Not relevant.

4.3.2 Terrestrial bioaccumulation

Not relevant.

4.3.3 Summary and discussion of bioaccumulation

The octanol/water partition coefficient of disodium disulphite is very low, for this reason the substance has no potential for bioaccumulation.

4.4 Secondary poisoning

The very low logKow indicates that the substance is not bioaccumulative.

5 HUMAN HEALTH HAZARD ASSESSMENT

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

The evaluating Member State has no information that would raise particular concern about this endpoint. The information presented by the Registrant is relevant and acceptable, and the evaluating Member State agrees to the conclusion made by the Registrant.

Details on the toxicokinetics of the substance can be found in the Annex of the Report (confidential information).

5.1.1 Non-human information

Not relevant.

5.1.2 Human information

Not relevant.

5.1.3 Summary and discussion on toxicokinetics

Not relevant.

5.2 Acute toxicity

5.2.1 Non-human information

5.2.1.1 Acute toxicity: oral

Acute toxicity data are reported in two key studies provided by the Registrant and several literature data are available for rats and other species. Oral LD_{50}s in the range of 1131 - 3200 mg/kg bw in rats have been reported. The acute LD_{50} value by oral exposure in rat used for regulatory purposes is 1540 mg/kg bw. In Cosmetic Ingredients Review (CIR 2003) Eastman Kodac Co. reported in 1980 the acute oral LD_{50} value of 1131 and 1903 mg/kg for female and male rats, respectively. Considering that the details of the study providing the lower value are not available, and the classification and labelling requirements will not change using this value, the evaluating Member State can agree with the use of the oral LD_{50} value reported by the Registrant.

Based on this LD_{50} value the harmonized classification as in Regulation 1272/2008/EC in category of Acute Tox. 4 can be confirmed.

The study reports of the acute oral toxicity experiments revealed that unusual gross abnormalities were not found in surviving rats, so application of STOT SE category based on acute oral toxicity is not relevant.

References:

Cosmetic Ingredient Expert Review Panel (2003). Final Report on the Safety Assessment of Sodium Sulfite, Potassium Sulfite, Ammonium Sulfite, Sodium Bisulfite, Ammonium Bisulfite, Sodium Metabisulfite, and Potassium Metabisulfite. International Journal of Toxicology, 22 (S2): 63-88.

5.2.1.2 Acute toxicity: inhalation

One read-across study equivalent or similar to OECD 403 for sodium sulphite (CAS 7757-83-7) has been reported in rats by the Registrant which indicated an LC_{50} >5.5 mg/l (limit test). During exposure nothing abnormal was detected. After exposure substance-contaminated heads, and unstable, staggering gait were observed. After one day nothing abnormal was detected.
In Cosmetic Ingredient Review (CIR 2003) acute inhalation toxicity study performed by Chen et al from 1987 was evaluated. In this study Guinea pigs were exposed to sodium sulphite aerosol (MMAD 1.36 µm) head only for 1 hour at 0.474, 0.669 and 0.972 mg/m^3 concentration levels. Respiratory mechanics were measured in unanesthetized animals before, during and after exposure. At highest dose the resistance increased dose dependently (50% in high dose) and the 19% decrease of compliance occurred. Another group of guinea pigs was exposed whole-body to the same aerosol at 0.204, 0.395, and 1.152 mg/m^3. After exposure, lung volume, diffusion capacity for carbon monoxide, and wet lung weight were evaluated in anesthetized, tracheotomised animals. Compared to controls, total lung capacity, vital capacity, functional residual capacity, residual volume, and diffusion capacity for carbon monoxide were all decreased in exposed guinea pigs. A dose-related increase in wet lung weight was found (Chen et al., 1987).

Groups of eight guinea pigs were exposed head-only for 1 hour to an ammonium sulphite/ ammonium sulphate aerosol at concentrations of 50, 250, and 450 mg/m^3. The aerosol had an MMAD of approximately 2 to 3 µm and the pH was greater than 5; chemical composition was 60% to 80% sulphite with the remainder being sulphate. Sulphur dioxide concentrations were monitored and never exceeded 1 ppm; chamber ammonia gas concentrations exceeded 50 ppm throughout the study and occasionally reached 150 ppm. All guinea pigs survived the exposure. The median lethal concentration (LC_{50}) for ammonia sulphite exceeded 400 mg/m^3 (Rothenberg et al. 1986).

Beagle dogs (five female and three male) were exposed nose-only for 1 hour to 1 mg/m^3 of aerosolized ammonium sulphite mixed with sulphate. Sulfur dioxide and ammonia gas concentrations were monitored and were less than 0.5 and 5 ppm, respectively. No significant difference was observed between pre-exposure and post-exposure tracheal mucous clearance rates. Citing results of other studies, the investigators noted that ammonium sulphite seemed to be less toxic than sulfuric acid on an equivalent mass basis. The investigators also noted that ammonium sulphite was rapidly oxidized in air, thereby lessening its environmental health effects (Rothenberg et al. 1986).

Groups of six male Sprague-Dawley rats were exposed for 3 days to sodium sulphite aerosols at concentrations of 0.1, 1, 5, or 15 mg/m^3 (sulfur dioxide equivalents of 0.2 to 2.7 ppm). The particle size was 1 µm. Two control groups were exposed to either 15 mg/m^3 sulphate aerosol or filtered air.

Responses were measured as follows: tracheal explants were cultured to measure glycoprotein secretion rates, lung homogenates were analysed for protein, DNA and RNA concentrations, and the wet weight to dry weight ratios of the right apical lung lobes were determined. Increased glycoprotein secretion was observed in rats dosed with 25 mg/m^3, and increased wet to dry weight ratios of right apical lobes were observed in rats dosed with 21 mg/m^3. The investigators concluded that the rats responded with "mild pulmonary edema." Exposure to 25 mg/m^3 resulted in an irritation response by the tracheal epithelium. The investigators emphasized that their aerosol generation technique produced "well-characterized sulphite aerosols containing little or no contaminating [sulfur dioxide]." Earlier studies of sulfur dioxide gas were considered inadequate to evaluate sulphites and disulphites because sulfur dioxide was removed by the upper respiratory tract and did not penetrate to the deep lung (Last, Dasgupta, and Etchison 1980).

As stated in the Guidance on CLP, the generic term respiratory tract irritation (RTI) covers two different effects: “sensory irritation” and “local cytotoxic effects”. The Guidance also points out that classification in STOT SE Category 3 for respiratory tract irritation is generally limited to local cytotoxic effects. The results of the inhalation toxicity studies performed by Chen at al. in 1987 and Last et al in 1980 support the existence of local cytotoxic effect of a structurally closely related substance, sodium sulphite, so the classification of disodium disulphite into STOT SE Category 3 for RTI may be warranted.

References:

Chen LC, Lam HF, Ainsworth D, Guty J, Amdur MO (1987). Functional changes in the lungs of guinea pigs exposed to sodium sulfite aerosols. Toxicology and Applied Pharmacology. 1987 Jun 15;89(1):1-8.

Cosmetic Ingredient Expert Review Panel (2003). Final Report on the Safety Assessment of Sodium Sulfite, Potassium Sulfite, Ammonium Sulfite, Sodium Bisulfite, Ammonium Bisulfite, Sodium Metabisulfite, and Potassium Metabisulfite. International Journal of Toxicology, 22 (S2): 63-88.

Last JA, Dasgupta PK, Etchison JR (1980). Inhalation toxicology of sodium sulfite aerosols in rats. Toxicol Appl Pharmacol, 55(2):299-34.

Rothenberg SJ, Dahl AR, Barr EB, Wolff RK (1986). Generation, behavior, and toxicity of ammonium sulfite aerosols. Journal of the Air Pollution Control Association, 36:55-59.

5.2.1.3 Acute toxicity: dermal

No indication of concern has been raised about this endpoint.

5.2.1.4 Acute toxicity: other routes

No indication of concern has been raised about this endpoint.

5.2.2 Human information

OECD SIDS Report concluded that relating to irritation of disodium disulphite 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 still not 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).

It is also stated in the OECD SIDS report that 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 was considered to be low.

References:

OECD (2001). SIDS Initial Assessment Report for SIAM 13 (Bern, 6 - 9 November 2001) - Disodium disulfite, CAS: 7681-57-4. UNEP Publications.

5.2.3 Summary and discussion of acute toxicity

The information related to the acute oral toxicity of the disodium disulphite presented by the Registrant is sufficient for evaluation. Therefore the evaluating Member State agrees to the conclusion made by the Registrant.

Considering the results of the acute inhalation toxicity studies in Guinea pigs, Beagle dogs and Sprague-Dawley rats at relatively low concentration levels of sodium sulphite and ammonium sulphite, and the human observations reported in section *5.3.3. Respiratory tract* in relation to the irritation effect of disodium disulphite (itching, rhinitis, nasal congestion) the application of category STOT SE 3 for respiratory tract irritation to disodium disulphite seems to be necessary.

5.3 Irritation

5.3.1 Skin

A comprehensive read-across concept has been developed for sulphites, hydrogensulphites and diisulphites, based on the pH-dependent equilibrium in aqueous solutions. Since the nature of the cation is not assumed to contribute substantially to differences in toxicity and solubility, only the chemical and biological properties of the anion are considered as relevant determinants. Based on the described equilibrium correlations, the evaluating Member State considered the unrestricted read-across between the groups of sulphites, hydrogensulphites and disulphites as justified.

Six reliable *in vivo* skin irritation studies were identified that are considered adequate (read-across) information (key studies).

One *in vivo* study of potassium sulphite on skin irritation was performed according to OECD TG 404. The test article showed no skin irritating properties. No erythema or edema were seen in any of

the treated rabbits at 24, 48, 72 hours after the beginning of the study. In two animals very slight erythema was observed at the 4-hour reading, which had disappeared at the 24 hour reading.

One further *in vivo* skin irritation study of sodium sulphite was equivalent or similar to OECD TG 404. No skin irritating effect of sodium sulphite could be determined.

Three study reports equivalent or similar to OECD TG 404, for ammonium hydrogensulphite, sodium hydrogensulphite and potassium hydrogensulphite indicated no skin irritation when applied as aqueous solution (70%, 40% and 32%; substances as such are not existent in dry form). Erythema and edema scores were zero after 24, 48 and 72h for all test substances.

Skin irritation of disodium disulphite solution was tested in a single 4 h dermal application (Broughton, 1973) according to the criteria of the Federal Hazardous Substances Act, Section 191.11. The animals were immobilised in restrainers and their trunks were wrapped in a nonabsorbent binder for the exposure period. Application of 0.5 mL aqueous solution of the test substance under gauze patches (1 inch square) to intact skin sites on the back of albino rabbits (New Zealand White, six animals) afforded no signs of irritation (Draize scoring) after 4, 24 and 48 hours. According to OECD TG 404 examination for signs of erythema and edema and the responses should be scored at 30-60 minutes, and then at 24, 48, and 72 hours after patch removal. Despite minor reporting and experimental deficiencies/deviations in study design, the reference fulfils the basic requirements for scientific data used in chemicals risk assessment.

Based on the outcome of the read-across studies, it can be concluded, that there is no concern for skin irritation.

References:

Broughton WS (1973). Skin irritation test with sodium metabisulfite in rabbits with cover letter dated 04/13/94 Testing laboratory: Hazleton Laboratories Inc., 3200 Leesburg Turnpike, Vienna, Virginia 22180, U.S.A. Report No.: OTS0572413 Report date: 1973-10-11.

5.3.2 Eye

The evaluating Member State has no information that would raise new concern about this endpoint. The information provided by the Registrant is sufficient for evaluation. The evaluating Member State agrees with the conclusion made by the Registrant that according to the EC Regulation No. 1272/2008, disodium disulphite is classified as a serious eye irritant (Eye Dam.1, H318).

5.3.3 Respiratory tract

Non-human information on respiratory tract irritation was discussed in section *5.2.1.2. Acute toxicity:inhalation*. Based on the results of the inhalation toxicity studies performed in guinea pigs, dogs and rats the application of category STOT SE 3 for respiratory tract irritation to disodium disulphite seems to be necessary.

Human Information: OECD SIDS Report concluded that relating to irritation of disodium disulphite 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 symptoms are still not 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).

Disodium disulphite was administered to 29 children with chronic asthma in a single-blind challenge. The children ranged in age from 5.5 to 14 years and were essentially evenly divided by sex; 28 of the 29 were atopic for airborne allergens. A positive response was judged by a reduction in pulmonary function. The patients were challenged both with capsules at doses up to 100 mg and citric acid solution containing disodium disulphite at doses up to 50 mg. Disulphite hypersensitivity was detected in 19 children; all reacted to disulphite in solution, and none responded when it was administered in capsule form. Most of the responders experienced immediate reactions, which consisted initially of a burning sensation in the throat, tight cough, wheezing, and signs of respiratory distress. Seven of the 19 had a history which suggested sensitivity to disulphite in foods. The authors considered that the lack of response to disulphite in capsules and the rapid onset of bronchial symptoms suggested that inhalation of sulfur dioxide was the trigger. (Towns and Mellis, 1984)

The Joint Expert Committee on Food Additives (JECFA) of WHO/FAO has also evaluated the possible adverse effects of sulphites in 2011. The Committee also reviewed case studies and challenge tests for idiosyncratic sensitivity to sulphiting agents and noted the life-threatening nature of the adverse effects in some cases. It recommended that, where a suitable alternative method of preservation exists, its use should be encouraged, particularly in those applications in which the use of sulphites may lead to high acute intake. The Committee also reiterated the view expressed at the twenty-seventh meeting (Annex 1, reference 62, section 2.4) that appropriate labelling is the only feasible means of protecting individuals who cannot tolerate certain food additives. (WHO/FAO; Joint Expert Committee on Food Additives (JECFA): Food Additive Series 42: Preservative: Sulfur dioxide and sulphites)

Steiner et al in 2008 examined the disodium disulphite induced airways disease in the fishing and fish-processing industry. The authors stated that disodium disulphite is recognized as a potential cause of airway irritation and possibly occupational asthma, but awareness of its use in the fishing and fish-processing industry is low. They described three cases of occupational airways disease due to disodium disulphite exposure and reviewed the literature. Three patients, one trawlerman and two prawn processors, developed work-related airways disease due to exposure to disodium disulphite, one with irritant-induced asthma with a positive-specific bronchial challenge associated with very high sulphur dioxide exposures, one with occupational asthma and one with vocal cord dysfunction and underlying asthma. Of the nine cases recorded in the literature, most were non-atopic and responses to specific bronchial challenge when undertaken showed an immediate response. Exposures to sulphur dioxide in these settings are very high, in excess of 30 ppm. The authors concluded that disodium disulphite should be regarded as a cause of occupational airways disease and its use in the fish and prawn-processing industry investigated further to better identify risks from exposure and handling of the agent in the workplace. (Steiner et al, 2008)

References:

Steiner M, Scaife A, Semple S, Hulks G, Ayres JG (2008). Sodium metabisulphite induced airways disease in the fishing and fish-processing industry. Occupational Medicine, Oxford Journals, Volume 58, Issue 8, Pp. 545-550.

Towns SJ, Mellis CM (1984). Role of acetyl salicylic acid and sodium metabisulfite in chronic childhood asthma. Pediatrics 73: 631-637.

WHO/FAO; Joint Expert Committee on Food Additives (JECFA): Food Additive Series 42: Preservative: Sulfur dioxide and sulfites (WHO Food Additives Series 42). Available from, as of July 28, 2011: http://www.inchem.org/pages/jecfa.html.

5.3.4 Summary and discussion of irritation

Based on the negative results of studies conducted with similar substances, it can be concluded, that disodium disulphite does not require classification as skin irritant.

However, with regard to the respiratory tract, considering the results of the acute inhalation studies in Guinea pigs and Sprague-Dawley rats at relatively low concentration levels to sodium sulphite related to the lung edema, irritation of tracheal epithelium and the human observations (burning sensation in the throat, tight cough and wheezing) reported in relation to the irritation effect of disodium disulphite (itching, rhinitis, nasal congestion) the classification of disodium disulphite to STOT SE Category 3 for respiratory tract irritation seems to be necessary.

5.4 Corrosivity

On the basis of data on irritation above, the substance is not to be considered as corrosive.

Disodium disulphite does not need to be classified for skin irritation.

According to the EC Regulation No. 1272/2008 and subsequent regulations, the substance is classified as a serious eye irritant (Eye Dam.1, H318).

5.5 Sensitisation

5.5.1 Skin

One reliable animal study, according to OECD guideline 429 (Skin Sensitisation: Local Lymph Node Assay, modified according to Ehling et al. 2005) and according to GLP has been reported by the Registrant. Treatment with disodium disulphite at concentrations of 10%, 25% or 50% did not reveal statistically significantly increased values for lymph node cell count, all stimulation indices for the lymph node cell count were beneath the threshold value of 1.4. In addition, the lymph node weight was not increased. Hence, the substance was classified as not sensitising.

However, existing human data should also be considered for classification of the substances as skin sensitizer as described in the Guidance on the Application of the CLP Criteria, Annex I: 3.4.2.2.2.1.

The following literature data can be used for evaluating the possible skin sensitising potential of disodium disulphite:

The Cosmetic Ingredient Expert Review Panel issued the Final Report on the Safety Assessment of Sodium Sulfite, Potassium Sulfite, Ammonium Sulfite, Sodium Bisulfite, Ammonium Bisulfite, Sodium Metabisulfite, and Potassium Metabisulfite in the International Journal of Toxicology in 2003. In this review report the results of Yang et al (1986), Peterson and Menné (1992) and Vena et al (1994) were included. Studies of Combe Incorporated performed in 1996 and in 1998 were also included.

Yang, Purchase, and Rivington (1986) reported that results of skin tests, provocative oral challenge test, and passive transfer tests suggested that some disulphite-sensitive reactions can be IgE mediated.

Petersen and Menné (1992) patch tested 1762 dermatologic patients with sodium sulphite 1% petrolatum (pet.). Following 2 days of occlusive exposure, positive reactions were observed in 25 patients (1.4% incidence). Seven of the 25 tested positive only to sodium sulphite (the European standard series was also tested). Only 3 of the 25 patients had previous contact with ketoconazole cream (contains sodium sulphite). The investigators did not consider it worthwhile to routinely patch test with sodium sulphite because the "clinical relevance of the positive reactions to sodium sulphite remains to be established."

Vena, Foti, and Angelini (1994) reported the results of patch testing 2894 eczematous patients over a 2-year period. Positive reactions to disodium disulphite 1% pet. (following a 2-day occlusive exposure) were noted in 50 patients (1.7% incidence). All 50 patients also reacted to potassium disulphite 1 % pet., and to sodium disulphite 1% and 5% pet. Only two reacted to sodium sulphite 1 % pet. Prick and intradermal tests of 20 patients with a disodium disulphite solution (10 mg/ml) were negative and oral challenge of five patients with 30 and 50 mg disodium disulphite did not provoke a flare-up of dermatitis or patch test. The dermatitis was considered occupational in seven cases. Five of the remaining 43 cases were considered allergic contact dermatitis resulting from the use of topical preparations.

In the study of Combe incorporated from 1996 a hair-coloring agent with 0.64% sodium sulphite was used in a repeat insult open patch test involving 100 participants. The panelists recieved 0.2 ml or 0.2 g of the test material directly onto a designated area of the back. The procedure was repeated until nine consecutive applications had been made for every Monday, Wednesday, and Friday for 3 consecutive weeks. Reactions were scored just before the next application. The panelists were then allowed a 10- to 14-day nontreatment period, after which a challenge or retest application was applied once to a previously unexposed site. Retest doses were equivalent to any of the original nine exposures and were scored 24 and 48 h after application. Comparisons were made between the sensitizing doses and the retest doses. No adverse reactions were observed and according to the investigators, the test material cannot be considered a primary irritant or primary sensitizer (Combe Incorporated 1996).

Samples of 0.5% sodium sulphite in a topical feminine cream were patch tested by Combe Incorporated in 1998 using 100 panelists. The semiocclusive patch, containing 0.2 ml or 0.2 g of the test material, was affixed directly onto the back and removed after 24 h. The procedure was repeated until nine consecutive applications had been made for every Monday, Wednesday, and Friday for 3 consecutive weeks. Reactions were scored just before the next application. The panelists were then allowed a 10- to 14-day nontreatment period, after which a challenge or retest application was applied once to a previously unexposed site. Retest doses were equivalent to any of the original nine exposures and were scored 24 and 48 h after application. No adverse reactions were observed and according to the investigators, the test material cannot be considered a primary irritant and primary sensitizer (Combe Incorporated 1998).

Madan et al. (2007) determined that positive patch tests to disodium disulphite are frequent. Standard series patch testing to disodium disulphite in 1751 patients showed 71 reactions interpreted as positive and allergic. 33 (46.5%) reactions were originally reported as relevant and 38 (53.5%) were of unexplained relevance depending on the presence or absence of identifiable sources responsible for the presenting dermatitis. An additional detailed study of the sources of disodium disulphite in the environment and a retrospective analysis of these results have been undertaken to identify further, possibly overlooked sources of disodium disulphite exposure based

on the occupational and recreational history. Most of the positive reactions in the relevant group were attributed to the use of Trimovate cream (63%). 5 patients (13%) with positive reactions in the unexplained relevance group were potentially exposed to disodium disulphite in local anaesthetic solutions while at work. 3 patients in the unexplained relevance group (7.8%) and 4 (12.1%) in the relevant group had potential for occupational exposure to disodium disulphite as bakers or caterers. Overall, occupational exposure was considered as a possible source of sensitization in 10 (26.3%) patients in the unexplained relevance group. Madan et al. propose that sensitization to disodium disulphite from parenteral solutions and occupational exposure from food handling may account for some of the otherwise unexplained positive patch test reactions. A detailed occupational history should be therefore be sought in otherwise unexplained positive reactions to disodium disulphite.

Roberts et al. (2012) investigated the possible in cutaneo reaction chemistry of disodium disulphite. The authors stated, that disodium disulphite is an unusual but not infrequent contact allergen whose chemistry suggests a previously unrecognized protein modification mechanism involving nucleophilic attack by sulphite di-anions on target electrophilic centres in skin proteins. The chemical properties required for sensitization by nucleophilic attack on skin proteins are quite restrictive, so the domain of nucleophilic sensitizers is expected to be small. Thiourea derivatives are among the sensitizers likely to act by this mechanism.

Garcia-Gavin et al. (2012) performed a retrospective study on patients patch tested with a sulphite. Between 1990 and 2010, 2763 patients were patch tested with disodium disulphite. The reactions were considered to be relevant if there was a clear relationship between the dermatitis and sulphite exposure. One hundred and twenty-four (4.5%) of 2763 patients patch tested positively to disodium disulphite. The most frequent localizations of the lesions were the face (40.3%) and the hands (24.2%). Six patients also reported systemic symptoms. Thirteen cases (10.5%) were occupational, 10 of them presenting with hand eczema. Disodium disulphite was the single allergen found in 76 cases (61.3%). The reactions were considered to be relevant in 80 cases (64.5%), of which 11 were occupational. The authors concluded that allergic contact dermatitis caused by sulphites is frequent and often relevant. One should be aware of possible relevant sources of exposure, particularly in occupational settings such as hairdressing and the food industry, and in pharmaceutical and cosmetic products. Patch testing with disodium disulphite, which seems to be the best indicator for sulphite contact allergy, is also useful in cases of immediate reactions to sulphite-containing products.

Vitaliti G, et al in 2014 reported the case of a five-year-old female child, admitted to Pediatric Acute and Emergency Department of their hospital for urticaria and anaphylaxis secondary to disodium disulphite sensitisation. The importance of this case report is the knowledge of the possibility of a disodium disulphite allergy also in childhood. The underlying mechanism remains unknown, because to our knowledge, their report is the first case ever described in literature in such early childhood.

The available human information on the positive patch tests for sulphites including disodium disulphite showed increasing tendency in incidence. While Petersen and Menné found positive patch tests in 1992 with incidence of 1.4 %, Garcia-Gavin et al. in 2012 found 4.5% of 2763 patients patch tested positively to disodium disulphite. Vitaliti G, et al in 2014 reported a case study showing the possibility of a disodium disulphite allergy also in childhood.

It should also be considered that in 1986 Yang et al perceived that disodium disulphite-sensitive reactions can be IgE mediated. Roberts et al in 2012 determined that disodium disulphite is an unusual but not infrequent contact allergen whose chemistry suggests a previously unrecognized protein modification mechanism involving nucleophilic attack by sulphite di-anions on target electrophilic centres in skin proteins.

References:

Combe Incorporated (1996). 100 human subject insult open patch test skin irritation/sensitization evaluation. Unpublished data submitted by CTFA.

Combe Incorporated (1998). 100 human subject insult semi-occlusive patch test skin irritation/sensitization evaluation. Unpublished data submitted by CTFA.

Cosmetic Ingredient Expert Review Panel (2003). Final Report on the Safety Assessment of Sodium Sulfite, Potassium Sulfite, Ammonium Sulfite, Sodium Bisulfite, Ammonium Bisulfite, Sodium Metabisulfite, and Potassium Metabisulfite. International Journal of Toxicology, 22 (S2): 63-88.

Ehling G, Hecht M, Heusener A, Huesler J, Gamer AO, van Loveren H, Maurer T, Riecke K, Ullmann L, Ulrich P, Vandebriel R, Vohr HW (2005). An European inter-laboratory validation of alternative endpoints of the murine local lymph node assay: 2nd round. Toxicology; 212:69-79

Garcia-Gavin J, Parente J, Goossens A (2012). Allergic contact dermatitis caused by sodium metabisulfite: a challenging allergen. A case series and literature review. Contact Dermatitis, doi:10.1111/j.1600-0536.2012.02135.x.

Madan V, Walker SL, Beck MH (2007). Sodium metabisulfite allergy is common but is it relevant? Contact Dermatitis 57 (3): 173-6.

Petersen CS, Menné T (1992). Consecutive patch testing with sodium sulphite in eczema patients. Contact Dermatitis, 27:344-345.

Roberts DW, Basketter D, Kimber I, White J, McFadden J, White IR (2012). Sodium metabisulfite as a contact allergen--an example of a rare chemical mechanism for protein modification. Contact Dermatitis, 66(3):123-7. doi: 10.1111/j.1600-0536.2011.02038.x.

Vena GA, Foti C, Angelini G (1994). Sulfite contact allergy. Contact Dermatitis, 31 :172-175.

Vitaliti G, Guglielmo F, Giunta L, Pavone P, Falsaperla R (2014). Disodium disulphite allergy with multiple food and drug hypersensitivities in a five-year-old child: A case report and literature review. Allergol Immunopathol (Madr.), doi:10.1016/j.aller.2013.10.003 http://dx.doi.org/10.1016/j.aller.2013.10.003.

Yang WH, Purchase EC, Rivington RN (1986). Positive skin tests and Prausnitz-Küstner reactions in metabisulfite-sensitive subjects. J Allergy Clin Immunil. 78(3 pt 1):443-449.

5.5.2 Respiratory system

OECD SIDS (2001) report concluded that 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 was considered to be low.

Lin et al in 2011 investigated the effects of sodium sulphite and its interaction with a house dust mite (Dermatophagoides pteronyssinus, Der p) on allergic sensitization and airway inflammation. BALB/c mice were divided into four groups: control (n = 10), mite intranasal (mIN, n = 12), sodium sulphite intranasal (sIN, n = 12) and mIN + sIN (n = 12). In non-control groups, the mice were sensitized on day 8 and day 15 with mite allergen subcutaneously. Mite allergen was then

administrated intranasally from day 15 to day 22 in mIN and mIN+sIN groups. Sodium sulphite was administrated in sIN and mIN + sIN groups intranasally from day 1 to day 22. Plasma Der p-specific IgE, IgG2a, lung histopathology and cytokine levels (IL-5 and IFN-γ) were analyzed. In comparison between mIN (or sIN) and mIN + sIN group, Der p-specific IgE levels were significantly higher in mIN + sIN group ($p < 0.01$). Besides, Der p-specific IgG2a level was significantly lower in mIN + sIN group than mIN (or sIN) group ($p < 0.01$). The peribronchiolar, alveolar and total inflammatory scores were increased in the mIN + sIN group comparing with the control group ($p < 0.05$, $p < 0.01$, $p < 0.01$, respectively). Lung supernatant in mIN + sIN group has higher IL-5/IFN-γ ratio than control, mIN or sIN group (all $p < 0.05$).The study of Lin et al. concluded that sodium sulphite may enhance allergic sensitization as well as airway inflammation in mite allergen sensitized BALB/c mice.

References:

Lin HK, Tsai JJ, Wen MC, Tsai MC, Chen CJ, Fu LS (2011). Sodium sulfite aggravated allergic sensitization and airway inflammation in mite allergen sensitized BALB/c mice. Human & Experimental Toxicology; 30(10):1682-9.

OECD (2001). SIDS Initial Assessment Report for SIAM 13 (Bern, 6 - 9 November 2001) - Disodium disulfite, CAS: 7681-57-4. UNEP Publications.

5.5.3 Summary and discussion on sensitisation

One reliable animal study, according to OECD guideline 429 (Skin Sensitisation: Local Lymph Node Assay, modified according to Ehling et al. 2005) and according to GLP has been reported by the Registrant. The study results showed no sensitising potential of the test substance. Hence, disodium disulphite was classified as not skin sensitising.

Extensive data base has been reviewed in the updated registration dossier showing many cases of contact allergies and patch test reactions to disodium disulphite and occasionally also to potassium disulphite are described. Evidently patients who react to disodium disulphite react also to sodium disulphite. It should also be considered that in most cases predisposed patients showed reactions to the applied sulphite substances. The prevalence of sulphite sensitivity in the general population is unknown, but it appears to be rare among non-asthmatics. It should also be noted that the estimates of the percentage of asthmatics characterised as sensitive to oral sulphite challenge range from less than 4% up to 66%. An immunological pathogenesis has not been proven for these reactions and is assumed - if at all - only for a small minority of affected persons. However, the available human information on the positive patch tests for sulphites including disodium disulphite showed increasing tendency in incidence. While Petersen and Menné found positive patch tests in 1992 with incidence of 1.4 %, Garcia-Gavin et al. in 2012 found 4.5% of 2763 patients patch tested positively to disodium disulphite. Vitaliti G, et al in 2014 reported a case study showing the possibility of a disodium disulphite allergy also in childhood.

Based on the evaluated literature data it is unlikely that disodium disulphite is a skin sensitiser or induce respiratory sensitization but may enhance symptoms of asthma in sensitive individuals. The information related to the skin and respiratory sensitizing properties of the disodium disulphite presented by the Registrant is sufficient for evaluation and the evaluating Member State agrees to the conclusion made by the Registrant. It is supported by the review of the available data performed by the German MAK Commission in 2014, who also concluded that in view of the widespread use of disodium disulphite, and therefore the numerous possibilities for contact in everyday life and the

occupational field, the number of persons epidermally sensitised is, however, very small. Disodium disulphite is therefore not considered as dermal sensitiser.

5.6 Repeated dose toxicity

5.6.1 Non-human information

The hazard class of STOT RE 1; H372: Causes damage to organs has been notified among the aggregated self classifications in the C&L Inventory, and the evaluating Member State considered that this raised some concern about this endpoint.

5.6.1.1 Repeated dose toxicity: oral

5.6.1.2 Repeated dose toxicity: inhalation

A read-across study, a chronic rat inhalation toxicity study (Gunnison, 1988) is available on the effect of inhaled sulfur dioxide and systemic sulfite on the induction of lung carcinoma in rats by benzo[a]pyrene. Male Sprague-Dawley CD rats were exposed in chambers to nominal concentrations of 0, 10 or 30 ppm SO_2 for 6 hours per day, 5 days per weeks for 21 weeks. Thereafter, the rats were observed for the development of tumours in the respiratory tract for 737 days. Systemic exposure to sulphite/bisulphite was accomplished by inducing sulphite oxidase deficiency by means of high tungsten to molybdenum ratio in the diet. Sulphite oxidase deficiency results in an accumulation of endogenously generated sulphite. Complete necropsy was performed on all animals with particular attention given to the respiratory tract. No NOAEC could be derived from the study. No significant adverse effects have been reported from SO_2 exposure.

Eight male beagle dogs were continuously exposed to a 1 mg/m^3 disulphite aerosol for 290 days (Takenaka et al. 1990). The generation of the aerosol was detailed by Karg et al. (1988), who specified an MMAD of 0.63 pm. The extrapulmonary airway was examined microscopically following treatment. Three unexposed dogs were also examined. Hyperplastic foci were observed in the respiratory region of the posterior nasal cavity in seven exposed dogs. Changes included a thickened epithelial layer due to epithelial proliferation, loss of secretory material, and moderate mononuclear cell infiltration. One of three control dogs had slight focal secretory cell proliferation with mononuclear cell infiltration. Laryngeal changes characterized by a focal loss of cilia and slight subepithelial mononuclear cell infiltration were observed in four exposed dogs. Focal disappearance of ciliated cells in the transitional region between cartilaginous and membranous trachea was observed in exposed and control dogs. However, an increased number of nonciliated cells was also noted in the membranous portion of the trachea of exposed dogs and was not observed in control dogs. The tracheal changes, as observed in electron micrographs, were likely caused by a disorder in epithelial cell development rather than by cell degeneration. Repeated exposures to sulphite aerosols were considered to have adverse effects on the extrapulmonary airways of beagle dogs. No NOAEC could be derived from the study.

A chronic repeated dose inhalation toxicity study was also available on dogs (Ferron et al, 1990). Eight Beagle dogs were exposed in chambers to an aerosol concentration of 1 mg/m^3 $Na_2S_2O_5$ for 290 days. Prior to this exposure the animals were housed in chambers under clean air conditions for 320 days. Selected parameters of lung clearance, biochemistry, cytology, and morphology were

determined during both periods to find sensitive parameters for early changes of lung function. Three out of eight dogs showed significant changes in clearance rate of moderately soluble particles during the sulphite exposure compared to the clearance rate during clean air exposure. No NOAEC could be derived from the study.

Data waiving was submitted for repeated dose inhalation toxicity study by the registrant.

References:

Ferron, G.A.; et al. (1990) Long-term exposure of dogs to a sulphite aerosol.J. Aerosol Sci. 21, S479-S482.

Gunnison, A.F.; et al. (1988).The effect of inhaled sulfur dioxide and systemic sulfite on the induction of lung carcinoma in rats by benzo[a]pyrene. Environ. Res. 46, 59-73

Karg E, Erbe F, Ferron GA, Haider B, Heyder J, Kreyling WG, Peter J, Tuch T, Witte W (1988). Facilities for chronic exposure of dogs to sulfite aerosols. Journal of Aerosol Science, Volume 19, Issue 7, Pages 971–973.

Takenaka S, Heilmann P, Ruprecht L, Heinzann U, Murray AB, Fürst G, Heini A, Heyder J (1990). Long-term exposure of dogs to a sulphite aerosol: IV. Effects on extrapulmonary airway morphology. Journal of Aerosol Science, Volume 21, Supplement 1, Pages S483–S486.

5.6.1.3 Repeated dose toxicity: dermal

The evaluating Member State has no information that would raise particular concern about this endpoint.

5.6.1.4 Repeated dose toxicity: other routes

The evaluating Member State has no information that would raise particular concern about this endpoint.

5.6.2 Human information

There are no reports indicating reliable information on human repeated dose toxicity in the public domain.

5.6.3 Summary and discussion of repeated dose toxicity

The information related to the toxic properties of the disodium disulphite after repeated dose oral exposure as presented by the Registrant is sufficient for evaluation and the evaluating Member State agrees to the conclusion made by the Registrant.

Data waiving was submitted for repeated dose inhalation toxicity study by the Registrant. However, a rat and two dog studies for chronic repeated dose inhalation toxicity were referred in the registration documentation. Repeated exposure to sulphite aerosols were considered to have adverse effects on the extrapulmonary airways of beagle dogs at 1 mg/m^3 dose level. Hyperplastic foci were observed in the respiratory region of the posterior nasal cavity in exposed dogs. Changes included a thickened epithelial layer due to epithelial proliferation, loss of secretory material, and moderate

mononuclear cell infiltration. Laryngeal changes characterized by a focal loss of cilia and slight subepithelial mononuclear cell infiltration were observed in the exposed dogs. Focal disappearance of ciliated cells in the transitional region between cartilaginous and membranous trachea was observed in exposed and control dogs.

However, incidences of changes in lung capacity parameters, mild pulmonary edema and change of the tracheal epithelium were noted after using fine aerosol containing fine respirable particles in the inhalation toxicity studies. As disodium disulphite is not used in sprays, the evaluating Member State has no concern related to the inhalation toxicity of the substance after repeated exposure.

5.7 Mutagenicity

5.7.1 Non-human information

5.7.1.1 In vitro data

Gene mutation test in bacteria was performed with disodium disuphite on Salmonella typhimurium strains TA 1535, TA 1538, TA 98 and TA 100 and in Escherichia coli WP2 (uvrA) by doses up to 10000 µg/plate, with and without metabolic activation. No mutagenic effect was observed. (Klimisch reliability factor 1) (Simmon V.F. 1978).

Another Ames test was performed with disodium disulphite on S. typhimurium strains TA 1535, TA 100, TA 1537 and TA 98 by doses up to 50 mg/plate, only with metabolic activation, respectively. No mutagenic activity was observed. Cytotoxicity was not measured or reported with the main experiment. (Klimisch reliability factor 2) (Ishidate M. 1984)

In a further test, disodium disuphite was assessed on Salmonella typhimurium strains TA92, TA1535, TA100, TA1537, TA94 and TA98 by doses up to 5000 µg/plate, with and without metabolic activation. No mutagenic activity was observed. (Klimisch reliability factor 1) (Engelhardt G. 1989)

Sister chromatid exchange (SCE) assay and chromosome aberration assay were performed with disodium disulphite on human peripheral blood cells (human lymphocytes) by doses up to 300 µg/mL without metabolic activation. Disodium disulphite induced a significant increase of SCEs and chromosome aberrations at all concentrations and treatment periods (24 and 48 h) compared to negative control. These effects were dose-dependent. The assay was not conducted in GLP. (Klimisch reliability factor 2) (Rencüzogullari E. 2001.)

In another study about sodium bisulphite induced cytogenetic damage, frequencies of chromosomal aberrations (CA), sister-chromatid exchanges (SCE), and micronuclei (MN) were examined in human blood lymphocytes exposed to sodium disulphite (sulfur dioxide) at various concentrations ranging from $5x10^{-5}$ M to $2×10^{-3}$ M, without metabolic activation. Authors only investigated chromatid breaks in the CA experiments. Exposure duration was 48 hours for CA and 72 hours for MN experiments. Sodium bisulphite solution (0.1 M, pH 7.0) was freshly prepared before use by dissolving a 0.075 M: 0.025 M mixture of Na_2SO_3 and $NaHSO_3$ (purity not given) into RPMI medium. The mitotic index was assessed in a separate experiment, for which the incubation duration was not given. They found that sodium bisulphite caused an increase in SCE and MN in human blood lymphocytes in a dose-dependent manner, and also induced mitotic delays and decreased mitotic index. For CA, the results indicated that sodium bisulphite induced an increase of

chromatid-type aberrations in lymphocytes from three of four donors in a dose-dependent manner. However, positive controls were not used in the experiment. (Klimisch reliability factor 3) (Meng Z. 1992.)

A study examined the genotoxic effect of potassium metabisulphite (PMB) using chromosome aberration, sister chromatid exchange, micronucleus tests in human lymphocytes, without metabolic activation. The human lymphocytes were treated with 25, 50, 100, and 200 µg/ml of PMB for 24 and 48 hr. PMB induced abnormalities such as structural and numerical (total) CAs, SCEs, and MN formations in the lymphocytes of the 24- and 48-hr treatment periods. MN percentage was not increased in a dose-dependent manner, thus, a clear positive outcome is equivocal. The assay shows a dose- and time-dependent increase of structural CA. In addition, PMB showed a cytotoxic effect by decreasing the replication index (RI), mitotic index (MI) and nuclear division index (NDI) in human lymphocytes. (Klimisch reliability factor 2) (Yavuz-Kocaman A. 2008).

Mammalian cell gene mutation assay was performed with disodium disulphite at the hprt locus on mouse lymphoma L5178Y cells with and without metabolic activation, concentrations ranging from 100 to 1902 µg/mL, according to GLP. Three experiments were performed, none of them showed statistically significant increases in mutant frequency and there were no significant linear trends, indicating a negative result. (Klimisch reliability factor 1)

References:

Engelhardt G (1989). Report on the Study of Natriumdisulfit (ZST Test Substance No.: 89/380) in the AMES TEST (Standard Plate Test and Preincubation Test with Salmonella typhimurium) (Unpublished report).

Ishidate M JR, Sofuni T, Yoshikawa K, Hayashi M, Nohmi T, Sawada M, Matsuoka A (1984). Primary mutagenicity screening of food additives currently used in Japan. Food and Chemical Toxicology, 8: 623-636.

Meng Z, Zhang L (1992). Cytogenetic damage induced in human lymphocytes by sodium bisulfate. Mutation Research, 298:63-69.

Rencüzogullari E, Ila HB, Kayraldiz A, Topaktaş M (2001). Chromosome aberrations and sister chromatid exchanges in cultured human lymphocytes treated with sodium metabisulfite, a food preservative. Mutation Research, 490(2):107-12.

Simmon VF, Eckford SL (1978). Microbial mutagenesis testing of substances: compound report: F76-004, sodium meta-bisulfite. SRI Project LSU-6909, PB89-193684 (Unpublished report).

Yavuz-Kocaman A, Rencuzogullari E, Basrilla H, Topaktas M (2008). The genotoxic effect of potassium metabisulfite using chromosome aberration, sister chromatid exchange, micronucleus tests in human lymphocytes and chromosome aberration test in bone marrow cells of rats. Environmental and Molecular Mutagenesis, 49:276–282.

5.7.1.2 In vivo data

Micronucleus assay was performed with sodium sulphite on bone marrow cells of male mice. The test substance was administered once subcutaneously at dose levels of 250, 500 and 1000 mg/kg

bw. The animals were sacrificed 24 and 48 h later (high group and vehicle control group) or 24 h later (small and middle group). An inhibition of erythropoiesis was detected at dose of 1000 mg/kg bw in the 48 h sacrifice interval. Sodium sulphite proved to be negative in this test. The assay was conducted in compliance with the principles of GLP. (Klimisch reliability factor 1)

Micronucleus test, chromosome aberration test and sister chromatid exchange test were performed on bone marrow cells of Chinese hamsters and mice with sodium pyrosulphite. Half of the animals were fed a low molybdenum diet and given drinking water supplemented with sodium tungstate. The sulphite oxidase activity fell to the limit of sensitivity of the assay in these animals. The doses were in the SCE test 1x 660 mg/kg bw p.o. in water or in unfermented grape-juice, or 12x 50mg/kg subcutaneously at 20 min intervals at standard diet (both species). After low molybdenum, high tungsten diet the doses were 330 mg/kg p.o. (hamster) and 165 mg/kg (mouse). In the micronucleus and chromosome aberration tests the doses were 2 x 660 mg/ kg bw p.o. in water or in unfermented grape juice 30 and 6 h before the animals were killed (both species, normal animals), 2 x 330 mg/kg in water or in juice p.o. (sulphite-oxidase-deficient hamsters) and 2 x 165 mg/kg p.o. in water or in juice (sulphite-oxidase-deficient mice). Every test gave negative result. (Klimisch reliability factor 2) (Renner et al., 1983).

Dominant lethal test was performed on male Sprague-Dawley rats. The animals were given sodium bisulphite in diet for 10 weeks before mating. The doses were 45, 15 and 4.5 mg/kg/day. 20-20 rats from the treatment groups and 40 rats from the vehicle control group were mated with two virgin females for 7 days. After a week the females were replaced with 2 new females. The test produced no consistent responses to suggest that sodium bisulphite is mutagenic to the rat. (Klimish reliability factor 2)

Dominant lethal and heritable translocation tests were performed on male mice, and dominant lethal test was conducted on female mice. Males were treated daily (except holydays) with 400 or 300 mg/kg sodium bisulphite intraperitoneally. The higher dose was given 20 times, the lower dose 38 times. Female mice were treated by a single i.p. injection of 550 mg/kg bw sodium bisulphite and mated to untreated males within 4.5 days after treatment. Sodium bisulphite proved to be negative in these tests. No data on GLP are available. (Klimisch reliability factor 2) (Generoso et al., 1978)

Micronucleus assay and comet assay were performed with disodium disulphite on male and female mice by single oral dose of 0.5; 1 or 2 g/kg bw. Animals were sacrificed 24 h later. Micronuclei were detected in blood reticulocytes and in polychromatic erythrocytes of the bone marrow. In the comet assay the DNA damage was determined in liver, blood and bone marrow cells, the slides were stained by silver staining and the damage index was assessed visually. The micronucleus assay gave significantly positive results in the high dose groups in booth cell types to an equal degree. In the comet test significant increases in damage index and damage frequency values were detected in the 1 g/kg and 2g/kg group. No data on GLP are available. (Klimish reliability factor 2 - micronucleus assay; 3 - COMET test.) (Carvalho et al. 2011).

Chromosome aberration test was performed with disodium disulphite on bone marrow cells of rats (3 male and 3 female per group) by single 250, 500, 750 and 1000 mg/kg bw dose orally or intraperitoneally. The animals were sacrificed 6, 12 and 24 h later. Disodium disulphite increased the chromosomal aberrations dose dependently, significantly by i.p. and p.o. administration. The administration by i.p. was more effective than p.o. Results for the negative and positive controls are not reported. No data on GLP are available. (Klimisch reliability factor 3)

Chromosome aberration test was performed with potassium disulphite on bone marrow cells of rats (two males and two females per group) by single 150, 300 and 600 mg/kg bw dose intraperitoneally. Urethane (400 mg/kg bw) was used as the positive mutagen. Colchicine (3 mg/kg

bw) was injected intrapeitoneally 2 hr before the animals were sacrificed. The animals were sacrificed 12 and 24 h later. Potassium disulphite increased the chromosomal aberrations dose dependently, significantly. No data on GLP are available. (Klimisch reliability factor 3) (Yavuz-Kocaman et al. 2008).

References:

Carvalho IM, Melo Cavalcante AA, Dantas AF, Pereira DL, Costa Rocha FC, Andrade TJ, Da Silva J (2011). Genotoxicity of sodium metabisulfite in mouse tissues evaluated by the comet assay and the micronucleus test. Mutation Research, 720: 58-61.

Generoso WWM, Huff SW, Cain KT (1978). Tests on induction of chromosome aberrations in mouse germ cells with sodium bisulfate. Mutation Research, 56: 363-365.

Renner HW, Wewer J (1983). Attemps to induce cytogenetic effects with sulphite in sulphite oxidase- deficient Chinese hamsters and mice. Food and Chemical Toxicology, 21/2: 123-127.

Yavuz-Kocaman A, Rencuzogullari E, Ila HB, Topaktas M (2008). The Genotoxic Effect of Potassium Metabisulfite Using Chromosome Aberration, Sister Chromatid Exchange, Micronucleus Tests in Human Lympocytes and Chromosome Aberration Test in Bone Marrow Cells of Rats. Environmental and Molecular Mutagenesis, 49: 276-282.

5.7.2 Human information

There are no reports on mutagenicity of disodium disulphite in humans. Observations with SO_2 inhalation are not included since inhalation of disodium disulphite is very improbable.

5.7.3 Summary and discussion of mutagenicity

Possible mutagenic properties of disodium disulphite were critically analyzed based upon the available relevant data published in scientific periodicals or referred to in the relevant OECD SIDS Report (2001) and in the US EPA Registration Eligibility Decision – Inorganic sulphites (2007). The summarized opinion of the above mentioned reports is, that genetic toxicity studies indicate disodium disulphite is equivocal in *in vitro* testing, but is not genotoxic in the *in vivo* testing. The evaluating Member State came to the following conclusion on mutagenicity.

Disodium disulphite proved to be not mutagenic in bacterial reverse mutation tests by doses up to 10000 µg/plate with and without metabolic activation (Simmon V.F. 1978; Engelhardt G. 1989) and by doses up to 50 mg/plate with metabolic activation (Ishidate M. 1984).

Sister chromatid exchange assays and chromosome aberration assays were performed on human lymphocytes with disodium disulphite (Rencüzogullary E. 2001) and with potassium disulphite (Yavuz-Kocaman A. 2008) without metabolic activation. Both tests gave positive results at both endpoints.

A micronucleus test was performed on human lymphocytes without metabolic activation (Yavuz-Kocaman A. 2008). The frequencies of micronuclei increased significantly, dose independently in all concentrations (25, 50, 100 and 200 µg/ml). So the result is equivocal.

In vitro mammalian cell gene mutation assay was performed with disodium disulphite with and without metabolic activation on mouse lymphoma cells. (Stone V. 2010). Disodium disulphite gave negative result in this test.

In vivo micronucleus test, chromosome aberration test and sister chromatid exchange test were performed on bone marrow cells of Chinese hamsters and mice with disodium disulphite. The doses were given subcutaneously or per os (Renner et al. 1983). Every test gave negative result.

Another micronucleus assay on bone marrow cells of mice with sodium sulphite was negative. The test substance was administered once subcutaneously. (Schultz et al. 2008).

In vivo comet assay and micronucleus assay were performed with disodium disulphite on mice by single oral dose (Carvalho et al. 2011). Animals were sacrificed 24h later. Comets were stained via silver staining and visually examined. In the comet test significant increases in damage index and damage frequency were detected. According to the most recent OECD Guideline (TG 489): "After electrophoresis, the DNA is visualized using appropriate fluorescent stain. Preparations should be analyzed using microscopic and full or semi-automated image analysis systems." These deficiencies make the comet test not reliable. In the micronucleus test the frequency of micronucleated peripheral blood and bone marrow cells was unusually almost the same at 24h. Although according the OECD Guideline samples should be drawn not earlier than 36 hours after exposure when examining the peripheral blood, the 24h treatment for bone marrow cells is suitable. The evaluating Member State accepts the positive result of the micronucleus test.

Dominant lethal test was performed on rats with sodium bisulphite by oral administration. (Stanford Research Institute, 1979). The test produced no consistent responses to suggest that sodium bisulphite is mutagenic to rat.

Another dominant lethal test was performed with sodium bisulphite on male and female mice, together with heritable translocation assay in males. (Genoroso et al. 1978). The test substance was given intraperitoneally. Sodium sulphite proved to be negative in this test.

Disodium disulphite proved to be positive in chromosome aberration tests on bone marrow cells of rats by per os or intraperitoneal administration. (Kayraldiz et al. 2007). They used only 3 male and 3 female per group (OECD TG 475: five animals per group). Results for the negative and positive controls are not reported. This publication is not reliable for hazard and risk assessment.

Potassium disulphite proved to be positive in chromosome aberration test on bone marrow cells of rats by intraperitoneal administration (two males and two females per group, OECD TG 475: five animals per group). (Yavuz-Kocaman et al. 2008). Because of the intraperitoneal administration and the small number of the animals this publication is not reliable for hazard and risk assessment.

The *in vitro* mutagenicity tests with sulphite gave equivocal results. Bacterial reverse mutagenicity tests were negative, two sister chromatid exchange assays and chromosome aberration assays were positive and the *in vitro* mammalian cell gene mutation assay gave negative result.

Reliable *in vivo* mutagenicity tests with per os and subcutaneous administration gave negative results except one micronucleus assay on bone marrow cells of mice. Two *in vivo* micronucleus and two chromosome aberration assays with sulphite on bone marrow cells were negative. Two dominant lethal tests on rats and mice gave no positive result.

Based on the available data the evaluating Member State considers that the concern for mutagenicity is not substantiated, as there is no consistent evidence of induction of genetic toxicity with relevance to humans for sulphites.

References:

Carvalho IM, Melo Cavalcante AA, Dantas AF, Pereira DL, Costa Rocha FC, Andrade TJ, Da Silva J (2011). Genotoxicity of sodium metabisulfite in mouse tissues evaluated by the comet assay and the micronucleus test. Mutation Research, 720: 58-61.

Engelhardt G (1989). Report on the Study of Natriumdisulfit (ZST Test Substance No.: 89/380) in the AMES TEST (Standard Plate Test and Preincubation Test with Salmonella typhimurium) (Unpublished report).

Generoso WWM, Huff SW, Cain KT (1978). Tests on induction of chromosome aberrations in mouse germ cells with sodium bisulfate. Mutation Research, 56: 363-365.

Ishidate M JR, Sofuni T, Yoshikawa K, Hayashi M, Nohmi T, Sawada M, Matsuoka A (1984). Primary mutagenicity screening of food additives currently used in Japan. Food and Chemical Toxicology, 8: 623-636.

Kayraldiz A, Topaktas M (2007). The in Vivo Genotoxic Effects of Sodium Metabisulfite in Bone Marrow Cells of Rats. Russian Journal of Genetics. 43/8: 905-909.

OECD (2001). SIDS Initial Assessment Report for SIAM 13 (Bern, 6 - 9 November 2001) - Disodium disulfite, CAS: 7681-57-4. UNEP Publications.

Rencüzogullari E, Ila HB, Kayraldiz A, Topaktaş M (2001). Chromosome aberrations and sister chromatid exchanges in cultured human lymphocytes treated with sodium metabisulfite, a food preservative. Mutation Research, 490(2):107-12.

Renner et al. 1983Renner HW, Wewer J (1983). Attemps to induce cytogenetic effects with sulphite in sulphite oxidase- deficient Chinese hamsters and mice. Food and Chemical Toxicology, 21/2: 123-127.

Schultz M, Landsiedel R (2008). Micronucleus test in bone marrow cells of the mouse. BASF Project No.: 26M0250/084046.

Simmon VF, Eckford SL (1978). Microbial mutagenesis testing of substances: compound report: F76-004, sodium meta-bisulfite. Unpublished report: PB89-193684, SRI Project LSU-6909. Testing laboratory: SRI International, 333 Ravenswood Avenue, Menlo Park, CA 94025. Report no.: FDA/CFSAN-89/83. Report date: 1978-04-01.

Stanford Research Institute (1979). Study of the Mutagenic Effects of Sodium Bisulfite (76-72) by the Dominant Lethal Test in Rats. SRI Project LSU-7740.

Stone V (2010). Mutation at the hprt locus of mouse lymphoma L5178Y cells (MLA) using the MicrotitreR fluctuation technique (Unpublished study report).

Yavuz-Kocaman A, Rencuzogullari E, Ila HB, Topaktas M (2008). The Genotoxic Effect of Potassium Metabisulfite Using Chromosome Aberration, Sister Chromatid Exchange, Micronucleus Tests in Human Lympocytes and Chromosome Aberration Test in Bone Marrow Cells of Rats. Environmental and Molecular Mutagenesis, 49: 276-282.

5.8 Carcinogenicity

5.8.1 Non-human information

5.8.1.1 Carcinogenicity: oral

Most of the carcinogenicity studies are negative with sodium metabisulfite, but one of the *in vivo* studies suggested that sodium metabislufite has tumour promoting activity. Also in one human cohort study the brain tumour incidencies was increased. Therefore the evaluating Member State found it necessary to assess this endpoint.

Three different studies were performed with disodium disulphite or potassium disulphite. None of the experiments suggested neoplastic effects of the test materials.

24 months study was performed with 1% and 2% potassium disulphite (in drinking water) and with male and female mice (50 male and 50 female/group). The maximum tolerated dose was 2% potassium disulphite. According to the study no neoplastic effect was observed (Tanaka T et al., 1994).

104 (F0 and F1 generation) and 30 weeks study was evaluated with Wistar rats (20 male/20 fimale/group) in the study of Til et al (1972). Disodium disulphite concentrations was 0; 0.125; 0.25; 0.5; 1 and 2% (maximum tolerated dose). There was no neopastic effect detected using the test material. The incidences of thyroid and pituitary tumors were increased in treated males with time, but no dose–response relationship was observed.

Disodium disulphite was studied in three generations of rats with 750 and 375 ppm conentrations. The experiments lasted for 2.5 years through mating, pregnancy and lactation over 3 generations. According to the post-mortem analysis no treatment related effect was observed (Locket, Natoff, 1960),

In the single-dose study of Furihata et al (1989) male Fischer rats were given 0.45; 0.89; 1.34 g/kg bw potassium sulphite and 0.5; 0.8; 1.1; and 1.4 g/kg bw potassium disulphite. According to the study both potassium sulphite and disulphite have tumour promoting activity via increasing ornithine decarboxylase activity and induction of DNA synthesis.

References:

Furihata C, Yamakoshi A, Takezawa R, Matsushima T (1989). Various sodium salts, potassium salts, a Calcium salt and an Ammonium salt induced ornithine decarboxylase and stimulated DNA synthesis in rat stomach mucosa. Japanese Journal of Cancer Research, 80, 424-429.

Lockett MF, Natoff IL (1960). A study of toxicity of sulphite. Journal Pharmacy and Pharmacology, 12: 488-96, cited in: 30th Meeting of the Joint FAO/WHO Expert Committee on Food Additives (1986). Toxicological Evaluation of Certain Food Additives and Contaminants. WHO Food Additives Series 21.

Tanaka T, Fujii M, Mori H, Hirono I (1979). Carcinogenicity Test of Potassium Metabisulfite in Mice. Ecotoxicology and Environmental Safety, 3(4), 451-453.

Til HP, Feron VJ, de Groot AP (1972). The Toxicity of Sulfite. I. Long-term Feeding and Multigeneration Studies in Rats. Food and Cosmetics Toxicology, 10(3), 291-310.

5.8.1.2 Carcinogenicity: inhalation

A 21 weeks study was evaluated with Sprague-Dawley male rats. The first group was exposed to 10 ppm and 30 ppm of sulfur dioxide, the second group was exposed to sulfur dioxide and benzo(a)pyrene simultaneously, the third one was exposed to benzo(a) pyrene and sulphite/bisulphite anions that accumulated systemically from endogenous generation in rats with induced sulphite oxidase deficiency.

After two years the rats were observed for the development of tumours in the respiratory tract. The probability of dying with squamous cell carcinoma was calculated by the logrank analysis. The data from these groups were not statistically different and neither inhalation exposure to sodium dioxide nor systemic exposure to sulphite/bisulphite anions affected the induction of carcinoma of the lung (Gunnison, A.F, 1988).

References:

Gunnison AF, Sellakumar A, Synder EA, Currie D (1988). The effect of inhaled sulfur dioxide and systemic sulfite on the induction of lung carcinoma in rats by benzo[a]pyrene. Environmental Research, 46, 59-73.

5.8.1.3 Carcinogenicity: dermal

There is no information that disodium disulphite affects the integumentary system.

5.8.2 Human information

In a retrospective study (Robinson C.F et al, 1986) workers of pulp and paper mill was evaluated. Exposure level was unknown, so exposure-response relationship was not possible to establish.
The incidences of lymphosarcomas, reticulosarcomas and stomach cancers were increased but the results were non-significant.
In a cohort study with pulp and paper mill workers (Andersson E et al, 1998) there was an increased mortality from asthma and brain tumours. There was no explanation for the increased risk for brain tumours.

References:

Andersson E, Nilsson T, Persson B, Wingren G, Torén K (1998). Mortality from asthma and cancer among sulfite mill workers. Scandinavian Journal of Work, Environment & Health, 24 (1), 12-17.

Robinson CF, Waxweiler RJ, Fowler DP (1986). Mortality among production workers in pulp and paper mills. Scandinavian Journal of Work, Environment & Health, 12 (66), 552-560.

5.8.3 Summary and discussion of carcinogenicity

Several animal tests were performed both with disodium disulphite and structurally similar potassium disulphite with regard to their possible carcinogenic effects, but none of these studies gave evidence that would indicate carcinogenic property of disodium disulphite. However, there is a report on retrospective human information on pulp and paper mill workers available where a slightly increased tumour incidence was found, but that was in a multi chemically exposed working environment, and no relationship could be established to disodium disulphite itself.

5.9 Toxicity for reproduction

5.9.1 Effects on fertility

5.9.1.1 Non-human information

In a three-generation study (Til et al., 1972; Klimisch reliability factor: 2 – reliable with restrictions; key study) disodium disulphite was administered in the diet to rats in concentrations of 0.125, 0.25, 0.5, 1.0 and 2.0% (corresponding to a nominal dose of 49, 108, 220, 460 and 955 mg/kg bw/day according to the Chemical Safety Report) for periods up to 2 years. The diet was enriched with 50 ppm thiamine to prevent thiamine deficiency due to destruction of this vitamin by sulphite. $Na_2S_2O_5$ and thiamine content was monitored, the losses during storage up to the time of consumption were 22, 14, 12, 8 and 4.5% $Na_2S_2O_5$ and 2.7, 1.7, 8.3, 14.5 and 15.4% thiamine in the diets containing 0.125, 0.25, 0.5, 1.0 and 2.0% sulphite, respectively.

Several parameters were not examined during the study, such as sperm parameters, estrous cyclicity, offspring pathology, etc.

Occult blood was found in the faeces in all generation groups given 1% sulphite or more. In 10% of the females in the 0.25% group and 10% of the males in the 0.5% group slight indications of intestinal blood loss were apparent in the F0 generation at week 32 only. However this symptom was not observed later in these groups or in other generations receiving the same dose level. In females treated with 0.5% sulphite occult blood was not noted during the study.

Pathological changes were seen in gastric morphology in all generations at the two highest dose levels. At these doses hyperplasia and inflammation were observed in both the fore- and glandular stomach. At 0.5% treatment-related lesions were seen only in the forestomach of a few F2-generation rats. The NOAEL for local effects could therefore be set at 0.25% (according to IUCLID data equivalent to a nominal concentration of 108 mg/kg bw/day disodium disulphite or 72 mg/kg bw/day SO_2).

Relative kidney weight was slightly elevated in F2-generation females treated with 2% disodium disulphite, but functional or histological changes were not observed.

A marginally reduced haemoglobin content, haematocrit value and erythrocyte count occurred in F0-generation females at the dose level of 2%. F1-generation males at 2% showed an increased leucocyte count at week 102. All other haematological values were within normal ranges.

Slight growth retardation was observed in F1 and F2 generation rats both before and after weaning at the dose level of 2%. Body weight of the F0 generation was not reduced in any treatment group.

A significant reduction in the number of F2 pups in the first litter was observed at and above 0.5% sulphite. However there was no dose-response and the effect did not occur in the second litters. During lactation pup body weight of the 2% group was reduced compared to the control group. Decreased body weight was also seen at doses of 1% or below, however there was no distinct dose-related response.

The NOAEL for fertility effects was found to be above 2% (corresponding to 955 mg/kg bw/day $Na_2S_2O_5$ or 640 mg/kg bw/day SO_2 according to IUCLID data) due to the lack of any evident effects on fertility or reproduction up to this dose level.

Another study is available (Lockett and Natoff, 1960; Klimisch reliability factor: 2 – reliable with restrictions) where disodium disulphite was administered to rats via drinking water for up to 2.5 years (3 generations). The doses were 375 and 750 ppm SO_2 as disodium disulphite. Several parameters are missing from this study, e.g. sperm parameters, estrous cyclicity, or offspring parameters were not recorded. Disodium disulphite was not found to be toxic to the reproduction in this study up to the level of 750 ppm. However even at the highest dose level there were absolutely no treatment related effects present, indicating that the dose levels were relatively low. The NOEL identified in this study was 750 ppm which corresponded according to the authors to an average of 53 mg/kg bw/day nominal concentration.

In a study performed on Swiss albino mice (Pal and Bhunya, 1992; Klimisch reliability factor: 3 – not reliable) disodium disulphite was administered intraperitoneally to four male animals for each dose level. The doses were 200, 300 and 400 mg/kg bw/day $Na_2S_2O_5$ and were divided into five injections, each one given at an interval of 24 hours on five consecutive days. Animals were sacrificed 35 days after the first injection. According to the authors a dose-related increase in the level of sperm shape abnormalities was observed. The percentage of aberrant sperm was 2.20, 4.25 and 5.50% at the dose levels of 200, 300 and 400 mg/kg bw, respectively, compared to the level of 2.06% of the control group. However, the Registrant argued that the effect of disodium disulphite on sperm shape is biologically implausible for the following reasons: In another study also performed on Swiss albino mice (Acharya et al., 2002), the control group had abnormal sperm values of 5%, whereas a positive substance (cadmium chloride) produced abnormal values of 20-25%. In another study with mice (Rasgele, 2014) the control had approximately 5% of abnormalities and the positive control (Mitomycin C) resulted in abnormalities of 20-25%. A study investigating the age-dependent changes in sperm shape abnormalities (Krzanowska, 1981) noted aberrant sperm percentages of 6.8-20.5% in untreated C57, CBA and KE mice of the same age as used by Pal and Bhunya. Based on the above arguments the evaluating Member State accepts the disregarding of the Pal & Bhunya study. Although the effects seem dose dependent, even at the highest dose the level of abnormalities was only 5.5%, which falls into the range of background control data found in the literature. A concern regarding this endpoint is not fully substantiated based on these results.

The study of Mohamad (2011) on disodium disulphite was insufficiently reported; detailed data could not be found and was thus disregarded for the evaluation.

Table 6: Overview of studies on fertility

Method	Animal model	Results	Remarks	Reference
Three-generation study No guideline followed	Rat (Wistar)	NOAEL parental: 0.25% (equivalent to 108 mg/kg bw/day$Na_2S_2O_5$), based on hyperplastic and inflammatory effects in the fore- and	reliability: 2 (reliable with restrictions) key study	Til et al., 1972

Oral: diet Doses: 0.125%, 0.25%, 0.5%, 1.0%, 2.0% and control (equivalent to: 49, 108, 220, 460 and 955 mg/kg bw/day $Na_2S_2O_5$) Exposure: 104 weeks (F0 and F1) and 30 weeks (F2)		glandular stomach and occult blood in faeces observed at 0.5% and above NOAEL reproductive: > 2% (equivalent to 955 mg/kg bw/day$Na_2S_2O_5$), no evident effects on reproduction		
Combined repeated dose and three-generation reproductive toxicity study No guideline followed Oral: drinking water Doses: 375 ppm, 750 ppm and control Exposure: up to 2.5 years	Rat (uniform strain bred for cancer research)	No effects seen. NOEL parental: 750 ppm (equivalent to 53 mg/kg bw/day) NOEL reproductive: 750 ppm (equivalent to 53 mg/kg bw/day)	reliability: 2 (reliable with restrictions) supporting study	Lockett and Natoff, 1960
Sperm-shape abnormality assay Intraperitoneal Doses: 200, 300, 400 mg/kg bw/day $Na_2S_2O_5$ and control Exposure: once daily, for 5 consecutive days	Mouse (albino Swiss)	Dose-dependent increase in the level of sperm shape aberrations compared to control (2.20, 4.25 and 5.50% at 200, 300 and 400 mg/kg bw, respectively). Results up to the highest dose level fall in the range of background control data from literature. NOAEL not identified.	reliability: 3 (not reliable) disregarded study	Pal and Bhunya, 1992
2 month RDT study Other information not specified	Rat, unspecified	Insufficiently reported	disregarded information	Mohamad, 2011
Sperm-shape abnormality assay Test substance: cadmium chloride Intraperitoneal	Mouse (Swiss)	Sperm-shape abnormalities: Control: 5% Cadmium chloride: 20-25%	supporting study	Acharya et al., 2002
Sperm-shape abnormality assay Test materials: pesticides Positive control: Mitomycin C Intraperitoneal	Mouse, unspecified	Sperm-shape abnormalities: Control: 4.8-5.3% Positive control (Mitomycin C): 26.4-28.8%	supporting study	Rasgele, 2014
Sperm abnormality ration in relation to age Untreated	Mouse (C57, CBA, KE)	Sperm-shape abnormalities at 10 weeks: 6.8% (CBA), 17.8% (C57), 20.5% (KE)	supporting study	Krzanowska, 1981

References:

Acharya UR, Das SS, Mishra M (2002). Role of Vitamin C and E on Sperm Abnormality and Sperm Count in Cadmium Treated Swiss Mice. Cytologia, 67(1), 47-52.

Krzanowska H (1981). Sperm head abnormalities in relation to the age and strain of mice. Journal of Reproduction and Fertility, 62(2), 385-392.

Lockett MF, Natoff IL (1960). A study of toxicity of sulphite. Journal Pharmacy and Pharmacology, 12: 488-96.

Mohamad SSI (2011). Some Toxicological Studies on (Sodium Metabisulphite) as Food Preservatives in Male Albino Rats. Benha University, Egypt (Unpublished thesis).

Pal BB, Bhunya SP (1992). Genotoxic effect of a preservative, sodium metabisulphite as revealed by mammalian in vivo bioassays. Cytologia 57: 455 - 461.

Rasgele PG (2014). Abnormal sperm morphology in mouse germ cells after short-term exposures to acetamiprid, propineb, and their mixture. Archives of Industrial Hygiene and Toxicology, 65(1), 47-56.

Til HP, Feron VJ, de Groot AP (1972). The Toxicity of Sulfite. I. Long-term Feeding and Multigeneration Studies in Rats. Food and Cosmetics Toxicology, 10(3), 291-310.

5.9.1.2 Human information

No human data are available.

5.9.2 Developmental toxicity

5.9.2.1 Non-human information

The evaluating Member State considers the available studies sufficient for evaluation based on the read-across concept for sulphites, disulphites, hydrogensulphites and thiosulphates. In a study performed on rats (Ema et al., 1985; Klimisch reliability factor: 2 – reliable with restrictions) dipotassium disulphite was administered via the diet in doses of 0.1%, 1.0% and 10% (equivalent to 130, 1320 and 2860 mg/kg bw/day $K_2S_2O_5$). Based on suppressed maternal body weight gain and reduced food consumption observed at 10% the maternal NOAEL was set at 1% (equivalent to 1320 mg/kg bw/day $K_2S_2O_5$). In the 10% group the fetal body weight was significantly lower than that of the control group and the postnatal survival rate of the offspring was slightly decreased. The authors concluded that the reason for these effects was probably maternal malnutrition. The NOAEL for fetotoxicity was identified as 1% (1320 mg/kg bw/day); the test material was not considered to have any teratogenic effects.

The effects of sodium sulphite heptahydrate have also been examined in rats (Itami et al., 1989; Klimisch reliability factor: 2 – reliable with restrictions) fed diets containing doses of 0.32%, 0.63%, 1.25%, 2.5% or 5% test material (corresponding to a nominal concentration of

approximately 200, 400, 900, 1750, 2900 mg/kg bw/day Na_2SO_3 x $7H_2O$ or 100, 200, 450, 850, 1450 mg/kg bw/day Na_2SO_3, or 50, 100, 225, 440, 725 mg/kg bw/day SO_2). Maternal toxicity was evidenced by decreased body weight gain and decreased food consumption at 5%. The NOAEL for maternal toxicity was therefore 2.5%. No evidence of teratogenicity was found in the study. A significant reduction in the fetal body weight of both sexes was observed in all dose groups except the 2.5% group. Skeletal and internal variations and delayed ossification was seen in some groups, without statistical significance. The slight effect on fetal toxicity could have been a consequence of maternal malnutrition and/or disturbance in metabolism caused by treatment. The NOAEL for fetotoxicity was below 0.32%, however these effects were not dose-dependent and were not present in the live-birth part of the study. The NOAEL for teratogenicity was above the highest dose of 5%.

Several other studies have also been submitted, performed with oral administration of disodium disulphite, sodium thiosulphate, sodium hydrogensulphite or dipotassium disulphite by gavage to rats, rabbits, mice or hamsters (Food and Drug Research Laboratories, 1972-1975; NTIS, 1972-1974). In none of these studies could a NOAEL value be identified, probably due to the relatively low dose levels. No clear maternal, fetotoxic or teratogenic effects were observed in any of these experiments.

Table 7: Overview of studies on developmental toxicity

Method	Animal model	Results	Remarks	Reference
Test substance: dipotassium disulphite; read-across No guideline followed Oral: diet Doses: 0.1%, 1.0%, 10% and control (equivalent to 130, 1320 and 2860 mg/kg bw/day $K_2S_2O_5$) Exposure: from day 7 to day 14 of pregnancy	Rat (Wistar)	NOAEL maternal: 1% (equivalent to 1320 mg/kg bw/day), based on reduced body weight gain and food consumption at 10%. NOAEL fetotoxicity: 1% (equivalent to 1320 mg/kg bw/day), based on lower fetal body weight and reduced postnatal survival rate at 10%. NOAEL teratogenicity: >10% (equivalent to 2860 mg/kg bw/day), no effects observed.	reliability: 2 (reliable with restrictions) key study	Ema et al., 1985
Test substance: sodium sulphite heptahydrate; read-across Similar to OECD Guideline 414 (Prenatal Developmental Toxicity Study). Oral: diet Doses: 0.32%, 0.63%, 1.25%, 2.5%, 5% and control (equivalent to 200, 400, 900, 1750 and 2900 mg/kg bw/day Na_2SO_3 x $7H_2O$) Exposure: from day 8 to day 20 of pregnancy	Rat (Wistar)	NOAEL maternal: 2.5% (equivalent to 1750 mg/kg bw/day Na_2SO_3 x $7H_2O$), based on decreased body weight gain and food consumption at 5%. NOAEL fetotoxicity: <0.32% (equivalent to 200 mg/kg bw/day Na_2SO_3 x $7H_2O$), based on reduced fetal body weight, skeletal and internal variations and delayed ossification. NOAEL teratogenicity: >5% (equivalent to 2900 mg/kg bw/day Na_2SO_3 x $7H_2O$), no effects observed.	reliability: 2 (reliable with restrictions) key study	Itami et al., 1989

Test substance: sodium thiosulphate; read-across Similar to OECD Guideline 414 (Prenatal Developmental Toxicity Study). Oral: gavage Doses: 4.0, 19.0, 86.0, 400 mg/kg bw/day and control (nominal concentration) Exposure: from day 6 to day 15 of pregnancy	Rat (Wistar)	No maternal, fetotoxic or teratogenic effects observed. NOAEL maternal: > 400 mg/kg bw/day NOAEL fetotoxicity: > 400 mg/kg bw/day NOAEL teratogenicity: > 400 mg/kg bw/day	reliability: 2 (reliable with restrictions) key study	Anonymus, 1972a
Test substance: sodium hydrogensulphite; read-across Similar to OECD Guideline 414 (Prenatal Developmental Toxicity Study). Oral: gavage Doses: 1, 5, 24, 110 mg/kg bw/day and control (nominal concentration) Exposure: from day 6 to day 15 of pregnancy	Rat (Wistar)	No maternal, fetotoxic or teratogenic effects observed. NOAEL maternal: > 110 mg/kg bw/day NOAEL fetotoxicity: > 110 mg/kg bw/day NOAEL teratogenicity: > 110 mg/kg bw/day	reliability: 2 (reliable with restrictions) key study	Anonymus, 1972b
Test substance: dipotassium disulphite; read-across Similar to OECD Guideline 414 (Prenatal Developmental Toxicity Study). Oral: gavage Doses: 1.55, 7.19, 33.4, 155 mg/kg bw/day and control (nominal concentration) Exposure: from day 6 to day 15 of pregnancy	Rat (Wistar)	No maternal, fetotoxic or teratogenic effects observed. NOAEL maternal: > 155 mg/kg bw/day NOAEL fetotoxicity: > 155 mg/kg bw/day NOAEL teratogenicity: > 155 mg/kg bw/day	reliability: 2 (reliable with restrictions) key study	Anonymus, 1975
Test substance: disodium disulphite Similar to OECD Guideline 414 (Prenatal Developmental Toxicity Study). Oral: gavage Doses: 1.23, 5.71, 26.5, 123 mg/kg bw/day and control (nominal concentration)	Rabbit (Dutch)	No maternal, fetotoxic or teratogenic effects observed. NOAEL maternal: > 123 mg/kg bw/day NOAEL fetotoxicity: > 123 mg/kg bw/day NOAEL teratogenicity: > 123 mg/kg bw/day	reliability: 2 (reliable with restrictions) key study	Anonymus, 1974a

Exposure: from day 6 to day 18 of pregnancy				
Test substance: sodium thiosulphate; read-across Similar to OECD Guideline 414 (Prenatal Developmental Toxicity Study). Oral: gavage Doses: 2.5, 5.8, 27.0, 125.4, 580 mg/kg bw/day and control (nominal concentration) Exposure: from day 6 to day 18 of pregnancy	Rabbit (Dutch-belted)	No maternal, fetotoxic or teratogenic effects observed. NOAEL maternal: > 580 mg/kg bw/day NOAEL fetotoxicity: > 580 mg/kg bw/day NOAEL teratogenicity: > 580 mg/kg bw/day	reliability: 2 (reliable with restrictions) key study	Anonymus, 1974b
Test substance: sodium hydrogensulphite; read-across Similar to OECD Guideline 414 (Prenatal Developmental Toxicity Study). Oral: gavage Doses: 1, 4.64, 21.6, 100 mg/kg bw/day and control (nominal concentration) Exposure: from day 6 to day 18 of pregnancy	Rabbit (Dutch-belted)	No maternal, fetotoxic or teratogenic effects observed. NOAEL maternal: > 100 mg/kg bw/day NOAEL fetotoxicity: > 100 mg/kg bw/day NOAEL teratogenicity: > 100 mg/kg bw/day	reliability: 2 (reliable with restrictions) key study	Anonymus, 1974c
Test substance: sodium thiosulphate; read-across Similar to OECD Guideline 414 (Prenatal Developmental Toxicity Study). Oral: gavage Doses: 5.5, 25.5, 118.0, 555 mg/kg bw/day and control (nominal concentration) Exposure: from day 6 to day 15 of pregnancy	Mouse (CD-1)	No maternal, fetotoxic or teratogenic effects observed. NOAEL maternal: > 555 mg/kg bw/day NOAEL fetotoxicity: > 555 mg/kg bw/day NOAEL teratogenicity: > 555 mg/kg bw/day	reliability: 2 (reliable with restrictions) key study	Anonymus, 1972a
Test substance: sodium hydrogensulphite; read-across Similar to OECD Guideline 414 (Prenatal Developmental Toxicity Study). Oral: gavage	Mouse (CD-1)	No maternal, fetotoxic or teratogenic effects observed. NOAEL maternal: > 150 mg/kg bw/day NOAEL fetotoxicity: > 150 mg/kg bw/day NOAEL teratogenicity: > 150	reliability: 2 (reliable with restrictions) key study	Anonymus, 1972b

Doses: 2, 7, 32, 150 mg/kg bw/day and control (nominal concentration) Exposure: from day 6 to day 15 of pregnancy		mg/kg bw/day		
Test substance: dipotassium disulphite; read-across Similar to OECD Guideline 414 (Prenatal Developmental Toxicity Study). Oral: gavage Doses: 1.25, 5.47, 26.9, 125 mg/kg bw/day and control (nominal concentration) Exposure: from day 6 to day 15 of pregnancy	Mouse (CD-1)	No maternal, fetotoxic or teratogenic effects observed. NOAEL maternal: > 125 mg/kg bw/day NOAEL fetotoxicity: > 125 mg/kg bw/day NOAEL teratogenicity: > 125 mg/kg bw/day	reliability: 2 (reliable with restrictions) key study	Anonymus, 1975
Test substance: sodium thiosulphate; read-across Similar to OECD Guideline 414 (Prenatal Developmental Toxicity Study). Oral: gavage Doses: 4.0, 19.0, 86.0, 400 mg/kg bw/day and control (nominal concentration) Exposure: from day 6 to day 10 of pregnancy	Hamster (Golden)	No maternal, fetotoxic or teratogenic effects observed. NOAEL maternal: > 400 mg/kg bw/day NOAEL fetotoxicity: > 400 mg/kg bw/day NOAEL teratogenicity: > 400 mg/kg bw/day	reliability: 2 (reliable with restrictions) key study	Anonymus, 1972a
Test substance: sodium hydrogensulphite; read-across Similar to OECD Guideline 414 (Prenatal Developmental Toxicity Study). Oral: gavage Doses: 1, 6, 26, 120 mg/kg bw/day and control (nominal concentration) Exposure: from day 6 to day 10 of pregnancy	Hamster (Golden)	No maternal, fetotoxic or teratogenic effects observed. NOAEL maternal: > 120 mg/kg bw/day NOAEL fetotoxicity: > 120 mg/kg bw/day NOAEL teratogenicity: > 120 mg/kg bw/day	reliability: 2 (reliable with restrictions) key study	Anonymus, 1972b

References:

Anonymous (1972a). Study of the mutagenic effects of sodium meta-bisulfite (71-22). Testing laboratory: Stanford Research Insititue, Menlo Park, California 94025, U. S. A. Report no.: FDA 71-267.

Anonymous (1972b). Teratologic evaluation of FDA 71-35 (sodium thiosulfate). Testing laboratory: Food and Drug Research Laboratories, 60 Evergreen Place, New Jersey. Report no.: FDABF-GRAS-046. Report date: 1972-10-29.

Anonymous (1972c). Teratologic evaluation of FDA 71-20 (sodium bisulfite). National Technical Information Service (NTIS), U. S. Department of Commerce, PB-221788, East Orange, New Jersy, USA.

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

Anonymous (1974b). Teratologic evaluation of sodium thiosulfate in rabbits. National Technical Information Service (NTIS), U. S. Department of Commerce, PB-267 194. Report date: 1974-09-17.

Anonymous (1974c). Teratological evaluation of FDA 71-20 (sodium bisulfite) in rabbits. NTIS-PB-267 195.

Anonymous (1975). Teratological evaluation of FDA 71-21 (potassium metabisulfite) in mice and rats. Testing laboratory: Food and Drug Research Laboratories, Inc., Route 17C, Waverly, New York. Report no.: PB-245 529. Report date: 1975-03-21.

Ema M, Itami T, Kanoh S (1985). Effect of potassium metabisulfite on pregnant rats and their offspring. Journal of the Food Hygienic Society of Japan, 26, 454-459.

Itami T, Ema M, Kawasaki H, Kanoh S (1989). Evaluation of teratogenic potential of sodium sulfite in rats. Drug and Chemical Toxicology, 12, 123-135. (cited in OECD SIDS sodium dithionite, Oct. 2004).

5.9.2.2 Human information

No human data are available.

5.9.3 Summary and discussion of reproductive toxicity

Effects on fertility

In the key study on disodium disulphite (Til et al., 1972) doses of 0.125, 0.25, 0.5, 1.0 and 2.0% of test material (corresponding to a nominal concentration of 49, 108, 220, 460 and 955 mg/kg bw/day according to the Chemical Safety Report) were administered to rats for periods up to 2 years. The NOAEL identified from this study was 0.25% (according to IUCLID data equivalent to a nominal concentration of 108 mg/kg bw/day disodium disulphite or 72 mg/kg bw/day SO_2) based on local effects in the fore- and glandular stomach and occult blood in faeces observed at 0.5% and above. This NOAEL value is taken into account for the risk assessment of disodium disulphite. No effects

were seen on fertility or reproduction, thus the NOAEL for these effects was above the highest dose of 2.0% (955 mg/kg bw/day) for all generations.

The study of Lockett and Natoff (1960) also did not reveal any reproductive effects of disodium disulphite. In this study the test material was administered to rats in the drinking water in doses of 375 and 750 ppm SO_2. However even at the highest dose level there were absolutely no treatment related effects present, indicating that the dose levels were relatively low. The NOEL identified in this study was 750 ppm which corresponded according to the authors to an average of 53 mg/kg bw/day nominal concentration.

Two other studies on disodium disulphite were not considered adequate for the evaluation. In an intraperitoneal study on mice doses of 200, 300 and 400 mg/kg bw/day $Na_2S_2O_5$ were given to four male animals per dose level. The injections were given at 24 hour intervals on five consecutive days. According to the authors a dose-related increase in the level of sperm shape abnormalities was observed. The percentage of aberrant sperm was 2.20, 4.25 and 5.50% at the dose levels of 200, 300 and 400 mg/kg bw, respectively, compared to the level of 2.06% of the control group. However literature data shows that historical control data of the same mouse strain is usually around 5% (Acharya et al., 2002) and in other mouse strains of the same age control values of 6.8-20.5% of abnormal sperm were found (Krzanowska, 1981). A positive response of cadmium chloride in the above mentioned Acharya study or the positive result of Mitomycin C in another study (Rasgele, 2014) appeared as 20-25% of aberrant sperm. Considering these data it may be plausible that the results of Pal and Bunya (1992) are of no biological significance. A concern regarding this endpoint is not fully substantiated.

The available studies did not follow any guidelines and several parameters were not examined (e.g. sperm parameters, estrous cyclicity, offspring pathology, etc.). Nevertheless, based on the weight of evidence of the information discussed above, the evaluating Member State considers that there is no concern for reproductive toxicity.

Developmental toxicity

A read-across concept was proposed for sulphites, disulphites, hydrogensulphites and thiosulphates. Teratogenicity studies were accepted based on this approach. In a study performed on rats (Ema et al., 1985) where dipotassium disulphite was administered via the diet in doses of 0.1%, 1.0% and 10% (equivalent to 130, 1320 and 2860 mg/kg bw/day $K_2S_2O_5$) a maternal NOAEL of 1% (equivalent to 1320 mg/kg bw/day $K_2S_2O_5$) was identified. The critical signs were suppressed maternal body weight gain and reduced food consumption observed at 10%. The reduced fetal body weight observed at the dose of 10% may have appeared as a secondary effect of maternal malnutrition. The NOAEL for fetotoxicity was 1% (1320 mg/kg bw/day); the test material was not considered to have any teratogenic effects.

In another study sodium sulphite heptahydrate was fed in the diet to rats (Itami et al., 1989) in doses of 0.32%, 0.63%, 1.25%, 2.5% or 5% test material (corresponding to a nominal concentration of approximately 200, 400, 900, 1750, 2900 mg/kg bw/day Na_2SO_3 x $7H_2O$ or 100, 200, 450, 850, 1450 mg/kg bw/day Na_2SO_3). The maternal NOAEL was 2.5% based on decreased body weight gain and decreased food consumption at 5%. Slightly reduced fetal body weight was observed at all doses, thus the NOAEL for fetotoxicity was below 0.32%. However these effects were not dose-dependent and were not present in the live-birth part of the study. No evidence of teratogenicity was found in the study, the NOAEL for teratogenicity was above the highest dose of 5%.

Several other studies have also been submitted, performed with oral administration of disodium disulphite, sodium thiosulphate, sodium hydrogensulphite or dipotassium disulphite by gavage to rats, rabbits, mice or hamsters (Food and Drug Research Laboratories, 1972-1975; NTIS, 1972-

1974). In none of these studies could a NOAEL value be identified, probably due to the relatively low dose levels. No clear maternal, fetotoxic or teratogenic effects were observed in these Food and Drug Research Laboratories and NTIS experiments.

Based on the available studies there does not seem to be effects on developmental toxicity or teratogenicity therefore the evaluating Member State does not consider that there is a concern regarding developmental toxicity.

5.10 Endocrine disrupting properties

The evaluating Member State has no information that would raise particular concern about this endpoint.

5.11 Other effects

The evaluating Member State found no indication of concern about the other effects of disodium disulphite.

5.12 Combined effects

The evaluating Member State has no information that would raise particular concern about this endpoint.

5.13 Derivation of DNEL(s) / DMEL(s)

5.13.1 Overview of typical dose descriptors for all endpoints

The Registrants considered every endpoint but assigned dose descriptor only for repeated dose toxicity (oral).

Qualitative assessments were made concerning the other effects. Read-across was used exclusively or in combination with studies on disodium disulphite in the determination of acute toxicity values, skin irritation, respiratory tract sensitisation, carcinogenity and reproductive toxicity.

5.13.2 Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptor for critical health effects

The documentation submitted by the Registrant was assessed by the evaluating Member State, as well as other available, relevant, additional information. Based on the evaluation of the data the evaluating Member State identified no concern. The basis of long term, systemic effects, inhalation DNELs is a three-generation chronic toxicity study in rats (Till et al. 1972) that the evaluating Member State considers appropriate. The assessment factors used in the calculations (metabolic rate (allometric scaling): 1x; remaining inter-species variability: 2.5x) are justified because the relevant human exposure route was inhalatory. The assessment factors for intra-species variability (3x and 5x) are not the ECHA Guidance Ch. R8 recommendations but the 2003 ECETOC values (ECETOC

2010). The evaluating Member State assessed this approach in view of the exposed population and the characteristics of the substance and has not identified any concern. The calculation for inhalation exposure DNELs (225 mg/m^3 for workers and 66 mg/m^3 for general population) were executed properly. The evaluating Member State notes that these values exceeded the limit that is generally used for inert dusts. In the exposure assessment for inhalation exposure of workers the Registrants based their modelling on a DNEL that is 22 or 6.6 times lower and conform to the widely accepted occupational exposure limit value for inert dust: 10 mg/m^3. The evaluating Member State concluded that conforming to this inhalatory value provides adequate control of the risk.

To derive the long term, systemic effects, oral other animal studies were used (NOAEL 108 mg/kg bw/d). (Till et al. 1972) (Feron et al. 1972). The evaluating Member State concluded that the assessment factors used (inter-species variability: 2.5x; intra-species variability: 5x), the calculation and the DNEL (8.6 mg/kg bw/d) is appropriate.

The substance was classified as irritating to the eye (Category 1) based on a study on rabbits (Kieczka 1984).

The Registrants have considered the dermal uptake route negligible. The evaluating Member State completely agrees, as the physicochemical characteristics of the substance would not allow substantial permeation through the intact skin.

The Registrants have not found information to derive levels concerning local effects due to inhalation. The evaluating Member State has found no information that the substance caused local effects in general. Only in a specific subgroup (asthmatics) were adverse effects reported (worsening of symptoms). The evaluating Member State concludes that the limit value for inert dusts should provide appropriate protection for the general and working population.

The Registrants considered the examination of local effects from short and long term dermal exposure not required. The evaluating Member State concluded that there was no concern of substance specific health effects that would require the examination of these endpoints.

The Registrants collated a substantial list of studies (mainly case reports) on disulphites and dermatitis. The Registrant's key study, which was negative, was carried out on animals. (Haferkorn 2010). Furthermore the Registrant emphasises that several international and European scientific bodies have concluded that sulphites do not cause sensitivity. The evaluating Member State notes that disodium disulphite contact allergen testing is not an uncommon examination in occupational dermatology (De Groot, 2004) and allergic skin reactions by disodium disulphite at work is repeatedly discussed in scientific journals (García-Gavín et al. 2012, Kaaman et al. 2010, Sasseville-El-Helou 2009, Aalto-Korte et al. 2009). The evaluating Member State evaluated all available and relevant information, with special emphasis of the 1997 review by the MAK Commission (DFG, 2014) and the lymph node assay (Haferkorn, 2010), and concludes that skin sensitising properties of disodium disulphite is not a concern.

References:

Aalto-Korte K, Suuronen K, Alanko K (2009). Sodium metabisulfite - a contact allergen? Contact Dermatitis, 60(2):115-7.

DFG (2014). Sulfites. The MAK-Collection Part I, MAK Value Documentations 2014, Wiley-VCH Verlag GmbH & Co. KGaA

De Groot AC (2004). Patch-Test Concentrations and Vehicles for Testing Contact Allergens. Condensed Handbook of Occupational Dermatology. Springer-Verlag Berlin, Heidelberg, p. 510.

ECETOC (2010). Guidance on Assessment Factors to Derive a DNEL. ECETOC, Brussels, 2010. pp. 30-35. ECETOC (2010). Guidance on Assessment Factors to Derive a DNEL. ECETOC, Brussels, 2010. pp. 30-35.

Feron VJ, Wensvoort P (1972). Gastric lesions in rats after the feeding of sulphite. Pathologia Europaea, 7(2), 103-111.

García-Gavín J, Parente J, Goossens A (2012). Allergic contact dermatitis caused by sodium metabisulfite: a challenging allergen: a case series and literature review. Contact Dermatitis, 67(5):260-9.

Haferkorn J (2010). Sodium metabilsulfite: Skin sensitisation: Local lymph node assay in mice. LPT Laboratory of Pharmacology and Toxicology GmbH & Co. KG, Redderweg 8, 21147 Hamburg 25740, Sulfur Dioxide based Chemicals REACH Consortium (SDIOC), EEIG 2010-09-21.

Kaaman AC, Boman A, Wrangsjö K, Matura M (2010). Contact allergy to sodium metabisulfite: an occupational problem. Contact Dermatitis, 63(2):110-2.

Kieczka H (1984). Report on the acute irritation to the eye of the white rabbit based on OECD. BASF Aktiengesellschaft, Dept. of Toxicology, D-6700 Ludwigshafen/Rhein, FRG 84/200 BASF SE 84/200, 1984-11-05.

Sasseville D, El-Helou T (2009). Occupational allergic contact dermatitis from sodium metabisulfite. Contact Dermatitis, 61(4):244-5.

Stingeni L, Bianchi L, Lisi P (2009). Occupational airborne allergic contact dermatitis from potassium metabisulfite. Contact Dermatitis, 60(1):52-3.

Til HP, Feron VJ, de Groot AP (1972). The Toxicity of Sulfite. I. Long-term Feeding and Multigeneration Studies in Rats. Food and Cosmetics Toxicology, 10(3), 291-310.

Til HP, Feron VJ, de Groot AP, Vanderwal P (1972). The toxicity of sulphite. II. Short- and long-term feeding studies in pigs. Food and Cosmetics Toxicology, 10(4), 463-473.

5.14 Conclusions of the human health hazard assessment and related classification and labelling

After reviewing the available data on acute toxicity, the evaluating Member State considers that the application of STOT SE category based on acute oral toxicity is not relevant. However based on the LD_{50} value the harmonized classification of the substance according to EC Regulation No. 1272/2008 in category of Acute Tox. 4 can be confirmed.

Considering the results of the acute inhalation toxicity studies in Guinea pigs, Beagle dogs and Sprague-Dawley rats at relatively low concentration levels of sodium sulphite and ammonium sulphite, and the human observations reported in section *5.3.3. Respiratory tract* in relation to the irritation effect of disodium disulphite (itching, rhinitis, nasal congestion) the application of category STOT SE 3 for respiratory tract irritation to disodium disulphite seems to be justified.

Based on the negative results of read-across studies, it can be concluded, that disodium disulphite does not require classification as skin irritant.

One reliable animal study, according to OECD guideline 429 (Skin Sensitisation: Local Lymph Node Assay, modified according to Ehling et al. 2005) and according to GLP has been reported by the Registrant. The study results showed no sensitising potential of the test substance. Hence, the test substance was classified as not skin sensitising.

Extensive data base has been reviewed in the updated registration dossier showing many cases of contact allergies and patch test reactions to disodium disulphite and occasionally also to potassium disulphite are described. Evidently patients who react to disodium disulphite react also to sodium bisulphite. It should also be considered that in most cases predisposed patients showed reactions to the applied sulphite substances. The prevalence of sulphite sensitivity in the general population is unknown, but it appears to be rare among non-asthmatics. It should also be noted that the estimates of the percentage of asthmatics characterised as sensitive to oral sulphite challenge range from less than 4% up to 66%. An immunological pathogenesis has not been proven for these reactions and is assumed - if at all - only for a small minority of affected persons. However, the available human information on the positive patch tests for sulphites including disodium disulphite showed increasing tendency in incidence. While Petersen and Menné found positive patch tests in 1992 with incidence of 1.4 %, Garcia-Gavin et al. in 2012 found 4.5% of 2763 patients patch tested positively to disodium disulphite. Vitaliti G, et al in 2014 reported a case study showing the possibility of a disodium disulphite allergy also in childhood.

Based on the evaluated literature data it is unlikely that disodium disulphite is a skin sensitiser or induce respiratory sensitization but may enhance symptoms of asthma in sensitive individuals. The review of the available data performed by the German MAK Commission in 2014 also concluded that in view of the widespread use of disodium disulphite, and therefore the numerous possibilities for contact in everyday life and the occupational field, the number of persons epidermally sensitised is, however, very small. Disodium disulphite is therefore not considered to be dermal sensitiser.

Possible mutagenic properties of disodium disulphite were critically analyzed based upon the available relevant data published in scientific periodicals or referred to in the relevant OECD SIDS Report (2001) and in the US EPA Registration Eligibility Decision – Inorganic sulphites (2007). The summarized opinion of the above mentioned reports is, that genetic toxicity studies indicate disodium disulphite is equivocal in *in vitro* testing, but is not genotoxic in the *in vivo* testing. The evaluating Member State carefully assessed numerous relevant studies on mutagenicity of disodium disulphite, and concluded that there is no consistent evidence of induction of genetic toxicity with relevance to humans for sulphites. The evaluating Member State considers that the available information is robust enough to clarify the mutagenicity concern and also that classification of disodium disulphite seems not warranted.

No animal tests gave evidence that would indicate carcinogenic property of disodium disulphite. Although there is a report on retrospective human information on pulp and paper mill workers available where a slightly increased tumour incidence was found, but that was in a multi chemically exposed working environment, and no relationship could be established to disodium disulphite itself.

In the key study on disodium disulphite (Til et al., 1972) no effects were seen on fertility or reproduction, thus NOAEL for these effects was above the highest dose for all generations. The study of Locket and Natoff (1960), where the test material was administered to rats in the drinking water, did not reveal any reproductive effects of disodium disulphite. Even at the highest dose level there were absolutely no treatment related effects present, indicating that the dose levels were relatively low. Two other studies on disodium disulphite were not considered adequate for the evaluation.

Teratogenicity studies were accepted based on the read-across concept, which was proposed for sulphites, metabisulphites, hydrogensulphites and tiosulphates. In a study performed on rats (Ema et al., 1985), where dipotassium disulphite was administered via diet, showed a maternal NOAEL of 1%. The test material was not considered to have any teratogenic effects. In another study (Itami et al., 1989), sodium sulphite heptahydrate was fed in the diet to rats, showed slightly reduced fetal body weight, thus the NOAEL for fetotoxicity was below 0,32%. However no evidence of teratogenicity was found in the study, the NOAEL for teratogenicity was above the highest dose of 5%.

Several other studies have also been submitted, performed with oral administration of disodium disulphite, sodium thiosulphate, sodium hydrogensulphite or dipotassium disulphite by gavage to rats, rabbits, mice or hamsters (Food and Drug Research Laboratories, 1972-1975; NTIS, 1972-1974). In none of these studies could a NOAEL value be identified, probably due to the relatively low dose levels. No clear maternal, fetotoxic or teratogenic effects were observed in these Food and Drug Research Laboratories and NTIS experiments.

As a conclusion, based on the available studies the evaluating Member State considers that the available information is robust enough to clarify the reproduction concern and classification of disodium disulphite seems not warranted either.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO CHEMICAL PROPERTIES

As the possible exposure way is the inhalation, the granulometry was assessed. The concept of read-across was analyzed as it was used for prediction of endpoint information.

1. Granulometry

It is important to mention that the granulometry of a substance is highly dependent on the industrial processing methods and possibly also on handling of the material, any published data on granulometry will be pertinent only to the particular sample or process.

1.1 General data of the registered substance

Disodium disulphite is an inorganic material and appears as a white crystalline or powder and has a SO_2 odour (Lide D.R, 2008 and O'Neil, M.J., 2006). The Total Dustiness (airborne fraction) of the registered substance represented at 18.55 mg/g (DMT) based on experimental data. The mass median aerodynamic diameters (mono-modal distribution) of airborne fraction was calculated (equals MMAD = 23.110 µm), which is, in principle, used to compare particles of different sizes, shapes and densities and it is a useful parameter to predict where in the respiratory tract such particles may be deposited. The median particle size L_{50} of the test items deduced from the particle size distributions is 66.8 µm based on experimental data. The particle size L10 of the test items deduced from the particle size distributions is 9.4 µm based on experimental data. The particle size L90 of the test items deduced from the particle size distributions is 238.5 µm based on experimental data.

1.2 Dustiness

The dustiness or the property of the materials to produce airborne dust is a relative term. The value of the dustiness of disodium disulphite interprets as medium dustiness comparing to pellet like solids with the low dustiness or a solid producing dust cloud presenting high dustiness.

1.3 Particle Size

It is well known that in generally, inhalable fractions are the ones with dimension below 100 µm. The upper respiratory tract (nose, oral cavity, throat and larynx) blocks particles which are over 30 µm, and they are excreted with mucus. Taking into account that median particle size of the registered substance is 66.8 µm, the particles of disodium disulphite deposits in the upper respiratory tract most likely with inertial impaction, meaning that the impaction tends to occur where the airways direction changes.

1.4 Mass median aerodynamic diameters

Calculation of MPPD was carried out to predict where in the respiratory tract such particles may be deposited based on MMAD. The MPPD model has the capability to calculate the deposition and clearance of monodisperse (geometric standard deviation σg of particle distribution ≤1.3) and polydisperse (σg > 1.3) aerosols in the respiratory tract of humans and rats for particles ranging from ultrafine (0.01µm) to coarse (20µm). The model is based upon “single-path” and “multipath” formalisms for tracking air flow and calculating aerosol deposition in the lung. The single-path method calculates deposition in a typical path per airway generation, while the multipath method calculates particle deposition in all airways of the lung to provide regional-, lobar-, and airway-

specific estimates. Within each airway, deposition is calculated using theoretically derived efficiencies for deposition within the airway or airway bifurcation by the following mechanisms: diffusion, sedimentation, and impaction (Jarabek A.M, 2005). Fractional deposition in human respiratory tract (MPPD model, based on calculated MMAD):

- Head (ET): 55.3 %
- Tracheobronchial (TB): 0.3 %
- Pulmonary (PU): 0.4 %

1.5 Conclusion

To conclude, it can be stated that the particles of the registered substance are most likely to deposit in the upper respiratory tract and they are excreted with mucus.

2. Odour

Disodium disulphite has an SO_2-like odor, which will not necessary means the present of SO_2. Disodium disulphite decomposes to SO_2 by heat, so the concentration of the presented SO_2 in air will depend on the ambient temperature. This property should be taken into account when considering the protection of health at work-places and fire-fighters.

References:

Jarabek AM (2005). Dosimetric Adjustments for Interspecies Extrapolation of Inhaled Poorly Soluble Particles (PSP). Inhalation Toxicology, 17:317–334.

Lide DR (2008). CRC Handbook of Chemistry and Physics (88th ed.). CRC Press.

O'Neil MJ (2006). The Merck Index, An encyclopedia of chemicals, drugs and biological (14th ed.). NJ: Merck & Co., Inc..

7 ENVIRONMENTAL HAZARD ASSESSMENT

7.1 Aquatic compartment (including sediment)

Disodium disulphite has been tested on a wide range of aquatic organisms for all three trophic levels. Therefore, all ecotoxicity data that were generated using a (di)sulphite compound with low-toxic counter ions (e. g., potassium, sodium), can be pooled together and – when expressed as SO_3^{2-}, used in a read-across approach for all (di)sulphite compounds. There are some acute data concerning aquatic toxicity of the substance, however chronic data are really rare. To take a precautionary approach, acute toxicity of disodium disulphate to freshwater algae is characterized by two values, LC_{50} 43.8 mg/L and LC_{10} 33.3 mg/L, while a NOEC value is used to describe its chronic toxicity to Daphnia sp. (NOEC ≥ 10 mg/L). These are derived from the values LC_{50} 36.8 mg/L, LC_{10} 28 mg/L (alga), and 8.41 mg/L (Daphnia) expressed as SO_3^{2-} chosen for Chemical Safety Assessment and calculation of the PNEC.
Based on the observations made during the scientific evaluation of disodium disulphite, the evaluating Member States is of the opinion that regarding this endpoint the statements and the conclusions of the Registrant can be supported.

7.1.1 Toxicity data

7.1.1.1 Fish

7.1.1.1.1 Short-term toxicity to fish

Short-term fish toxicity tests of sulphites and disulphites were performed on several species (*Leucius idus, Danio rerio, Oncorhynchus mykiss*). Tested compounds were potassium sulphite, potassium disulphite, and sodium sulphite. Data obtained from these studies can be used for read-across. In the available scientific publications the measured LC_{50} values for fish range from 177.8 mg/L to 681.2 mg/L (119.6 mg/L to 490 mg/L expressed as sulphite). The results of acute toxicity tests strongly depend on test organisms, and on forms of sulphite, and the test condition. The mortality was related to the sulphite-induced oxygen reduction of the test medium: concentration levels that previously lead to in 100% mortality showed no effect at all when the test media was aerated during the test period. The low pH of the test media also can cause mortality. The low pH was caused by the sulphite. The lowest values of LC_{50} have been determined under the above mentioned conditions accordingly.
The results of acute toxicity tests of disodium disulphite on fish species are summarised in the Table 8.

Table 8: Summary of short term toxicity data on fish

Fresh water					
Fish species	**Method**	**Duration**	**Results**	**Reference / Cited by**	**Remarks/ Test substance**
Oryzias latipes	OECD TG 203	96 h	LC_{50}>100 mg/L	OECD SIDS 2001	limit test/ disodium

					disulphite
Salmo gairdneri	German Industrial Standard Guidelie No DIN 38412	96 h	LC_{50}=177.8 mg/L (test material) (geometric means: 147 mg/L (0 % mortality) and 215 (100% mortality))	Registration dossier	- disodium disulphite
Danio rerio	OECD TG 203	96 h	464 mg/L<LC_{50}<1000 mg/L	Registration dossier	read-across potassium disulphite
Leucius idus	DIN 38412, part L15, June 1982	96 h	LC_{50}=316 mg/L (geometric means: 216 mg/L (0 % mortality) and 464 (100% mortality))	Registration dossier	read-across, sodium sulphite

The most sensitive species to the disodium disulphite based on the data available in the literature was the Rainbow trout (*Salmo gairdneri*).
The LC_{50} of disodium disulphite (96h) to the Rainbow trout was found to be 177.8 mg/L (geometric mean of two concentration levels 147 mg/L (0% mortality) and 215 mg/L (100% mortality).
These experimental results were measured under well-defined conditions in static test system. The mortality of the fish and the test concentration were also monitored and measured daily.

There are some other relevant studies which can be seen in the Table 8. Some of them were carried out with other substances, but they are accepted because of the read-across.
Some study showed that in most examinations the mortality was linked to the sulphite-induced oxygen reduction of the test medium. In some studies it can be found that concentration levels that previously resulted in 100% mortality showed absolutely no effect when the test media was aerated for the period of the test. For the test with the *Salmo gairdneri*, experiential mortality was linked to very low pH levels in the test medium after the addition of the test substance. At concentration level of 215 mg/L (90% mortality), pH levels were between 4.3 and 5.6.
Because the read-across and comparability the LC_{50} values expressed as sulphite, these values are used for the derivation of PNEC.
The value of 149.5 mg SO_3^{2-}/L is put forward for the environmental classification of sulphite/disulphite compounds.
As it is the lowest LC_{50} data available in the literature it can be used as a worst case for the aquatic assessment of disodium disulphite.
Therefore the conclusion of the Registrant can be supported.

References:

OECD (2001). SIDS Initial Assessment Report for SIAM 13 (Bern, 6 - 9 November 2001) - Disodium disulfite, CAS: 7681-57-4. UNEP Publications.

7.1.1.1.2 Long-term toxicity to fish

There is no information on long-term toxicity to fish with disodium disulphite in the existing and available literature. In a study by Egeler (2010) reliable chronic toxicity data in GLP-OECD Guideline 210 early-life stage study were described, using sodium sulphite (Na_2SO_3) as test substance, see Table 9.

Table 9: Summary of long-term toxicity data on fish

Fresh					

water					
Fish species	**Method**	**Duration**	**Results**	**Reference / Cited by**	**Remarks/ Test substance**
Danio reiro	OECD 210 (flow through-system)	34 d	NOEC >= 316 mg/L (test mat. (nominal) based on: hatching success, mortality (post-hatch success), numbers of healthy fish, length of surviving fish, dry weight of the surviving fish	Egeler P (2010)	sodium sulphite

Under the experimental conditions of this study, a concentration-response relationship was not observed. Five different concentrations were tested, but no adverse effects on hatching, post–hatch mortality, health, length and dry weight of surviving fish (*Danio rerio*) were observed. Accordingly, a chronic 34d-NOEC of ≥316 mg test substance/L for fish (≥200.5 mg SO_3^{2-}) is recommended for this endpoint.

According to the explanation of the Registrant, the tested substance (sodium sulphite) does not reduce the pH of the test media below a level causing adverse effects, neither does the O2 concentration fall under the critical level. For these reasons the Registrant uses a four times lower concentration for the chemical safety assessment.
The value is EC_{10} or NOEC: 50 mg/L (SO_3^{2-})
The evaluating Member State considers that the argument of the Registrant is acceptable.

References:

Egeler P (2010). Sodium sulfite: a study on the toxicity to Early-Life stages of zebra fish. Study report for SDIOC EWIV Sulfur Dioxide based Chemicals REACH Consortium. Testing laboratory: ECT Oekotoxikologie GmbH, Böttgerstrasse 2-14, D-65439 Flörsheim/Main, Germany. Report no.: 10CL1FV. Owner company: SDIOC EWIV Sulfur Dioxide based Chemicals REACH Consortium. Report date: 2010-10-01.

7.1.1.2 Aquatic invertebrates

7.1.1.2.1 Short-term toxicity to aquatic invertebrates

The acute toxicity data of disodium disulphite to aquatic invertebrates are presented in Table 10.

Table 10: Summary of short term toxicity data on aquatic invertebrates

Fresh water					
Invertebrate species	**Method**	**Duration**	**Results**	**Reference / Cited by**	**Remarks/ Test substance**
Daphnia magna	79/831/EEC, appendix V, part C	48 h	88.8 mg/L	Registration dossier	-/ disodium disulphite
Daphnia magna	-	48 h	273 mg/L	Dowden BF, Bennet HJ (1965)	read-across/sodium sulphite

Based on the available studies, the toxicity EC_{50}(48h) of disodium disulphite to aquatic invertebrates are between 88.8 mg/L and 273 mg/L. The invertebrates are more sensitive than vertebrate organisms. The test animals were *Daphnia magna* in both studies.

Dowden and Bennett (1965) reported the effects of sodium sulphite on *Daphnia magna*. The presented 48h-TLm_{50} of 273 mg/L was higher than the results of the Registrant with *Daphnia magna* according to standard methods, where the effective mean concentration (EC_{50}) after 48-hour exposure was 88 mg/L, which is the lowest value among all the toxicity values for different endpoint in the available literature.

In the view of the evaluating Member State the data provided by the Registrant is reliable and sufficient in order to establish that the reported EC_{50} value is considered to be as a key endpoint for further analysis. The Registrant used the same data for its chemical safety assessment. The toxic effects were linked to oxygen depletion. The Registrant used the value of 74.9 mg SO_3^{2-}/L, which was put forward for the environmental classification of sulphite/disulphite compounds.

The evaluating Member State, based on the available information, considers that the above arguments and the values are acceptable.

References:

Dowden BF, Bennett HJ (1965). Toxicity of selected chemicals to certain animals. Journal of the Water Pollution Control Federation, 37(9), 1308-1316.

7.1.1.2.2 Long-term toxicity to aquatic invertebrates

Long-term aquatic invertebrate toxicity test was performed on the species of water flea (*Daphnia magna* Straus*).* The tested material was disodium disulphite. The test substance was investigated in a 21 day semi-static test in the following concentrations: 10 mg/L; 5 mg/L; 1 mg/L. The validity criteria were fulfilled by the test. During the 21 days period, the minimum of the pH was 7.5, the maximum value was 8.0, and the oxygen content was formed between 8.0 – 15.5 (mg/L). The results of the chronic toxicity do not show any significant difference nor mortality or reproduction in the applied concentrations of the test substance.
The results of the long-term toxicity test of disodium disulphite on *Daphnia magna* are summarised in Table 11.

Table 11: Summary of long term toxicity data on Daphnia magna

Species	Method	Duration	Test substance	Results	Reference
Daphnia magna Straus	EEC Guideline XI/681/86, Draft 4 (similar to OECD 211)	21 days	Disodium disulphite	NOEC : > 10 [mg/L] LC_0 : > 10 [mg/L]	Registration dossier

Additional studies are not mentioned in the available scientific literature, thus the NOEC should be up to 10 mg/L. During the risk assessment, considering the worst case, 10 mg/L is used for the calculation of the PNEC (EC_{10} = 8.41 mg SO_3^{2-}/L).

7.1.1.3 Algae and aquatic plants

The reported data from disodium disulphite and sodium sulphite were performed on several algae species (*Scenedesmus subspicatus, Scenedesmus brasiliensis, Chlorella vulgaris, Chlamydomonas reinhardii*).
Following results of the Registrant (see Table below), the validity criteria were fulfilled by the test; in the control culture, the cell density increased 54 times after 72 hours. At this investigation the nominal concentrations were: 7.8, 15.6, 31.3, 62.5, 125.0, 250.0 and 500.0 mg/L. The results of acute-toxicity tests of disodium disulphite on *Scenedesmus subspicatus* are summarised in Table 12.

Table 12: Summary of EC values on algae

EC values (biomass) mg/L	EC values (growth rate) mg/L	EC values (72 hours) mg/L
E_bC_{10}: 37.88	E_rC_{10}: 33.27	EC_{20}: 39.2
E_bC_{50}: 47.78	**E_rC_{50}: 43.78**	**EC_{50}: 48.1**
E_bC_{90}: 60.25	E_rC_{90}: 57.60	EC_{90}: 60.0

Sodium sulphite was investigated in the study of Stamm A (1980) with three different algae species: *Chlorella vulgaris, Scenedesmus brasiliensis, Chlamydononas reinhardtii*. The following nominal concentrations were used: 0.1; 0.2; 0.3; 0.4; 0.5; 1; 2; 10 mM [SO_3]. The total exposure duration was 96 hours, the average pH was 6.2. The reported EC_{50} values were taken from a graph and were calculated between 0.5 and 1 mM (63 and 126 mg test item/L). The reported 96h-NOEC-value was 37.8 mg test item/L. The results of the acute toxicity tests on algae species are summarised in Table 13.

Table 13: Summary of short term toxicity data on algae

Species	Method	Duration	Test substance	Results	Reference (reliable)
Scenedesmus subspicatus	OECD 201	72 h	Disodium disulphite	EC_{50}=43.8 mg/L EC_{10}=33.3 mg/L	Registration dossier
Scenedesmus brasiliensis, Chlorella vulgaris Chlamydomonas reinhardii	no guideline followed	96 h	sodium sulphite	NOEC= 37.8 mg/L EC_{50}= 63-126 mg/L	Stamm A (1980)

In the hazard and effects assessment of disodium disulphite, the data which was reported by BASF (1989) study were taken forward. It can be explained by the facts,

- that *Scenedesmus subspicatus* was more sensitive than the three other algae species
- reported study by Stamm A (1980) was not followed any guideline contrary to the tests executed by the Registrant /OECD Guideline No. 201/
- effects levels reported by Stamm (1980) were graphic estimates.

The values of 36.8 and 28.0 mg SO_3^{2-}/L were put forward for the environmental classification of disulphite compounds.

References:

Castenholz RW (1977). The effect of sulfide on the Blue Green Algae of Hot Springs. II. Yellowstone National Park. Microbial Ecology, 3(7), 79-105 (author communication used).

OECD (2001). SIDS Initial Assessment Report for SIAM 13 (Bern, 6 - 9 November 2001) - Disodium disulfite, CAS: 7681-57-4. UNEP Publications.

OECD (2008). SIDS Initial Assessment Report for SIAM 26, Sodium sulfite, CAS: 7757-83-7, Draft of March 2008.

Stamm A (1980). Der Einfluss von Sulfit auf das Wachstum und die CO2-Fixierung einzelliger Grünalgen. Environmental Pollution, 22(2), 91-99.

7.1.1.4 Sediment organisms

Because of the potential oxidation of sulphite to sulphate under environmental conditions, and its physicochemical properties which make adsorption to sediments unlikely, the derivation of a PNEC for the sediment compartment is not feasible.
There are no relevant test designs and toxicological data.
The Koc value is 2.447 and it means that the substance has very high mobility in sediment/soil (OECD 2001).

7.1.1.5 Other aquatic organisms

There are no toxicity data for other aquatic organisms with disodium disulphite in the dossier and also in the known literature.

7.1.2 Calculation of Predicted No Effect Concentration (PNEC)

7.1.2.1 PNEC water

The PNEC values for the water compartment can be calculated from toxicity data by using assessment factors. The $PNEC_{water}$ given by the Registrant is 1 mg/L based on the long-term NOEC for *Daphnia magna* and an assessment factor of 10. In spite of the fact that the long-term fish test is missing, the argumentation of the Registrant is accepted. In this reason, the evaluating Member State adopts the assessment factor.

$PNEC_{water}$ ($Na_2S_2O_5$) = 1 mg/L
$PNEC_{water}$ (SO_3^{2-}) = 0.84 mg/L

7.1.2.2 PNEC sediment

There are no toxicity data available for the sediment. Therefore, the PNEC value for sediment has been calculated based on equilibrium partitioning method and $PNEC_{water}$, according to the ECHA Guidance (Chapter R.10.5). The calculated PNEC for sediment is 0.84 mg disodium disulphite/kg wet weight.

7.2 Terrestrial compartment

7.2.1 Toxicity test results

7.2.1.1 Toxicity to soil macro organisms

There are no toxicity data for soil macro organism with disodium disulphite in the dossier or in the known literature. Physico-chemical properties of disodium disulphite e.g. the low K_{OC} (2.447; OECD 201) predestines the compound that may not stay in the terrestrial compartment but behaves as mobile substance in soil and leaches into the groundwater. The short half-life of disodium disulphite in water (a maximum of 77h (in worst case)) due to the rapid oxidation from sulphite to sulphate underlines that it is not relevant to investigate the macroorganism toxicity in soil. The evaluating Member State agrees with the above opinion of the Registrant.

References:

OECD (2001). SIDS Initial Assessment Report for SIAM 13 (Bern, 6 - 9 November 2001) - Disodium disulfite, CAS: 7681-57-4. UNEP Publications.

Tsunogai S (1971). Oxidation rate of sulfite in water and its bearing on the origin of sulfate in meteoric precipitation. Geochemical Journal, 5, 175-185.

7.2.1.2 Toxicity to terrestrial plants

According to the known literature disodium disulphite has been investigated under terrestrial circumstances on tomato leaves with different concentrations. Disodium disulphite brought degradation in green pigment and protein in tomato leaves. In the treated leaves the chlorophyll content was reduced by 71.15 % and protein by 42.85 % at a concentration of 660 µg/mL as compared with the controls.
Since exposure of terrestrial plants with disodium disulphite is unlikely as it has been mentioned above in 7.2.1.1 as well, the evaluating Member State accepts the Registrant's opinion that toxicity to plants is not a significant concern.

References:

OECD (2001). SIDS Initial Assessment Report for SIAM 13 (Bern, 6 - 9 November 2001) - Disodium disulfite, CAS: 7681-57-4. UNEP Publications.

7.2.1.3 Toxicity to soil micro-organisms

There are no toxicity data for soil micro-organism with disodium disulphite in the dossier or in the known literature. See the argumentation above in 7.2.1.1 which is also applicable to this endpoint.

7.2.1.4 Toxicity to other terrestrial organisms

There are no toxicity data for other terrestrial organisms with disodium disulphite in the dossier or in the known literature.

7.2.2 Calculation of Predicted No Effect Concentration (PNEC soil)

PNEC derivation for the terrestrial compartment is not feasible.

7.3 Atmospheric compartment

No data are available on biotic effects in the atmosphere.

7.4 Endocrine disrupting properties

The evaluating Member State has no information that would raise any concern about this endpoint.

7.5 Microbiological activity in sewage treatment systems

7.5.1 Toxicity to aquatic micro-organisms

Aquatic micro-organisms test with disodium disulphite and sodium sulphite were investigated in 3 different tests.
Test results are summarised in the following table.

Table 14: Summary of toxicity to aquatic micro-organisms

Fresh water					
Species	**Method**	**Duration**	**Results**	**Reference / Cited by**	**Remarks/ Test substance**
Pseudomonas putida	DIN 38412, part 8 equal with ISO 10712:1995	17 h	EC10=30.8 mg/L EC50=56.1 mg/L	Registration dossier	disodium disulphite
activated sludge microorganisms of a predominantly domestic sewage	OECD Guideline 209	3 h	NOEC>=1000 mg/L EC50>1000 mg/L	Egeler P. et al (2010)	read-across sodium sulphite

mixed bacteria culture	growth inhibition test using aerobic bacteria	16 h	IC50=2000 mg/L	Alsop et al (1980)	read-across sodium sulphite

According to the OECD 2001 disodium disulphite may lead chemical consumption of oxygen in biological sewage treatment plants.
A 17-hour long test was performed by the Registrant on *Pseudomonas putida*. The tested material was disodium disulphite ($Na_2S_2O_5$), the results are EC_{10}=30.8 mg/L and EC_{50}=56.1 mg/L.
The two other tests showed that mixed bacteria test systems were less sensitive to sodium sulphite (Na_2SO_3) than *Pseudomonas putida* to disodium disulphite ($Na_2S_2O_5$). These results converted to disodium disulphite ($Na_2S_2O_5$) using read-across are NOEC=754 mg/L and IC_{50}=1508 mg/L.
Although *Pseudomonas putida* test was not according to GLP, but equal with ISO 10712:1995, so it is acceptable for the evaluation and the test substance was disodium disulphite.
Registrant argues that OECD 209 test result (NOEC=754 mg/L) is to describe the substance behaviour in the sewage treatment plant.
The evaluating Member State however considers that the data of the 17-hour long test shall be used as a worst case scenario, characterising microbiological activity in sewage treatment systems of disodium disulphite, EC_{10}=30.8 mg/L, as this test result is reliable and highly relevant and the test can be considered as a key study, because in this case there was no read-across.

References:

Alsop GM, Waggy GT, Conway RA (1980). Bacterial growth inhibition test. Journal of the Water Pollution Control Federation, 52(10): 2452-2456.

Egeler P, Goth M (2010). Sodium sulfite: a study on the respiration inhibition of activated sludge. Study conducted for SDIOC EWIV Sulfur Dioxide based Chemicals REACH Consortium. Testing laboratory: ECT Oekotoxicologie GmbH, Böttgerstrasse 2-14, 65439 Flörsheim/Main, Germany. Report no.: 10CL3XA. Owner company: SDIOC EWIV Sulfur Dioxide based Chemicals REACH Consortium. Report date: 2010-10-01.

OECD (2001). SIDS Initial Assessment Report for SIAM 13 (Bern, 6 - 9 November 2001) - Disodium disulfite, CAS: 7681-57-4. UNEP Publications.

7.5.2 PNEC for sewage treatment plant

Calculating PNEC for sewage treatment plant an assessment factor of 1 is applied on the EC_{10} value of growth inhibition test on *Pseudomonas putida*, $PNEC_{stp}$=30.8 mg/L.

7.6 Non compartment specific effects relevant for the food chain (secondary poisoning)

Disodium disulphite has low bioaccumulation potential, besides under environmental conditions rapidly formed sulfate from sulphite. The evaluating Member State agrees with the Registrant that the secondary poisoning is an unlikely exposure pathway.

7.7 Conclusion on the environmental hazard assessment and on classification and labelling

There are some acute data concerning aquatic toxicity of the substance, however chronic data are really rare. Observed toxic effects may be caused by either sulphite toxicity or lack of oxygen or a combination of both. The invertebrates are the most sensitive trophic level. As worst case endpoint for the toxicity of disodium disulphite to freshwater algae, LC_{50} 43.8 mg/L and LC_{10} 33.3 mg/L and chronic Daphnia NOEC ≥ 10 mg/L. It arises from values the LC_{50} 36.8 mg/L, LC_{10} 28 mg/L (alga), and 8.41 mg/L (Daphnia chronic) expressed as SO_3^{2-}. The used assessment factors are 10.

No data are available for sediment dwelling organisms. PNEC for sediment is calculated using the equilibrium partitioning method based on the $PNEC_{water}$ for disodium disulphite. The calculated PNEC for sediment is 0.84 mg/kg wet weight.

Two different test systems were investigated for aquatic micro-organisms. The test material of the respiration inhibition test performed with activated sludge microorganisms (OECD 209) is sodium sulphite and the result is converted to 754 mg disodium disulphite /L as NOEC. The growth inhibition test with *Pseudomonas putida* is not a GLP test (ISO 10712:1995), but the test material was disodium disulphite. The PNEC is derived from results obtained in the most sensitive test system available, therefore PNEC for STP microorganisms is 30.8 mg disodium disulphite /L.

There are no key studies available for terrestrial ecosystem. The physico-chemical properties of disodium disulphite indicate that the substance is mobile in soil and rapidly oxidize to sulphate. Due to the low exposure potential in soil, the toxicity to terrestrial organisms is not a significant concern.

Considering the above data the evaluating Member State's view is that the available and reliable long-term aquatic tests, in particular the *Daphnia magna* test, which was accepted as the worst case, indicates that the original concern is not substantiated, and classification of the substance as toxic to the aquatic environment is not justified, as the NOEC was higher than the criteria (higher than 1 mg/L) for classification, the NOEC was 10 mg/L.

8 PBT AND VPVB ASSESSMENT

8.1 Assessment of PBT/vPvB properties – Comparison with the criteria of Annex XIII

Not relevant.

Disodium disulphite is an inorganic substance and according to Annex XIII of Regulation 1907/2006/EC a PBT and vPvB assessment shall apply to all organic substances, including organo-metals.

9 EXPOSURE ASSESSMENT

9.1 Human Health

The Registrants considered all relevant sectors and occupations. The risk characterisation ratios (exposure estimate/derived no-effect level) are below 1.

The evaluating Member State considered possible exposure scenarios and concluded that the CSR contains every relevant use. Taking into consideration the physical properties of the substance, the technologies and the modelling tools, the characterisations of exposures with the tools are conservative enough and no concern was raised. The evaluating Member State recommends the use of gloves as a good practice.

9.1.1 Exposure assessment for worker

The Registrants used the MEASE tool, which is intended for the exposure assessment of inorganic compounds and metals. The tool is not externally validated. The latest review of available exposure assessment tools found MEASE conservative enough for powders, although no correlation could be found between calculated and real exposures (van Tongeren, Lamb, Miller et al., 2014). A major uncertainty factor in exposure assessment is expertise in using the given tool (van Tongeren, Lamb, Cherrie et al., 2014).

The evaluating Member State has taken into consideration that the Registrants are the developer of the MEASE tool thus the most professional usage and expertise are probable.

The evaluating Member State welcomes that the Registrants prudently draw attention to the possibility of SO_2 formation.

9.1.1.1 Overview of uses and exposure scenarios

The Registrants considered sources of exposures (processes and/or working activities) in the following scenarios:

a. Manufacture and industrial uses of slurries/pastes, low dusty solids/powders, medium dusty solids/powders, high dusty solids/powders

b. Professional uses of slurries/pastes, low dusty solids/powders, medium dusty solids/powders, high dusty solids/powders of disodium disulphite as such or in preparation

c. Industrial use of disodium disulphite in the wood and furniture industry

For spraying of slurries/pastes in occupational settings the Registrant assumed medium emission.

Considering the registered uses, the evaluating Member State accepts that the above are the relevant exposure scenarios.

9.1.1.2 Scope and type of exposure

Inhalation, dermal and oral exposures, eye contact are conceivable.

Oral exposure is unlikely if occupational hygiene standards are met and eating, drinking and smoking is prohibited in the working areas. Thus this route was not calculated in details.

Dermal exposure cannot be a substantial source of systemic dose due to the physicochemical nature of the substance. The Registrant considered the local dermal effect irrelevant. The evaluating Member State's position is that, when contact with the substance is abundant, it is good practice to recommend the use of gloves not only for mechanical and heat protection but also to minimise the chance of development of the rare allergic reaction.

The calculated inhalation systematic DNEL was higher than the generally agreed OEL for inert dusts. Thus the later (10mg/m^3) was applied. Local exhaust ventilation and respiratory protective equipments were the usual risk management measures against inhalation.

Eye protection was generically addressed by personal protective equipment, which the evaluating Member State considers appropriate.

The evaluating Member State concluded that the exposures and the risks can be controlled if the risk management measures are used accordingly.

9.1.1.2.1 Monitoring data

Exposure to disodium disulphite takes place in various settings. The Registrant supplied no data on workplace exposure measurements.

9.1.1.2.2 Modelled data

The MEASE tool is considered sufficiently conservative for the exposure assessment of powders (van Tongeren, Lamb, Miller et al., 2014). The Registrant used the low dustiness scenario as the default scenario, based on their rotating drum dustiness testing. However, various scenarios forecasted high emission. Level of separation, localised controls were considered and the need of respiratory protection was calculated accordingly. The Registrant recommended eye protection. Gloves and skin protection was not specified.

9.1.2 Exposure assessment for consumer

9.1.2.1 Overview of uses and exposure scenarios

The following consumer uses were considered: consumer use of disodium disulphite in photographic applications: Pouring of liquid concentrate; Pouring of powder formulation; Tank processing; Tray processing of films

Exposure from the general environment is unlikely because disodium disulphite readily converts into sulphates or SO_2. Alimentary exposure is possible as a natural by-product or food additive but this scenario is exempt from REACH.

9.1.2.2 Scope and type of exposure

Inhalation, dermal and oral exposures, eye contact are conceivable.

DNEL 8.6 mg/kg bw/day was calculated but oral exposure is likely only in cases of misuse.

Dermal exposure cannot be a substantial source of systemic dose due to the physicochemical nature of the substance. The Registrant considered the local dermal effect irrelevant. The evaluating Member State's position is that it is good practice to recommend the use of gloves when contact with the substance is abundant in order to minimise the chance of development of the rare allergic reaction.

The calculated inhalation systematic DNEL was higher then the generally agreed OEL for inert dusts. Thus the later (10mg/m^3) was applied. The evaluating Member State adopts this approach.

The Registrant performed a qualitative assessment for exposure to the eye because disodium disulphite is classified as irritating to eyes.

The evaluating Member State concluded that the exposures and the risks can be controlled if the risk management measures are used accordingly.

9.1.2.2.1 Monitoring data

The Registrants supplied no monitoring data.

9.1.2.2.2 Modelled data

The Registrant used the ECETOC TRA tool, which is able to assess consumer exposure as well. The latest review found ECETOC TRA conservative enough for powders, and the correlation was good between calculated and real exposures (van Tongeren, Lamb, Miller et al., 2014).The model is based on the observations on another material used in photographic applications. The calculated exposures were far beyond any DNEL derived. Aerosol formation was disregarded. Accidental exposure of the eyes (splashing, dusting) is possible, thus protection is recommended.

References:

van Tongeren M, Lamb J, Cherrie, J, Hesse, S, Hahn, S eteam Project: Implications from the results and practical recommendations for model developers, users and regulators. The ETEAM

Conference - Challenges and Perspectives of Tier 1 Exposure Assessment, 25./26.03.2014 in Dortmund. http://www.baua.de/en/Topics-from-A-to-Z/Hazardous-Substances/Workshops/ETEAM-2014/pdf/ETEAM-2014-10.pdf?__blob=publicationFile&v=1

van Tongeren M, Lamb J, Miller B, MacCalman L, Cherrie J. eteam Project: Results of external validation exercise. The ETEAM Conference - Challenges and Perspectives of Tier 1 Exposure Assessment, 25./26.03.2014 in Dortmund. http://www.baua.de/en/Topics-from-A-to-Z/Hazardous-Substances/Workshops/ETEAM-2014/pdf/ETEAM-2014-08.pdf

9.2 Environmental exposure assessment

The adopted emission scenario in the environmental exposure assessment presented by the Registrant was not detailed properly and no further information was made available about the environmental releases.

Nonetheless, considering that in view of the evaluating Member State the classification of disodium disulphite as aquatic chronic 3 is not justified, as highlighted in Chapter 7, the evaluating Member State came to the conclusion that the basis of its initial concern (i.e. self-classification notified in the C&L inventory) on environmental exposure was not justified in case of the evaluated substance. The evaluating Member State has no other information on possible concern with regard to environmental exposure by disodium disulphite.

Consequently, and taking into account that the environmental exposure assessment is not mandatory based on the Regulation No. 1907/2006/EC, Article 14, the evaluating Member State disregards its initial concern on environmental exposure.

9.3 Combined exposure assessment

Not relevant.

10 RISK CHARACTERISATION

10.1 Human Health

10.1.1 Workers

The estimated inhalation exposures to disodium disulphite (risk characterization ratios) are within the safe area for workers in every identified operation, when all specified risk management measures and operational conditions are in place and followed.

The evaluating Member State deems protection against dermal exposure necessary to prevent local effects.

Should there be change in technology and/or risk management measures, and in case of special vulnerable individuals (e.g. asthmatics), the risk may need to be reassessed.

10.1.2 Consumers

According to the estimation the health risk of consumers is negligible if use is proper. Furthermore, the sole identified consumer use is small, semi-professional group (amateur analogue photographers) where increased technology and safety awareness is expected. Nonetheless, the evaluating Member State would support addressing basic skin protection for consumers too.

10.1.3 Indirect exposure of humans via the environment

Indirect exposure due to identified uses of the substance is highly improbable because disodium disulphite readily transforms into sulphate or SO_2. Furthermore, exposure to disodium disulphite is common from foods.

10.2 Environment

Not relevant.

10.3 Overall risk characterisation

Not relevant.

10.3.1 Human health (combined for all exposure routes)

There is no concern due to the exposure if the conditions detailed in section 9 are met, except for basic skin protection for which the evaluating Member State suggest recommending the use of protective gloves.

10.3.2 Environment (combined for all exposure routes)

Not relevant.

11 OTHER INFORMATION

The environmental exposure assessment presented by the registrant has not been accepted by the evaluating Member State, because the adopted emission scenario is not properly detailed. The release to water is calculated based on the maximum tonnage of sodium disulphite used per year per site and the highest environmental release category (ERC 4). The calculations assumed that 98.2% of the disodium disulphite react/oxidise during the processes. However, the ERC 4 scenario states that 100% of the substance reaches the STP.

The evaluating Member State considers that in principle the emission scenarios should be given for every process. Alternative is to have detailed justification on the maximum rate of release (stated release rate is 1.8%) for all processes.

Considering that the basis of an initial concern on environmental exposure was the potential classification of disodium disulphite as hazardous to aquatic environment, which classification proved to be not justified during the evaluation, the evaluating Member State considers, that more detailed/revised environmental exposure assessment would be only of little added value.

12 REFERENCES

Title	Author	Publication/source details	Date
4.3			
SIDS Initial Assessment Report for SIAM 13 - Disodium disulfite, CAS: 7681-57-4	OECD	UNEP Publications	2001
5.2.1.1			
Final Report on the Safety Assessment of Sodium Sulfite, Potassium Sulfite, Ammonium Sulfite, Sodium Bisulfite, Ammonium Bisulfite, Sodium Metabisulfite, and Potassium Metabisulfite	Cosmetic Ingredient Expert Review Panel	International Journal of Toxicology, 22 (S2): 63-88	2003
5.2.1.2			
Functional changes in the lungs of guinea pigs exposed to sodium sulfite aerosols	Chen LC, Lam HF, Ainsworth D, Guty J, Amdur MO	Toxicology and Applied Pharmacology. 1987 Jun 15;89(1):1-8	1987
Final Report on the Safety Assessment of Sodium Sulfite, Potassium Sulfite, Ammonium Sulfite, Sodium Bisulfite, Ammonium Bisulfite, Sodium Metabisulfite, and Potassium Metabisulfite	Cosmetic Ingredient Expert Review Panel	International Journal of Toxicology, 22 (S2): 63-88.	2003
Inhalation toxicology of sodium sulfite aerosols in rats	Last JA, Dasgupta PK, Etchison JR	Toxicol. Appl. Pharmacol., 55(2):299-34	1980
Generation, behavior, and toxicity of ammonium sulfite aerosols	Rothenberg SJ, Dahl AR, Barr EB, Wolff RK	Journal of the Air Pollution Control Association, 36:55-59.	1986
5.2.2			
SIDS Initial Assessment Report for SIAM 13 (Bern, 6 - 9 November 2001) - Disodium disulfite, CAS: 7681-57-4	OECD	UNEP Publications	2001
5.3.1			
Skin irritation test with sodium metabisulfite in rabbits with cover letter dated 04/13/94	Broughton WS	Hazleton Laboratories Inc., 3200 Leesburg Turnpike, Vienna, Virginia 22180, U.S.A	1973

Title	Author	Publication/source details	Date
5.3.3			
Joint Expert Committee on Food Additives (JECFA): Food Additive Series 42: Preservative: Sulfur dioxide and sulfites (WHO Food Additives Series 42)	WHO/FAO	http://www.inchem.org/pages/jecfa.html	2011
Role of acetyl salicylic acid and sodium metabisulfite in chronic childhood asthma	Towns SJ, Mellis CM	Pediatrics 73: 631-637	1984
Sodium metabisulphite induced airways disease in the fishing and fish-processing industry	Steiner M, Scaife A, Semple S, Hulks G, Ayres JG	Occupational Medicine, Volume 58, Issue 8, Pp. 545-550. Oxford Journals	2008
5.5.1			
100 human subject insult open patch test skin irritation/sensitization evaluation	Combe Incorporated	Unpublished data submitted by CTFA	1996
100 human subject insult semi-occlusive patch test skin irritation/sensitization evaluation	Combe Incorporated	Unpublished data submitted by CTFA	1998
Final Report on the Safety Assessment of Sodium Sulfite, Potassium Sulfite, Ammonium Sulfite, Sodium Bisulfite, Ammonium Bisulfite, Sodium Metabisulfite, and Potassium Metabisulfite	Cosmetic Ingredient Expert Review Panel	International Journal of Toxicology, 22 (S2): 63-88	2003
Allergic contact dermatitis caused by sodium metabisulfite: a challenging allergen. A case series and literature review	Garcia-Gavin J, Parente J, Goossens A	Contact Dermatitis, doi:10.1111/j.1600-0536.2012.02135.x	2012
Consecutive patch testing with sodium sulphite in eczema patients	Petersen CS, Menné T	Contact Dermatitis, 27:344-345	1992
Positive skin tests and Prausnitz-Küstner reactions in metabisulfite-sensitive subjects	Yang WH, Purchase EC, Rivington RN	J Allergy Clin Immunil. 78(3 pt 1):443-449	1986

Title	Author	Publication/source details	Date
Sodium metabisulfite allergy is common but is it relevant?	Madan V, Walker SL, Beck MH	Contact Dermatitis 57 (3): 173-6	2007
Sodium metabisulfite as a contact allergen--an example of a rare chemical mechanism for protein modification	Roberts DW, Basketter D, Kimber I, White J, McFadden J, White IR	Contact Dermatitis, 66(3):123-7. doi: 10.1111/j.1600-0536.2011.02038.x	2012
Sodium metabisulphite allergy with multiple food and drug hypersensitivities in a five-year-old child: A case report and literature review	Vitaliti G, Guglielmo F, Giunta L, Pavone P, Falsaperla R	Allergol Immunopathol (Madr.), doi:10.1016/j.aller.2013.10.003	2014
Sulfite contact allergy	Vena GA, Foti C, Angelini G	Contact Dermatitis, 31 :172-175	1994
5.5.2			
Sodium sulfite aggravated allergic sensitization and airway inflammation in mite allergen sensitized BALB/c mice	Lin HK, Tsai JJ, Wen MC, Tsai MC, Chen CJ, Fu LS	Hum Exp Toxicol. 10:1682-9. doi: 10.1177/0960327111398673. Epub	2011
SIDS Initial Assessment Report for SIAM 13 - Disodium disulfite, CAS: 7681-57-4	OECD	UNEP Publications	2001
5.6.1.2			
Long-term exposure of dogs to a sulphite aerosol	Ferron GA et al.	Aerosol Sci. 21, S479-S482	1990
The effect of inhaled sulfur dioxide and systemic sulfite on the induction of lung carcinoma in rats by benzo[a]pyrene	Gunnison AF et al.	Environ. Res. 46, 59-73	1988
Facilities for chronic exposure of dogs to sulfite aerosols	Karg E, Erbe F, Ferron GA, Haider B, Heyder J, Kreyling WG, Peter J, Tuch T, Witte W	Journal of Aerosol Science, Volume 19, Issue 7, Pages 971–973	1988
Long-term exposure of dogs to a sulphite aerosol: IV. Effects on extrapulmonary airway morphology	Takenaka S, Heilmann P, Ruprecht L, Heinzann U, Murray AB, Fürst G, Heini A, Heyder J	Journal of Aerosol Science, Volume 21, Supplement 1, Pages S483–S486	1990
5.7.1.1			
Report on the Study of Natriumdisulfit (ZST Test Substance No.:	Engelhardt G	Unpublished report	1989

Title	Author	Publication/source details	Date
89/380) in the AMES TEST (Standard Plate Test and Preincubation Test with Salmonella typhimurium)			
Primary mutagenicity screening of food additives currently used in Japan	Ishidate M JR, Sofuni T, Yoshikawa K, Hayashi M, Nohmi T, Sawada M, Matsuoka A	Food and Chemical Toxicology, 8: 623-636	1984
Cytogenetic damage induced in human lymphocytes by sodium bisulfate	Meng Z, Zhang L	Mutation Research, 298:63-69	1992
Chromosome aberrations and sister chromatid exchanges in cultured human lymphocytes treated with sodium metabisulfite, a food preservative	Rencüzogullari E, Ila HB, Kayraldiz A, Topaktaş M	Mutation Research, 490(2):107-12	2001
Microbial mutagenesis testing of substances: compound report: F76-004, sodium meta-bisulfite	Simmon VF, Eckford SL	SRI Project LSU-6909, PB89-193684 (Unpublished report)	1978
The genotoxic effect of potassium metabisulfite using chromosome aberration, sister chromatid exchange, micronucleus tests in human lymphocytes and chromosome aberration test in bone marrow cells of rats	Yavuz-Kocaman A, Rencuzogullari E, Basrilla H, Topaktas M	Environmental and Molecular Mutagenesis, 49:276–282	2008
5.7.1.2			
Genotoxicity of sodium metabisulfite in mouse tissues evaluated by the comet assay and the micronucleus test	Carvalho IM, Melo Cavalcante AA, Dantas AF, Pereira DL, Costa Rocha FC, Andrade TJ, Da Silva J	Mutation Research, 720: 58-61	2011
Tests on induction of chromosome aberrations in mouse germ cells with sodium bisulfate	Generoso WWM, Huff SW, Cain KT	Mutation Research, 56: 363-365	1978
Attemps to induce cytogenetic effects with sulphite in sulphite oxidase- deficient Chinese hamsters and	Renner HW, Wewer J	Food and Chemical Toxicology, 21/2: 123-127	1983

Title	Author	Publication/source details	Date
mice			
The Genotoxic Effect of Potassium Metabisulfite Using Chromosome Aberration, Sister Chromatid Exchange, Micronucleus Tests in Human Lympocytes and Chromosome Aberration Test in Bone Marrow Cells of Rats	Yavuz-Kocaman A, Rencuzogullari E, Ila HB, Topaktas M	Environmental and Molecular Mutagenesis, 49: 276-282	2008
5.8.1.1			
A study of toxicity of sulphite. Journal Pharmacy and Pharmacology, 12: 488-96	Lockett MF, Natoff IL	cited in: 30th Meeting of the Joint FAO/WHO Expert Committee on Food Additives (1986). Toxicological Evaluation of Certain Food Additives and Contaminants. WHO Food Additives Series 21	1960
Various sodium salts, potassium salts, a Calcium salt and an Ammonium salt induced ornithine decarboxylase and stimulated DNA synthesis in rat stomach mucosa	Furihata C, Yamakoshi A, Takezawa R, Matsushima T	Japanese Journal of Cancer Research, 80, 424-429	1989
Carcinogenicity Test of Potassium Metabisulfite in Mice	Tanaka T, Fujii M, Mori H, Hirono I	Ecotoxicology and Environmental Safety, 3(4), 451-453	1979
The Toxicity of Sulfite. I. Long-term Feeding and Multigeneration Studies in Rats	Til HP, Feron VJ, de Groot AP	Food and Cosmetics Toxicology, 10(3), 291-310	1972
5.8.1.2			
The effect of inhaled sulfur dioxide and systemic sulfite on the induction of lung carcinoma in rats by benzo[a]pyrene	Gunnison AF, Sellakumar A, Synder EA, Currie D	Environmental Research, 46, 59-73	1988
5.8.2			
Mortality from asthma and cancer among sulfite mill workers	Andersson E, Nilsson T, Persson B, Wingren G, Torén K	Scandinavian Journal of Work, Environment & Health, 24 (1), 12-17	1998
Mortality among production workers in pulp and paper mills	Robinson CF, Waxweiler RJ, Fowler DP	Scandinavian Journal of Work, Environment & Health, 12 (66), 552-560	1986
5.9.1.1			
Role of Vitamin C and E on Sperm Abnormality and Sperm	Acharya UR, Das SS, Mishra M	Cytologia, 67(1), 47-52	2002

Title	Author	Publication/source details	Date
Count in Cadmium Treated Swiss Mice			
Sperm head abnormalities in relation to the age and strain of mice	Krzanowska H	Journal of Reproduction and Fertility, 62(2), 385-392	1981
A study of toxicity of sulphite	Lockett MF, Natoff IL	Journal Pharmacy and Pharmacology, 12: 488-96	1960
Some Toxicological Studies on (Sodium Metabisulphite) as Food Preservatives in Male Albino Rats	Mohamad SSI	Benha University, Egypt (Unpublished thesis)	2011
Abnormal sperm morphology in mouse germ cells after short-term exposures to acetamiprid, propineb, and their mixture	Rasgele PG	Archives of Industrial Hygiene and Toxicology, 65(1), 47-56	2014
The Toxicity of Sulfite. I. Long-term Feeding and Multigeneration Studies in Rats	Til HP, Feron VJ, de Groot AP	Food and Cosmetics Toxicology, 10(3), 291-310	1972
Genotoxic effect of a preservative, sodium metabisulphite as revealed by mammalian in vivo bioassays	Pal BB, Bhunya SP	Cytologia 57: 455 - 461	1992
5.9.2.1			
Effect of potassium metabisulfite on pregnant rats and their offspring	Ema M, Itami T, Kanoh S	Journal of the Food Hygienic Society of Japan, 26, 454-459	1985
Teratologic evaluation of FDA 71-35 (sodium thiosulfate)	Anonymus	Food and Drug Research Laboratories 60 Evergreen Place, New Jersey. Report no.: FDABF-GRAS-046. Report date: 1972-10-30	1972a
Teratological evaluation of FDA 71-21 (potassium metabisulfite) in mice and rats	Anonymus	Food and Drug Research Laboratories Route 17C, Waverly, New York. Report no.: PB-245 529. Report date: 1975-03-21	1975
Evaluation of teratogenic potential of sodium sulfite in rats	Itami T, Ema M, Kawasaki H, Kanoh S	Drug and Chemical Toxicology, 12, 123-135	1989
Teratologic evaluation of FDA 71-20 (sodium bisulfite)	Anonymus	National Technical Information Service (NTIS) U. S. Department of Commerce, PB-221788, East Orange, New Jersey, USA	1972b
Teratologic Evaluation of Compound FDA 71-22, Sodium	Anonymus	National Technical Information Service (NTIS) U. S. Department of Commerce, PB-267 194, July 1974	1974a

Title	Author	Publication/source details	Date
Metabisulfite in Rabbit			
Teratologic evaluation of sodium thiosulfate in rabbits.	Anonymus	National Technical Information Service (NTIS) U. S. Department of Commerce, PB-267 194. Report date: 1974-09-17	1974b
Teratological evaluation of FDA 71-20 (sodium bisulfite) in rabbits	Anonymus	NTIS-PB 267195	1974c
5.13.2			
Sodium metabisulfite - a contact allergen?	Aalto-Korte K, Suuronen K, Alanko K	Contact Dermatitis, 60(2):115-7	2009
Patch-Test Concentrations and Vehicles for Testing Contact Allergens. Condensed Handbook of Occupational Dermatology	De Groot AC	Springer-Verlag Berlin, Heidelberg, p. 510	2004
Gastric lesions in rats after the feeding of sulphite	Feron VJ, Wensvoort P	Pathologia Europaea, 7(2), 103-111	1972
Allergic contact dermatitis caused by sodium metabisulfite: a challenging allergen: a case series and literature review	García-Gavín J, Parente J, Goossens A	Contact Dermatitis, 67(5):260-9	2012
Sodium metabilsulfite: Skin sensitisation: Local lymph node assay in mice	Haferkorn J	LPT Laboratory of Pharmacology and Toxicology GmbH & Co. KG, Redderweg 8, 21147 Hamburg 25740, Sulfur Dioxide based Chemicals REACH Consortium (SDIOC), EEIG 2010-09-21	2010
Contact allergy to sodium metabisulfite: an occupational problem	Kaaman AC, Boman A, Wrangsjö K, Matura M	Contact Dermatitis, 63(2):110-2	2010
Report on the acute irritation to the eye of the white rabbit based on OECD	Kieczka H	BASF Aktiengesellschaft, Dept. of Toxicology, D-6700 Ludwigshafen/Rhein, FRG 84/200 BASF SE 84/200, 1984-11-05	1984
Occupational allergic contact dermatitis from sodium metabisulfite	Sasseville D, El-Helou T	Contact Dermatitis, 61(4):244-5	2009
Occupational airborne allergic contact dermatitis from potassium metabisulfite	Stingeni L, Bianchi L, Lisi P	Contact Dermatitis, 60(1):52-3	2009
The Toxicity of Sulfite. I. Long-term Feeding and Multigeneration Studies in Rats	Til HP, Feron VJ, de Groot AP	Food and Cosmetics Toxicology, 10(3), 291-310	1972

Title	Author	Publication/source details	Date
The toxicity of sulphite. II. Short- and long-term feeding studies in pigs	Til HP, Feron VJ, de Groot AP, Vanderwal P	Food and Cosmetics Toxicology, 10(4), 463-473	1972
6			
Dosimetric Adjustments for Interspecies Extrapolation of Inhaled Poorly Soluble Particles (PSP)	Jarabek AM	Inhalation Toxicology, 17:317–334	2005
The Merck Index, An encyclopedia of chemicals, drugs and biological (14th ed.)	O'Neil MJ	NJ: Merck & Co., Inc.	2006
7.1.1.1.1			
SIDS Initial Assessment Report for SIAM 13 - Disodium disulfite, CAS: 7681-57-4	OECD	UNEP Publications	2001
7.1.1.1.2			
Sodium sulfite: A Study on the Toxicity to Early-Life Stages of Zebrafish	Egeler P	n/a	2010
7.1.1.2.1			
Toxicity of selected chemicals to certain animals	Dowden BF, Bennett HJ	Journal of the Water Pollution Control Federation, 37(9), 1308-1316	1965
7.1.1.3			
The effect of sulfide on the Blue Green Algae of Hot Springs. II. Yellowstone National Park	Castenholz RW	Microbial Ecology, 3(7), 79-105 (author communication used)	1977
SIDS Initial Assessment Report for SIAM 26, Sodium sulfite, CAS: 7757-83-7	OECD	Draft of March 2008	2008
SIDS Initial Assessment Report for SIAM 13 - Disodium disulfite, CAS: 7681-57-4	OECD	UNEP Publications	2001
Der Einfluss von Sulfit auf das Wachstum und die CO2-Fixierung einzelliger Grünalgen	Stamm A	Environmental Pollution, 22(2), 91-99	1980
7.2.1.1			
SIDS Initial Assessment Report for SIAM 13 - Disodium disulfite, CAS: 7681-57-4	OECD	UNEP Publications	2001

Title	Author	Publication/source details	Date
Oxidation rate of sulfite in water and its bearing on the origin of sulfate in meteoric precipitation	Tsunogai S	Geochemical Journal, 5, 175-185	1971
7.2.1.2			
SIDS Initial Assessment Report for SIAM 13 - Disodium disulfite, CAS: 7681-57-4	OECD	UNEP Publications	2001
7.5.1			
Bacterial growth inhibition test	Alsop GM, Waggy GT, Conway RA	Journal of the Water Pollution Control Federation, 52(10): 2452-2456	1980
Sodium sulfite: A study on the respiration inhibition of activated sludge	Egeler P, Goth M	n/a	2010
SIDS Initial Assessment Report for SIAM 13 - Disodium disulfite, CAS: 7681-57-4	OECD	UNEP Publications	2001
9.1.2.2.3			
eteam Project: Results of external validation exercise	van Tongeren M, Lamb J, Miller B, MacCalman L, Cherrie J	The ETEAM Conference - Challenges and Perspectives of Tier 1 Exposure Assessment, 25./26.03.2014 in Dortmund.	2014

13 ABBREVIATIONS

CA: Chromosome aberrations

CAS: Chemical Abstracts Service

CLP: Classification, labelling and packaging

CMR: Carcinogenic, mutagenic or toxic to reproduction

CoRAP: Community Rolling Action Plan

CSR: Chemical safety report

DMEL: Derived minimal effect level

DMT: Deutsche Montane Technologie

DNA: Deoxyribonucleic acid

DNEL: Derived no-effect level

EC: European Community

EC_{10}: Effective Concentration of a toxic substance at 10% mortality rate of the affected community being observed

EC_{50}: Median effective concentration

ECETOC TRA: European Centre for Ecotoxicology and Toxicology of Chemicals Targeted Risk Assessment

ECHA: European Chemicals Agency

FAO: Food and Agriculture Organization

GLP: Good laboratory practice

GSD: Geometric standard deviation

HERAG: Health Risk Assessment Guidance for Metals

IUCLID: International uniform chemical information database

IUPAC: International Union of Pure and Applied Chemistry

K_{oc}: Carbon-Water Partitioning Coefficient

LC_{10}: Lethal concentration to 10% of the population

LC_{50}: Median Lethal Concentration

LD_{50}: Median lethal dose

MEASE: Metals estimation and assessment of substance exposure

MI: Mitotic index

MMAD: Mass Median Aerodynamic Diameter

MN: Micronuclei

MPPD: Multiple-Path Particle Dosimetry

MSCA: Member state competent authority

NDI: Nuclear division index

NOAC: No Observed Adverse Effects Concentration

NOAEL: No observed adverse effect level

NOEC: No observed effect concentration

OECD: Organisation for Economic Co-operation and Development

OEL: Occupational exposure limit

PBT: Persistent, bioaccumulative and toxic

PMB: Potassium metabsulphite

PNEC: Predicted no-effect concentration

PPE: Personal protective equipment

ppm: Part per million

REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals

RI: Replication index

RMO: Risk Management Options

RNA: Ribonucleic acid

RPMI: Roswell Park Memorial Institute

RTI: Respiratory tract irritation

SCE: Sister chromatid exchange

SEV: Substance evaluation report

SIDS: Screening information data set

STP: Sewage treatment plant

SVHC: Substance of very high concern

TLm: Tolerance Limit

US EPA: United States Environmental Protection Agency

UVCB: Substance of unknown or variable composition

vPvB: Very persistent and very bioaccumulative

WHO: World Health Organization

ANNEX: CONFIDENTIAL INFORMATION

This annex is confidential and not included in the public version of this report.