

CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

International Chemical Identification:

Sulfur dioxide

EC Number: 231-195-2

CAS Number: 7446-09-5

Index Number: 016-011-00-9

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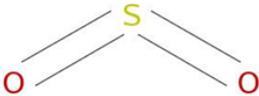
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1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	Sulfur dioxide
Other names (usual name, trade name, abbreviation)	Sulphur dioxide
ISO common name (if available and appropriate)	-
EC number (if available and appropriate)	231-195-2
EC name (if available and appropriate)	Sulfur dioxide
CAS number (if available)	7446-09-5
Other identity code (if available)	-
Molecular formula	SO ₂
Structural formula	
SMILES notation (if available)	O=S=O
Molecular weight or molecular weight range	64.0638 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	<i>Not relevant</i>
Description of the manufacturing process and identity of the source (for UVCB substances only)	<i>Not relevant</i>
Degree of purity (%) (if relevant for the entry in Annex VI)	<i>Not relevant</i>

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)
Sulfur dioxide	100 %	Press. Gas (Note U), Skin Corr. 1B, H314 Acute Tox. 3*, H331	

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Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
none				

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
none					

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	016-011-00-9	sulfur dioxide	231-195-2	7446-09-5	Press. Gas Skin. Corr. 1B Acute Tox. 3*	H314 H331	GHS06 GHS05 GHS04 Dgr	H314 H331		*	Note 5 Note U
Dossier submitters proposal					Retain: Press. Gas Skin. Corr. 1B Add: Skin Sens. 1 Muta. 2 STOT-SE 3 Modify: Acute Tox 3	Retain: H314 Add: H317 H341 H335 Modify: H331	Retain: GHS04 GHS05 GHS06 Dgr Add: GHS08	Retain: H314 Add: H317 H341 H335 Modify: H331		Add: Inhalation: ATE: 1041 ppmV (gases)	Retain: Note 5 Note U
Resulting Annex VI entry if agreed by RAC and COM					Press. Gas Acute Tox. 3 Skin Corr. 1B Skin Sens. 1 Muta. 2 STOT-SE 3	H331 H314 H317 H341 H335	GHS06 GHS05 GHS04 GHS08 Dgr	H331 H314 H317 H341 H335		Inhalation: ATE: 1041ppmV (gases)	Note 5 Note U

Table 6: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	Hazard class not applicable	No
Flammable gases (including chemically unstable gases)	Data conclusive but not sufficient for classification	Yes
Oxidising gases	Data conclusive but not sufficient for classification	Yes
Gases under pressure	Press. Gas, Note U	Yes
Flammable liquids	Hazard class not applicable	No
Flammable solids	Hazard class not applicable	No
Self-reactive substances	Hazard class not applicable	No
Pyrophoric liquids	Hazard class not applicable	No
Pyrophoric solids	Hazard class not applicable	No
Self-heating substances	Hazard class not applicable	No
Substances which in contact with water emit flammable gases	Hazard class not applicable	No
Oxidising liquids	Hazard class not applicable	No
Oxidising solids	Hazard class not applicable	No
Organic peroxides	Hazard class not applicable	No
Corrosive to metals	Hazard class not applicable	No
Acute toxicity via oral route	Hazard class not assessed in this dossier	No
Acute toxicity via dermal route	Hazard class not assessed in this dossier	No
Acute toxicity via inhalation route	Acute Tox 3, H331	Yes
Skin corrosion/irritation	Hazard class not assessed in this dossier	No
Serious eye damage/eye irritation	Hazard class not assessed in this dossier	No
Respiratory sensitisation	Data conclusive but not sufficient for classification	Yes
Skin sensitisation	Skin Sens. 1, H317	Yes
Germ cell mutagenicity	Muta. 2, H341	Yes
Carcinogenicity	Data conclusive but not sufficient for classification.	Yes
Reproductive toxicity	Hazard class not assessed in this dossier	No
Specific target organ toxicity-single exposure	STOT-SE 3, H335	Yes
Specific target organ toxicity-repeated exposure	Hazard class not assessed in this dossier	No
Aspiration hazard	Hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	Hazard class not assessed in this dossier	No
Hazardous to the ozone layer	Hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING**4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL**

The substance is an active substance in the meaning of regulation (EU) 528/2012 and shall normally be subject to harmonised classification and labelling.

5 IDENTIFIED USES

Sulfur dioxide is used as a fungicide in the context of BPR. Additionally, it has a broad spectrum of uses within industrial settings including winemaking, water treatment and metal purification.

6 DATA SOURCES

For the toxicological evaluation following data sources were used:

- Competent Authority Report (2017). Sodium sulfitemetabisulfite releasing sulfur dioxide dossier. Evaluation of active substances.
- REACH registration dossier (accessed in ECHA-REACH-IUCLID: 30 March 2017) on sulfur dioxide (joint submission dated 13 Sep 2010) including the respective CSR.

7 PHYSICOCHEMICAL PROPERTIES

Table 7: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	colourless biting gas	Holleman-Wiberg (1995)	Literature data, information about weight of evidence assessment are given in the IUCLID dossier (If it is not stated otherwise, this comment applies to all endpoints of this table).
Melting/freezing point	-75.5 °C	Lide, D.R. (Ed.) (2007)	Literature data
Boiling point	-10 °C	Holleman-Wiberg (1995) Lide, D.R. (Ed.) (2007)	Literature data
Relative density	2.619 g/L (25 °C), gaseous	Lide, D.R. (Ed.) (2007)	Calculation of ideal gas density in grams per litre at 25°C and 101.325 kPa
Vapour pressure	3271 hPa at 20°C	Sax N.; Lewis R.J. 1987.	Vapour pressure is defined as the pressure exerted by a vapour above a liquid. This definition means that vapour pressure data is not relevant for sulfur dioxide because it is a gas under the physical conditions it is being used as a biocide

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Property	Value	Reference	Comment (e.g. measured or estimated)
Surface tension			For SO ₂ which is not stable in water the determination of the surface tension is technically not feasible. Sulfur dioxide dissolves in water and forms sulfurous acid.
Water solubility	ca. 22.86 g/100 g water at 101.3 kPa (0 °C, pH 0.63) (calculation) ca. 11.4 g/100 g water at 101.3 kPa (20 °C, pH 0.78) (calculation) Sulfur dioxide dissolves in water and forms sulfurous acid.	Holleman-Wiberg (1995)	
Partition coefficient n-octanol/water			As SO ₂ reacts reversible with water to form sulfurous acid (H ₂ SO ₃) the partition coefficient of SO ₂ could not be determined, as in water H ₂ SO ₃ is build.
Flash point	Not applicable		Study scientifically unjustified. Due to the fact, that sulfur dioxide is a gas, this endpoint can be waived.
Flammability	non-flammable gas	ISO 10156:2010	Study scientifically not necessary Sulfur dioxide is a non-flammable gas as described in ISO 10156:2010, see Table 1.
Explosive properties	Not applicable		Study scientifically unjustified. Testing is only applicable for solids and liquids. Therefore, gases are out of the scope of the Explosives hazard class.
Self-ignition temperature	Not relevant		Study scientifically not necessary. The study does not need to be conducted because the substance is a gas having no flammable range with air.
Oxidising properties	non-oxidising gas	ISO 10156:2010	Study scientifically not necessary. Sulfur dioxide is a non-oxidising gas as described in ISO 10156:2010, see Table 1.
Granulometry			Due to the fact, that sulfur dioxide is a gas, this endpoint can be waived.

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Property	Value	Reference	Comment (e.g. measured or estimated)
Stability in organic solvents and identity of relevant degradation products			Study does not need to be conducted for inorganic substances
Dissociation constant			Sulfur dioxide will not dissociate into two or more chemical species, instead sulfur dioxide reacts reversible with water to form sulfurous acid (H ₂ SO ₃), with an equilibrium constant $K \lll 1.0E-9$
Viscosity			Sulfur dioxide is gaseous, which is why viscosity cannot be determined.

8 EVALUATION OF PHYSICAL HAZARDS

8.1 Explosives

Hazard class not applicable. The study does not need to be conducted because the substance is a gas.

8.2 Flammable gases (including chemically unstable gases)

Flammability shall be determined by tests or, for mixtures where there are sufficient data available, by calculation in accordance with the methods adopted by ISO (see ISO 10156 as amended, Gases and gas mixtures — Determination of fire potential and oxidising ability for the selection of cylinder valve outlets).

8.2.1 Short summary and overall relevance of the provided information on flammable gases (including chemically unstable gases)

Sulfur dioxide is a non-flammable gas as described in ISO 10156:2010.

8.2.2 Comparison with the CLP criteria

Flammable gas means a gas or gas mixture having a flammable range with air at 20 °C and a standard pressure of 101,3 kPa.

8.2.3 Conclusion on classification and labelling for flammable gases

Sulfur dioxide has no flammable range with air, thus it does not require classification as flammable gas.

8.3 Oxidising gases

8.3.1 Short summary and overall relevance of the provided information on oxidising gases

Sulfur dioxide is a non-oxidising gas as described in ISO 10156:2010.

8.3.2 Comparison with the CLP criteria

Oxidising gas means any gas or gas mixture which may, generally by providing oxygen, cause or contribute to the combustion of other material more than air does.

8.3.3 Conclusion on classification and labelling for oxidising gases

Sulfur dioxide does not cause or contribute to the combustion of other material more than air does, thus it does not require classification as oxidising gas.

8.4 Gases under pressure

8.4.1 Short summary and overall relevance of the provided information on gases under pressure

The critical temperature is the temperature above which a pure gas cannot be liquefied, regardless of the degree of compression.

Critical temperature of sulfur dioxide: 157.5 °C [CHEMSAFE (2016)]

8.4.2 Comparison with the CLP criteria

Gases under pressure are gases which are contained in a receptacle at a pressure of 200 kPa (gauge) or more at 20 °C, or which are liquefied or liquefied and refrigerated. They comprise compressed gases, liquefied gases, dissolved gases and refrigerated liquefied gases.

Liquefied gas: A gas which, when packaged under pressure, is partially liquid at temperatures above – 50 °C. A distinction is made between: (i) high pressure liquefied gas: a gas with a critical temperature between – 50 °C and + 65 °C; and (ii) low pressure liquefied gas: a gas with a critical temperature above + 65 °C.

8.4.3 Conclusion on classification and labelling for gases under pressure

Sulfur dioxide requires classification as “Gases under pressure” when put on the market in accordance with Note U. Due to the critical temperature of 157.5 °C, sulfur dioxide shall be classified as Press. Gas (Liq.), H280: Contains gas under pressure; may explode if heated.

8.5 Flammable liquids

Hazard class not applicable. The study does not need to be conducted because the substance is a gas.

8.6 Flammable solids

Hazard class not applicable. The study does not need to be conducted because the substance is a gas.

8.7 Self-reactive substances

Hazard class not applicable. The study does not need to be conducted because the substance is a gas.

8.8 Pyrophoric liquids

Hazard class not applicable. The study does not need to be conducted because the substance is a gas.

8.9 Pyrophoric solids

Hazard class not applicable. The study does not need to be conducted because the substance is a gas.

8.10 Self-heating substances

Hazard class not applicable. The study does not need to be conducted because the substance is a gas.

8.11 Substances which in contact with water emit flammable gases

Hazard class not applicable. The study does not need to be conducted because the substance is a gas.

8.12 Oxidising liquids

Hazard class not applicable. The study does not need to be conducted because the substance is a gas.

8.13 Oxidising solids

Hazard class not applicable. The study does not need to be conducted because the substance is a gas.

8.14 Organic peroxides

Hazard class not applicable. The study does not need to be conducted because the substance is a gas.

8.15 Corrosive to metals

Hazard class not applicable. The study does not need to be conducted because there is no established suitable test method for gases.

8.15.1 Short summary and overall relevance of the provided information on the hazard class corrosive to metals

Anhydrous sulfur dioxide is generally considered non-corrosive to steel and other common metals, however it reacts with atmospheric moisture and water to form corrosive acids (sulfurous acid, which will rapidly convert to sulfuric acid) and this cause rapid corrosion of some metals.

8.15.2 Comparison with the CLP criteria

Neither the corrosivity of gases nor the formation of corrosive gases is currently covered by CLP.

8.15.3 Conclusion on classification and labelling for corrosive to metals

No classification and labelling is proposed.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Sulfur dioxide

Only non-guideline-conform study on toxicokinetics were available. As the dossier relies nearly exclusively on published literature information, the vast amount of studies deal with some aspects of toxicokinetics, but were often conducted for other/special purposes. Therefore, data from various kinds of studies were compiled to provide some information on classical toxicokinetic endpoints (absorption, distribution, metabolism, elimination).

Please also note that all references to concentration on ppm unit refers to gas volume (ppmV).

Table 8: Summary table of toxicokinetic studies

Method Guideline, GLP status, Reliability	Species, Strain, Sex, No/Group	Test substance Dose levels Duration of exposure	Results	Remarks (e.g. major deviations)	Reference
Sulfur dioxide					
Non-guideline; non-GLP; Reliability 2 Key study	Healthy human volunteers (age: 27 – 39 y), M, 7 in total (1 group)	SO ₂ , mean: 16.1±4.1 ppm (conc. of SO ₂ in the mask, mean of 13 samples), 25 – 30 min exposure, inhalation via mask	Conc. within the nose: 13.8±3.4 ppm (n = 19 determinations); conc. in pharynx: not detectable 0.3 ppm estimated in comparison to controls. Essentially complete initial deposition in nasal mucosa, desorption and expiration via air ~15 %, estimated systemic absorption 85 %.	Temperature: 21°C, determination of SO ₂ concentrations via changes in electro conductivity	Speizer and Frank 1966 Arch Environ Health 12: 725-728
Non-guideline; non-GLP Reliability 2 Key study	Rat, Sprague Dawley, M, 40-48/group	SO ₂ , 0, 10, 30 ppm: 6 h/d; 5 d/wk, 21 wks; measured conc.: 10.1 ± 0.3 29.9 ± 1.2 (means of daily average); Recovery period: 4 wks following treatment	Conc. of R-S-SO ₃ ⁻ + SO ₃ ²⁻ in trachea: 30 ppm: 173 ± 59 nmol/g wet weight. 30 ppm (recovery period): 65 ± 16 nmol/g wet weight. In large bronchi: 30 ppm: 156 ± 78 nmol/g wet weight. No accumulation of sulfite in plasma in rats with intact sulfit oxidase at wk 6, 14, and 21 of exposure.	Concentrations determined in lung only slightly higher than in controls – finding is in accordance with results of studies demonstrating nasopharyngeal absorption (Speizer & Frank 1966, Anonymous38, 1969, see above).	Anonymous40
Non-guideline; non-GLP Reliability 2 Key study	Rabbit, New Zealand White, F, 4/group	SO ₂ : Group 1: 10.3 ± 0.5 ppm SO ₂ for 10 days Group 2: 9.7 ± 0.4 ppm for 3.7 days Inhalation exposure	Plasma concentration at equilibrium (nmol/mL): 21 – 59 (n = 8) Half-life (days; min - max): 0.8 – 8.7 mean: 3.2 ± 2.3, equilibrium at approx. 3-5 days	Exponential clearance of exogenous S-sulfonate proceeded to a conc. of approx. 10 nmol/ mL above endogenous conc. followed by a plateau for	Anonymous42

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Method Guideline, GLP status, Reliability	Species, Strain, Sex, No/Group	Test substance Dose levels Duration of exposure	Results	Remarks (e.g. major deviations)	Reference
				several days – afterwards decrease to endogenous conc.	
Non-guideline; non-GLP Reliability 2 (e.g. untypical study design) Key study	Dog, no information on strain and sex, 10 per group	³⁵ SO ₂ ; Inhaled ³⁵ SO ₂ (min – max): 7.2 – 132.3 µcurie ³⁵ S Inhalation via tracheal cannulation	Distribution in organs % of administered ³⁵ S (20 – 30 min after end of exposure; min – max): Trachea: 1.6 – 20.3 % Lung: 1.8 – 6.9 % Liver: 2.8 – 27.4 % Spleen: 0.1 – 5.4 % Kidney: 0.2 – 12.4 % Brain: 0.2 – 7.2 % Lymph nodes of pulmonary hilar: 0.003 – 1.7 %	Uncommon administration	Anonymous57
Non-guideline; non-GLP Reliability 2 (reporting deficiencies) Key study	Dog, Mongrel, no information on sex, 5 or 4 per group, respectively	³⁵ SO ₂ ; Inhalation exposure Group 1; 5 dogs: exposure: 22 ± 2 ppm Group 2; 4 dogs: exposure: 50 ppm, exposure duration: 30 or 60 min	Absorption: Percentage of dialyzable ³⁵ S in plasma: 64.4 ± 2.3 % (SE), content of ³⁵ S after precipitation: 74.7 % ± 8.8 % (SE). Blood levels increased continuously during exposure (60 min exposure) Excretion: Within a 3 hour post-exposure period, radioactivity of whole blood decreased little despite continuous renal excretion of ³⁵ S. An average of 84.4 % of the urinary- ³⁵ S was in the form of inorganic sulfate; 92.4 % was present as total sulfate. Main excretion via urine: total ³⁵S mean: 92.4 %, as inorganic sulfate (³⁵S) mean: 84.4 %; 7.6 % as esters of sulfuric acid; rest not determined (e.g. neutral sulfur) Protein binding predominantly to α-globulins and albumin Binding to RBC: 35.1 % ± 3.6 % (SE; in vivo) of which 2/3 intracellular, 63.6 % ± 10.3 % (SE; in vitro)		Anonymous37
Non-guideline; non-GLP, Reliability 2	Rat, Wistar, M, 4 - 16/group	Sulfur dioxide; 0; 5; 50; 100 ppm 5 h /day; 7 – 28 days	Depletion of GSH due to formation of S-sulfo-glutathione as detoxification product. GSH depleted in lung, liver, kidney and heart tissue at 5 or 100 ppm sulfur dioxide	* Rats exposed to 50 ppm SO ₂ maintained tissue GSH status	Anonymous44

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Method Guideline, GLP status, Reliability	Species, Strain, Sex, No/Group	Test substance Dose levels Duration of exposure	Results	Remarks (e.g. major deviations)	Reference
Key study			(sulfitolysis of GSSG to GSSO ₃ ²⁻ *. Enzyme activity: Lung activity of GCS (γ-glutamylcysteine synthetase), GPx (glutathione peroxidase), GRed (glutathione reductase) and γ-glutamyltranspeptidase reduced; Liver: GRed and GPx sign. reduced.		
Non-guideline, non-GLP Reliability 2 Key study	Rabbit, NZW, M; 8 rabbits in total 1 Rhesus Monkey/ ♀;	SO ₃ ²⁻ : Injected doses: 0.15, 0.30 and 0.60 mmol SO ₃ ²⁻ /kg bw; Single injections	Rapid equilibration of the central and tissue compartments, Rapid distribution and elimination, rate constants: 0.1 – 1.0 /min, clearance and elimination inversely related to dose - sulfate inhibits SO <i>in vitro</i> . Sulfite distribution fits two-compartment model. Clearance by direct oxidation to sulfate – metabolic clearance: 22 mL/min/kg bw.	-	Gunnison and Palmes 1976. Toxicol. Appl. Pharmacol. 38:111-126.
Non-guideline; non-GLP, Reliability 2 inhalation whole body	Mouse (Kunming albino)/ ♂; # of animals not clearly given (3 animals / group suggested): 4 equal groups of mice 3 groups exposed to SO ₂ , 1 control group.	Sulfur dioxide in mg/m ³ ; 0) control 1) 14 ± 1.25 2) 28 ± 1.98 3) 56 ± 3.11 corresp. to 0; 5.3±0.5; 10.5±0.7; 21.1 ±1.2 ppm Exposure duration: 4 hours per day, 7 days.	Dose-dependent increases of sulfite levels in tissues μg/mg protein): Brain: 0): 0.174±0.008 1): 0.275±0.05 2): 0.299±0.073 3): 0.352±0.06 Heart: 0): 0.147±0.004 1): 0.236±0.029 2): 0.362±0.061 3): 0.397±0.062 Lung: 0): 0.187±0.015 1): 0.335±0.059 2): 0.354±0.018 3): 0.512±0.055	-	Anonymous45
Non-guideline; non-GLP; Reliability 2	Adult dogs, 7 in total (1 group. cross-over design), 5 evaluated, sex and strain not reported	SO ₂ , 1 - 50 ppm; 5 min exposure: inhalation via mask (nose or mouth) airways surgically isolated,	Nose breathing: Initial nasal retention of sulfur dioxide almost complete (99 %) in dogs irrespective of concentration (1-50 ppm) and of air flow Mouth breathing: Uptake by mouth: 95 % on average at 3.5 L/min; < 50 % at 35 L/min	Initial and systemic uptake of SO ₂ depends on airflow and mode of breathing (mouth vs nose, fast or slow breathing).	Anonymous38

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Method Guideline, GLP status, Reliability	Species, Strain, Sex, No/Group	Test substance Dose levels Duration of exposure	Results	Remarks (e.g. major deviations)	Reference
		Airflow: 3.5 and 35 L/min	airflow, higher desorption from respiratory tissue Mouth breathing and high flow rates (e.g. when exercising) results in increased exposure of lower airways		
Non-guideline; non-GLP; Reliability 4	Healthy male volunteers, N = 15, age not reported	SO ₂ , slowly increasing concentrations up to 1, 5, and 25 ppm on days 1, 2, 3 respectively, 6 h exposure Inhalation	< 1 % of conc. reached the oropharynx; 99 % absorption by nose. Concentration dependent decrease in mucus flow rate	SO ₂ concentration in expired air not determined. Study predominantly to study respiratory function.	Andersen et al. 1974 Arch. Environ. Health 28: 31-39
Non-guideline; non-GLP Reliability 4	Rabbit, Strain not specified, A):10 in total cross-over design; B) 5 in total, cross-over design	SO ₂ , inhalation in exposure chamber – 2 methods: A (air sucked from cannulated trachea - : 100, 250 ppm B (cannulated trachea, free breathing) 100 – 200 ppm / 300 ppm	Efficient absorption of SO ₂ in the upper respiratory tract: 100-200 ppm: 95 – 98 % absorption by nasal cavities 300 ppm: 51 – 86 % absorption by nasal cavities, only 2 – 5 % reached the trachea.	-	Dalhemn and Strandberg 1961; Int J Air Water Pollut 4: 154-167
Non-guideline; non-GLP Reliability 2	Rats/Wistar/ no data on sex; 10/group, 7 groups exposed.	SO ₂ , 40 to 750 ppm. analytical concentration: 41 ± 2 ppm, 64 ± 4 ppm, 83 ± 2 ppm, 145 ± 1 ppm, 231 ± 3 ppm, 426 ± 4 ppm and 751 ± 17 ppm.; inhalation via mask	Capacity to retain SO ₂ , inversely related to exposure concentration (range 41 to 751 ppm). Absorption at the 1 ppm level would be anticipated to be about 93 % (exponential extrapolation of retention for lower sulfur dioxide concentrations).	-	Anonymous19
Non-guideline; non-GLP, Reliability 2	Human healthy volunteers, M, 13/group (group 1: 13 non smokers, mean age: 22). 7/group	SO ₂ , Group 1: 12 subjects: 0, 0.3; 1.0, 3.0, ppm (cross-over design):	Plasma levels increased by 1.1 ± 0.16 nmol S-sulfonate/ ml plasma (mean + SE) for each 1-ppm SO ₂ increment in chamber.	-	Gunnison and Palmes 1971

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Method Guideline, GLP status, Reliability	Species, Strain, Sex, No/Group	Test substance Dose levels Duration of exposure	Results	Remarks (e.g. major deviations)	Reference
	(group 2: 7 heavy smokers, mean age: 34)	Group 1: 12 subjects 120h continuous exposure: inhalation in chamber: 1 subject: 3.0, 6.0 ppm 48 h exposure Group 2: 96 h continuous exposure: 0, 0.3; 1.0, 3.0 ppm;			
Non-guideline; non-GLP Reliability 2	Rabbits (New Zealand White)/ ♂; 3-11 animals/group 12 rabbits exposed to 3 ppm	SO ₂ , 0, 3, 10 ppm: measured conc. max. ± 5 %)	Conc. of R-S-SO ₃ ⁻ + SO ₃ ²⁻ in trachea (nmole/g dry wt) at: 10 ppm and exposure duration (hr): 0 hr: 14±11 1 hr: 39±14 3 hr: 107±36 10 hr: 100±58 24 hr: 116±54 48 hr: 152±37 72 hr: 163±37 3 ppm: 3 hr: 45±17 24 hr: 61±41(n.s. from 3 hours exposure)	Several rabbits showed signs of infections and had clearly higher elevated levels of R-S-SO ₃ ⁻ + SO ₃ ²⁻ at 48 and 72 hr: 294±147 – they were evaluated separately and excluded from overall evaluation.	Anonymous46
Non-guideline; non-GLP, reliability 4	2 dogs, no information on sex and strain	³⁵ SO ₂ ; 15 ppm, 42.5 min exposure 33 ppm, 40 min exposure	≥90 % ³⁵ SO ₂ per unit of gas-air mixture inhaled was retained in the respiratory tract 2 days following inhalative exposure. Still detectable 7 days after exposure. ³⁵ SO ₂ readily excreted in urine, not detected in faeces	Exposure via tracheal tube. Adverse effects: decrease in lung compliance and increases in pulmonary resistance	Anonymous56 1960b
	1 dog	³⁵ SO ₂ ; 11.2 ppm, 20 min exposure	Distribution in organs 40 min following end of exposure: Trachea: 7.2 % Lung: 6.9 % Liver: 27.4 % Spleen: 5.4 % Kidney: 2.8 % Brain: 0.6 %	Dogs tracheostomied	
	1 dog	³⁵ SO ₂ ; 29.8 ppm, 35 min exposure	Distribution in organs 40 min following end of exposure		

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Method Guideline, GLP status, Reliability	Species, Strain, Sex, No/Group	Test substance Dose levels Duration of exposure	Results	Remarks (e.g. major deviations)	Reference
			Trachea: 6.0 % Lung: 2,4 % Liver: 10.2 % Spleen: 1.0 % Kidney: 1.9 % Brain: -		
Sulfites and sulfates					
Non-guideline; non-GLP Reliability 2 Key study	Rabbit (New Zealand White), F	8.9 or 26 Na₂S₂O₅ $\mu\text{mol/mL}$ drinking water, corresponding to approx. 0.9 or 2 mmol sulfite/kg bw/d, corresp. to approx.. 72 or 160 mg/kg bw/d sulfite Oral exposure	Plasma concentration at equilibrium (nmol/mL; min - max) at 8.9 $\mu\text{mol/mL}$: 24 – 31 (n = 2); mean concentration at equilibrium: 28 \pm 5 Half-life (days; min – max): 0.45 – 1.69 at 26 $\mu\text{mol/mL}$: 46 – 120 (n = 8); mean concentration at equilibrium: 82 \pm 25 Half-life (days; min – max): 1.12 – 1.58 Mean half-life: 1.3 \pm 0.3 days (n = 10)	Exponential clearance of exogenous S-sulfonate proceeded to a conc. of approx. 10 nmol/ mL above endogenous conc. followed by a plateau for several days – afterwards decrease to endogenous conc.	Anonymous42
	Rabbit (New Zealand White), F, 4	0.9 mmol Na ₂ S ₂ O ₅ /kg bw Intravenous exposure	T _{max} : 20-40 min C _{max} : 110 – 180 nmol/mL		
Non-guideline, non-GLP Reliability 2 Key study	Human, 8 healthy male subjects, bw: 59.1 – 99.0 kg	Sodium sulfate (³⁵ S), 60 – 80 μCi ³⁵ S/mL, administered volume: 1 mL, i.v. and p.o.	Volume of distribution: Intravenous: 16.8 \pm 1.1 L Oral: 15.3 \pm 1.2 L Excreted within 24 h: Intravenous: 86.3 \pm 1.8 oral: 79.9 \pm 2.2 Time to reach equilibrium with C_{max}: Intravenous: 60 – 90 min Oral: 60 – 105 min	Slow absorption from the GI tract over 10-30 min, followed by a rapid absorption phase until C _{max} is reached.	Bauer 1976 J. Appl. Physiol 40:648-650
Non-guideline, non-GLP	Rat, Wistar, F, Group 1: n=8 Group 2: n=12 4 treatment	Group 1: Na ₂ S ₂ O ₅ , 2000 ppm (as SO ₂) in	Excretion in urine within 4 h following	-	Anonymous55

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Method Guideline, GLP status, Reliability	Species, Strain, Sex, No/Group	Test substance Dose levels Duration of exposure	Results	Remarks (e.g. major deviations)	Reference
Reliability 2	groups a) NaCl b) Na ₂ S ₂ O ₃ x 5 H ₂ O c) Na ₂ SO ₄ x 10 H ₂ O d) Na ₂ S ₂ O ₅ Group 3: n=12, as group 2 but i.p. administration	drinking water, Group 2: p.o. gavage, single dose; volume administered: 5 % of bw Group 3: i.p.; volume admin.: 3 % of bw; single dose urine collection 4 h following administration	- oral application (group 2): sulfur (%): a) NaCl: - b) Na ₂ S ₂ O ₃ : 23.1±3.11 c) Na ₂ SO ₄ : 7.1±1.15 d) Na ₂ S ₂ O ₅ : 55.1±6.24 - i.p. application (group 3) sulfur (%): a) NaCl: - b) Na ₂ S ₂ O ₃ : 84.9±11.7 c) Na ₂ SO ₄ : 87.7±14.16 d) Na ₂ S ₂ O ₅ : 88.6±5.29 urinary excretion predominantly as inorganic sulfate		
Non-guideline, non-GLP Reliability 2	Human ileostomied, healthy subjects 3M/3F; mean age: 60 (48 – 74 y), mean weight 63 kg (57 – 76 kg) 3 healthy subjects, age and weight not reported	Sulfate, dietary exposure; 1.6 – 16 mmol/d	Maximum net intestinal absorption of dietary sulfate: Ileostomied subjects - plateau at 5 mmol/day with dietary intakes of 7 mmol/day; Healthy subjects: > 16 mmol/day; Urinary excretion of sulfate correlation lineary with dietary sulfate: 97 % excreted via urine , 19.4 mmol/ day excretion from endogenous sulfate production (zero dietary sulfate) Faeces: Faecal losses of sulfate <0.5 mmol/day in the normal subjects at all doses.		Florin et al. 1991; Gut; 32:766-73
Non-guideline, non-GLP Reliability 2	Human, 5 healthy men, age: 25 – 36 y, bw: 66 – 79 kg	18.1 g Sodium sulfate (equiv. 8 g anhydrous sodium sulfate, single oral dose or 4 divided oral doses in hourly intervals	Baseline sulfate excretion (prior to external sulfate intake; min – max: 13.0±2.1 – 24.3±6.5 mmol/24 h Mean excretion after single dose (cumulative, % of dose): 24 h: 36.4±15.4 48 h: 49.5±15.6 72 h: 53.4±15.8 Mean excretion after divided doses (cumulative, % of dose): 24 h: 43.5±12.0 48 h: 53.1±7.5 72 h: 61.8±7.8	Values are amounts of excreted sulfate minus baseline values. No radiolabelling of sulfur.	Cochetto and Levy 1981, J Pharm Sci. 70/3: 331-333

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Method Guideline, GLP status, Reliability	Species, Strain, Sex, No/Group	Test substance Dose levels Duration of exposure	Results	Remarks (e.g. major deviations)	Reference
Non-guideline, non-GLP Reliability 2	Human, 18 healthy volunteers 10M/8F; age: 16- 62 y; Dog, Mongrel; 16	H₂SO₄ (³⁵ S), 20 µCi ³⁵ S/mL administered volume: 1 mL, i.v.	T_{1/2,elimination} (average) human: 5.9 h, dog: 7.5 h Clearance human: 24-49 mL/min Clearance dog: not reported V_D human (18 min): 5.2 – 14.6 L V_D dog (25-30 min): 1.12 – 4.27 L	-	Walser et al. 1953 J. Clin. Invest. 32: 299-311
Non-guideline, non-GLP Reliability 2	Human, 33 healthy volunteers 25M/8F; age: 17- 72 y; A) 11 soldiers: mean age: 18.6±1.6 y B) 9 young male students: mean age: 26.3±3.5y C) 5 elderly men: mean age: 62.6±1.7 D) 8 elderly women: mean age: 65.3±7.8 y	Na₂SO₄ (³⁵ S), 100 µCi ³⁵ S i.v. single dose	V_D: A: 13.4±1.5 L B: 12.0±2.1 L C: 10.6±1.3 L D: 10.7±1.5 L	-	Ryan et al. 1956 J Clin Invest. 35(10):1119-30
Non-guideline, non-GLP Reliability 2	Mammals (pig, sheep, bovine, horse, rat, rabbit (without further details).	No exposure, general investigation on sulfite oxidase distribution	High activities of sulfite oxidase in liver, kidney and heart of mammals (tissues with a high catabolic activity for amino acids) - very low activities in brain, spleen, lung and testis.	-	Cabré, F. et al., 1990, Biochem Medicine Metabol Biol. 43:159-62

9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

Sulfur dioxide:

Absorption

Inhalation is the predominant route of exposure for SO₂ as a gaseous substance. Sulfur dioxide is rapidly absorbed in the moist epithelium of the upper respiratory tract. Virtually all of the inspired sulfur dioxide was absorbed by the nasal mucosa following nasal respiratory exposure in seven healthy men. A part of approximately 15 % was subsequently desorbed and eliminated with exhaled air (Speizer and Frank 1966).

³⁵S enters the circulation from the mucosa of the upper airways. Radioactivity of whole blood decreased little during postexposure periods of up to 3 hours (Anonymous37). Anonymous57 detected ³⁵S in the airway tissues

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of a dog one week after the animal had been exposed to $^{35}\text{SO}_2$ through a tracheal cannula. However, dogs not exposed via the trachea retained most of the inhaled ^{35}S in the nasal mucosa following nasal exposure and blood levels were below the limit of detection (Anonymous57).

In tracheal tissue in the rat a concentration-dependent steady-state of sulfite and S-sulphonates was reached within 6 weeks of exposure to 10 or 30 ppm sulfur dioxide in rats. Tracheal concentrations declined as exposure stopped but were still elevated after a 4-week post exposure period. S-sulphonate compounds (RS-SO_3^-) were not detectable in blood in this study (Anonymous40), whereas plasma S-sulphonate levels increased progressively during exposure with SO_2 until equilibrium was reached (Anonymous42; Gunnison and Palmes 1971).

Plasma contained more ^{35}S than red blood cells. During the postexposure period, plasma levels decreased slightly whereas level of ^{35}S in red blood cells increased (see also Anonymous39). Approximately one third of the plasma ^{35}S was bound to proteins (albumin; Anonymous37).

Following nasal exposure to sulfur dioxide in dogs, the blood concentrations reached its maximum at the end of the short exposure period of 38 min (Anonymous39).

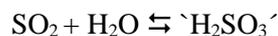
Anonymous38 and Brain (1970, cited by US EPA 2007) investigated the oral and nasal absorption of SO_2 in the surgically isolated upper respiratory tract of anesthetized dogs. Radiolabelled SO_2 at concentrations of 1; 10; and 50 ppm were passed separately through mouth and nose at a flow of 3.5 and 35 L/min, respectively. Nasal absorption was complete independent of air flow, whereas oral absorption of SO_2 was 95 % on average at 3.5 L/min but only 34 % at 34 L/min. However, differences might be due to methodological variations as it was apparently difficult to fix the mask closely over the snout of the dogs.

Distribution

Absorbed sulfur dioxide metabolites are readily distributed throughout the body (distribution and elimination rate constants: 0.1 – 1.0/min; Gunnison and Palmes 1976). Clearance and elimination inversely related to dose following nasal administration (Anonymous39; Anonymous37) or exposure via tracheal cannulation (Anonymous56). In the latter investigation, radioactivity levels were highest in trachea, lungs, and liver followed by spleen, kidney brain and the pulmonary hilar lymphnodes. Within the blood, ^{35}S is distributed in the plasma and in the cellular compartments (Anonymous38; Anonymous39). Gunnison and Palmes (1974) showed a positive correlation with air concentrations of sulfur dioxide and plasma levels of S-sulphonate in human subjects following continuous exposure to 0.3, 1.0, 3.0, 4.2, or 6.0 ppm SO_2 in a chamber for periods of up to 120 hours.

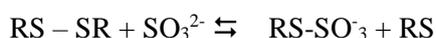
Metabolism

Sulfur dioxide readily dissolves in water forming sulfurous acid which dissociates to form bisulfite and sulfite ions in a ratio depending on the pH of the solution (Menzel et al. 1986).



Following absorption, inhaled sulfur dioxide dissolves on the walls of the moist airways (Gunnison & Jacobsen 1987). Sulphite (sulfite, bisulphate) reacts with cellular molecules especially by sulphitolytic cleavage of disulfide bonds in molecules such as cysteine, albumin, and glutathione (Gunnison & Jacobsen 1987; Menzel et al. 1986).

Sulphitolytic reaction:



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At pH 7.4 the forward reaction is essentially irreversible. Detection of elevated levels of S-sulphonate (RS-SO₃) compounds in an organ or tissue is an indication for recent exposure to sulfite (Gunnison & Jacobsen 1987).

Sulphite oxidase (SO) catalyses the oxidation of sulfite to sulphate with ferricytochrome c being the physiological electron acceptor. Sulphite oxidase is located in the intermembrane space of mitochondria. Sulphite oxidation is performed in the Mo (molybdenum) centre, and the reducing equivalents are passed on the b5 haem, where, in turn, the terminal electron carrier cytochrome c_(ox) is reduced. This is the final step in the oxidative degradation of the sulfur containing amino acids cysteine and methionine. The enzyme also plays an important role in detoxifying exogenously supplied sulfite and sulfur dioxide (Feng et al. 2007).

High activity of this enzyme has been found in the liver, kidney, and heart, whereas activity is low in brain, spleen, lungs, and testis (Anonymous40). Human lung has an approximately 135-fold lower capacity to oxidise sulfite than human liver (Beck-Speier et al. 1985). Sulphite oxidase activity was high in liver and hepatocytes and low activity was detectable in lung samples and in phagocytic cells. ATP level decreased following 30 min incubation (pH 6, 37°C) with sulfite dependent on the SO activity of the tissue of approximately 10 % in hepatocytes and rat liver slices compared to an decrease > 90 % in rat lung slices, alveolar and peritoneal macrophages (Anonymous41). Sulfite was cleared by direct oxidation with a metabolic clearance rate of 22 mL/min/kg bw (Gunnison and Palmes, 1974)

Compared to other animal species, rats have approximately three and five time greater SO activity than rabbits and rhesus monkeys (e.g. Anonymous46). Sulphite oxidase activity in liver was determined to be highest in rats (rat > horse > cattle > sheep > rabbit > pig) whereas pigs showed the highest SO activity in the kidney (Cabr e et al. 1990). Hepatic SO activity in rats is about 10-20 fold higher than that in humans.

Rats with impaired SO activity showed higher *in vivo* plasma concentrations of sulfite than normal rats (Anonymous40). SO activity has been shown to be lower in young than in adult rats as molybdenum - which is the cofactor of sulfite oxidase - is present in low levels in newborns (Johnson and Rajagopalan 1976). Deficiency of SO leads to accumulation of SO₃²⁻, a strong nucleophile, capable of reaction with a wide variety of cell components (Feng et al. 2007).

Glutathione (GSH) is suggested to play a role in SO₂ detoxification through the sulphitolysis of glutathione disulphide (GSSG) to S-sulphoglutathione (GSSO₃²⁻). Repeated inhalation exposure to 5 ppm of SO₂ did lead to depletion of GSH pools in lung, liver, heart, and kidney (Anonymous44). In addition, a variety of authors demonstrated depletion of GSH levels and increased lipid peroxidation and oxidative stress in various organs (lung, heart, liver, kidneys, spleen, retina, lens tissue, testis, intestinal tissues, various regions of the brain, testicles; e.g. Anonymous47; Anonymous43; Anonymous48; Anonymous53 ; Anonymous51, Anonymous11; Anonymous49) following repeated exposure to SO₂ in various species (guinea pig, rabbit, mouse, rat). These results are in agreement with the wide distribution of metabolites of sulfur dioxide within the body.

Elimination

The majority of inhaled sulfur dioxide was excreted in the urine as inorganic sulphate (84.4 %) with a total urinary excretion of 92.4 % (Anonymous37). Anonymous39 determined maximal levels in urine approximately 90 min following onset of a 30-min exposure. In the study performed by Anonymous37, blood concentrations were steadily increased during exposure of 60 min whereas peak excretion in urine was not reported but apparently depends on exposure duration. Mean half-life of SO₂ was: 3.2 ± 2.3 days with an equilibrium at approx. 3-5 days following inhalation exposure to approximately 10 ppm SO₂ in rabbits (Anonymous42).

Sulphite/bisulfite:

Absorption

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Sodium metabisulfite: Ji et al (1995) determined endogenous plasma concentrations of $4.87 \pm 2.49 \mu\text{mol/L}$ as total plasma sulfites of 76 donors (reference range for total serum sulfite in normal subjects is $0 - 9.85 \mu\text{mol/L}$). Two subjects received an oral single dose (with vegetable juice) of 20 mg/kg bw of sodium metabisulfite (no information on the content of sulfite of vegetable juice). A rapid rise in total serum sulfite was observed which reached a maximum of 112 and $38 \mu\text{mol/L}$ in subject 1 and 2, respectively within approximately 30 min.

Sodium sulphate: Maximal plasma concentration with equilibrium was reached within 60 – 105 min following oral application of sodium sulphate in healthy male volunteers whereas equilibrium with maximal plasma concentrations are achieved within 60 – 90 min following intravenous application. A biphasic absorption is assumed with a slow phase from the GI within 10 – 30 min followed by rapid absorption in which plasma peak levels are reached (Bauer 1976).

Distribution

Sulfite distribution (investigated in rabbits) can be described by a two-compartmental model, characterized by rapid equilibration of the central and tissue compartments with elimination occurring predominantly by the metabolic route from the central compartment. The authors suggest that the fast component represents the diffusion of a low molecular weight S-sulphonate from the blood vessels while the slow component probably corresponds to clearance of protein S-sulphonate (Gunnison and Palmes 1976).

Metabolism

Inhaled, ingested or injected sulfite is metabolized by sulfite oxidase to sulphate.

Only small amount of unchanged sulfite is cleared via kidney and excreted with urine following single i.v. injection of sodium metabisulfites in rabbits (Gunnison and Palmes 1976). In human polymorphonuclear leukocytes (neutrophils) two alternative pathways have been observed following incubation of human neutrophils with sulfite in vitro: one enzymatic route dependent on sulfite oxidase and one non-enzymatic route which involves intermediate formation of sulfur trioxide anion radicals (Constantin et al. 1996).

Endogenous sulphate production

Endogenous production of sulphate in the lung may take place in the human alveolar epithelial cells with cysteine dioxygenase (CDO) and sulfite oxidase (SO) being the responsible enzymes for possible pulmonary in situ production. Sulphate can then be converted to the substrate for phase II sulphotransferases or be used for the sulphation of structural components of the alveolus. Sources for endogenous sulphate production are sulfur containing amino acids, predominantly cysteine (Millard et al. 2003). The authors showed that both enzymes were expressed in alveolar cells but whether the activity of the enzymes would be sufficient for endogenous sulphate production remains speculative.

Elimination

Mean urinary excretion from endogenous produced sulphate (oxidation from S-amino acids) amounted to approximately 15 mmol/day in healthy volunteers (Florin et al. 1991). Maximum net intestinal absorption in ileostomised subjects reached a plateau at 5 mmol/day with dietary intakes of 7 mmol/day and above. Provided colonic absorption of sulphate is similar in healthy volunteers, a net absorption of 10 mmol/day was calculated during a period of high sulphate (16.6 mmol/day) intake. The authors assumed that diet and intestinal absorption are the principal factors affecting the amounts of sulphate reaching the colon. Endogenous secretion of sulphate by colonic mucosa may also contribute to the amounts of sulphate determined in the colon of healthy and ileostomised subjects (Florin et al. 1991).

Similar to sulfur dioxide, orally ingested sodium metabisulfite, sodium sulphate and hydrated sodium bisulphate in rats are predominantly excreted via the kidney as anorganic sulphate. Approximately 55 % of $\text{Na}_2\text{S}_2\text{O}_5$ is excreted within 4 hours following oral administration compared to 89 % following percutaneous administration (Bhagat and Lockett 1960).

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Protein binding

Sulfite binds to fibronectin and to serum albumin in vitro and in vivo (Gregory and Gunnison 1984).

Conclusions:

The sulfites oral absorption can be considered 100 % (approx. 80 % within 24 h) based on sulfur dioxide high solubility in water and on the most reliable study on oral and intravenous administration of sulfites (sodium sulphate), which demonstrated urinary excretion of 80 % of dose within 24 hours (Bauer 1976). Complete absorption can be assumed.

Studies on dermal absorption of sodium metabisulfite were not available. Default values according to EFSA guidance on dermal absorption (EFSA 2012) are applied. Based on physico-chemical properties of sodium metabisulfite, the substance is not likely to penetrate skin to a large extent as the substance is highly water soluble (negative $\log P_{ow}$). Therefore, dermal absorption of sulfites, metabisulfites, bisulfites and sulphates can be assumed as below 25 / 75 % (at concentrations > 5 % and ≤ 5 %, resp.) based on the EFSA Guidance on Dermal Absorption (2012). With respect to the gaseous appearance of sulfur dioxide, exposure via skin is not a relevant exposure route. Sulfur dioxide has a harmonised classification as Skin Corr. 1B, H314.

Various studies indicate complete inhalation absorption of SO_2 (Anonymous38; Anonymous39; Andersen et al. 1974, Anonymous37). Sulfur dioxide is highly soluble in water. It is, therefore, readily absorbed by the mucous of the upper respiratory tract. Parts of the absorbed SO_2 is subsequently exhaled (~ 15 %) via expired air. The values considered were 85 – 92 %.

Inhaled and ingested sulfur dioxide/sulfites are systemically available. Distribution in blood in plasma and cellular compartments. Accumulation of sulfite in plasma is not to be expected.

Sulphite oxidase is the most important enzyme in sulfite metabolism, oxidizing SO_3^{2-} to SO_4^{2-} . Liver, kidney, and heart are tissues with high activity of sulfite oxidase, whereas e.g. lung, brain, spleen, and testes show low activity (Gunnison & Jacobson 1987). Deficiency of sulfite oxidase results in accumulation of SO_3^{2-} which is a strong nucleophile that can react with a variety of cell components (Feng et al. 2007). Inhaled sulfur dioxide dissolves on the walls of the moist airways producing a mixture of sulfite, bisulfite, and hydrogen ions. Lung is the predominant target organ for local effects of SO_2 exposure (port of entry) presumably due to its low activity of sulfite oxidase. Organs with low activity of sulfite oxidase are suggested to be target organs.

All studies which addressed elimination following sulfur dioxide or sulphate exposure identified urinary excretion of inorganic sulfur as predominant route of elimination. Amount of expired SO_2 .

10 EVALUATION OF HEALTH HAZARDS

Taking into account that sulfur dioxide has an existing harmonized classification, only the endpoints which need to be amended are addressed¹. Therefore, only the data for acute toxicity by inhalation, skin irritation, respiratory sensitisation, skin sensitisation, carcinogenicity and germ cell mutagenicity assessments are presented. The REACH Registration report on Sulfur dioxide was also taken into account (c.f., section 6) and is generally in agreement with the information presented in this CLH report.

Sulfur dioxide is a well-known pollutant in ambient air as result from anthropogenic and natural emissions. In addition, sodium metabisulfite has a long tradition as preservation agent and antioxidant in food and cosmetics

¹ECHA- Guidance on the preparation of dossiers for harmonised classification and labelling, vs 2.0 (2014), section 3.4.3.1, page 18: “The dossiers proposing revisions to Annex VI entries need only focus on the specific hazard classes that are proposed to be revised. If one or several of the CMR and respiratory sensitisation hazard classes were not assessed in the past when the current harmonised classification was adopted and included in Annex VI, it may be considered (in line with Article 36(1), CLP) that these are included in the updated dossier, in addition to the hazard class(es) for which the revision is proposed. The process for updating Annex VI entries is the same for active substances used in BP and PPP as for other substances, and hence CLH dossiers proposing a revision of an existing entry for active substances in BP and PPP do not need to include data on all hazard classes but only data relevant for the revision proposal”.

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(e.g. Us-EPA 2008, JECFA 1964/65/66, Nair et al. 2003). Furthermore, considerable quantities of sulfite are generated in the body by normal catabolic processing of sulfur-containing amino acids (e.g. cysteine) and other sulfur-containing substances (Gunnison and Jacobsen 1987).

Consequently, extensive research has been performed on the toxicology of sulfur dioxide and sulfites and a vast amount of human and animal toxicity data has been accumulated. Unfortunately, little of the available data has been acquired and reported in a way complying with current OECD and EU guidelines for the testing of chemicals. Therefore, appropriate care needs to be taken in its interpretation. Nevertheless, it provides the information required for an assessment of the human health effects of sulfur dioxide and sodium metabisulfite.

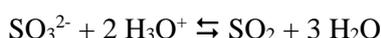
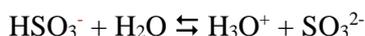
As sodium metabisulfite is another substance, its classification has to be addressed in a separate CLH dossier.

As human health effect assessment bases almost completely on published information, reliability can rarely be scored better than "reliable with restrictions" which is equivalent to Klimisch score 2. As a consequence, key studies are generally defined on the basis of studies with reliability scores of 2 if the results of these are supported by other studies.

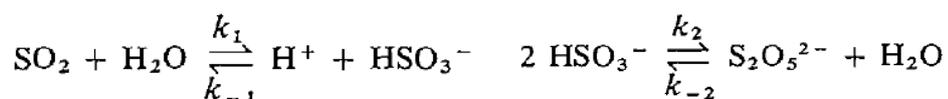
Not all references available were considered relevant for hazard assessment. Due to the vast amount of studies submitted and additionally retrieved from scientific literature search, the DS refrained from listing of all studies that were not used for hazard assessment (e.g. due to poor reliability).

Read-across concept for sulfur dioxide, sulfites, hydrogensulfites, in aqueous solution:

Quadrivalent-sulfur substances (S^{IV} , sulfurous acid: H_2SO_3 and salts of sulfite: SO_3^{2-}) and bisulfite (HSO_3^-) are produced when SO_2 dissolves in water and exist in a pH-sensitive equilibrium as shown in the following equations (Anonymous46, Shapiro 1972, Hayon et al. 1972; Beets and Voss, 1970). In addition, the active substance is sulfur dioxide generated by hydrolysis in situ of sodium metabisulphite. The following reactions occur, when sulphur dioxide is generated:



At pH 0.9, 24.7°C (Beets and Voss, 1970):



$$K_{-1} = 2.48 \pm 0.27 \times 10^9 \text{ mole}^{-1} \text{ s}^{-1}$$

$$K_2 = 7.00 \pm 0.21 \times 10^2 \text{ mole}^{-1} \text{ s}^{-1}$$

$$K_1 = 1.06 \pm 0.13 \times 10^8 \text{ s}^{-1}$$

$$K_{-2} = 10^4 \text{ s}^{-1}$$

This dossier concerns SO_2 as gas and in aqueous solution. A comprehensive read-across concept was developed for sulfur dioxide, sulfites, and hydrogensulfites. It is expected that the cation (i.e., sodium, potassium, ammonium) contributes to a lesser extent to the toxicity and solubility (all compounds are very soluble in water). Therefore, chemical and biological properties of the "sulfite" anion are predominantly considered as relevant determinant and information from sulphates with other cations than sodium are included in the evaluation.

The species that dominates among these rapidly interconvertible hydration products depends primarily upon pH but also on ionic strength and temperature (Gunnison and Jacobsen, 1987). Therefore, sulfur dioxide is transported through aqueous systems at neutral pH almost totally in its hydrated form. Because of this rapid

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hydration, the interactions of sulfur dioxide with biological molecules in an aqueous medium are probably those of sulfite and bisulfite.

Acidification will liberate sulfur dioxide vapours; in alkalis, sulfites, bisulfites, and metabisulfites are produced (Green, 1976). At concentrations > 1M, bisulfite anions will dimerize with the elimination of water to form metabisulfite (S₂O₅)²⁻; at low concentrations metabisulfite will hydrolyse to form bisulfite (HSO₃)⁻ (Shapiro 1983; Gunnison and Jacobsen 1987, Nair et al., 2003).

10.1 Acute toxicity - oral route

Endpoint not addressed.

10.2 Acute toxicity - dermal route

Endpoint not addressed.

10.3 Acute toxicity - inhalation route

Currently, there are no acute inhalation studies available according to OECD Guideline 403, but sufficient information on acute inhalation toxicity can be derived from some older studies (Anonymous17, Anonymous23; Anonymous24). The most reliable studies with the lowest LC₅₀ values were re-assessed and the conclusion was the same as the previous classification on Acute Tox. Cat. 3.

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Table 9: Summary table of animal studies on acute inhalation toxicity

Summary table of animal studies on acute inhalation toxicity with sulfur dioxide																	
Method, Guideline, GLP status, Reliability	Species, Strain, Sex, No/group	Test substance, form (gas, vapour, dust, mist) Actual and nominal concentration, Type of administration (nose only / whole body/ head only)	Results LC ₅₀	Remarks (e.g. major deviations)	Reference												
Pre-guideline OECD 403, Non-GLP, Reliability 2. Key study	Rat, CD outbred, M, 8/group	Sulfur dioxide (CAS 7446-09-5), air containing SO ₂ , 4 h exposure: whole-body dose levels: 224; 593; 965; 1168; 1319 ppm	Effects of various concentrations of inhaled SO ₂ on the mortality of rats: <table border="1"> <thead> <tr> <th>Concentration of SO₂ (ppm)</th> <th>2-week mortality</th> </tr> </thead> <tbody> <tr> <td>224</td> <td>0/8</td> </tr> <tr> <td>593</td> <td>0/8</td> </tr> <tr> <td>965</td> <td>3/8</td> </tr> <tr> <td>1168</td> <td>5/8</td> </tr> <tr> <td>1319</td> <td>8/8</td> </tr> </tbody> </table> 965 ppm < LC ₅₀ < 1168 ppm (approx. 2.57 mg/L < LC ₅₀ < 3.11 mg/L) at 965 ppm and higher: Respiratory difficulties followed by exhaustion and death	Concentration of SO ₂ (ppm)	2-week mortality	224	0/8	593	0/8	965	3/8	1168	5/8	1319	8/8	Acute Tox 3 A LC50 value of 1041 ppmV was calculated post-hoc by log-probit regression using BMDS software version 2.6.0.1.	Anonymous17
Concentration of SO ₂ (ppm)	2-week mortality																
224	0/8																
593	0/8																
965	3/8																
1168	5/8																
1319	8/8																
Method: Specific investigation on time-course of airway hyperreactivity and inflammatory changes in bronchoalveolar lavage (BAL) after exposure to high concentration; Non-guideline;	Dogs (Beagle)/ (M+F); 8 animals in total (4/group – control and treated).	Sulfur dioxide (CAS 7446-09-5); air containing SO ₂ 2-h exposure: endotracheally intubated, artificially respired Conc.: 400 ppm	LC ₀ (2 h): > 400 ppm; an immediate increase of bronchial responsiveness to histamine that lasted for about 2 hours post-exposure. Cell numbers in BAL were increased up to 1 hour for epithelial cells and from 1-4 hours for neutrophils. There	-	Anonymous18												

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Summary table of animal studies on acute inhalation toxicity with sulfur dioxide					
Method, Guideline, GLP status, Reliability	Species, Strain, Sex, No/group	Test substance, form (gas, vapour, dust, mist) Actual and nominal concentration, Type of administration (nose only / whole body/ head only)	Results LC ₅₀	Remarks (e.g. major deviations)	Reference
Non-GLP; Reliability of 2.			was no significant change of lymphocytes, macrophages, eosinophils, goblet cells, or mast cells in lavages.		
Method: investigation of ventilatory parameters and histological changes of the respiratory tract; Non-guideline; Non-GLP; Reliability of 2.	Rats (Wistar) / no data on sex; Seven groups of ten rats. Further control group.	Sulfur dioxide (CAS 7446-09-5); air containing SO ₂ 2-h exposure: head only, inhalation by face mask Conc.: 41 ± 2 ppm, 64 ± 4 ppm, 83 ± 2 ppm, 145 ± 1 ppm, 231 ± 3 ppm, 426 ± 4 ppm and 751 ± 17 ppm	LC ₀ (2 h): > 700 ppm LOAEC (2 h): 40 ppm (decrease of respiratory rate); Effects: sneezing, coughing and lachrymation, intermittent burst of quick and deep inspirations and expirations; 750 ppm: animals became grievously labored 0 and 40 ppm: no adverse histological changes of lungs 64-231 ppm: 10-30 % of the lungs showed pulmonary edema; 426-751 ppm: 70-80 % of the lungs showed pulmonary edema A positive correlation between the frequency of occurrence of pulmonary damage and the concentration of SO ₂ was shown.	-	Anonymous19
Method: investigation on time-course of inflammatory changes; Non-guideline; Non-GLP; Reliability of 2.	Dogs (Beagle)/ (F+M); 7 animals.	Sulfur dioxide (CAS 7446-09-5) air containing SO ₂ 2-h exposure: endotracheally intubated, artificially respired	LOAEC: 200 ppm; no mortality Airway hyperreactivity to histamine induced in dogs after a 2 hour inhalation of 200 ppm sulfur dioxide was associated with significant	-	Anonymous20

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Summary table of animal studies on acute inhalation toxicity with sulfur dioxide					
Method, Guideline, GLP status, Reliability	Species, Strain, Sex, No/group	Test substance, form (gas, vapour, dust, mist) Actual and nominal concentration, Type of administration (nose only / whole body/ head only)	Results LC ₅₀	Remarks (e.g. major deviations)	Reference
		Conc.: 200 ppm	inflammatory changes lasting up to the end of the observation period of 22 h.		
Method: investigation of respiratory rate; Non-guideline; Non-GLP; Reliability of 2.	Mice (dd strain)/ no data on sex 4 mice / test concentration, 7 test groups (including controls).	Sulfur dioxide (CAS 7446-09-5) air containing SO ₂ 10-min exposure: whole body Conc.: 0, 23, 38, 75, 128, 250, 500 ppm	LOAEC: 23 ppm; Sensory irritation, decrease of respiratory rate.	-	Anonymous21
Method: investigation of microscopic lesions of respiratory tract; Non-guideline; Non-GLP; Reliability of 2.	Mice (Ha/ICR)/ ♂; 3 DF-mice and 2 CO-mice/timepoint of sacrifice; controls: 9 DF-mice, 7 CO-mice	Sulfur dioxide (CAS 7446-09-5) Air containing SO ₂ Exposure period: 4, 24, 48, 72 hours continuously (gas): whole body Conc.: 10 ppm	LOAEC: 10 ppm (24 h exp., not after 4h exp.); Severe injury of respiratory and olfactory epithelium of the nasal cavity (oedema, necrosis and desquamation).	-	Anonymous22
Method: investigation of survival time and histological changes of the lower respiratory tract; Non-guideline; Non-GLP; Reliability of 2.	Rats (Sprague Dawley)/ ♂; 12 animals/dose.	Sulfur dioxide (CAS 7446-09-5) Exposure period: until death: whole body Conc.: 1.975, 3.498, 5.052 ppm	LC ₁₀₀ : 1975 ppm: 198 min; 3.498 ppm: 72 min; 5.052 ppm: 41 min; Deaths: time-dependent, 100% mortality at all concentrations.; Early deaths: acute asphyxia; Late deaths: pulmonary failure (oedema, consolidation of lung tissue).	-	Anonymous23

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Summary table of animal studies on acute inhalation toxicity with sulfur dioxide					
Method, Guideline, GLP status, Reliability	Species, Strain, Sex, No/group	Test substance, form (gas, vapour, dust, mist) Actual and nominal concentration, Type of administration (nose only / whole body/ head only)	Results LC50	Remarks (e.g. major deviations)	Reference
			Mean survival time: Susceptibility to lethal toxic action of SO ₂ highest in mice, intermediate in guinea pigs, least in rats		
Method: investigation of survival time and histological changes of the lower respiratory tract; Non-guideline; Non-GLP; Reliability of 2.	Mice (Connaught Medical research laboratory mice) /♂; 12 animals/dose.	Sulfur dioxide (CAS 7446-09-5) Exposure period: until death: whole body Conc.: 610, 913, 1178 ppm	LC ₁₀₀ : 610 ppm: 286 min; 913 ppm: 75 min, 1178 ppm: 39 min; Mortality: time-dependent, 100% at all concentrations ; Early deaths: acute asphyxia; Late deaths: pulmonary failure (oedema, consolidation of lung tissue). Mean survival time: Susceptibility to lethal toxic action of SO ₂ highest in mice, intermediate in guinea pigs, least in rats	-	Anonymous23
Method: investigation of survival time and histological changes of the lower respiratory tract; Non-guideline; Non-GLP; Reliability of 2.	Guinea pigs/♂; 12 animals/dose.	Sulfur dioxide (CAS 7446-09-5) Exposure period: until death: whole body Conc.: 2.207, 2.508, 2.750 ppm	LC ₁₀₀ : 2.207 ppm: 68 min; 2.508 ppm: 39 min; 2.750 ppm: 36 min. Mortality: time-dependent, 100% at all concentrations; Early deaths: acute asphyxia; Late deaths: pulmonary failure (oedema, consolidation of lung tissue). Mean survival time: Susceptibility to lethal toxic action of SO ₂ highest in mice,	-	Anonymous23

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Summary table of animal studies on acute inhalation toxicity with sulfur dioxide					
Method, Guideline, GLP status, Reliability	Species, Strain, Sex, No/group	Test substance, form (gas, vapour, dust, mist) Actual and nominal concentration, Type of administration (nose only / whole body/ head only)	Results LC50	Remarks (e.g. major deviations)	Reference
			intermediate in guinea pigs, least in rats		
Method: investigation of mortality and histological changes of the respiratory tract; Non-guideline; Non-GLP; Reliability of 2.	Hamsters (Syrian) /♂; No. of animals: 8 at 40 ppm, 12 at 40 ppm + carbon, 8 controls (without carbon).	Sulfur dioxide (CAS 7446-09-5) Exposure time 4h: whole body Conc.: 40 ppm SO ₂ , 40 ppm SO ₂ + 0.74 g carbon dust/m ³ , control: 0.74 g carbon dust/m ³	Exposure to SO ₂ alone: No leucocyte recruitment Exposure to SO ₂ and carbon dust: Numerous polymorphonuclear leukocytes within bronchial walls and in lumen (in part reversible)	Experiments with hamsters are not reliable (pneumonia, pathogenic bacteria in trachea/lungs). Repeated exposure of hamsters to SO ₂ was also reported. A LC ₅₀ value cannot be derived due to reporting deficiencies. Epithelial changes in trachea and large bronchi were observed after exposure to 100, 200, 400 ppm for up to 6 weeks.	Anonymous24
Method: investigation of ciliary beat in trachea; Non-guideline; Non-GLP; Reliability of 2.	Rabbits (no data on strain and sex); 10 animals/ dose.	Sulfur dioxide (CAS 7446-09-5) 45-min exposure: Head-only or whole body Conc. (nominal and analytical): about 100, 200, 300 ppm or about 100, 250 ppm	NOAEC (NOEC): 100 ppm (analytical: 99 ppm); LOAEC (LOEC): 200 ppm (analytical 210 ppm); (based on ciliar activity stop) high retention of sulfur dioxide in nose, mouth and pharynx; only about 1-2 % of the initially inhaled sulfur dioxide (at up to 250 ppm, analytical: 241 ppm) reached tracheal region	-	Anonymous25
Method: investigation of haematological changes;	Rats (Swiss) /♂; 50 animals (experimental group) /51 animals (control).	Sulfur dioxide (CAS 7446-09-5) 24-h exposure:	LOAEC: 0.87 ppm: haematocrit ↑; Sulfhaemoglobin ratio ↑;	-	Anonymous26

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Summary table of animal studies on acute inhalation toxicity with sulfur dioxide					
Method, Guideline, GLP status, Reliability	Species, Strain, Sex, No/group	Test substance, form (gas, vapour, dust, mist) Actual and nominal concentration, Type of administration (nose only / whole body/ head only)	Results LC ₅₀	Remarks (e.g. major deviations)	Reference
Non-guideline; Non-GLP; Reliability of 2.		whole body Conc.: 1 ppm (nominal)	Viscosity (whole blood/packed cell): ↓; Erythrocyte counts, Hb methemoglobin, mean corpuscular volume and mean corpuscular hemoglobin concentration (no significant difference).		
Method: fixed concentration procedure; Non-guideline; Non-GLP; Reliability of 2.	Rats (Sprague Dawley)/ ♂; 15 animals (pretreated with tracer particles, divided into 3 groups [one control, one SO ₂ , one HCHO] after exposure).	Sulfur dioxide (CAS 7446-09-5) 4-h exposure (SO ₂ gas after inhalation of radioactive tracer particles): nose only Conc.: 20.1 ± 0.6 ppm	LOAEC: 20.1 ppm; delayed upper respiratory tract particle clearance whereas clearance from the deep lung was not affected.	-	Anonymous27
Method: investigation of ultrastructural histological changes in different regions of the respiratory tract; Non-guideline; Non-GLP; Reliability of 2.	Rats (Wistar)/ ♂; 5 gnotobiotic rats, 5 further gnotobiotic control rats.	Sulfur dioxide (CAS 7446-09-5) 8-h exposure: whole body Conc.: 800 ppm (2.16 g/m ³)	LOAEC: 800 ppm; upper trachea represented the most affected region of epithelial damage; gradient of decreasing cellular damage was observed in the tracheobronchial tree in peripheral direction accompanied by decreasing mitotic and metabolic activity of surviving cells.	-	Anonymous28

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Summary table of animal studies on acute inhalation toxicity with sulfur dioxide					
Method, Guideline, GLP status, Reliability	Species, Strain, Sex, No/group	Test substance, form (gas, vapour, dust, mist) Actual and nominal concentration, Type of administration (nose only / whole body/ head only)	Results LC ₅₀	Remarks (e.g. major deviations)	Reference
Method: investigation of time-dependence and reversibility of histological changes in nose tissues; Non-guideline; No data on GLP; Reliability: 2 (reliable with restrictions).	Mice (ICR) / ♀; 56 healthy mice: 44 mice were exposed to SO ₂ , 12 were used as controls	Sulfur dioxide (CAS 7446-09-5) 30-, 60- and 120-min exposure: whole body Conc.: 20 ppm	LOAEC: 20 ppm; severe injury of respiratory and olfactory epithelium of the nasal cavity (depending on exposure/observation time); The changes were primarily degenerative rather than inflammatory.	-	Anonymous29
Method: investigation of blood pressure; Non-guideline followed; Non-guideline; No data on GLP; Reliability: 2 (reliable with restrictions).	Rats (Wistar) / ♂; 10/conc. group (3 exposure groups and 3 control groups)	Sulfur dioxide (CAS 7446-09-5) 6-h exposure: Whole body Conc.: 28.6 ± 1.0 mg/m ³ (about 10 ppm) 57.3 ± 2.0 mg/m ³ (about 20 ppm) 114.4 ± 2.0 mg/m ³ (about 40 ppm)	NOAEC: 10 ppm; LOAEC: 20 ppm; Dose-dependent significant decreases of blood pressure in comparison to control values.	-	Anonymous31
Sodium metabisulfite: Studies with sodium metabisulfite aerosol in mice (Anonymous33), sodium sulfite aerosol in mice (Anonymous34), rats (Anonymous35), and guinea pigs (Anonymous36) were not conducted to derive an LC ₅₀ .					

10.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

The LC₅₀ value of 965 ppm < LC₅₀ < 1168 ppm originates from the most reliable study (eq. to Klimisch score of 2) available for sulfur dioxide (Anonymous17). Although the study was conducted prior to OECD 403 it is considered sufficient for classification and labelling. No further acceptable study reporting LC₅₀ values for sulfur dioxide is available. At 965 ppm and higher, the animals presented respiratory difficulties followed by exhaustion and death. A LC₅₀ value of 1041 ppmV was estimated by the DS post-hoc using log-probit regression. The value requires classification according to Reg (EC) No. 1272/2008: Acute Tox. 3, H331: Toxic if inhaled.

10.3.2 Comparison with the CLP criteria

The following table presents the critical results for acute inhalative toxicity used for classification and labelling and further lists the criteria required from CLP regulation.

Toxicological result*	CLP criteria
<p>Sulfur dioxide: rat, M:</p> <p>Inhalation LC₅₀: 965 ppm < LC₅₀ < 1168 ppm (approx. 2.57 mg/L < LC₅₀ < 3.11 mg/L)</p> <p>Based on log-probit regression an ATE of 1041ppmV is proposed.</p>	<p>Cat. 4 (H332): 2500 < LC₅₀ ≤ 20000 (ppmV)</p> <p>Cat. 3 (H331): 500 < LC₅₀ ≤ 2500 (ppmV)</p> <p>Cat. 2 (H330): 100 < LC₅₀ ≤ 500 (ppmV)</p> <p>Cat. 1 (H330): LC₅₀ ≤ 100 (ppmV)</p>

*Only studies used for classification are listed.

10.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Based on the results listed above, the proposed classification and labelling for the inhalation LC₅₀ endpoint is:

Sulfur dioxide:

Acute Tox. 3, H331: Toxic if inhaled. (ATE: 1041 ppmV)

10.4 Skin corrosion/irritation

Hazard class not assessed in this dossier.

10.5 Serious eye damage/eye irritation

Sulfur dioxide has a harmonised classification: Skin Corr. 1B; H314: Causes severe skin burns and eye damage.

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10.6 Respiratory sensitisation

For justification on a Read-across from metabisulfite, please refer to section 10.

Table 10: Summary table of animal studies on respiratory sensitisation

Sulfur dioxide/Sodium metabisulfite

Method, Guideline, GLP status, Reliability	Species, Strain, Sex, No/group	Test substance Dose levels, Duration of exposure	Results	Reference
Method: <i>in vivo</i> (specific investigation of effect of low-level sulfur dioxide exposure on allergic sensitisation to inhaled allergen); Non-guideline; No data on GLP; Reliability: 2 (type of study)	Guinea pig (Dunkin-Hartley); (A) ovalbumin (OA) and sulfur dioxide exposure, N=12 ♂, (B) sulfur dioxide exposure, N=12 ♂, (C) ovalbumin exposure, N=11 ♂, Controls: (D) saline exposure, N=7 ♂	Sulfur dioxide; 0.1 ppm sulfur dioxide on 5 consecutive days, 5 h/d (Groups A and B) and 0.1 % ovalbumin aerosol in exposure chamber for 45 min on day 3, 4 and 5 (Groups A and C).	No allergic response was observed in case of SO ₂ exposure only. The OA-and SO ₂ -exposed group showed airway obstruction. Results confirm findings with respect to SO ₂ and OA reported by Anonymous2 (1988).	Park et al., 2001; Ann Allergy Asthma Immunol.. 86:62-7
Method: <i>in vivo</i> (specific investigation of effect of sulfur dioxide on allergic sensitisation to inhaled allergen); Non-guideline; Non-GLP; Reliability: 2 (type of study)	Guinea pig (Perlbright-White); Three groups of animals were exposed to different concentrations: (A): N=6 ♀ (B): N=5 ♀ (C): N=6 ♀ (D): Control group N=14 ♀	Sulfur dioxide followed by ovalbumine exposure on day 3; Conc. of SO ₂ : (A): 0.1 ± 0.05 ppm (B): 4.3 ± 1.2 ppm (C): 16.6 ± 3.5 ppm; Exposure duration: 8 hours on 5 consecutive days.	Low concentrations of SO ₂ can facilitate local allergic sensitisation against ovalbumine in guinea pigs. 67 – 100 positive bronchial reactions to inhaled OA, depending of SO ₂ concentrations, compared to 7 % in controls without prior SO ₂ exposure.	Anonymous2
Method: <i>in vivo</i> (specific investigation of effect of sulfur dioxide on allergic sensitisation to inhaled allergen and effect of anti-inflammatory agents); Non-guideline; GLP; Reliability: 2 (type of study).	Guinea pig (Perlbright-White); - Number of animals: N = 6 ♀/group; 4 groups - Controls: N = 6 ♀	Sulfur dioxide; Exposure: 5 ppm sulfur dioxide on 5 consecutive days, 8 hours/day, in exposure chamber; Concomitant exposure to ovalbumin and anti-inflammatory agents: - indomethacin; - methylprednisolone; - nebulized nedocromil sodium - control: clean air and OA	Sulfur dioxide-induced enhancement of allergic sensitisation to ovalbumine was inhibited by treatment with anti-inflammatory agents simultaneously to sulfur dioxide exposure (mechanism not investigated).	Anonymous3

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Method, Guideline, GLP status, Reliability	Species, Strain, Sex, No/group	Test substance Dose levels, Duration of exposure	Results	Reference
Method: <i>in vivo</i> (specific investigation of effect of 5 ppm sulfur dioxide exposure on allergic sensitisation to injected allergen), Non-guideline; No data on GLP; Reliability: 2 (type of study).	Guinea pig (Hartley); 12 ♂/group, 3 groups in total	Sulfur dioxide (or NO ₂); Mean concentration: 4.92 ± 0.51 ppm; (NO ₂ : 4.76 ± 0.48 ppm Duration of exposure: 4 h/d, 5 d/w; 30 exposures; Simultaneous exposure to <i>Candida albicans</i> (sensitisation agent) from the 1 st day of treatment.	Exposure to SO ₂ increased sensitisation rate to <i>C. albicans</i> resulting in significantly increased numbers of animals with prolonged expiration and/or inspiration and in a decrease of respiratory rate. Delayed-type dyspneic symptoms even lead to mortality in 3/12 sulfur dioxide exposed animals.	Anonymous ⁴

Table 11: Summary table of human data on respiratory sensitisation

(Please refer to section 12 for further details (tables and figures) on key studies.)

Type of data/report, Reliability	Test substance	Relevant information about the study	Observations	Reference
Published study Reliability: 2 (reporting deficiencies). Key study	Sodium metabisulfite , oral administration in capsules: 0, 5, 10, 25, 50, 100, 200 mg, concentration increase every 30 min	Single-blind study design: 44 patients with history of sulfite sensitive asthma, 27 asthmatics without sulfite sensitivity, 8 controls without asthma	39 % of patients with a history of sulfite-sensitive asthma showed significant bronchoconstriction after ingestion of metabisulfite (PD ₂₀ FEV ₁ : 34±56 mg; min: 5, max: 200 mg; n=17); specificity: 100 %, sensitivity: ca. 40 % Onset of SMB reaction minimal 60, maximal 210 min, average 150 min.	Hein et al. 1996 Pneumologie 50/6: 394-8
Published study Reliability: 2 (reporting deficiencies). Key study	Metabisulfite (MB) (sodium or potassium) oral administration: 50 mg in 30 mL 0.5 % citric acid (pH2) and SO₂ inhalation : 0.5; 1.5; 5 ppm (or 3 ppm if large decrease in	Single-blind, placebo controlled 3 groups of 10 subjects, each 1: asthmatics sensitive to oral MB, 2: asthmatics, not sensitive to oral MB, 3: non-asthmatics controls	% fall after MB: Group 1: 35±14; group 2: 6±6; group 3: 5±3 Pc20 SO ₂ (ppm): group 1: 1.19±0.78 (0.5 – 2.9); group 2: 2.3±1.42; group 3: >5; Pc20 SO ₂ does not correlate with	Delohery et al. 1984 Am Rev Respir Dis; 130:1027-32

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Type of data/report, Reliability	Test substance	Relevant information about the study	Observations	Reference
	PEFR occurred) for 4 min on separate days	Endpoint 20 % decrease in PEFR (Pc20, SO ₂ , PD ₂₀ MB)	MB PEFR fall. Asthmatics whose asthma is provoked by ingestion of acid MB solutions, are not supersensitive to inhaled SO ₂ gas SO ₂ sensitivity does not correlate with histamine reactivity.	
Published study Reliability: 2 (reporting deficiencies). Key study	Potassium metabisulfite: aerosol challenge: 0.05; 0.5; 5.0 mg/mL; 2 mL inhaled Oral challenge: 10, 25, 50 mg	Objective: Responses in 8 asthmatic patients (2M/6F) to aerosolised metabisulfite Endpoint: 50 % change in specific airway resistance	Bronchospastic response at 1.2 ppm Aerosol challenge 2/8 negative; 3/8 positive at 0.5 mg/mL, and 5.0 mg/mL, respectively 3/8 positive reactors to 0.5 mg/mL aerosol reacted at 10, 25, 50 mg oral SMB, respectively. All patients negative in prick tests.	Schwarz and Chester 1984; J Allergy Clin Immunol. 74:511-3
Published study (Survey (asthmatic and non-asthmatic patients; inhalation exposure route), reliability not assignable	Sodium metabisulfite (aerosol): in increasing doubling concentrations (0.3 to 160 mg/ml) in normal saline	13 asthmatic (9M, 4F) and five atopic non-asthmatic subjects, , endpoint: PD ₂₀ FEV ₁	>20 mg/ml metabisulfite: Mild irritation and cough noticed by all volunteers. 3 subjects (2 asthmatics, 1 non-asthmatic) did not achieve PD ₂₀ no further response. Inhalation of > 160 mg/ml of metabisulfite not possible due to cough and irritation. Molar Sign. linear correlation between , PD ₂₀ FEV ₁ metabisulfite and methacholine (r = 0.714; p < 0.05) but	Nichol et al. 1989; Thorax. 44: 1009-1014

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Type of data/report, Reliability	Test substance	Relevant information about the study	Observations	Reference
			<p>potency of metabisulfite approx.. 6x lower than of methacholine. PD20 FEV₁ response reproducible over days and weeks.</p>	
<p>Published case reports Reliability: 2 (type of study: case report).</p>	<p>Sulphites, unspecified Case 2: sodium bisulfite</p>	<p>4 cases of occupational exposure to sulfites Case 1: F, 36 y, involved in production of beverages and oenology Case 2: M, 41 y, printer, atopic history, sulfite related asthma Case 3: sex and age not specified, press photographer Case 4: sex not specified, 25 y, atopic, console operator, history,</p>	<p>Case 1: Rhinorrhoea, anosmia, ageusia negative skin tests, blood basophilia, nasal eosinophilia, IgE negative Case 2: Obstructive rhinorrhoea, anosmia, ageusia, basophilia, asthma, eczema Case 3: urticaria, IgE negative, basophilia, histamine release Case 4: asthma (severe crisis), no eosinophilia, positive for basophilie, obstruction not beta2 reversible, sulfite specific IgE increased</p>	<p>Vallon et al. 1995. Allergie et Immunologie 27/3:83-7</p>
<p>Published case reports Reliability: 2 (type of study: case report).</p>	<p>Sodium bisulfite, sodium metabisulfite Oral challenge: 0.1, 0.5, 1, 5 mg SMB in 5 mL water</p>	<p>Patient (1F, age: 18 y) with perennial asthma and intra-alveolar infiltration of eosinophils and histiocytes – diagnosis: chronic eosinophilic pneumonia Symptom treatment with isoeharine aerosol and metoclopramide (containing sodium bisulfite resp. SMB). Double-blind oral challenge with SMB</p>	<p>After treatment intubation for acute respiratory failure required. Oral challenge: 10 min following 5 mg SMB, FEV₁ decreased 52 %</p>	<p>Twarog et al. 1982. JAMA 248: 16:2030-1</p>
<p>Published study: oral challenge with sulfites</p>	<p>Potassium bisulfite, capsule: 1, 5, 10, 25, 50, 100, 200 mg) at 30 min intervals</p>	<p>56 asthmatic children (35M/21F) age: 6 – 14 y (10.2 ± 3.4)</p>	<p>Positive reactions after challenge with solution: 2 of 56</p>	<p>Boner et al. 1990; J. Allergy Clin. Immunol. 85:479-83</p>

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Type of data/report, Reliability	Test substance	Relevant information about the study	Observations	Reference
Reliability: 2 (reporting deficiencies).	solution: 30 mL of 0.5 % citric acid with 1, 10, 25, 50, 100 mg at 15 min intervals	Pulmonary function tests at 2, 5, 15 min following each dose and at 30, 60, 90 min following dosing Endpoint: Pc20 FEV ₁	children (3.6 % 1x at 50 mg, 1x at 100 mg) Capsules: 4 positive reactions at 200 mg	
Published study Reliability: 2 (reporting deficiencies).	Potassium metabisulfite in capsules	Prospective single-blind screening study: 120/83 non-/steroid dependent asthmatics Endpoint: Pc20 FEV ₁	5 non-steroid dependent and 9 steroid dependent with positive reactions Best estimate of prevalence of sulfite sensitivity in asthmatics is 3.9 %	Bush et al. 1986. Am J Med. 81: 816-820
Published study Reliability: 2 (reporting deficiencies).	Sodium metabisulfite , potassium metabisulfite, sodium bisulfite (and tartrazine)	40 patients with clinical diagnosis of chronic urticaria: 29 F; 7M; 4-62 y	63.8 % (23/36) with positive oral challenge tests 36.1 % (13/36) to sodium metabisulfite, 33.3 % (12/36) to sodium bisulfite and 30.5 % (11/36) to potassium metabisulfite. (47.2 % (17/36) positives to tartrazine)	Jimenez-Aranda et al. 1996 Rev Alerg Mex 43/6:152-6
Published study Reliability: 2 (reporting deficiencies).	Sodium metabisulfite (SMB) diluted in lemon juice: 1, 10, 25, 50, 75, 100, 150 mg MBS in 15 mL of lemon juice	Oral challenge tests with sodium metabisulfite diluted in lemon juice at pH 4.2 and at pH 3.3 if no reaction at pH 4.2). Spanish and Dutch pickled onions used for oral challenge in 7/9 patients. Total # of patients: 18 (10M/8F; age 12-23 y)	MBS, pH 4.2: positive response in 6 patients (33.3 %); at pH 3.3: positive 3/12 patients. 3/7 positive responses to Spanish pickled onions (SO ₂ conc: 765 and 1182 ppm) no reaction against Dutch pickled onions; SO ₂ conc.: 200 ppm). Inhalation of SO ₂ while consuming food with high SMB conc. with acid pH is considered as critical conditions	Gastaminze et al. 1995. Clin Exp Allergy. 25(8):698-703.
Case reports				

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Type of data/report, Reliability	Test substance	Relevant information about the study	Observations	Reference
Published case report Reliability: 2 (type of study: case report).	Potassium metabisulfite	Case report and double blind placebo-controlled food challenge, 49 y male patient	Case of severe hypotension after food ingestion Anaphylaxis following potassium metabisulfite challenge (300 mg; approx. 4 mg/kg bw)	Cifuentes et al. 2013; Int. Arch. Allergy Immunol. 162/1:94-6
Published case report Reliability: 2 (type of study: case report).	Sulphites in food and wine, challenge with potassium metabisulfite: 1, 5, 10, 25, 50, 100 mg in capsules, skin prick test with 10 and 1 mg/mL	F, age: 22 y with reported 2-y-history of episodes of urticaria-angiooedema Challenge test: sequential administration at 30 minutes intervals, FEV ₁ and blood pressure determined every 10 min	Urticaria and angioedema of face, neck, upper thorax, dysphonia without asthma skin prick test: negative oral challenge: positive at 25 mg dose: urticaria on face and upper thorax after 12 min, nasal itching, rhinorrhoea, dysphonia, relief of symptoms after s.c. adrenaline injection Prevalence in asthmatics: 2 - 6 %	Belchi-Hernandez et al. 1993; Ann Allergy; 71/3:230-2

10.6.1 Short summary and overall relevance of the provided information on respiratory sensitisation

Sulfur dioxide (SO₂) and sulfites including sodium metabisulfite have been recognised to induce bronchial hyperresponsiveness (BHR), in sensitive and healthy persons (e.g. van Schoor and Pauwels 2000 and tables above). Subjects with mild asthma develop airflow limitation at a lower threshold concentration of SO₂ and with greater magnitude than do non-asthmatic subjects (Sheppard et al., 1980). In an animal study, repeated exposure of guinea pigs to sulfur dioxide (0.1 ppm) alone did not result in a sensitisation response, although animals pretreated with ovalbumin developed asthmatic reactions (Park et al., 2001). Similar findings were observed by Anonymous₂, Anonymous₃ and Anonymous₄.

Cases of sulfite induced asthma (mild and life-threatening) are described in literature for decades in the general population and in occupationally exposed workers (e.g. van Schoor et al. 2000, John and Linn 2010). Severe life-threatening asthmatic, urticarial and anaphylaxis-like attacks have been documented after exposure to sulphiting agents while eating a restaurant meal, different foods, drinking wine or after receiving parenteral medication containing sulfites as preservatives (Gillman, 1982; Schwartz and Chester, 1984, Delohery et al., 1984; Nichol et al., 1989; Wüthrich and Huwyler, 1989; Wright et al., 1990; Wüthrich et al., 1993; Vallon et al., 1995; Jiménez-Aranda et al., 1996; Gastaminza et al., 1995; Kounis et al., 2014; Cifuentes et al., 2013; Cussans et al., 2015). Patients, who also have had asthma attacks and gastrointestinal distress after eating restaurant meal, were mostly positive to sodium metabisulfite challenge by inhalation, although some persons were negative by aerosol and oral challenge despite their history (Schwartz and Chester, 1984). Some asthmatic persons can develop airways obstruction to ingested sodium metabisulfite while the other asthmatics do not (Delohery et al., 1984). Nichol et al. (1989) reported that asthmatic and non-asthmatic but atopic persons reacted similarly to challenge by sodium metabisulfite aerosol in a dose-dependent manner. It seems that inhaled sulfite aerosols can induce asthma in sensitive persons, although this effect is not restricted to patients with a clinical history of sulfite sensitivity or to subjects who demonstrated sensitivity to oral ingestion of metabisulfite (van Schoor et al., 2000; Schwartz and Chester, 1984).

Cases of metabisulfite induced asthma in occupationally exposed persons have been reported in radiographer (Merget and Korn, 2005), wine tester, pressman, photographer (Vallon et al., 1995), technician handling chemicals in a water treatment plant (Valero et al., 1993) and in persons who worked in fishing and fish processing industry (Steiner et al., 2008; Pougnet et al., 2010; Uriarte et al., 2015). The patients reacted positive to inhalation challenge by sodium metabisulfite (Merget and Korn, 2005; Steiner et al., 2008; Uriarte et al., 2015), whereby control non-occupationally exposed asthmatic persons could also possess a high susceptibility to sodium metabisulfite and sulfur dioxide (Merget and Korn, 2005).

In conclusion, exposure to aerosolized sodium metabisulfite can induce asthma-like symptoms mostly in sulfite-sensitive population. Sensitisation of healthy subjects is also described, especially following frequent exposure e.g. in occupational settings.

Furthermore, sulfur dioxide exposure elicitates asthma-like symptoms in sulfite-sensitive populations and/or asthmatics.

According to Guidance on the Application of the CLP Criteria (Version 4.1 – June 2015), “*Substances shall be classified as respiratory sensitizers if there is evidence in humans that the substance can lead to specific respiratory hypersensitivity. This is further described in the CLP Annex I, 3.4.2.1.2*”

“Annex I: 3.4.2.1.2 Human evidence

Annex I: 3.4.2.1.2.1. Evidence that a substance can lead to specific hypersensitivity will normally be based on human experience. In this context, hypersensitivity is normally seen as asthma, but other hypersensitivity reactions such as rhinitis/conjunctivitis and alveolitis are also considered. The condition will have the clinical character of an allergic reaction. However, immunological mechanisms do not have to be demonstrated....”

The underlying mode of action is still under debate. Different mechanisms may be involved in SO₂-induced asthma which at least partly differs in humans and animals. As long as an allergic mechanism cannot be excluded, the afore-mentioned criteria from CLP guidance (2015) apply. Inflammatory processes are clearly

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involved in hypersensitivity reactions (e.g. see citation below). Classification for respiratory irritation alone is not sufficient to protect vulnerable persons.

Possible mode of actions of sulfur dioxide were described by US EPA and are cited here as follows (US EPA Report: Integrated Science Assessment for sulfur oxides – Health Criteria, September 2008 and references cited therein):

“In humans, the mechanisms responsible for SO₂-induced bronchoconstriction are not fully understood. In non-asthmatics, near complete attenuation of bronchoconstriction has been demonstrated using the anticholinergic agents atropine and ipratropium bromide (Snashall and Baldwin, 1982; Tan et al., 1982; Yildirim et al., 2005). However, in asthmatics, these same anticholinergic agents (Field et al., 1996; Myers et al., 1986), as well as short- and long-acting β 2-adrenergic agonists (Gong et al., 1996; Linn et al., 1988), theophylline (Koenig et al., 1992), cromolyn sodium (Myers et al., 1986), nedocromil sodium (Bigby and Boushey, 1993) and leukotriene receptor antagonists (Gong et al., 2001; Lazarus et al., 1997) only partially blocked SO₂-induced bronchoconstriction (see Annex Table D-1, (U.S. EPA, 1994c). That none of these therapies have been shown to completely attenuate the effects of SO₂ implies the involvement of both parasympathetic pathways and inflammatory mediators in asthmatics. Strong evidence of this was borne out in a study by Myers et al. (1986), in which asthmatic adults were exposed to SO₂ following pretreatment with cromolyn sodium (a mast cell stabilizer), atropine (a muscarinic receptor antagonist), and the two medications together. While both treatments individually provided some protection against the bronchoconstrictive effects of SO₂, there was a much stronger and statistically significant effect following concurrent administration of the two medications. It has been proposed that inflammation contributes to the enhanced sensitivity to SO₂ seen in asthmatics by altering autonomic responses (Tunnicliffe et al., 2001), enhancing mediator release (Tan et al., 1982) and/or sensitizing C-fibers and RARs (Lee and Widdicombe, 2001). Whether local axon reflexes also play a role in SO₂-induced bronchoconstriction in asthmatics is not known (Groneberg et al., 2004; Lee and Widdicombe, 2001; Widdicombe, 2003). However, differences in respiratory tract innervation between rodents and humans suggest that C-fiber mediated neurogenic inflammation may be unimportant in humans (Groneberg et al., 2004; Widdicombe and Lee, 2001; 2003).”

In addition to the observations indicating the presence of direct allergic reactions by exposure to SO₂ and metabisulfite, an important feature of the clinical syndrome asthma, the airway hyperresponsiveness (AHR) has to be considered as well. The variable part of AHR is associated with acute inflammation, the persistent component of AHR is connected with chronic inflammation and airway remodeling (Cockcroft and Davis, 2006). However, the mechanism of action is in both cases far from clear and can include factors such as mast cells and histamine release like in allergic reactions. Atopic IgE-mediated allergic responses are the most common inducers of AHR. The indirect stimuli such as chemicals inducing indirect AHR were considered to be more clinically relevant.

Acute toxicity inhalation studies are available and demonstrate clinical signs of AHR induced by SO₂ in dogs (Anonymous18; Anonymous20). Although these studies were attributed to the endpoint acute toxicity inhalation, the observation of AHR signs as a syndrome of asthma in this endpoint is not foreseen to be included by the CLH template nor is it in the endpoints respiratory irritation or respiratory sensitization. However, DS decided to assign AHR effects such as bronchoconstriction to Specific Target Organ Toxicity (STOT SE 3: Respiratory Tract Irritation) and propose classification for this endpoint. Moreover, AHR is a severe adverse outcome that should in any case be considered not only for risk assessment but also for classification and labelling (Cockcroft, D.W. and Davis, B.E., 2006).

10.6.2 Comparison with the CLP criteria

Toxicological result	CLP criteria
<p>Sulfur dioxide:</p> <p>-human data, metabisulfite oral administration and sulfur dioxide inhalation: : 0.5; 1.5; 5 ppm for 4 min on separate days (Delohery et al. 1984): Inhalation elicitation: \leq 0.5 ppm (1.3 mg/m³)</p>	<p><u>Category 1 :</u></p> <p>Substances shall be classified as respiratory sensitisers (Category 1) where data are not sufficient for sub-categorisation in accordance with the following criteria :</p>

Toxicological result	CLP criteria
<p>-human data, 4-8 % of asthmatics are intolerant to sulfites according to Hein et al. 1996. Prevalence of asthmatics in Europe: between 1.6 % in Romania and 7 % in France (OECD statistics 2012), corresponding to a prevalence of sulfite sensitive subjects between 0.064 and 0.56 %. The frequency of occurrence is only roughly estimated.- elicitation of asthma-like symptoms/bronchoconstriction following SO₂ inhalation</p> <p>- sulfur dioxide is used as an example of respiratory tract irritant substance in the Guidance on the Application of the CLP Criteria (2017, section 3.8.5.1.3., page 456), based on the broad, well documented human experience on irritating effect to respiratory system.</p> <p>- as described above, airway responses cannot be solely assigned to the corrosive properties of the substance already covered by Skin Corr 1 classification.</p> <p>Proposed classification as Respiratory Tract Irritant Cat. 3 (see section 10.11)</p>	<ul style="list-style-type: none"> - if there is evidence in humans that the substance can lead to specific respiratory hypersensitivity ; and/or - if there are positive results from an appropriate animal test <p><u>Sub-category 1A :</u></p> <ul style="list-style-type: none"> - Substances showing a high frequency of occurrence in humans; or a probability of occurrence of a high sensitisation rate in humans based on animal or other tests. Severity of reaction may also be considered. <p><u>Sub-category 1B :</u></p> <ul style="list-style-type: none"> - Substances showing a low to moderate frequency of occurrence in humans; or a probability of occurrence of a low to moderate sensitisation rate in humans based on animal or other tests. Severity of reaction may also be considered.

10.6.3 Conclusion on classification and labelling for respiratory sensitisation

Sulfur dioxide is considered not to be a sensitiser itself, but unequivocally exacerbates existing asthma in sulfite-sensitive populations and/or asthmatics by the inhalation route and after single exposure to concentrations ≤0.5ppm. Thereby, sulfur dioxide can cause asthma symptoms and breathing difficulties as described in hazard sentence H334: “*May cause allergy or asthma symptoms or breathing difficulties if inhaled.*”. As sulfur dioxide is not an allergen itself and requires an existing allergy is a prerequisite for the observed asthma symptoms, classification as respiratory sensitisation does not apply according to current CLP criteria and guidance. However, the DS would like to point out that the observed effects are not completely in line with the criteria in CLP regulation. The definition of sensitisation under CLP is quoted in the CLP guidance (2017, p 333) as follows:

“Annex I: 3.4.1.3. *For the purpose of section 3.4, sensitisation includes two phases: the first phase is induction of specialised immunological memory in an individual by exposure to an allergen. The second phase is elicitation, i.e. production of a cell-mediated or antibody-mediated allergic response by exposure of a sensitised individual to an allergen.*

Annex I: 3.4.1.4. *For respiratory sensitisation, the pattern of induction followed by elicitation phases is shared in common with skin sensitisation. [...].”*

In contrast, regarding the clinical character of the observed symptoms the following will apply (citation from CLP guidance 2017, p 333): “**Annex I: 3.4.2.1.2 Human evidence**

Annex I: 3.4.2.1.2.1. *Evidence that a substance can lead to specific hypersensitivity will normally be based on human experience. In this context, hypersensitivity is normally seen as asthma, but other hypersensitivity reactions such as rhinitis/conjunctivitis and alveolitis are also considered. The condition will have the clinical character of an allergic reaction. However, immunological mechanisms do not have to be demonstrated.*“

It is further noted that respiratory sensitisation may be induced not only by inhalation but also by skin contact (Dotson et al. 2015 as quoted from CLP guidance 2017).

In summary, sulfur dioxide does not meet the criteria given in the CLP regulation and respective guidance (see citation above) for respiratory sensitisation. Nevertheless, it should be evaluated how the hazard potential of substances inducing asthma-like symptoms through inducing airway-hyperresponsiveness, such as sulfur dioxide, can be adequately reflected by classification under the CLP regulation.

10.7 Skin sensitisation

For justification of Read-across from metabisulfite please refer to section 10. Moreover, case reports are published describing contact dermatitis from sodium metabisulfite suspected to be caused by sulfur dioxide evaporated from sodium metabisulfite solutions (e.g. Jacobs and Rycroft 1995, Vallon et al. 1995) and not by direct skin contact to the solution.

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Table 12: Summary table of animal studies on skin sensitisation

Method, Guideline, GLP status, Reliability	Species, Strain, Sex, No/group	Test substance, Vehicle, Dose levels, Route of exposure (topical/intradermal, if relevant), Duration of exposure	Results (EC3-value or amount of sensitised animals at induction dose)	Remarks (e.g. major deviations)	Reference
OECD 429 GLP; Reliability: 1	Mouse (NMRI / CrI:NMRI); 6 animals/group (♀).	Sodium metabisulfite (purity: 99.1 %); vehicle: Application: 25 µL on the dorsum of animal's left and right ears (10 % w/w, 25 % w/w, and 50 % w/w); Duration of exposure: 3 consecutive days)	Not sensitising: all stimulation index (SI) values are under the trigger values for C&L: 10 % w/w: SI: 0.854 (cell count); SI: 0.800 (lymph node weight); SI: 0.934 (ear weight) 25 % w/w: SI: 0.970 (cell count); SI: 1.200 (lymph node weight); SI: 1.086 (ear weight) 50 % w/w: SI: 0.878 (cell count); SI: 1.171 (lymph node weight); SI: 1.020 (ear weight)	Alternative endpoints were chosen: lymph node weight, lymph node cell count, ear weight, ear thickness: modified OECD 429, method according to Ehling et al. 2005 Study not considered a key study due to minor relevance regarding human exposure. Sufficient studies with human exposure available.	Anonymous1

Table 13: Summary table of human data on skin sensitisation (Please refer to section 12 for further details (tables and figures) on key studies.)

Type of data/report, Reliability	Test substance	Relevant information about the study	Observations	Reference
Published case series and literature review Key study	Sodium metabisulfite 2 %, later 1 % in petrolatum	Retrospective study with 2763 patients patch-tested between 1990 and 2010	124 (4.5 %) positive results (77F/47M), most frequently on the face and the hands, median age: 50; 13 cases (10.5 %) occupational exposure.	Garcia-Gavin et al. 2012; Contact Dermatitis 67:260-9
Published report Key study	Sodium metabisulfite and sodium sulfite	Prospective small study in a patient population patch tested with sodium sulfite 1 % pet. and SMB 1 % pet.	183 patients tested: 5.5 % (n=10) positive to sodium metabisulfite, 3.8 % (n=7) positive to sodium sulfite.	Oliphant et al. 2012 Contact Dermatitis 66/3:128-30
Published retrospective analysis of positive patch test cases Key study	Sodium metabisulfite (SMB); 1 % in petrolatum	1751 patients in a Contact Dermatitis Investigation Unit in Manchester, UK	71 (4.1 %) positive reactions, interpreted as allergic. 33/71 with identifiable source (group A), 38 with unknown sources (group B). 47	Madan, V., Walker, S.L., Beck, M.H. 2007, Contact Dermatitis; 57:173-6.

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Type of data/report, Reliability	Test substance	Relevant information about the study	Observations	Reference
			cases with known sources after reanalysis (3 %). Sensitization to sodim metabisulfite from parenteral solutions and occupational exposure from food handling may account for some of the otherwise unexplained positive patch test reactions.	
Published study	Sodium metabisulfite 1 % in petrolatum (1 % pet.), prick and intradermal testing with 10 mg/mL If positive: subsequently tested with sodium sulfite, sodium bisulfite 1 %/5 % pet, potassium metabisulfite 1 % pet.	2894 (953M/1941F) consecutive patients Incidence of delayed hypersensitivity (type IV allergy) in patients with eczematous dermatitis	50/2894 (1.7 % positive reactions), also positive after potassium metabisulfite and sodium bisulfite but only 2 (4 %) positive after sodium sulfite, no positive reaction after prick test or intradermal test or oral challenge with 30 and 50 mg sodium metabisulfite - 7 patients with occupational contact.	Vena et al. 1994; Contact Dermatitis. 31:172-5
Published retrospective study at Department of Occupational and Environmental Dermatology in Stockholm, Sweden	Sodium metabisulfite 2 % in petrolatum	1518 consecutive patients (839; 55.3 % F; 679, 44.8 % M) patch test	51/1518 patients (3.4 %) reacted positive to SMB	Kaaman et al. 2010; Contact Dermatitis. 63: 110-112
Retrospective case review	Sodium metabisulfite 2 % in petrolatum	1751 patients are patch tested to the standard series, including SMB [1 % in petrolatum (pet.)].	71/1751 patients (4.1 %) reacted positive to SMB	Madan et al. 2007. Contact Dermatitis. 63/2:110-112
Published study	Sodium metabisulfite, potassium metabisulfite, sodium bisulfite (and tartrazine)	40 patients with clinical diagnosis of chronic urticaria: 29 F; 7M; 4-62 y	63.8 % (23/36) in positive oral challenge tests 36.1 % (13/36) to sodium metabisulfite, 33.3 % (12/36) to sodium bisulfite and 30.5 % (11/36) to potassium metabisulfite. (47.2 % (17/36) positives to tartrazine)	Jimenez-Aranda et al. 1996 Rev Allerg Mex 43/6:152-6
Case reports (probably IgE-mediated allergic reactions)				
Published case report	Potassium metabisulfite	Case report and double blind placebo-controlled food challenge, 49 y male patient	Case of severe hypotension after food ingestion Anaphylaxis following potassium metabisulfite challenge (300 mg; approx.. 4 mg/kg bw)	Cifuentes et al. 2013; Int. Arch. Allergy Immunol. 162/1:94-6

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Type of data/report, Reliability	Test substance	Relevant information about the study	Observations	Reference
Published case report	Sulfites in food and wine, challenge with potassium metabisulfite: 1, 5, 10, 25, 50, 100 mg in capsules, skin prick test with 10 and 1 mg/mL	F, age: 22 y with reported 2-year-history of episodes of urticaria-angioedema Challenge test: sequential administration at 30 minutes intervals, FEV ₁ and blood pressure determined every 10 min	Urticaria and angioedema of face, neck, upper thorax, dysphonia without asthma skin prick test: negative oral challenge: positive at 25 mg dose: urticaria on face and upper thorax after 12 min, nasal itching, rhinorrhoea, dysphonia, relief of symptoms after s.c. adrenaline injection Prevalence in asthmatics: 2 - 6 %	Belchi-Hernandez et al. 1993; Ann Allergy; 71/3:230-2
Published case reports	Potassium metabisulfite 10 and 50 mg oral challenge	4 asthmatic patients acutely sensitive to potassium metabisulfite (present in restaurant food)	Severe wheezing, chest tightness, flushing, weakness + 1 case of generalised urticarial, angioedema of the tongue and constriction of the chest.	Gillman 1982; Epitomes – Allergy 137/2: 120-1
Published case report	Sodium metabisulfite 1 % in patch test	54 y, M with 6-week history of a non-pruritic rash affecting axillae and groins following food consumption in restaurants	Positive reaction to 1 % SMB in patch test According to authors: first reported case of type IV allergy following consumption of high-sulfite diet.	Cussans et al. 2015 Contact Dermatitis; Jun 2015 (epub)
Case report + oral and skin provocative tests	Sodium metabisulfite 10 mg/mL in PBS in patch test; Prick and intradermal testing with 10-fold serial dilutions. Oral challenge: 1, 5, 10, 25, 50, 100, 200 mg SMB	34 y, F with of metabisulfite-induced anaphylaxis : convincing evidence of an IgE-mediated mechanism of action	Symptoms: urticaria, angioedema, nasal congestion, and apparent nasal polyp swelling following provocative challenge with sodium metabisulfite. Skin test to metabisulfite was positive as was a basophil histamine release test when the patient's cells were incubated with metabisulfite. Oral challenge test with 50 mg SMB resulted in angioedema, urticarial, nasal congestion. After 3 rd oral challenge reactions occurred already with 1 mg SMB and 10 mg SMB in 4 th and 5 th oral challenge after 6 months.	Sokol and Hydick, 1990 Annals of Allergy 65:233-238

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Type of data/report, Reliability	Test substance	Relevant information about the study	Observations	Reference
Case report	Sodium metabisulfite; oral challenge with single dose of 50 mg SMB	47 y, M with recurrent severe episodes of acute urticarial, angioedema and dyspnoea. + Placebo-controlled oral challenge test with 50 mg SMB resulted in an acute urticaria attack.	Placebo-controlled oral challenge test with 50 mg SMB resulted in an acute urticaria attack.	Wüthrich et al. 1993. Dermatology 187: 290-292

Reliability of the studies is “not assignable” according to Klimisch, because no OECD guideline was followed. However, all listed studies are considered reliable from the scientific point of view. PEF_R: Peak expiratory flow rates, PD₂₀ FEV₁: provocative dose that produce 20 % decrease in FEV₁, SMB: Sodium metabisulfite.

10.7.1 Short summary and overall relevance of the provided information on skin sensitisation

Sodium metabisulfite is widely used as an antioxidant in oral, topical, and parenteral pharmaceutical formulations; it is also widely used in food products (Rowe et al., 2009) and cosmetics (Nair and Elmoore, 2003). Although it is extensively used in a variety of preparations, sodium metabisulfite and other sulfites have been associated with a number of severe to fatal adverse reactions. There are reports of hypersensitivity, anaphylaxis, and even death from Kounis syndrome from sulfite administration (Kounis et al., 2014). Anaphylactoid shock has been reported during epidural anesthesia for cesarean section, in which the responsible agent was metabisulfite, as additive agent of adrenaline-containing local anesthetic (Soulat et al., 1991, cited in Kounis et al., 2014). The reactions are usually hypersensitivity-type reactions and include bronchospasm, angioedema, anaphylactoid reactions, urticaria, and asthmatic attacks (Jacobs and Rycroft, 1995; Wüthrich et al., 1993). Allergy to sulfite antioxidants is estimated to occur in 5–10 % of asthmatics, although adverse reactions may also occur in non-asthmatics with no history of allergy (Rowe et al., 2009). According to Nair and Elmoore (2003) between 2 % and 5 % of asthmatics are sulfite-sensitive.

Sokol and Hydick (1990) reported a case of a patient with a history of allergic rhinitis who demonstrated anaphylactic clinical reaction to sodium metabisulfite after eating a restaurant meal. The patient demonstrated urticaria, angioedema, nasal congestion, and apparent nasal polyp swelling following provocative challenge with sodium metabisulfite. Skin test to metabisulfite was positive in all cases (Sokol and Hydick, 1990). Sokol and Hydick presented also a literature review of allergic IgE-mediated reactions in sensitive individuals. IgE mediated nature of basophil activation was also detected in patients with sulfite intolerance (Saint-Laudy et al., 1994). Wüthrich and Huwyler (1994) suggested also IgE-dependent mechanism of allergic reactions in their patients, while Belchi-Hernandez et al. (1993) found that IgE mediated mechanism was not involved in eliciting of urticaria -angioedema, nasal itching, rhinorrhea, and dysphonia in a patient who consumed sulfite containing foods and drinks. They believe that the stimulation of cholinergic receptors, either directly by sulfites or by accumulation due to partial sulfite oxidase deficiency, could cause the clinical manifestations of sulfite-induced allergic reactions (Belchi-Hernandez et al., 1993). The IgE-mediated allergy has not been demonstrated either in a recent study in a patient who reacted with anaphylaxis (severe hypotension) after consuming sulfite containing foods (Cifuentes et al., 2013). The patient reacted with anaphylaxis to potassium metabisulfite in an oral provocative test. In the last study, the patient had a diagnosis of monoclonal mast cell activation syndrome (MCAS) and therefore, the authors suggest that monoclonal MCAS may be involved in the mechanism of sulfite-intolerance (Cifuentes et al., 2013).

Other cases of severe, life-threatening asthmatic and urticarial reactions are described in asthmatic patients after ingestion of wine, salads and other foods containing sulfites (Gillman, 1982; Wüthrich and Huwyler, 1989; Wüthrich et al., 1993; Jiménez-Aranda et al., 1996). All the patients with chronic urticaria and asthma reacted positively to sodium metabisulfite in oral provocation test. Furthermore, a case of a type IV systemic allergic reaction to dietary sulfites is reported in a patient who had a high dietary intake of sulfite-rich foods (Cussans et al., 2015).

Roberts et al. (2012) proposed a probable mechanism for the in cutaneo modification of proteins by sodium metabisulfite which involves the sulfite di-anion acting as a nucleophile towards electrophilic centres in proteins. This is a rare mechanism, as most known skin-sensitizing chemicals behave as electrophiles.

Sodium metabisulfite is present as antioxidant in oral, topical and parenteral medicines (Riemersma et al., 2004). In this regard, several cases of contact allergic reaction to local anesthetics containing sodium metabisulfite are reported in sensitive persons: two cases of Burning Mouth Syndrome in two patients who underwent several dental interventions (Levanti et al., 1996) and in a patient receiving an anaesthetic injection for a biopsy (Riemersma et al., 2004). Other cases of contact sensitivity have been attributed to the use of hydrocortisone, hydroquinone (i.e. bleaching cream), ketoconazole creams as well as Trimovate® and Timodine® creams, in which sodium metabisulfite serves as a preservative (Madan et al. 2007; Huang and Chu, 2007). Sodium metabisulfite produced positive reactions in a patient under patch test after use of cosmetic creams (Malik et al., 2007).

Cases of occupational contact dermatitis are described in photographers, in a pharmaceutical technician, baker, caterer, salad maker, wine producer, agronomist, carpenter, chemical factory worker, radiographer and hairdresser (Vena et al., 1994; Jacobs and Rycroft, 1995; Lee and Nixon, 2001; Merget and Korn, 2005; Madan

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et al., 2007; Aalto-Korte et al., 2009; Madan and Beck, 2009; Sasseville and El-Helou, 2009). All the patients reacted positively to sodium metabisulfite in patch test. Madan and Beck (2009) believe that allergic skin reactions point more to a diagnosis of contact allergy rather than irritancy.

The incidence of delayed hypersensitivity reactions to sodium metabisulfite was investigated in several studies in a large number of patients. Vena et al. (1994) present results of patch testing of 2894 eczematous patients. Positive patch test to sodium metabisulfite was considered to be high: 50 out of 2894 subjects (1.7 %) reacted positively (Vena et al., 1994). The dermatitis was considered to be occupational in 7 cases, while only 5 out of the 43 non-occupational cases were considered to be relevant. According to the authors, the relevance of positive reactions is difficult to establish due to the ubiquity of the substance in drugs and foods. In another study of Madan et al. (2007) 71 out of 1751 patients (4.1 %) reacted positively to sodium metabisulfite, whereby 33 (46.5 %) were originally reported as relevant and 38 (53.5 %) were of unexplained relevance. A careful re-analysis of data by the authors revealed a higher incidence of potentially relevant cases due to sodium metabisulfite as it firstly was interpreted: cases of 47 patients were retrospectively regarded as relevant (instead of 33 after first analyses). In 2007, patch test positivity of 6.6 % (8 persons) to sodium metabisulfite was described in a consecutive series of 117 patients in Ireland (Malik et al., 2007; Davies and Johnson, 2011). 4 cases were considered relevant (3.4 %). In a retrospective study in 1518 patients with hand eczema, sodium metabisulfite produced positive reaction in 3.4 % of subjects in patch test (Kaaman et al., 2010). The majority of incidences could probably be ascribed to occupational exposure, although the relevance of positive cases was difficult to establish because not all patient records enabled a complete evaluation. In a cross-sectional study in 63 workers with occupational contact dermatitis at two Indonesian tanneries, sodium metabisulfite was found to be occupationally relevant sensitizer (2.6 % persons showed positive skin reactions) (Febriana et al., 2012). Garcia-Gavin and coworkers (2012) analysed results of patch testing of patients from 1990 to 2010 in a retrospective study and found that 124 (4.5 %) of 2763 were positive to sodium metabisulfite. Of these, 76 persons (61.3 %) reacted only to sodium metabisulfite, while the others presented one or more concomitant positive test reactions. The reactions were considered relevant in 80 cases of which 11 were occupational. A relationship of allergenicity of sodium metabisulfite and sodium sulfite was investigated in a study with 180 patients (Oliphant et al., 2012). The authors found that the majority of patients with positive reactions to sodium metabisulfite were also positive to sodium sulfite. It should be mentioned that sodium metabisulfite is part of the standard series of substances used in patch testing (e.g. Madan et al. 2007).

10.7.2 Comparison with the CLP criteria

The following table presents the critical results for skin sensitisation used for classification and labelling and further lists the criteria required from CLP regulation.

Toxicological result	CLP criteria
<p>Sulfur dioxide:</p> <p>Elicitation and Sensitisation cannot be differentiated on the basis of available data. Value for elicitation/sensitisation:</p> <p>dermal: $\leq 1\%$ (lower concentrations not tested in patch test), no elicitation at 10 mg/mL in prick/intradermal testing.</p> <p>Values represent LOAELs from a considerably study population in peer reviewed scientific journals.</p> <p>High frequency of occurrence in humans (2-5% unselected patients) and 5–10 % of asthmatics</p> <p>According to CLP, high frequency of occurrence: $\geq 1\%$ in unselected dermatitis patients,) classifies as Skin Sens 1A.</p>	<p><u>Category 1 :</u></p> <ul style="list-style-type: none"> – if there is evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons, or – if there are positive results from an appropriate animal test <p><u>Sub-category 1A :</u></p> <ul style="list-style-type: none"> – Substances showing a high frequency of occurrence in humans; or a probability of occurrence of a high sensitisation rate in humans based on animal or other tests. Severity of reaction may also be considered high frequency criteria :. <ul style="list-style-type: none"> - 0.2 % general population study - 1.0 % dermatitis patients (unselected, consecutive) - 2.0 % selected dermatitis patients (aimed testing, usually special test series).

Toxicological result	CLP criteria
	<p>Sub-category 1A (non-human data) :</p> <ul style="list-style-type: none"> - GPMT : <ul style="list-style-type: none"> ≥ 30 % responding at ≤ 0.1 % intradermal induction dose, or ≥ 60 % responding at > 0.1 % to ≤ 1 % intradermal induction dose <p><u>Sub-category 1B :</u></p> <ul style="list-style-type: none"> - Substances showing a low to moderate frequency of occurrence in humans; or a probability of occurrence of a low to moderate sensitisation rate in humans based on animal or other tests. Severity of reaction may also be considered. <p>Sub-category 1B (non-human data) :</p> <ul style="list-style-type: none"> - GPMT : <ul style="list-style-type: none"> ≥ 30 % to < 60 % responding at > 0.1 % to ≤ 1% intradermal induction dose, or ≥ 30 % responding at > 1 % intradermal induction dose

10.7.3 Conclusion on classification and labelling for skin sensitisation

The DS proposes classification of Sulfur dioxide as Skin sens. 1.

According to the guidance on the Application of CLP criteria (section 3.4.2.2.1.2., page 336, 2017), “when considering human evidence, it is necessary to take into account the size of the population exposed and the extent of exposure and frequency, and thus the consideration is on a case by case basis”.

However, the extent of exposure and the frequency of occurrence of allergic reactions in the general population cannot be established due to lack of information. Regarding the ubiquity of the substance in drugs, foods and cosmetics, a high extent of exposure to sodium metabisulfite can be assumed.

Even though the CLP criteria for unselected dermatitis patients are fulfilled and might require subcategorization to 1A, no subclassification is proposed on the basis of the afore mentioned assumption.

Furthermore, the available data are based on metabisulfite. As sulfur dioxide is a gas, skin sensitisation would be expected for an aqueous solution of sulfur dioxide due to the formation of (bi-)sulphite under such conditions. Positive reactions with sodium metabisulfite were predominantly observed after testing a 1 % solution in petrolatum. Classification for skin sensitisation category 1 is thus proposed for sulfur dioxide aqueous solutions.

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10.8 Germ cell mutagenicity

For justification of Read-across from metabisulfite, please refer to section 10.

Table 14: Summary table of mutagenicity/genotoxicity tests *in vitro* (Further details on key studies, such as data tables and figures, are provided in section 12 for clarity.)

Method, Guideline, GLP status, Reliability	Test substance, Doses	Relevant information about the study (e.g. cell type, strains)	Results	Remarks (e.g. major deviations)	Reference
Sulphite, bisulfite, metabisulfite					
In vitro gene mutation studies in bacteria					
Bacterial reverse mutation assay, similar to OECD 471 (1983) Non-GLP Rel. 2 (reporting deficiencies) Key study	<u>Plate incorporation method:</u> 0.3-3.3-33.3-100-333.3-1000-3333.3-10000 µg/plate sodium metabisulfite (± S-9 mix) Positive controls: Concurrent positive controls were run with each test in compliance with OECD 471 (see remarks)	<i>S. typhimurium</i> strains TA 1535, TA 1537, TA 1538, TA 98, TA 100 <i>E. coli</i> : WP2 (uvrA) Solvent: 0.067 M potassium phosphate buffer, pH 7.0	Negative Cytotoxicity : <u>TA 1535:</u> -S9: toxic range 100 - 10,000 µg/plate; +S9: toxic range 3,333 - 10,000 µg/plate <u>TA 100:</u> -S9: toxic range > 333.3 µg/plate +S9: only at the highest doses tested. <u>WP2:</u> +S9: Toxicity at the highest dose tested. No observed toxicity +/-S9	Difference in outcome to study performed by Pagano and Zeiger (1987) might be due to pH-effects (here: neutral pH) because apparently mutation was observed in medium with pH 5-6. No purity (but batch) is given in the report. Only two plates per concentration (SD not available; cytotoxicity difficult to determine). Positive controls for strains TA 1537 and TA1538 (+S9) were reported in the publication - Prival et al. 1991, but not in the study report	Simmon, V.F. and Eckford S.L. (1978), NTIS Report PB89-193684 Published as Prival et al. 1991; Mutation Research 260: 321-329

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Method, Guideline, GLP status, Reliability	Test substance, Doses	Relevant information about the study (e.g. cell type, strains)	Results	Remarks (e.g. major deviations)	Reference
Gene mutation in vitro and host-mediated assay; non-guideline Non-GLP; Reliability: 2 (no test guideline, missing relevant tester strains). Key study	Sodium metabisulfite ; 5 % (w/v) for <i>in vitro</i> part host mediated assay: single and repeated dose (5 days): 30, 700, 1200 mg/kg bw	<i>Salmonella typhimurium</i> G 46, TA 1530 Host animals: random-bred Swiss-Webster male mice (28 – 30 g bw), 10 mice/treatment group	Negative <i>in vitro</i> and in host-mediated assay	Positive control: 0.1 % EMS: ok Well conducted early non-guideline study	NTIS 1972 NTIS Report PB221825 Published as Maxwell and Newell; Mol. Environ. Aspects Mutagenesis, Proc. Publ., Rochester Int. Conf. Environ. Toxic. 6th, 223-252, 1974
Bacterial reverse mutation assay, complies with OECD 471 (1983) Non-GLP Rel. 2 (Reporting Deficiencies) Key study	<u>Preincubation test:</u> 500 µL of sodium metabisulfite dilutions up to 0.64M in sodium phosphate buffer (pH 5, 6, 7, or 8)	<i>S. typhimurium</i> : G46 (Target <i>hisG46</i>): TA92, TA1535, TA100, SB2802, SB2061, TR3243 (Target <i>hisD6610</i>): , TA88, TA110, TA90, TA97, D3052 (Target <i>hisD3052</i>), TA1538, TA98, C3076 (Target <i>hisC3076</i>), TA1537, TA1977 (strains recommended by OECD 471 are labelled)	Positive – slight but dose-related increase in # of revertants – increase < 2-fold, with 60 min incubation, >2-fold after 90 or 120 min incubation) Reproducible weak mutagenic response in <i>S. typhimurium</i> strains carrying the <i>his D6610</i> or <i>hisG46</i> mutations. Peak mutagenic response in G46 stains at 0.1 M and in TR3243 at 0.3 M. Number of induced revertants per dose, the <i>hisD6610</i> site was most responsive, with TA 97 being the most active. Mutagenic response highest with 0.1 M sodium phosphate buffer at pH 5.0-6.0. Base-pair substitution and frameshift mutations Base-pair substitution (deamination of cytosine): At higher concentrations (1 M): cytosin bisulfite adducts leading to base substitution At lower concentrations (approx. 0.01 M) deamination of cytosine via oxidative damage assumed.	Examination of conditions under which sodium bisulfite is mutagenic (pH 5-6, phosphate buffer, see results). Reporting deficiencies (e.g. purity of test substance lacking)	Pagano and Zeiger (1987). Mutation Research 179: 159-166

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Method, Guideline, GLP status, Reliability	Test substance, Doses	Relevant information about the study (e.g. cell type, strains)	Results	Remarks (e.g. major deviations)	Reference
Bacterial reverse mutation assay, OECD 471 (1983) Non-GLP Rel. 2 (relevant tester strain missing)	<u>Standard plate test:</u> 0-20-100-500-2500-5000 µg/plate 96-98 % pure sodium sulfite (anhydride) (± S-9 mix) <u>Preincubation test:</u> 0-20-100-500-2500-5000 µg/plate 96-98 % pure sodium sulfite (anhydride) (± S-9 mix)	<i>S. typhimurium:</i> TA 1535, TA 1537, TA 98, TA 100 Solvent: phosphate buffer, pH not reported	Negative Cytotoxicity: Only very slight bacteriotoxic effects were deduced from slight dose-related decrease in the number of revertants.	Missing tester strain: <i>S. typhimurium</i> TA 102 or <i>E. coli</i> WP2 uvrA (pKM101). Efficacy of S9-mix only tested with 2-aminoanthracene. It has to be noted that the test substance was dissolved in aqua dest. which results in alkaline conditions	Engelhardt, G. (1989), Project No.:40M0639/884492
Bacterial reverse mutation assay, similar to OECD 471 Non-GLP Rel. 2 (No positive control)	<u>Preincubation test:</u> Max. non-cytotoxic dose: 50 mg/plate 95 % pure sodium metabisulfite (anhydride) in phosphate buffer <u>(± S-9 mix)</u>	<i>S. typhimurium:</i> TA 92, TA 1535, TA 1537, TA 94, TA98, TA 100 Solvent: phosphate buffer, pH not reported	Negative Highest dose without observed cytotoxicity: 50 mg/plate. No results for cytotoxic doses presented.	Screening of various substances, no positive controls used but substances with positive results indicate functioning of test system. No negative controls (but many substances tested negative). No titer given. No individual number of colonies (mean, SD) or number of plates per dose given.	Ishidate et al. 1984; Fd Chem Toxic 22/8: 623-36
Bacterial reverse mutation assay, Non-guideline, non-GLP Rel. 2 (non-guideline study)	Sodium bisulfite (NaHSO ₃) 0, 0.1, 0.5, 1.0, 1.5, 2.0 M	<i>S. typhimurium:</i> G46 (Target <i>hisG46</i>), TA92, TA1950, TA2410, TS24, GW19	Positive for <i>S. typhimurium</i> strains carrying <i>hisG46</i> allele, greater mutagenic response in strains with wild-type DNA repair capacity	Preincubation and pH<7 required for a positive test result. Very high concentrations used.	De Giovanni-Donnelly (1985), Teratogenesis, Carcinogenesis, and Mutagenesis 5: 195-203
Bacterial reverse mutation assay with various <i>E. coli</i> mutants, non-guideline, non-GLP Rel. 4 (experimental study)	Sodium bisulfite (NaHSO ₃) 1 M in 0.2 M sodium acetate buffer, pH 5.2	<i>E. coli</i> strains K12 (TA mutant site) and 15 (CG mutant site)	Positive – specific mutagen for CG mutants, Frequency of revertants tester strains vs. control: 2- (min) – 31-fold (max) in strain 15 only	Optimal result after 30 min incubation at pH 5.2	Mukai et al. (1970), Biochem Biophys Res Commun. 39/5: 983-988

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Method, Guideline, GLP status, Reliability	Test substance, Doses	Relevant information about the study (e.g. cell type, strains)	Results	Remarks (e.g. major deviations)	Reference
<i>In vitro</i> cytogenicity study in eucaryotic cells					
Gene mutation in vitro and host mediated assay; non-guideline, non-GLP Rel. 2 (non-guideline) Key study	0.1 % sodium metabisulfite host mediated assay: single and repeated dose (5 days): 30, 700, 1200 mg/kg bw	<i>Saccharomyces cerevisiae</i> D3, 5 x 10 ⁷ cells/mL Host animals: random-bred Swiss-Webster male mice (28 – 30 g bw), 10 mice/treatment group	Negative <i>in vitro</i> and in host-mediated assay	Positive control; i.m.: 350 mg/kg w/v EMS (ethyl methane sulphonate), test result: positive	NTIS 1972 NTIS Report PB221825 Published as Maxwell and Newell; Mol. Environ. Aspects Mutagenesis, Proc. Publ., Rochester Int. Conf. Environ. Toxic. 6th, 223-252, 1974
<i>In vitro</i> cytogenicity study in mammalian cells					
Chromosomal aberration OECD 473 (1997) Non-GLP Rel. 1 Sister chromatid exchange in human lymphocytes, OECD 479 Key study	Potassium metabisulfite (PMB) (CAS No. 16731-55-8) in bidistilled water, pH controlled: no influence on medium pH (6.8 – 7.2)	Human peripheral blood lymphocytes (donors: 2 M, 2F, non-smokers, 22-23y)	Positive Reduction in MI to 56 – 60 – 45 – 42 % (for concentrations: 25 – 50 – 100 – 200 µg/mL) of concurrent negative control, positive control: MI: 43 % of neg. control; OECD 473 for PBLs: MI reduction to 45±5 % of controls Slightly positive: Concentration dependent significant increase in SCE but not twice as high as controls	All concentrations cytotoxic but MI is within OECD 473 (2014) proposal for cytotoxicity (human blood lymphocytes: 45±5 % of control), cytotoxicity not clearly dose related at 24 h.	Anonymous15
Chromosomal aberration, Sister Chromatid exchanges non-guideline, non-GLP Comparable to OECD 473 (1997) Rel. 2 (reporting deficiency, no historical data presented)	Sodium metabisulfite (CAS No. 7681-57-4) in bidistilled water 75, 150, 300 µg/mL pH controlled: no influence on medium pH (6.8 – 7.2)	Human peripheral blood lymphocytes (donors: 2 M, 2F, non-smokers, 18-19y) staining: fluorescence plus Giemsa technique	Positive: Conc. dependent increase of CA: aberrant cells (%) 24 h: 2-fold; 2.4-fold; 2.8-fold over control, positive control: MMC: 6.2-fold; 48 h: 1.8-fold; 2-fold, 4.8-fold; MMC: 12-fold	Reporting deficiencies: Lack of information on purity and stability (but substance purchased from Merck, identifiable with cat. no) of test substance. Conc.-dependent cytotoxicity (MI):	Rencüzogullari et al. 2001. Mutation Research 490: 107-112

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Method, Guideline, GLP status, Reliability	Test substance, Doses	Relevant information about the study (e.g. cell type, strains)	Results	Remarks (e.g. major deviations)	Reference
			Weak positive at non-cytotoxic concentrations SCE: dose-dependent increase in SCE/cell: 1.5-; 1.9-; 2.7-fold	24 h: 87 %; 94 %, 78 %; MMI: 48 %; 48 h: 105 %, 76 %, 17 %; MMI: 28 %	
Chromosome aberration non-guideline, non-GLP Rel. 2 (well conducted but cytogenetic assay in anaphase)	Sodium metabisulfite 2.5; 25; 250 µg/mL; positive control: 0.05 µg/mL triethylenemelamine (TEM)	Anaphase analysis of diploid human embryonic lung cells (WI-38)	Positive: Dose-related sharp increase in the number of aberrant cells at low and intermediate dose, cytotoxic effect at high dose Positive control TEM produced positive results	Authors suggested that the test system may produce false positive results as positive results obtained in vitro with various compounds could not be confirmed in vivo.	NTIS 1972 NTIS Report PB221825 Published as Maxwell and Newell; Mol. Environ. Aspects Mutagenesis, Proc. Publ., Rochester Int. Conf. Environ. Toxic. 6th, 223-252, 1974
Micronucleus assay in human lymphocytes, Pre-OECD 487 Non-GLP Rel. 2	NaHSO₃, Na₂SO₃ ; 1:3 M/M 0, 0.05, 0.10, 0.50, 1.0, 2.0 mM in RPMI 1640 medium, pH: 7.0	Human lymphocytes obtained from 4 donors	Positive: Concentration dependent increase of MN from 16.5±2.87; 21±2.65; 27.75±1.7; 33±3.37; 38.75±1.31 MNPCE (mean ± SE), doubling of control values in 3 out of 4 donors	Reporting deficiencies: Lack of information on purity and stability of test substance (but sodium bisulfite solution freshly prepared).	Meng and Zhang 1992, Mutation Research 298: 63-69 (no robust study summary provided)
Chromosomal aberration Non-GLP Rel. 2 (No positive control, reporting deficiencies)	Sodium metabisulfite (anhydride) in physiol. saline	Chinese Hamster fibroblast cell line (CHL)	Negative Highest dose without observed cytotoxicity: 0.125 mg/mL. Highest tested dose caused 50 % cytotoxicity, but no details on dosing reported.	Screening of various substances, no positive controls used but substances with positive results indicate reliability of test system	Ishidate et al. 1984; Fd Chem Toxic 22/8: 623-36
Chromosome aberration and Sister chromatide exchange Non-guideline study, Non-GLP Rel. 2 (reporting deficiencies, no substance information) roughly OECD 479	Sodium bisulfite (NaHSO₃) 0, 10, 20, 40 mM	Hamster foetal cells (HFC),	Negative for chromosome aberration Statistically significant, dose-related increases in SCE: 17.00±1.09 (control) vs. 22.35±1.53 (40 mM; mean ± SEM) in arrested HFC; 9.65±0.67 (control) vs. 14.00±1.11 (40 mM) in exponentially growing HFC.	Reporting deficiencies: Lack of information on test substance (CAS no., purity lacking). Untypical cell line used. No positive control used. OECD TG479 deleted April 2014	Popescu and DiPaolo 1988 Cancer Research 48:7746-7251
Chromosome aberration in mammalian oocytes	Sodium sulfite (Na₂SO₃) 0, 5, 50, 100, 150, 200, 250,	Oocytes from ewe, cow, and mouse	Chromosome aberration, meiotic inhibition	Positive <i>in vitro</i> effects were not confirmed <i>in vivo</i> in mice – but no positive control was	Jagiello et al. 1975 Environ Res. 9: 84-93

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Method, Guideline, GLP status, Reliability	Test substance, Doses	Relevant information about the study (e.g. cell type, strains)	Results	Remarks (e.g. major deviations)	Reference
Non-GLP, non-guideline study Rel. 4 (experimental study)	350, 500, 1000, 10000 µg/mL		Mouse oocytes: inhibition of entry into chromosome damage from 25 µg/mL onwards meiosis at ≥ 10 µg/mL Ewe and cow oocytes: atresia and chromosome breaks at ≥ 250 µg/mL, inhibition of meiosis at ≥ 500 µg/mL in cow oocytes, no inhibition in ewe oocytes.	included.	
<i>In vitro</i> gene mutation study in mammalian cells					
Mouse lymphoma assay, hprt locus OECD 476 (1997) Rel. 1 Key study	Sodium metabisulfite Experiment 1: 200, 300, 400, 600, 800, 1200, 1600, and 1902 µg/mL (+/- S9 mix) Experiment 2: 100, 300, 600, 900, 1200, 1500, and 1902 µg/mL (+/- S9 mix) Experiment 3: 200, 400, 800, 1000, 1200, 1400, 1600, 1700, 1800, and 1902 µg/mL (+S9 mix) Positive controls: -S9µg/mL: 0.10 and 0.15 itroquinoline 1-oxide (NQO) + S9: 2.00 and 3.00 µg/mL Benzo[a]pyrene (B[a]P)	Mouse lymphoma L5178Y tk +/- cells	Negative Experiment 1: Positive (at 1600 and 1902 µg/mL with metabolic activation, % relative survival: 74 % and 65 %, respectively). Experiment 2: Negative. Experiment 3: Negative.	Test was considered negative because positive results in Exp. 1 (+S9) were not reproducible	Stone, V. (2010) Covance Study Number: 8230958
Sulfur dioxide					
Bacterial reverse mutation assay, No- OECD TG Non-GLP Rel. 2 (only 1 tester strain, only one concentration)	50 ppm SO ₂ , exposure: 48 h, Coexposure: B(a)P in (0-5 µg/plate). Positive control: 5 µg 2-aminoanthracene	S. typhimurium TA 98 + metabolic activation (S9)	Negative , no increase in revertants when compared to negative controls. No increase of mutagenic activity while co-exposed to f benzo(a)pyrene.	in principle OECD 471 (1983), but only one tester strain used. Study was conducted to investigate coexposure of B(a)P and SO ₂ + NO _x	Pool-Zobel, B.L. et al. 1990. Exp. Pathol. 39, 207-212

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Method, Guideline, GLP status, Reliability	Test substance, Doses	Relevant information about the study (e.g. cell type, strains)	Results	Remarks (e.g. major deviations)	Reference
In vitro mammalian cell micronucleus test OECD 487 principle Rel. 2 (reporting deficiencies) Non-GLP	0.1, 0.5, 1.0 ppm SO ₂ (gas)	Human lymphocytes derived from 4 donors (no more details given) Positive control: Cyclophosphamide	Positive Frequency of micronuclei and SCE in human lymphocytes increased concentration-dependently at cytotoxic concentrations: 0, 0.1, 0.5, 1.0 ppm: MN median: 1.5, 2.0, 4.5, 5.5, pos. control: 9.5) (MI reduction vs. control: 65 %, 58 %, 31 %)	Reporting deficiencies. Not clear, whether metabolic activation was used. Positive control is for tests with metabolic activation	Üren et al. 2014 Toxicol Ind Health. 2014 30(4):311-5.

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Method, Guideline, GLP status, Reliability	Test substance, Doses	Relevant information about the study (e.g. cell type, strains)	Results	Remarks (e.g. major deviations)	Reference
Table 15: Summary table of in vivo genotoxicity studies (Please refer to section 12 for further details (tables and figures) on key studies.) Method, Guideline, GLP status, Reliability	Test substance, Doses	Relevant information about the study (e.g. species and strain, duration of exposure)	Observations	Remarks (e.g. major deviations)	Reference
Sulfur dioxide					
In vivo Comet Assay Rel. 2 (reporting deficiencies, no positive control) Comparable to OECD 489 Non-GLP Key study	14, 28, 56, 112 mg/m ³ SO₂ concentrations measured within the chambers by pararosaniline hydrochloride spectrophotometry every 30 min	Mouse, Kunming albino, 6 males and 6 females 6 hours/day for 7 days DNA damage measured as Olive tail moment (OTM): product of tail moment length and tail DNA %. Sampling time: immediately after last exposure Cell viability > 95 % shown with Trypan-blue dye-exclusion technique.	Positive Dose-dependent increase OTM from 14 mg/m ³ onwards in blood lymphocytes. Cells derived from brain, lung, liver, spleen, kidney, and intestine in both sexes and in testicles of males. No effects on food consumption and body weight gain; no deaths, morbidity or distinctive clinical signs.	No justification for dose selection, no positive control used or no information on historical positive control range, values expressed as mean ± SE instead SD, body weight gain and food consumption not reported.	Anonymous11 (2005)
In vivo Mouse Micronucleus test	1.00, 2.99, 10.26 and 30.55 ppm SO₂	Mouse, NMRI, 6 males and 6 females	Negative The number of micronuclei not increased; however not proven that the substance	Acceptability criteria for negative results according to OECD 474 not fulfilled ²	Anonymous6, (2008) also published as:

² The study was designed as re-evaluation of the published data by Meng et al. (2002) using comparable doses. In consequence, only non-toxic doses were applied and the study does not meet the requirements of OECD 474.

The concentration of SO₂ in exposure chamber was not analysed, exposure via gas cylinders with certified SO₂/N₂ concentrations; control via flow rates.

Dose-dependent increases in malondialdehyde levels in erythrocytes of exposed mice in another study under the same conditions (statistically significant at 10 and 30 ppm).

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Method, Guideline, GLP status, Reliability	Test substance, Doses	Relevant information about the study (e.g. cell type, strains)	Results	Remarks (e.g. major deviations)	Reference
Similar to OECD 474 GLP Rel. 2 Key study		4 hours/day for 7 days	reached the target organ. No signs of overall toxicity. PCE:NCE ratio unchanged.		Anonymous7, (2010)
In vivo Mouse Micronucleus test Similar to OECD 474 Non-GLP Rel. 2	14, 28, 56, 84 mg/m ³ (5, 10, 21, 32 ppm) SO ₂ concentrations measured within the chambers by pararosaniline hydrochloride spectrophotometry every 30 min	Mouse, Kunming albino, 10 males and 10 females 4 hours/day for 7 days Sampling time: 24 h	Positive Dose dependent increase in micronuclei in PCE, no sex differences. Increase statistically significant at 14 mg/m ³ SO ₂ and higher.	PCE:NCE ratio was monitored but not reported. No positive control used, only 1000 PCE per animal scored, OECD 474 requires 2000 (4000 according to OECD 474, Sep 2014), no information on historical positive and negative control range, no justification for dose selection	Anonymous8, (2002)
In vivo Mouse Micronucleus test Conduction similar to OECD 474 Non-GLP Rel. 2	28 mg/m ³ SO ₂ concentrations measured within the chambers by pararosaniline hydrochloride spectrophotometry every hour	Mouse, Kunming albino, 12 males and 12 females 6 hours/day for 5 days Sampling time: 24 h following last exposure	Positive Significant increase in micronuclei (mono-, bi, and polymicronuclei) in PCE at 28 mg/m ³ compared to controls.	Reporting deficiencies, e.g. PCE:NCE ratio not reported. (Study was conducted to test the protective effect of seabuckthorn seed oil (i.p.) – only one test concentration chosen)	Anonymous10 (2003)
In vivo Mouse Chromosome aberration test Similar to OECD 475 Non-GLP Rel. 2	7, 14, 28, 56, mg/m ³ SO ₂ (nominal) concentrations measured within the chambers by pararosaniline hydrochloride spectrophotometry every 30 min	Mouse, Kunming albino, 10 males and 10 females 4 hours/day for 7 days Sampling time: 24 h following last exposure; 2 h after cholchicine injection	Positive Dose and duration dependent increase in aberrant cells, dose dependent decrease of mitotic index in both sexes Chromosome and chromatide breaks at 56 mg/m ³ SO ₂ ; at lower concentrations chromatide breaks only sign. at ≥ 14 mg/m ³ .	Short comings: Results of positive controls not documented, reporting deficiencies, sampling time after cholchecin 2 h (OECD: 3-5 h).	Anonymous9 (2002).

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Method, Guideline, GLP status, Reliability	Test substance, Doses	Relevant information about the study (e.g. cell type, strains)	Results	Remarks (e.g. major deviations)	Reference
Sodium/potassium metabisulfite					
Chromosomal aberration OECD 474 (1997) Non-GLP Rel. 2 (i.p. insufficient no. of animals) Key study	Potassium metabisulfite (CAS No. 16731-55-8) in bidistilled water: 150, 300, 600, mg/kg bw, i.p. single dose	Albino rats 2M + 2 F per group, Sampling time: 12 h, 24 h	Positive: Dose related increase of aberrant cells	No 48 h sampling, only 2 animals per sex and group, pos. control: urethane	Anonymous15 2008;
In vivo Mouse Micronucleus test comparable to OECD 474 Rel 2 (only 1 sampling time for blood cells and bone marrow cells) Non-GLP Key study	Oral gavage single dose Pre-test and main tests: 0.5, 1.0, 2.0 g/kg bw Test substance: sodium metabisulfite	Mice CF1 outbred Pre-test for acute toxicity: 6/group (3F+3M) Main test: 10/group (5F+5M) Sampling time: 24 h	Positive Increased frequency of micronuclei in bone marrow and peripheral blood cells at 2g/kg (limit dose); significant reduction of PCE:NCE ratio at 2 g/kg	Pre-test: no signs of toxicity; no mortalities, purity of test substance not reported but can be identified by catalogue no.) MN: PCE:NCE ratio in controls unusually high	Anonymous14 (2011)
Chromosome aberration Non-GLP; Pre- comparable to Guideline OECD 474 Reliability: 1 (pre-guideline but well conducted) Key study	Sodium metabisulfite; 0, 30, 700, 1200 mg/kg. Single or multiple oral dosing (5 d).	Rat (Albino, random-bred, 200 g bw) M	Negative Dose dependent decrease in mitotic index	Dose dependent increases in cytotoxicity	NTIS 1972 NTIS Report PB221825 Published as Maxwell and Newell; Mol. Environ. Aspects Mutagenesis, Proc. Publ., Rochester Int. Conf. Environ. Toxic. 6th, 223-252, 1974
Dominant Lethal Gene Test); Non-GLP; comparable to Guideline OECD 478 Reliability: 1 (pre-guideline but well conducted) Key study	Sodium metabisulfite; 0, 30, 700, 1200 mg/kg. p.o. Positive control: Triethylenmelamine (TEM) 0.2 mg/kg i.p. single dose	Rat (Albino) M; Single or multiple dosing (5 d). 10 M/treatment group	No consistent responses attributed to treatment, occasional statistical differences between control and sodium meta-bisulfite-dosed groups at P < 0.01; P < 0.05, and P < 0.10 without time or dose-response effect. At P < 0.20 indications of an effect	-	NTIS 1972 NTIS Report PB221825 Published as Maxwell and Newell; Mol. Environ. Aspects

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Method, Guideline, GLP status, Reliability	Test substance, Doses	Relevant information about the study (e.g. cell type, strains)	Results	Remarks (e.g. major deviations)	Reference
			TEM: positive		Mutagenesis, Proc. Publ., Rochester Int. Conf. Environ. Toxic. 6th, 223-252, 1974
Comet assay comparable to OECD 489 Non-GLP Rel. 2 (no early sampling time, unusual scoring – see remarks, poor reporting)	Oral gavage single dose Pre-test and main tests: 0.5, 1.0, 2.0 g/kg bw Test substance: sodium metabisulfite	Mice CF1 outbred Pre-test for acute toxicity: 6/group (3F+3M) Main test: 10/group (5F+5M) Sampling time: 24 h	Positive <u>Comet assay</u> Dose dependent increase in DI and DF in % in blood, liver and bone marrow. Increase statically significant at 1 g/kg and 2 g/kg.	Pre-test: no signs of toxicity; no mortalities, purity of test substance not reported but can be identified by catalogue no.) Damage Index (DI): cells were allocated into five classes according to tail size (0=no tails and 4 = maximum tail length). DI for maximum damage = 400 Damage Frequency (DF) = number of cells with tail in %.; Deviations: 1 sampling time only at 24h, no individual animal data – DI is an unusual scoring for Comet assay	Anonymous14 (2011)
Chromosome aberration, micronucleus assay and sister chromatid exchange assay; Non-GLP; non-guideline Reliability: 2 (reporting deficiencies, no MI, only two doses tested).	Sodium metabisulfite , calculated as SO ₂ : Mouse: s.c.: 50 mg/kg , p.o.: 660 mg/kg (normal animal), 165 mg /kg in sulphit oxidase deficient animals) Hamster: .c.: 50 mg/kg , p.o.: 660 mg/kg (normal animal) 330 mg 165 mg SO ₂ /kg (SO deficient animals)	Chinese hamster, Charles River NMRI-mice) F + M In addition: up to 12 injections (subcutaneous).	Negative. No cytogenetic effect in all three assays in normal and SO deficient animals	No proof of proliferation (e.g. no mitotic index – MI – reported), not clear whether target organ was reached. Study cannot be regarded as key study as important information is lacking (see above)	Anonymous12 (1983)
Micronucleus assay	Sodium metabisulfite ,	Chinese hamster, Charles River	Negative. Frequency in micronucleated cells not increased in normal and SO	Not proven that target organ (bone marrow) was	Anonymous12

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Method, Guideline, GLP status, Reliability	Test substance, Doses	Relevant information about the study (e.g. cell type, strains)	Results	Remarks (e.g. major deviations)	Reference
Non-GLP; Reliability: 2 (reporting deficiencies, no MI, only two doses tested).	calculated as SO ₂ : Mouse: s.c.: 50 mg/kg , p.o.: 660 mg/kg (normal animal), 165 mg /kg in sulphit oxidase deficient animals) Hamster: s.c.: 50 mg/kg , p.o.: 660 mg/kg (normal animal) 330 mg 165 mg SO ₂ /kg (SO deficient animals)	NMRI-mice) F + M In addition: up to 12 injections (subcutaneous).	deficient animals	reached. Study cannot be regarded as key study as important information is missing. Treatment schedule does not comply with OECD 474 2014.	(1983)
Sodium sulfite					
In vivo mouse Micronucleus test OECD 474 GLP Rel. 2 (reporting and methodological deficiencies) Key study	Subcutane Sodium sulfite wasserfrei, food grade (E221) 250, 500, 1000 mg/kg bw in 10 mL/ kg bw Vehicle: purified water; Positive control: cyclophosphamide (clastogenicity), vincristin sulphate (spindle poison),	Mice CrI:NMRI, M single dose	Negative Frequency of micronuclei in erythrocytes not increased compared to vehicle controls; PCE:NCE reduced at 1000 mg/kg bw at 48 h following administration	Dose selection after pretest, deaths observed at 1500 mg/kg bw, no information on number of animals used in pretest. No signs of toxicity although mortality occurred at 1500 mg/kg bw in pretest. Route of exposure: s.c. not recommended for reactive substances test substance not stable in water reporting deficiencies: route of exposure s.c. in text, p.o. in annex	Anonymous13 2008;
In vivo Comet Assay Non-GLP Reliability. 2 (sampling time, substance identification, missing purity, i.p. administration, sampling time) OECD 489	Intraperitoneal Sodium sulfite: sodium bisulfite (3:1 M/M) <u>Main test</u> 125, 250, 500 mg/kg bw	Mouse, Kunming albino, 6 males Daily for 7 days Sampling time: 24 h	Positive Dose dependent increase in OTM in cells from brain, lung, heart, liver, stomach, spleen, thymus, bone marrow and kidney (p < 0.05 one way ANOVA). Strongest increase in brain, lung and heart. Significant difference vs control in all tissues already at the lowest applied dose of 125 mg/kg bw (p<0.05; Dunnett test)	Reporting deficiencies: CAS No. missing, lack of information on stability Purity of test substance not reported (purchased from Sigma, ± identifiable from catalog). Sampling time 24 h after last dosing (recommended: 2- 6 h)	Anonymous16 (2004)

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Method, Guideline, GLP status, Reliability	Test substance, Doses	Relevant information about the study (e.g. cell type, strains)	Results	Remarks (e.g. major deviations)	Reference
			At 125 mg/kg bw % of cells with DNA damage in all organs except for thymus and bone marrow ≥ 50 %. 50 % lethality at 1000 mg/kg bw observed in pretest		
Dominant-lethal and heritable translocation in mice Non-guideline, non-GLP Rel. 3 (no positive control, no proof that target organ was exposed)	Sodium bisulfite i.p. , vehicle (and neg. control): aqua dest. 300, 400 mg/kg bw/d, repeated dose : 300 mg/kg: 38 doses in 54 days; 400 mg/kg: 20 doses at 26 day; 550 mg/kg bw/d single dosed females; # mated females: 300 mg/kg: 60; controls: 76 400 mg/kg: 69, controls: 135 550 mg/kg: 29; controls: 32	Translocation study: male 101 x C3H F ₁ mice mated with SEC x C57BL F ₁ female mice immediately after last dosing Dominant lethal: mating with SEC x C57BL F ₁ females up to 14.5 days after last injection Dominant lethal in females: C3H x 101 F ₁ single dose i.p. of 550 mg/kg, mated to untreated males within 4.5 days after treatment	Negative No signs for induction of dominant lethal mutations or heritable translocation	No positive control used Dose selection on basis of pretest: 550 mg/kg as highest dose without mortality	Anonymous5, 1978;

Table 16: Summary table of human data relevant for germ cell mutagenicity(Please refer to section 12 (tables and figures) for further details on key studies.)

Summary table of human data on genotoxicity					
Type of data/ report, Reliability	Test substance	Relevant information about the study	Observations	Reference	
Occupational study on clastogenicity of workers in a sulfite pulp factory Rel 2 (reporting deficiencies)	SO ₂	Controls: 15 M (5 smokers) Test groups: SO ₂ group: 7 M (1 smoker) Pulp bleaching group: 6 M (1 smoker) Paper mill group: 6 M (3 smokers) Chromosome aberrations in 100 cells/individual following 72 h of cell culture	SO ₂ group: All types of aberrations were significantly increased in comparison to the control group with p<0.01 or p<0.001. Smoking was the only possible confounder recorded. Due to lack of evaluation/ matching for possible confounders and low number of participants, no final conclusion can be drawn from the study.	Nordenson et al (1980) Hereditas 93: 161-164. (published)	

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Summary table of human data on genotoxicity				
Type of data/ report, Reliability	Test substance	Relevant information about the study	Observations	Reference
		No data on exposure to SO ₂ reported.		
Occupational study on clastogenicity Human Bio-Monitoring of workers in aluminium industry	SO ₂	CA and SCE in high and low exposed workers (M; mean age: 47.9) (exposure not specified) Average daily SO ₂ exposure estimated 0.2-3.0 ppm, individual mean exposure level 1.0 +- 0.85 ppm;	Frequencies of CA and SCE were similar in all groups. However, due to lack of evaluation/ matching for possible confounders and low number of participants, no final conclusion can be drawn from the study. In addition, exposure towards SO ₂ was very low.	Sorsa, M. <i>et al.</i> (1982). <i>Hereditas</i> 97: 159-161.
Occupational study on genotoxicity Human Bio-Monitoring on workers in a fertilizer factory	SO ₂	MI, CA, SCE, satellite associations in workers (n = 42) and matched (age, sex, smoking, alcohol consumption) controls (n = 42) Average exposure reported to be 41.7 mg/m³ (15.7 ppm; 20°C, atmospheric pressure)	Exposed vs. controls (p<0.05): MI: 7.09 ± 0.79 vs . 4.34 ± 1.23 SCE: 7.27 ± 0.13 vs. 3.97 ± 0.12 CA w/o gaps (smokers): 3.52 ± 0.27 (n = 34) vs. 1.07 ± 0.16 (n = 27) CA w/o gaps (alcoholics): 3.24 ± 0.33 (n = 17) vs. 0.91 ± 0.13 (n = 23) Satellite associations/cell: 17.1 ± 1.2 vs. 8.1 ± 0.3 Exposure to high concentrations of SO ₂ is associated with genotoxic effects in workers.	Yadav and Kaushik. (1996). <i>Mutation Research</i> 359:25-29.
Occupational study on genotoxicity (micronuclei formation) Human Bio-Monitoring of workers in a sulfuric acid factory	SO ₂	Micronuclei formation in peripheral blood lymphocyte culture in workers (n = 40) and matched (age, sex, smoking) controls (n = 42, members/students of university)	Exposed vs. controls (p<0.001): Lymphocytes with MN: w/o: 0 % vs . 31 %	Meng and Zhang (1990). <i>Environmental and Molecular Mutagenesis</i> 15:218-220 (published)

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Summary table of human data on genotoxicity				
Type of data/ report, Reliability	Test substance	Relevant information about the study	Observations	Reference
		Range of exposure reported to be 0.34 mg/m³ to 11.97 mg/m³ (0.13 ppm and 4.5 ppm; 20°C, atmospheric pressure, respectively during the year)	<p>>0.1 %: 72.5 % vs . 16.7 %</p> <p>>0.2 %: 17.5 % vs. 0 %</p> <p>Higher frequency of MN in smokers in both groups, but always higher in exposed workers whether smoking or not.</p>	
Occupational study on genotoxicity (chromosome aberration, sister-chromatid exchange) Human Bio-Monitoring of workers in a sulfuric acid factory	SO₂	<p>CA and SCE in peripheral blood lymphocyte culture in workers (n = 40) and matched (age, sex, smoking) controls (n = 42, members/students of university)</p> <p>Range of exposure reported to be 0.34 mg/m³ to 11.97 mg/m³ (0.13 ppm and 4.5 ppm; 20°C, atmospheric pressure, respectively during the year)</p>	<p>Exposed vs. controls (p<0.01):</p> <p>CA chromosome type: 165 vs . 25 aberrant cells (2.1 ± 0.23 % vs. 0.3 ± 0.1 %)</p> <p>CA chromatid type: 77 vs. 24 aberrant cells (1.0 ± 0.2 % vs. 0.3 ± 0.1 %)</p> <p>CA total number of cells: 242 vs. 49 (3.0 ± 0.3 % vs. 0.6 ± 0.1 %)</p> <p>SCE per cell: 6.7 ± 0.2 vs. 2.7 ± 0.1</p> <p>No difference of CA and SCE between smokers and non-smokers.</p>	<p>Meng and Zhang (1989). Mutation Research 241:15-20 (published)</p> <p>(same cohort as in the study above)</p>

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Summary table of human data on genotoxicity				
Type of data/ report, Reliability	Test substance	Relevant information about the study	Observations	Reference
Method: chromosomal aberrations in anaphase of human embryonic lung cells (WI-38); No data on GLP; Reliability: 2 (non-guideline study but well conducted)	Sodium metabisulfite test concentrations not specified (without metabolic activation).	Human embryonic lung cells (WI-38).	Positive in anaphase, negative in metaphase (without metabolic activation).	NTIS 1972 NTIS Report PB221825 Published as Maxwell and Newell; Mol. Environ. Aspects Mutagenesis, Proc. Publ., Rochester Int. Conf. Environ. Toxic. 6th, 223-252, 1974

Reliability of the human biomonitoring studies is “not assignable” according to Klimisch, because no OECD guideline was followed. However, all listed studies are considered reliable from the scientific point of view.

10.8.1 Short summary and overall relevance of the provided information on germ cell mutagenicity

Several *in-vivo* studies confirmed a clastogenic effect observed *in vitro* with sulfur dioxide. All studies had short comings in testing protocols or – at least – reporting deficiencies. However, results derived from a recently performed micronucleus assay *in vivo* (Anonymous6 und Anonymous7, 2008/2010) are not regarded sufficient on a standalone basis to dismiss positive results from micronucleus and comet assays reported from several published studies (see table above). The conflicting results are in line with the observation that results are highly dependent on test conditions. Sulfur dioxide and bisulfite/metabisulfite participate in a large number of organic and inorganic reactions (e.g. Anonymous46, 1981), which is plausible as sulfur dioxide and sodium metabisulfite are reactive substances.

Gene mutation seen under special conditions *in vitro* (see chapter above) was not confirmed *in vivo* in a well-conducted dominant lethal gene test (NTIS 1972/Maxwell and Newell 1974). In conclusion, gene mutation effects seen *in vitro* were not confirmed *in vivo*.

Clastogenic effects *in vivo*:

Sulfur dioxide:

positive results:

Anonymous112005: Comet assay (regarded as key study)

Anonymous8 2002: Micronucleus

Anonymous10 2003: Micronucleus

Anonymous9 2002: Chromosome aberration

negative results:

Anonymous6 und Anonymous7, 2008/2010: Micronucleus (regarded as key study)

Conclusion: Equivocal results for sulfur dioxide *in vivo* – all studies reliability of 2.

Sodium/potassium metabisulfite:

positive results:

Anonymous15 2008: Chromosome aberration (regarded as key study, reliability 2)

Anonymous14 2011: Micronucleus (regarded as key study, reliability 2), Comet assay

negative results:

NTIS 1972/Maxwell and Newell 1974: Chromosome aberration (regarded as key study, reliability 1)

Anonymous12, 1983: Chromosome aberration, micronucleus

Conclusion: Equivocal results for sodium metabisulfite *in vivo* – negative key studies reliability 1, positive key studies reliability 2.

Sodium sulfite/sodium bisulfite:

positive results:

Anonymous16 2004: micronucleus i.p., comet assay i.p.

negative results:

Anonymous13: micronucleus, s.c. (regarded as key study, reliability 2)

Comet assays reported here (Anonymous14, Anonymous16) are difficult to interpret as essential information is lacking or at least not reported. In addition, sampling time was after 24 hours (instead of 2-6 hours following last treatment as recommended by OECD 489). Although this might be more important in negative test results, an indirect/cytotoxic effect cannot be excluded. No details or images were given on comets and cytotoxicity.

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A bone-marrow micronucleus test in NMRI mice (m/f) according to OECD TG 474 following inhalation exposure to sulfur dioxide (Anonymous6 und 7 2008a,b, 2010) is available. Animals were exposed (whole-body) to 0 (clean air), 2.7, 8, 27, or 80 mg/m³ (0, 1, 3, 10, or 30 ppm) SO₂ for 4h/day on 7 consecutive days. Exposure to SO₂ caused no acute toxicity, mortality, or reduction in body weight under test condition. Compared with the clean-air controls, haematological parameters such as haematocrit, haemoglobin, erythrocyte/platelet/total leukocyte counts, differential white blood cell counts, and indicators of blood formation (reticulocyte counts, ratio of polychromatic to normochromatic erythrocytes in the bone marrow) remained unchanged by SO₂ treatment. In contrast to various *in vivo* studies performed by Anonymous8 and coworkers (see description below), SO₂ did not induce micronuclei in polychromatic erythrocytes of the bone marrow. SO₂ treatment significantly enhanced malondialdehyde levels in erythrocyte lysates (TBARS method), indicating SO₂-mediated oxidative stress. In the studies, dose dependent increases of chromosomal aberrations and micronuclei were shown *in vivo*. The dossier submitter evaluates the studies published by Anonymous8 and coworkers as reliable with restrictions (reliability 2). The studies were published in recognised peer review journals for toxicology. Anonymous7 performed the study under comparable conditions in order to refute or confirm the studies published by Anonymous8 and coworkers with the consequence that test concentrations were not chosen according to the requirements of OECD TG 474 (e.g. no observed toxicity, no indication that bone marrow was reached).

The group of Anonymous8 and coworkers conducted several *in vivo* studies on the genotoxic potential of inhalation exposure to sulfur dioxide in Kunming mice (micronucleus assay: Anonymous8, Anonymous10, chromosome aberration: Anonymous9, comet assay: Meng et al. 2005). In the chromosomal aberration test, male and female Kunming mice were exposed to concentrations of 0 to 56 mg/m³ of SO₂ for 4 hours per day for a period of 7 days. A dose-dependent increase in chromatid-type aberrations at body weight concentrations (from 7 to 28 mg/m³ – significant from 14 mg/m³ onwards) and chromosome-type aberrations at higher concentrations (56 mg/m³), were observed in a context of high cytotoxicity (reduced mitotic index) from 14 mg/m³ onwards. Positive results with metabisulfites (sodium, potassium) in chromosome aberration assays were also reported in rats by other groups (Anonymous15, Anonymous14) as well as in lymphocytes of exposed workers (Yadav and Kaushik 1996).

In the micronucleus test (Anonymous8), animals of the same strain of mice were exposed to up to 84 mg/m³ of SO₂ under comparable experimental conditions as in the chromosomal aberration test (Anonymous9). Anonymous10 investigated concentrations of 0 to 28 mg/m³ of SO₂ for 6 hours per day for a period of 5 days. A dose-dependent increase in the frequency of micronuclei in the polychromatic erythrocytes was observed in both studies. No information on the ratio of PCE/NCE was reported. However, as dose-dependent micronuclei formation was observed, the test substance must have reached the bone marrow but no information was given on cytotoxicity. In the chromosome aberration study cytotoxicity was seen at doses above 14 mg/m³. Hence, it cannot be excluded that genotoxicity occurs at cytotoxic doses only.

In the comet assay (Anonymous11), male and female mice were treated with 14 - 112 mg/m³ (5 – 40 ppm) SO₂ for 6 h/day for 7 days, while control groups were exposed to filtered air. SO₂ caused significant increases in DNA damage (increased olive tail moment, OTM) in all the cell types derived from blood lymphocytes and cells from the brain, lung, liver, spleen, kidney, intestine, analysed from both sexes of mice and in testicles. Cell viability was high (>95 %) prior to exposure. In contrast to the high degree of cell viability in treated groups indicated by the trypan-blue assay, H & E staining and transmission electron microscopy showed cell toxicity induced by SO₂.

Studies with sulfites also indicated contradictory results. Anonymous14 conducted a micronucleus and a comet assay in order to evaluate the genotoxic potential of sodium metabisulfite on different tissues of the mouse. Positive results were only seen at the limit dose of 2000 mg/kg bw accompanied with indication for bone marrow toxicity (significant reduction in the ratio of polychromatic to normochromatic erythrocytes. In the comet assay positive results were obtained at 1000 and 2000 mg/kg bw in all tissues investigated (liver, bone marrow, blood). Negative findings in the micronucleus assay up to 1000 mg/kg bw (highest dose tested) were confirmed in an unpublished study with sodium sulfite (Anonymous13). The comet assay performed by Anonymous16 on the genotoxic potential of a mixture of sodium sulfite and sodium bisulfite, 3:1 M/M) in cells of various organs (brain, lung, heart, liver, stomach, spleen, thymus, bone marrow and kidney) of male mice showed dose-dependent increases in OTM from 125 mg/kg bw onwards. The dossier submitter regarded

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the study as not reliable as important information on the test substance are lacking. 50 % lethality were already observed at 1000 mg/kg bw which could not be shown in any of the other studies.

In conclusion, a genotoxic potential of sulfur dioxide and sodium metabisulfite cannot be ruled out. The higher sensitivity of the comet assay following inhalation of SO₂ might be explained by formation of reactive oxygen species and, hence, an indirect genotoxic mechanism which might explain predominantly negative results *in vitro*. Concentration dependent increased levels of MDA, an indication for lipid peroxidation, were shown in erythrocytes at 10 and 30 ppm (Anonymous7).

Conclusions:

Currently, sulfur dioxide has no harmonised classification for mutagenicity, but the available data indicate a genotoxic potential. The higher sensitivity of the comet assay following inhalation of SO₂ might be explained by formation of reactive oxygen species and, hence, an indirect genotoxic mechanism may be postulated which might explain predominantly negative results *in vitro*. Concentration dependent increased levels of MDA, an indication for lipid peroxidation, were shown in erythrocytes at 10 and 30 ppm (Anonymous7).

Therefore, the proposal Muta. 2 for sulfur dioxide is based on positive evidence obtained from experiments in mammals supported by some *in vitro* findings. In addition, there is some indication for genotoxicity in lymphocytes of exposed workers. Also there was strand-breaking activity in testes in an *in vivo* comet assay and genotoxic effects in occupational studies.

California EPA³ indicated that there was “considerable evidence that air pollution (with SO₂ used as an index measure in some studies) induces DNA damage in human sperm (...) as well as other cell types (...). The data from animal studies are also indicative of oxidative damage, including DNA damage in the testes caused by exposure to SO₂.”

10.8.2 Comparison with the CLP criteria

The following table lists the criteria for germ cell mutagens required from CLP regulation:

CLP regulation
<p>The classification in <u>Category 1A</u> is based on positive evidence from human epidemiological studies. Substances to be regarded as if they induce heritable mutations in the germ cells of humans.</p>
<p>The classification in <u>Category 1B</u> is based on:</p> <ul style="list-style-type: none">— positive result(s) from <i>in-vivo</i> heritable germ cell mutagenicity tests in mammals; or— positive result(s) from <i>in-vivo</i> somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. It is possible to derive this supporting evidence from mutagenicity/genotoxicity tests in germ cells <i>in vivo</i>, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or— positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people.
<p>The classification in <u>Category 2</u> is based on:</p> <ul style="list-style-type: none">— positive evidence obtained from experiments in mammals and/or in some cases from <i>in vitro</i> experiments, obtained from:— somatic cell mutagenicity tests <i>in vivo</i>, in mammals; or— other <i>in vivo</i> somatic cell genotoxicity tests which are supported by positive results from <i>in vitro</i> mutagenicity assays.

³ California Environmental Protection Agency, 2011: Evidence on the Developmental and Reproductive Toxicity of Sulfur Dioxide (Reproductive and Cancer Hazard Assessment Branch; Office of Environmental Health Hazard Assessment).

Note: Substances which are positive in *in vitro* mammalian mutagenicity assays, and which also show chemical structure activity relationship to known germ cell mutagens, shall be considered for classification as Category 2 mutagens.

Toxicological results and CLP classification

Muta. 2, based on positive evidence obtained from experiments in mammals *in vivo* supported *in vitro* findings. In addition, there indication for genotoxicity in lymphocytes of exposed workers. Also there was strand-breaking activity in testes in an *in vivo* comet assay and genotoxic effects in occupational studies.

The genotoxic potential of sulfur dioxide was dicussed in September 2018 for the biocide assement procedure. The majority of the HH-WG members agreed that on the basis of the available information, sulfur dioxide is genotoxic.

10.8.3 Conclusion on classification and labelling for germ cell mutagenicity

DS proposes to classify sulfur dioxide as Muta. 2.

10.9 Carcinogenicity

Following data and information are available on sulfur dioxide and related relevant compounds. For justification of read-across from metabisulfite, please refer to section 10.

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Table 17: Summary table of *in vivo* carcinogenicity studies in animals

Summary table of carcinogenicity studies in animals						
Method, Guideline, GLP status, Reliability	Species, Strain, Sex, No/ group	Test substance Dose levels, Route of exposure, Duration of exposure	NOAEL, LOAEL	Results (Please indicate any results that might suggest carcinogenic effects, as well as other toxic effects.)	Remarks (e.g. major deviations)	Reference
Metabisulphites						
Pre-guideline -carcinogenicity study cannot be evaluated with respect to requirements of OECD due to poor study reporting Rel. 2 (poor reporting)	Mouse ICR/JCL mice, 50 M/ 50 F per group	1 and 2 % potassium metabisulphite solutions ad libitum for 24 months, corresponding to 2500 – 3000 mg/kg bw K ₂ S ₂ O ₅ or 1450 – 1730 mg/kg bw/d SO ₂ equivalents	No data	No evidence for carcinogenicity, Number of lung tumours higher in 2 % group, but statistically not significant	Calculation in mg/kg bw based on mice body weight of 20 - 25 g and a daily water intake of 3 - 5 ml. Only number of tumors and no data on other endpoints reported.	Anonymous64.
Non-guideline study Rel. 3 (well conducted study but carcinogenicity part not reliable: high tumour incidences in control)	Rat Wistar-derived F0-generation: 20 males /20 females F1-generation: 10 males/ 10 females F2-generation: 10 males/15 females	0, 0.125, 0.25, 0.5, 1.0, or 2.0 % sodium metabisulphite in the diet (considering sulphite loss corresponding to approx. 49, 108, 220, 460, 955 mg/kg bw/d) Exposure of F ₀ and F ₁ rats: 104 weeks, F ₂ rats: 30 weeks)	Local: NOAEC: 0.25 % (0.215 when considering sulphite losses) Systemic: reduced bw: >0.25 % (108 mg/kg bw/d Na ₂ S ₂ O ₅ , 72 mg /kg bw/d SO ₂) LOAEC: 0.5 % (gastric lesions) LOAEL: systemic: 0.5 % (220mg/kg bw/d Na ₂ S ₂ O ₅ , 147 mg /kg bw/d SO ₂)	Local effects: ≥0.5 %: Lesions and inflammatory infiltration in forestomach in F2 generation , ≥1 %: Occult blood in faeces, hyperplasia and inflammation in fore- and glandular stomach, reduced thiamine content in liver 2 %: Haematological effects Systemic effects: >0.25 % Reduced bw in F2 animals (-9 %) considered adverse at 0.5 % (- 11 %) No compound-related tumour incidence was reported. The number of lymphoreticular pulmonary tumours in males decreased with increasing levels of sulphite in the diet. Incidence of thyroid and pituitary	Losses of sulphite in the diet: 22; 14; 12; 8, 4.5 % respectively. Local effects in the forestomach of rats are considered of minor relevance for human RC. Number of rats with tumours very high (10/24 malignant lymphoreticular tumour in controls, lower in treatment groups)	Anonymous62

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Summary table of carcinogenicity studies in animals						
Method, Guideline, GLP status, Reliability	Species, Strain, Sex, No/ group	Test substance Dose levels, Route of exposure, Duration of exposure	NOAEL, LOAEL	Results (Please indicate any results that might suggest carcinogenic effects, as well as other toxic effects.)	Remarks (e.g. major deviations)	Reference
				tumours in control group very low; higher values in various test groups in random manner corresponding to historical controls – no relationship between number, location or type of tumours and treatment		
Sulphur dioxide						
Carcinogenicity, Pre-guideline study, does not follow OECD 451 principles Rel. 2 (untypical study design)	Mouse (LX colony), Group 1) control: 41 M/39 F; 2) free radical group: 30M/30F, 3) SO ₂ : 35M/30 F	Group 1: Untreated controls Group 2: Free radical inhalation Group 3: SO ₂ inhalation: 500 ppm (1330 mg/m³) /5min, 5 days/week, life long exposure. Examination of mice that survived ≥ 300 days (authors stated that no primary tumours of the lung were seen in LX mice below this age)	No data	Adenoma : Group 1 (Control): M: 11/35 (31 %) F: 5/30 (17 %) Group 2 (free radical inhalation): M: 12/29 (41 %) F: 7/30 (23 %) Group 3 (SO ₂ inhalation): M: 15/28 (54 %) F: 13/30 (45 %) Primary carcinoma: Group 1 (Control): M: 2/35 (6 %) F: 0/30 Group 2 (free radical inhalation): M: 3/29 (10 %) F: 0/30 Group 3 (SO ₂ inhalation): M: 2/28 (7 %) F: 4/30 (18 %)	Authors used LX mice because they are highly susceptible to the induction of lung adenoma in response to urethane. Adenoma in this study: all primary tumours of the lung are counted as adenomas, primary carcinoma: tumours which invade blood vessels. (primary carcinoma were also listed under adenoma) Assessment only in mice that survived at least 300 days.	Anonymous65
Carcinogenicity Non-guideline study, does not follow OECD 451 principles Rel. 2 (no typical)	Rat SD C.D. M; no. per group: 1)43 2)26	Group 1: Control (filtered air) Group 2: Control (filtered air + intratracheal instillation of gelatine	SO ₂ : 30/>30 ppm:	Negative: No malignant tumours observed in control and SO ₂ groups; high frequency of tumours in all B(a)P groups. No influence of SO ₂ on tumour	Treatment duration too short for a guideline conform carcinogenicity study High incidence of tumours in B(a)P – treated groups	Anonymous60

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Summary table of carcinogenicity studies in animals						
Method, Guideline, GLP status, Reliability	Species, Strain, Sex, No/ group	Test substance Dose levels, Route of exposure, Duration of exposure	NOAEL, LOAEL	Results (Please indicate any results that might suggest carcinogenic effects, as well as other toxic effects.)	Remarks (e.g. major deviations)	Reference
carcinogenicity study)	3)20 4)18 5)72 6)72 7)74	vehicle) Group 3: 10 ppm SO ₂ Group 4: 30 ppm SO ₂ Group 5: B(a)P Group 6: B(a)P + 10 ppm SO ₂ Group 7: B(a)P + 30 ppm SO ₂ 6h/d; 5d/wk; 21 weeks (treatment); observation period: 105 weeks		frequency in B(a)P groups.	precluded detection of tumour enhancing effect of SO ₂ . However, no tumours observed in groups exposed to SO ₂ alone.	
Carcinogenicity Non-guideline study, does not follow OECD 451 principles Rel. 3	Rat strain and sex not specified. 45 – 48 / group; 20 / control group	Sulphur dioxide Carcinogenicity part of study: exposure: 500 ppm Exposure induced mortality – inhalation of irritants: 10, 51, 105, 567 ppm (corr. 26, 134, 276, 1488 mg/m ³ – 24 °C) 6h/d; 5d/wk; 12 – 113 days (lowest to highest concentration)	10/105 ppm (from cumulative mortality study)	Neoplastic effects: no effects (No neoplastic effects were observed in the groups solely exposed to sulphur dioxide.) Non-neoplastic findings: Exposure-induced cumulative mortality (%): 10 ppm vs. control: 5 vs. 15 (day 113) 51 ppm vs. control: 18 vs. 10 (day 113) 105 ppm vs. control: 40 vs. 5 (day 22) 567 ppm vs. control: 87 vs. 10 (day 12), 105 and 567 high incidences of bronchitis, congestion, and pneumonia, regenerative hyperplasia and early metaplasia 4 d after exposure at 105 ppm	Major deficiencies when compared with guideline conform carcinogenicity study: duration too short, group size, major reporting deficiencies, study design	Anonymous61

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Table 18: Summary table of human data relevant for carcinogenicity

Summary table of human carcinogenicity data			
Kind of study (e.g. case reports)	Examination methods, number of individuals examined	Results	References
Cohort study on mortality due to cancer in workers of a paper company	Standardised mortality ratios (SMR) of selected causes of death; 883 subjects	460 workers were still alive, 414 were death, and 9 were lost to follow up. Employment in pulp or paper mills is associated with excess mortality due to digestive (SMR = 152, pancreatic cancer: SMR = 305) and lymphopoietic cancers (SMR = 241). Findings are not clearly SO ₂ related as workers might have been exposed towards other compounds (hydrogen sulfide, methyl mercaptan, chlorine, chlorine dioxide esp. pulp mill workers).	Henneberger, P.K. <i>et al.</i> (1989) Brit. J. Ind. Med. 46: 658-664. (published)
Cohort study on mortality due to cancer in workers of pulp and paper workers in Finland	Mortality (SMR) compared to national mortality rates 3520 subjects, six subcohorts compared to 1290 sawmill workers (control group)	Higher mortality from ischaemic heart disease in workers in sulphite, sulphate, and paper mills, maintenance department, and power plants compared to sawmills (SMR 121). Finding generally for occupational exposure in pulp and paper workers but cannot be related to SO ₂ .	Jäppinen, P. (1987). Brit. J. Ind. Med. 44: 580-587. (published)
Cohort study on mortality due to cancer in workers of pulp and paper workers in the USA	Mortality (SMR) compared to national mortality rates 3572 subjects	No increased cancer mortality or any mortality was observed in the cohort. Cohort of sulphite mill workers: Risk for stomach cancer was elevated for workers employed for 20 years in sulphite mills but did not increase with duration of employment.	Robinson, C.F. <i>et al.</i> (1986). Scand. J. Work Environ. Health 12: 552-560. (published)
Cohort study on cancer incidence among pulp and paper mill workers in British columbia	SIR (Standardised incidence ratios) in comparison to cancer incidence in the cohort 1756 cancer cases Cohort: 28278 workers; 475787 person-years; years worked (mean): 11.6 years	Excess risks of prostate and stomach cancers, leukemias in kraft and sulphite processes, rectal cancer for work in sulphite process only. Mesotheliomas associated with asbestos. Pulp and paper workers may have been exposed to asbestos, biocides, formaldehyde, hypochlorite (Band et al. 1997)	Band et al. (2001). Scand J Work Environ Health. 27/2:113-119
Cohort study on male pulp and paper workers in Norway	SIR Cohort: 23780 workers at least one year exposure between 1920 and 1993 in Norway	Excess incidence of lung cancer among short- and long-term employees: SIR for sulphite mill workers 1.5, 95 % CI 1.09-1.99). Lung cancer can be attributed to smoking and asbestos exposures. Other work-related exposures: sulphur and chloride compounds, wood dust).	Langseth and Andersen (2000) Scand J Work Environ Health. 26/2: 99-105
Cohort study on workers in pulp and paper industry in 12 countries (Brazil, Denmark, Finland, France,	SMR based on age-specific and calendar period-specific national mortality rates and cancer mortality risk.	Positive relationship between weighted cumulative SO ₂ exposure and lung cancer mortality (p-value of test for linear trend = 0.009 among all exposed workers; p = 0.3 among workers with high exposure. Mortality from non-Hodgkin lymphoma and	Lee et al. (2002) Environ Health Perspect. 110:991-995

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Summary table of human carcinogenicity data			
Kind of study (e.g. case reports)	Examination methods, number of individuals examined	Results	References
<p>Japan, New Zealand, Norway, Poland, South Africa, Spain, Sweden, USA).</p> <p>Data from Brazil and South Africa not included in analysis</p>	<p>Cohort: 57 613 workers \geq 1 year employed in pulp and paper industry</p>	<p>from leukaemia increased among workers with high sulphur dioxide exposure, dose–response relationship with cumulative sulphur dioxide exposure suggested for non-Hodgkin lymphoma. Conclusion: exposure with high concentrations of SO₂ in pulp and paper industry may be associated with increased lung cancer risk. SO₂ may have a cancer promoting effect in combination with other carcinogens. Residual confounding may have occurred. (e.g. Smoking was not considered as possible confounder, asbestos only assessed at level of department). Controlled possible co-exposure: asbestos, combustion products, welding fumes.</p>	

10.9.1 Short summary and overall relevance of the provided information on carcinogenicity

Taking into account all available information including genotoxicity, there is sufficient evidence that genotoxic effects occur at cytotoxic concentrations. The lung is the primary target organ following inhalation exposure to SO₂ but also following oral exposure to sulphites (bisulphites, metabisulphites). SO₂ and sulphite toxicity predominantly occur in tissues with lower sulphite oxidase activity (e.g. lung). As sulphite is a reactive substance, a carcinogenic effect mediated by binding to biomolecules (DNA, proteins) is principally possible, especially in tissues with low activity of sulphite oxidase. However, no clear evidence can be retrieved from the literature. A potential cytotoxic effect on chromosome aberration was postulated by Popescu and DiPaolo (1988). Bisulphite inhibition of DNA replication might be involved in the observed occurrence of abnormal chromosomes. Neoplastically transformed cells exhibit persistent chromosome rearrangements. This observation is in accordance with in vitro chromosome aberrations, especially at cytotoxic concentrations.

No classification for carcinogenicity is proposed. IARC (1992) came to the following conclusion: Sulphur dioxide, sulphites, bisulphites, and metabisulphites are not classifiable as to their carcinogenicity to humans (Group 3). No carcinogenicity study has been published since then. A comprehensive cohort study (Lee et al. 2002) concluded that exposure to sulphur dioxide of employees in pulp and paper industry may be associated with increased cancer risk, especially for lung cancer. Results were adjusted for some confounders. Controlled possible co-exposure: asbestos, combustion products, welding fumes. Increased relative risk (RR) for coexposure with asbestos and high SO₂ exposure as well as co-exposure of welding fumes and high SO₂. Exposure with sulphur dioxide was not measured but estimated by using international industrial hygiene measurement data from mills included in the study and from nonparticipating European and North American mills. Misclassification to exposure groups cannot be ruled out, completely. The authors further discussed the lack of potential lifestyle confounders (e.g. smoking) as important limitation of the study but considered the possible confounding effect of smoking habits not outside the range of 0.5 - 1.5 (smoking habits of not exposed and exposed population may not differ substantially higher). The authors identified as main result of the analysis an association between SO₂ exposure and mortality from all neoplastic diseases and lung cancer. The well-designed analysis comprises cohorts of several other publications. Apart from stated limitations by the authors, there is also uncertainty from other confounding factors in the paper processing (which may include, according to Band et al. 1997, chloroform, arsenic, formaldehyde, chlorophenols).

10.9.2 Comparison with the CLP criteria

In conclusion, there is evidence for an increased cancer risk especially associated with high sulphite exposure in exposed workers of the pulp and paper industry. However, due to potential co-exposure to other substances, information is considered not sufficient for classification for carcinogenicity category 1A.

Some animal experiments with sulfur dioxide or sulfur dioxide releasing compounds are available. However these had limitations regarding study design or reporting when compared to OECD TG recommendations. There are some results indicating carcinogenic effects in non-standard assays.

In summary, taking into account the limitations of the available data on carcinogenicity, DS does not see sufficient evidence to propose classification for carcinogenic hazards, even though sulfur dioxide is proposed to be a genotoxic compound.

10.9.3 Conclusion on classification and labelling for carcinogenicity

No classification for carcinogenicity is proposed.

10.10 Reproductive toxicity

Endpoint not addressed.

10.10.1 Adverse effects on sexual function and fertility

Endpoint not addressed.

10.10.2 Adverse effects on development

Endpoint not addressed.

10.10.3 Adverse effects on or via lactation

Endpoint not addressed.

10.11 Specific target organ toxicity-single exposure

The selected published studies were used to evaluate the ability of sulfur dioxide to induce bronchoconstriction. Main pulmonary function parameters amongst studies were SRaw (specific airway resistance) and FEV_{1.0} (forced expiratory volume in one second). According to the American Thoracic Society (ATS), reductions in FEV_{1.0}, of <10, 10-20 %, and >20 % were graded as mild, moderate, or severe, respectively (Samet et al. 2000). Another useful assessment of airflow limitations is the ratio of FEV_{1.0} to FVC (forced vital capacity). The FEV₁/FVC ratio is normally greater than 0.75 to 0.8, and possibly greater than 0.90 in children. Any values less than these suggest airflow limitation (GINA Report 2012). As the majority of studies with sulfur dioxide did not provide data on FEV₁/FVC ratio, reductions in FEV_{1.0} and/or SRaw were used instead (criteria as described below). Changes in lung function parameters were identified at concentrations of 0.4 ppm with asthmatics being the most vulnerable group. Increases in SRaw of ≥ 100 % (according to criteria of the “German Society for Pneumology”) and moderate decreases of FEV_{1.0} of ≥ 10 % were used as criterion to define an adverse effect indicating airflow restriction following short-term exposure.

Table 19 Summary table of other studies relevant for respiratory sensitisation/ irritation

Summary of controlled human exposure studies with asthmatics and healthy volunteers exposed to SO ₂							
Reference / study characteristics	SO ₂ exposure			(Lung) function parameters	Ventilation rate	Results	Others/ Remarks
	Conc. mg/m ³	Conc. ppm	Duration min				
<p>Linn et al. 1987 / 85 volunteers in 4 clinical groups:</p> <p>1: normal subjects (15M 9F; age: 18 - 37)</p> <p>2: atopic subjects (12M 9F, age: 18 - 32)</p> <p>3: subjects with minimal or mild asthma (10M 6F, age: 20 - 33)</p> <p>4: subjects with moderate to severe asthma (10M 14 F; age: 18 - 35, 1x 46)</p> <p>Key study</p>	0.5 1.1 1.6	0.2 0.4 0.6	60	<p>PD₂₀ in FEV_{1.0}, SRaw at FRC, FVC, PEF, EKG, maximal mid expiratory flow, symptom score</p>	40 L/min (during exercise)	<p>Changes in pulmonary function FEV_{1.0} - in clinical groups (results of 1. round)</p> <p>Group 1: none</p> <p>Group 2: none</p> <p>Group 3:</p> <p>0.4 ppm: FEV_{1.0}: ↓ (-6 %), SRaw: ↑ (129 %)</p> <p>0.6 ppm: FEV_{1.0}: ↓ (-11 %), SRaw: ↑ (153 %)</p> <p>Increases control SRaw: 29 %</p> <p>Group 4:</p> <p>0.4 ppm: FEV_{1.0}: ↓ (-13 %), SRaw: ↑ (108 %)</p> <p>0.6 ppm: FEV_{1.0}: ↓ (-24 %), SRaw: ↑ (200 %)</p> <p>Increases control SRaw: 73 %</p> <p>Significant increase (p<0.0001) of symptom score with increasing SO₂ concentrations</p> <p>LOAEL: 0.4 ppm</p> <p>NOAEL: 0.2 ppm</p>	<p>Alternate 10 min exercise and resting periods within a 1-h exposure cycle.</p> <p>Pulmonary function prior to, early and late in exposure; cross-over study</p>
<p>Roger et al. 1985 / 28 non-smoking male asthmatics currently receiving no corticosteroid, cromolyn sodium or desensitization therapy, baseline SRaw: 2.2 - 12.8 cm H₂O x sec.; FEV_{1.0}/FVC = 56 - 89 %, age: 19 - 34</p>	0 0.6 5 1.3 2.6	0 0.2 5 0.5 1.0	75	<p>SRaw, FEV_{1.0}, FVC, FEV_{1.0}/FVC, V_{tg}, FEF₂₅₋₇₅, Exercise at a)0, b)25, and c)50 min after entering the chamber</p> <p>SRaw in a, b, c: 3, 5, 7, and 9 min post-exercise</p> <p>Symptome questionnaire</p>	<p>normalized to body surface: 21.4±0.4 L/m²/min</p>	<p>Significant increase (p≤0.005) following exercise at 0, 25, and 50 min at 0.5 ppm SO₂ (93 %, 63 %; 52 % compared to pre-exposure; 39 %, 28 %, 24 % compared to clean air exposure) and 1.0 ppm (191 %, 147 %, 116 % compared to pre-exposure; 100 %, 86 %, 68 % compared to clean air exposure)</p> <p>LOAEL: 0.5 ppm</p> <p>NOAEL: 0.25 ppm</p>	<p>Chamber: 4 x 6 x 3.2 m 26.1±0.3°C, no pre-selection of SO₂ sensitive asthmatics</p>

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Summary of controlled human exposure studies with asthmatics and healthy volunteers exposed to SO ₂							
Reference / study characteristics	SO ₂ exposure			(Lung) function parameters	Ventilation rate	Results	Others/Remarks
	Co nc. mg/ m ³	Co nc. pp m	Durat ion min				
moderate exercise: V _E = 42 L/min, double-blind Key study							
Linn et al. 1982 24 volunteers (13 M, 11 F), moderate exercise mild to moderate asthmatics (FEV _{1.0} /FVC: 1x 59 %; 2x 66-68 %, 21 normal), non-smokers, mean age: 23±4 y exposure: 2 exercise phases: 1) 0-10 min followed by body plethysmography 40-50 min followed by body plethysmography, rests in between Key study	0 0.7 1.3	0 0.2 5 0.5	60	FVC, FEV _{1.0} (D ₁₀), V _{tg} , SRaw, Raw	27±6 L/min during exercise	0.25 ppm: no significant changes observed 0.5 ppm: no significant changes observed LOAEL: >0.5 ppm NOAEL: 0.5 ppm	Chamber Temperature 23°C
Schachter et al. 1984, 10 healthy (4M 6F) and 10 asthmatic (5M 5F) volunteers age (healthy): 26.1±6.3 asthmatics: 27.3±5.1 FEV _{1.0} asthmatics: 2.66±0.52,	0 0.6 6 1.3 2.0 2.6	0 0.2 5 0.5 0.7 5 1.0	40	SRaw, FEV _{1.0} , V _{max50%} , MEF _{40%} ,		No statistically significant differences (P<0.05) in parameters examined without exercise. Changes with exercise (significant changes from baseline at resp. SO ₂ concentration, asthmatics): FEV_{1.0} (L): 1 min post exercise: 0.75 ppm: -8 % 1.00 ppm: -14 %	Chamber: 3x3.7x2.4 m All group changes in pulmonary function were transient, with values returning to near baseline within 10 min after cessation of exercise despite

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Summary of controlled human exposure studies with asthmatics and healthy volunteers exposed to SO ₂							
Reference / study characteristics	SO ₂ exposure			(Lung) function parameters	Ventilation rate	Results	Others/ Remarks
	Co nc. mg/m ³	Co nc. ppm	Durat ion min				
SRaw: 5.01±1.5 cmH ₂ O/L*sec. Key study						5 min post exercise: 1.00 ppm: -11 % SRaw (cm H₂O/L x sec) 1 min post exercise: 1.00 ppm: + 54 % 5 min post exercise: 0.75 ppm: + 30 % 1.00 ppm: + 68 % MEF_{40%} (L/s): 1 min post exercise: 0.75 ppm: - 22 % 1.00 ppm: - 27 % 5 min post exercise: 0.75 ppm: - 16 % 1.00 ppm: - 16 % V_{max50%} (L/s) 1 min post exercise: 0.25 ppm: - 5 % 0.75 ppm: - 11 % 1.00 ppm: - 22 % 5 min post exercise: 0.50 ppm: - 6 % LOAEL: 0.75 ppm NOAEL: 0.5 ppm	continued presence of SO ₂ . In healthy subjects, upper airway complaints predominated in the absence of pulmonary functional changes.
Sandström et al. 1988 / 8 healthy nonsmoking subjects, 21 – 29 y, normal lung function	1 5 10	0.4 2 4	20	Heart rate, breathing pattern, frequency of eye blinks, standardized questionnaire, spirometry: FVC, FEV _{1.0} , FEF ₂₅₋₇₅ , MTT	n.r.	Increase in nasal and throat irritation at 10 mg/m ³ in 5/8 subjects, no difference in spirometry parameters 90-100 heart beats/min, 18-23 breaths/min – no changes while exposed LOAEL: 4 ppm (throat irritation) NOAEL: 2 ppm	Chamber: 3.2x2.0x2.2 m Air volume: 14.1 m ³ , air exchange ca. every 2 min last 15 min on bicycle ergometer (75 W)
Sandström et al. 1989 / 12 healthy nonsmoking subjects, 22 – 30	0 10 20	0 4 8	20	Bronchoscopy; BAL Lung function	n.r.	4 ppm: Normal endobronchial findings and normal lung function, activation of	Chamber: 3.2x2.0x2.2 m Air volume: 14.1 m ³ , air

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Summary of controlled human exposure studies with asthmatics and healthy volunteers exposed to SO ₂							
Reference / study characteristics	SO ₂ exposure			(Lung) function parameters	Ventilation rate	Results	Others/ Remarks
	Conc. mg/m ³	Conc. ppm	Duration min				
y, normal lung function; 4 subjects/group						alveolar macrophages; mild symptoms from eye and nose (no details reported) 8 ppm: mucosal erythaema in the distal part of trachea and proximal main bronchi; normal lung function, mild lymphocytosis, mild symptoms from eye and nose (no details reported) LOAEL: 8 ppm (mucosal erythaema) NOAEL: 4 ppm	exchange ca. every 2 min
Sandström et al. 1989 / 22 healthy nonsmoking male subjects, 22 – 37 y, mean: 27 y; normal lung function	20	8	20	BAL, spirometry: FEV _{1.0}	n.r.	8 ppm: 4h following exposure: mucosal erythema in trachea and proximal main bronchi of all subjects (disappeared 72h after exposure) total lymphocytes ↑, mast cells ↑, 8h following exposure: total cell number ↑ peak at 24h (alveolar macrophages / monocytes, lymphocytes, mast cells ↑; eosinophils and neutrophils unaffected), non-significant decrease in FEV _{1.0} LOAEL: 8 ppm (mucosal erythema) NOAEL: <8 ppm	Chamber: 3.2x2.0x2.2 m Air volume: 14.1 m ³ , air exchange ca. every 2 min, last 15 min on bicycle ergometer (75 W)
Bedi et al. 1984 / 9 + 14 healthy (M) nonsmoking subjects, 19 – 28 y (mean: 21.8), normal lung function	0 2.6 5.8	0 1 2	120	FRC, FVC, FEV _{1.0,2.0,3.0} , SRaw, MMV, V _{tg} , ERV, IC, FEF ₅₀ , FEF ₂₅₋₇₅ , FEF ₇₅	40 L/min	No significant changes in lung function parameters observed. LOAEL: >2 ppm NOAEL: 2 ppm	Chamber: 1.8x2.4x2.6 m air exchange ca. every 5 min; 22 °C; 40 % rel. humidity

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Summary of controlled human exposure studies with asthmatics and healthy volunteers exposed to SO ₂							
Reference / study characteristics	SO ₂ exposure			(Lung) function parameters	Ventilation rate	Results	Others/Remarks
	Conc.	Conc.	Duration				
	mg/m ³	ppm	min				
Andersen et al. 1974; 15 healthy male volunteers; age: 20 – 28 y; 4 smoker; 11 non-smoker	0 2.6 13.2 65.8	0 1 5 25	360	Nasal mucus flow rate, cross-sectional nasal airway, rhinomanometry, FEV _{1.0} , FEF ₂₅₋₇₅ ,	n.r.	<p>1 ppm: cross-sectional nasal airway significantly ↓ (more pronounced after 1-3 hours than after 4-6 hours exposure), FEF₂₅₋₇₅ significantly ↓</p> <p>5 ppm: mucus flow rate significantly ↓, cross-sectional nasal airway ↓, FEF₂₅₋₇₅ significantly ↓</p> <p>25 ppm: mucus flow rate (significantly) ↓ up to mucostasis; cross-sectional nasal airway ↓ (29 %), FEV_{1.0} significantly ↓ (4 %), FEF₂₅₋₇₅ significantly ↓</p> <p>concentration dependent increase in severity of all parameters investigated</p> <p>LOAEL: 25 ppm NOAEL: 5 ppm</p>	Climate chamber, all volunteers were exposed together, no exercise; no information on air change; 23 ± 0.3°C; 50±5 % rel. humidity; clean air exposure day 0; 1.0; 5.0; 25.0 ppm at days 1 – 3 respectively. Study design different from majority of other studies
Van Thriel et al. 2010; 16 healthy, non-smoking volunteers (8M/8F); age: F: 24.3±5.2 y; M: 28.4±3.9; FEV _{1.0} /FVC: 71 – 96 %; FEV _{1.0} : F: 3.85±0.6 L M: 4.56±0.54 L	0 1.3 2.6 5,2	0 0.5 1.0 2.0	240	FEV _{1.0} , FVC, FEV _{1.0} /FVC, PWC130, nasal airway resistance, eye blink frequency	n.r.	<p>FEV_{1.0}/FVC: no effect observed.</p> <p>ΔFEV_{1.0}: all ≤ 10 %, majority ≤ 5 %, no significant changes in parameters investigated were observed in healthy volunteers.</p> <p>LOAEL: >2 ppm NOAEL: 2 ppm</p>	Chamber: 4. x 2.65 x 2.27 m; 23.9 °C No single or tabulated data reported
Linn et al. 1985 24 volunteers (15 M, 9 F) with COPD, exposure included 2x 15 min exercise, age: mean: 60 (49 – 68 y)	0 1.0 5 2.1	0 0.4 0.8	60	V _{tg} , SRaw, FVC, FEV _{1.0} , S _{aO2} , MMFR, VE and heart rate at S _{aO2} , symptom questionnaire		<p>SRaw: 0.0; 0.4; 0.8 ppm: 20.2; 17.8; 17.4 8 cm H₂O x sec, respectively</p> <p>FEV_{1.0}: no significant differences between groups;</p> <p>No evidence for a clinical or physiological effects of</p>	Influence of COPD higher than of SO ₂ exposure

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Summary of controlled human exposure studies with asthmatics and healthy volunteers exposed to SO ₂							
Reference / study characteristics	SO ₂ exposure			(Lung) function parameters	Ventilation rate	Results	Others/ Remarks
	Conc.	Conc.	Durat ion				
	mg/m ³	ppm	min				
FEV _{1.0} /FVC = 47 % (1x 70 %), 17 former heavy smoker, 6 smoker, 1 non-smoker						SO ₂ exposure in this patient collective. LOAEL: >0.8 ppm NOAEL: 0.8 ppm	
Linn et al. 1983 23 asthmatic volunteers (13 M, 10 F), heavy exercise FEV _{1.0} /FVC = 67 – 100 %, patients hyperreactive to metacholine	0 0.5 3 1.0 6 1.6	0 0.2 0.4 0.6	5	Electrocardiogram FVC V _{tg} , S _{Raw} , FEV _{1.0,2.0,3.0} , S _{aO2} , PEF _R , FVC, V _{max75,50} , 25	Mean: 48 L/min	0.2 ppm: no significant changes 0.4 ppm: S _{Raw} : ↑ (69 %) V _{max75/50/25} : significant decrease at 0.4 (-8 %/ -10 %/-12 %) 0.6 ppm: S _{Raw} : ↑ (129 %), FEV _{1.0} : ↓ (-13 %), V _{max75/50/25} : ↓ (-21 %/ -25 %/- 31 %) PEF _R : ↓ (-14 %) All compared to pre-exposure values; control: S _{Raw} : ↑ 36 %. LOAEL: 0.6 ppm NOAEL: 0.4 ppm	Exposure temperature 23°C, rel. humidity: 85 %
Linn et al. 1984 24 volunteers (13 M, 11 F), heavy exercise mild to moderate asthmatics, non-smokers	0 0.8 1.6	0 0.3 0.6	Ca. 8 min 3x/week; 3 weeks	V _{tg} , S _{Raw} , S _{Gaw}	50 L/min during exercise	0.3 ppm: S _{Raw} : ↑ (< 100 % compared to changes in controls); 0.6 ppm: S _{Raw} : ↑ (> 100 % compared to changes in controls) LOAEL: 0.6 ppm NOAEL: 0.3 ppm	Values for mg/m ³ at 21°C, only SO ₂ responder participated, exposure investigated at 21°C, 7°C, -6°C, additive effects on temperature observed, but temperature influence lower at higher SO ₂ concentrations
Linn et al. 1988 20 volunteers (13 M, 7 F), heavy exercise (FEV _{1.0} /FVC: 69 – 90 %), non-smokers,	0 0.8 1.6	0 0.3 0.6	10	FVC, FEV _{1.0} , S _{Raw} , symptom score	50	0.3 ppm: S _{Raw} ↑ (< 100 %), FEV _{1.0} ↓ (changes > 20 %) 0.6 ppm: S _{Raw} ↑ (>100 %), FEV _{1.0} ↓ (changes > 20 %)	No information on chamber size and conditions

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Summary of controlled human exposure studies with asthmatics and healthy volunteers exposed to SO ₂							
Reference / study characteristics	SO ₂ exposure			(Lung) function parameters	Ventilation rate	Results	Others/ Remarks
	Co nc. mg/ m ³	Co nc. pp m	Durat ion min				
age: 19-36 y Volunteers with minimal – moderate asthma (9 on medication)						LOAEL: 0.3 ppm (decrease FEV _{1.0}) NOAEL: <0.3 ppm	Study was conducted to test influence of pre-treatment on SO ₂ -induced bronchoconstriction. Values without medication were used in this table.
Horstman et al. 1986 / 27 non-smoking male asthmatics currently receiving no corticosteroid, cromolyn sodium or desensitization therapy, baseline SRaw: 6.8 cm H ₂ O x sec.; FEV _{1.0} /FVC = 72 %, age: 18 - 35	0 0.6 5 1.3 2.6 5.2	0 0.2 5 0.5 1.0 2.0 #	10	SRaw, FEV _{1.0} /FVC	normalised to body surface: V _E : 21 L/m ² /min	SO ₂ concentration required to induce an increase of 100 % of SRaw: 0.28 – 1.9 ppm (23 subjects) >2 ppm (4 subjects) median: 0.75 ppm, for 6 subjects: <0.5 ppm LOAEL: 0.28 ppm NOAEL: <0.28 ppm	Chamber: 4 x 6 x 3.2 m 26.1±0.3°C, no pre-selection of SO ₂ sensitive asthmatics ± the same cohort as in Roger et al. 1985
Gong et al. 1995 14 unmedicated SO ₂ sensitive asthmatics, non-smoker, age: 27±11; 19-50 y	0 1.3 2.6	0 0.5 1.0	10	Psychophysical measurements: BS; VAS, FEV _{1.0}	Exercise light: 30 medium: 36 heavy: 43 L/min	10 min SO ₂ exposure > 0.5 ppm and ventilation > 30 L/min can cause or intense asthma manifestations comparable to those usually expected from everyday stress. (Study with reporting deficiency, no tabulated results)	Chamber: 2.2 m ³ , pre-selection of SO ₂ sensitive asthmatics: ≥ 75 % SRaw increase at 1 ppm SO ₂ and heavy exercise
Study with workers at an apricot farm							
Koksall et al. 2003 / 69 volunteer male workers at 15 apricot farms, mean age: 31.29±14.66, 15 – 69 y, duration of work in sulfurization	285 – 192 0	10 7 – 72 2* me an 34 2 ±	≤ 60	Symptom score, FVC, FEV _{1.0} , FEV _{1.0} /FVC%, FEF ₂₅₋₇₅ , PEF _R , V _{max25/50/75}	n.r.	Asthma-like symptoms such as acute mucosal irritation, decrease in pulmonary functions, dyspnoea (80 %), cough (78 %), itchy or scratchy throat (36 %), eye and nose irritation (83/70 %)	Exclusion criteria: history of allergy or known pulmonary or systemic diseases (23

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Summary of controlled human exposure studies with asthmatics and healthy volunteers exposed to SO ₂							
Reference / study characteristics	SO ₂ exposure			(Lung) function parameters	Ventilation rate	Results	Others/Remarks
	Co nc. mg/ m ³	Co nc. pp m	Durat ion min				
process: 10.98 ± 10.83 y, 1 – 45 y, 45 smoker/24 non-smoker		19 5				FEV _{1.0} ↓ (1-40 % in 88 % of workers); significant decrease (p<0.05) in FVC%; p<0.001: FEV _{1.0} , FEV _{1.0} /FVC%, PEF _R , V _{max25/50/75} , LOAEL/ NOAEL: n.d.	subjects excluded)
Results derived from Reviews							
Goodman et al. 2010, data from 13 controlled clinical exposure studies with a total of 274 asthmatic volunteers	0 0.5- 2.7	0 0.2 - 1.0	n.r.	SRaw, FEV _{1.0}	30-90	≥ 0.4 ppm SRaw ↑ (≥ 100 %) and/or FEV _{1.0} ↓ (≥ 10 %) LOAEL: 0.4 ppm NOAEL: 0.2 ppm	Some studies already included as single studies in this table.
Johns and Linn 2011, data from 55 controlled clinical exposure studies with a total of 948 asthmatic volunteers	0 0.2 7 – 21. 3	0 0.1 - 8	1- 240?	SRaw, FEV _{1.0}	≤ 1	Increase in bronchomotor response with increasing SO ₂ concentrations with significant interindividual variability in response. LOAEL/NOAEL: n.d. Only few studies reported effects with SO ₂ concentrations < 0.4 ppm.	Some studies already included as single studies in this table.

BAL: bronchoalveolar lavage, BS: Borg scale, COPD: chronic obstructive pulmonary disease, EKG: electrocardiogram, ERV: Expiratory reserve volume; FEV_{1.0}: forced expiratory volume in 1 sec, FEF₂₅₋₇₅: mean expiratory flow during the middle half of FVC; FEF_{max}: maximal expiratory flow during FVC; FEF_{50/75}: instantaneous expiratory flows after 50 and 75 % of the FVC are exhaled, FRC: functional residual capacity, FVC: forced vital capacity, IC: inspiratory capacity; MEFV: maximal flow volume, MMFR: maximal midexpiratory flow rate, MTT: mean transit time, MV: minute ventilation, n.r. not reported, PC₈: Provocative concentration causing a SRaw increase of 8 units (L x cm H₂O/L/s), PEF_R: peak expiratory flowrate, PEFV: partial flow volume, MVV: maximal voluntary ventilation; PFT: pulmonary function tests, S_{aO2}, PWC130: physical capacity at a heart rate of 130 bpm; SG_{aw}: specific conductance in cm H₂O⁻¹sec⁻¹ (reciprocal of sRaw), sRaw: specific airway resistance, VAS: visual analog scale, V_E: minute ventilation, V_{max25/50/75}: flows at 25/50/75 % of vital capacity, V_{Ig}: thoracic gas volume

*: volume of sulfurization chambers and amount of sulfur differed between apricot farms

#: Subjects whose SRaw increase was < 100 % at 1.0 ppm were also exposed to 2.0 ppm;

10.11.1 Short summary and overall relevance of the provided information on specific target organ toxicity- single exposure

Sulfur dioxide is a corrosive substance with irritating properties at lower concentration. Irritation at lower concentrations is covered by the derived reference value for inhalation exposure. In animal studies there is some indication for respiratory tract irritation that is supported by human data. There are numerous data available on respiratory tract irritation of sulfur dioxide in humans. The studies are mainly of short-term durations in occupationally exposed workers, volunteers or represent medical surveillance data. Exposure of

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volunteers or occupationally exposed workers to sulfur dioxide at concentrations higher than 1 ppm caused complaints of dryness in the throat, nose, eyes and upper respiratory passages. Reductions in clearance rates and symptoms of discomfort as well as inflammatory reactions in the human lung were observed. Relative air humidity had no influence on effects at low exposure concentrations (until 6 ppmV). Generally, all pulmonary changes were reversible. However, significant changes in pulmonary function, dyspnoea, pain on deep breathing, severe conjunctivitis and airway obstruction were reported in people who survived after acute accidental exposure to extremely high concentrations of sulfur dioxide. Some changes were partially irreversible (e.g. damage of the ciliated epithelium with impairment of pulmonary clearance, increased sensibility to external irritants and infections). They showed also symptoms of chronic bronchitis. In dead persons, lung oedema, emphysematous changes with fundamental lesions of extensive peribronchiolar fibrosis and bronchiolitis obliterans were observed.

No statistically significant changes in physiology or symptoms could be attributed to sulfur dioxide exposure at concentrations of 1 ppm and lower in healthy subjects including smokers and volunteers with chronic obstructive pulmonary disease (COPD). Nevertheless, a wide range of sensitivities to sulfur dioxide was found among the asthmatic subjects (see Table 11 above).

Indication for respiratory tract irritation such as nasal and throat irritation was observed in healthy humans following exposure to 4 ppm sulfur dioxide (Sandström et al. 1988). Sulfur dioxide is classified as corrosive and classification for respiratory tract irritation is considered required. Also based on the broad, well documented human experience on irritating effect to respiratory system, sulfur dioxide is used as an example of respiratory tract irritant substance in the Guidance on the Application of the CLP Criteria (2017, section 3.8.5.1.3., page 456).

10.11.2 Comparison with the CLP criteria

Toxicological results	CLP criteria
<p>Sulfur dioxide:</p> <ul style="list-style-type: none"> - Broad, well documented human experience on irritating effect to respiratory system. - Corrosive substance with irritating properties at lower concentration - In animal studies there is some indication for respiratory tract irritation that is supported by human data - Transient effects observed <p>Proposed classification as STOT-SE3 (Respiratory Tract Irritant)</p>	<p>Category 1 (H370):</p> <p>Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following single exposure.</p> <p>Substances are classified in Category 1 for specific target organ toxicity (single exposure) on the basis of:</p> <p>(a) reliable and good quality evidence from human cases or epidemiological studies; or</p> <p>(b) observations from appropriate studies in experimental animals in which significant and/or severe toxic effects of relevance to human health were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below to be used as part of weight-of-evidence evaluation.</p> <p>Equivalent guidance value ranges for single dose exposures:</p> <p>Oral (rat): $C \leq 300$ mg/kg bw</p> <hr/> <p>Category 2 (H371):</p> <p>Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following single exposure.</p> <p>Substances are classified in Category 2 for specific target</p>

Toxicological results	CLP criteria
	<p>organ toxicity (single exposure) on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below in order to help in classification.</p> <p>In exceptional cases, human evidence can also be used to place a substance in Category 2.</p> <p>Equivalent guidance value ranges for single dose exposures:</p> <p>Oral (rat): $2000 < C \leq 300$ mg/kg bw</p> <p>Category 3 (H335):</p> <p>Transient target organ effects</p> <p>This category only includes narcotic effects and respiratory tract irritation. These are target organ effects for which a substance does not meet the criteria to be classified in Categories 1 or 2 indicated above. These are effects which adversely alter human function for a short duration after exposure and from which humans may recover in a reasonable period without leaving significant alteration of structure or function. Substances are classified specifically for these effects as laid down in 3.8.2.2.</p> <p>Annex I: 3.8.2.2.1 Criteria for respiratory tract irritation <i>The criteria for classifying substances as Category 3 for respiratory tract irritation are:</i></p> <p>(a) <i>respiratory irritant effects (characterized by localized redness, oedema, pruritis and/or pain) that impair function with symptoms such as cough, pain, choking, and breathing difficulties are included. This evaluation will be based primarily on human data.</i></p> <p>(b) <i>subjective human observations could be supported by objective measurements of clear respiratory tract irritation (RTI) (such as electrophysiological responses, biomarkers of inflammation in nasal or bronchoalveolar lavage fluids).</i></p> <p>(c) <i>the symptoms observed in humans shall also be typical of those that would be produced in the exposed population rather than being an isolated idiosyncratic reaction or response triggered only in individuals with hypersensitive airways. Ambiguous reports simply of "irritation" shall be excluded as this term is commonly used to describe a wide range of sensations including those such as smell, unpleasant taste, a tickling sensation, and dryness, which are outside the scope of classification for respiratory irritation.</i></p> <p>(d) <i>there are currently no validated animal tests that deal specifically with RTI, however, useful information may be obtained from the single and repeated inhalation toxicity tests. For example, animal studies may provide useful information in terms of clinical signs of toxicity (dyspnoea, rhinitis etc) and histopathology (e.g. hyperemia, edema, minimal inflammation, thickened mucous layer) which are reversible and may be reflective of the characteristic clinical symptoms described above. Such animal studies can be used as part of weight of evidence evaluation.</i></p>

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Toxicological results	CLP criteria
	<i>(e) this special classification would occur only when more severe organ effects including in the respiratory system are not observed.</i>

10.11.3 Conclusion on classification and labelling for STOT SE

DS proposes classification in STOT-SE Category 3, Respiratory tract irritant, H335 May cause respiratory irritation.

The classification criteria for Category 3 (Respiratory Tract Irritation) is fulfilled based on well documented experience in humans. RAC may also consider Category 1 of STOT-SE as significant (asthmatic effects on humans) for sulfur dioxide classification.

10.12 Aspiration hazard

No data available.

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11 REFERENCES

CHEMSAFE (2016): Database that contains safety characteristic data for fire and explosion prevention, evaluated and recommended by experts at BAM and PTB. CHEMSAFE is a joint project between BAM (Federal Institute for Materials Research and Testing, Berlin), PTB (Physikalisch-Technische Bundesanstalt, Braunschweig) and DECHEMA (Gesellschaft für Chemische Technik und Biotechnologie e.V., Frankfurt am Main); <http://dechema.de/en/chemsafe.html>

ISO 10156:2010: Gases and gas mixtures - Determination of fire potential and oxidizing ability for the selection of cylinder valve outlets; http://www.iso.org/iso/catalogue_detail.htm?csnumber=44817

Overall reference list (including data owner and confidentiality claim)

Part of the dossier

Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
8. TOXICOLOGICAL PROFILE FOR HUMAN AND ANIMAL INCLUDING METABOLISM						
8.1_01 Summary: Toxicological profile for humans and animals	Sulphites	Chemservice S.A.	2015	Read-across concept for sulphur dioxide, sulphites, hydrogensulphites and metabisulphites in aqueous solution Not GLP / Unpublished	Yes	Micro-Pak B.V.
8.1_02 Summary: Toxicological profile for humans and animals	Sulfites	Betts, R.H. and Voss, R.H.	1970	The kinetics of oxygen exchange between the sulphite ion and water	No	Published
8.3_02 Skin sensitisation	Sodium metabisulfite	Anonymous1	2010		Yes	SDIOC (Micro-Pak B.V. has LoA)
8.3_02 Skin sensitisation	Sodium metabisulfite	Haferkorn, J.	2010	Attachment of summary table (source indicated above for 8.3_02). GLP / Unpublished	Yes	SDIOC (Micro-Pak B.V. has LoA)
8.3_03 Skin sensitisation	Potassium metabisulfite	Gillman, S.A.	1982	Metabisulfite Sensitivity as a Cause of Asthma. West J Med. 1982; 137 (29): 120-1. Not GLP / Published	No	Published
8.3_04 Skin sensitisation	Sodium metabisulfite	Belchi-Hernandez, J., Florido-Lopez, F., Estrada-Rodriguez, J.L., Martinez-Alzamora, F., Lopez-Serrano, C.	1993	Sulphite-induced urticaria. Annals of Allergy, 71, 230-232. Not GLP / Published	No	Published

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		and J.A. Ojeda-Casas				
8.3_05 Skin sensitisation	Sodium metabisulfite	Jiménez-Aranda, G.S., Flores-Sandoval, G., Gómez-Vera, J. and M. Orea-Solano	1996	Prevalencia de urticaria crónica posterior a la ingestión de aditivos alimentarios en un hospital de tercer nivel. Revista Alergia México, Vol. XLIII, Num. 6, noviembre-diciembre 1996, 152-156. Not GLP / Published	No	Published
8.3_06 Skin sensitisation	Potassium metabisulfite	Cifuentes, L., Ring, J., Brockow, K.	2013	Clonal Mast Cell Activation Syndrome with Anaphylaxis to Sulphites. Int Arch Allergy Immunol: 2013; 162: 94–96. Not GLP / Published	No	Published
8.3_07 Skin sensitisation	Sodium metabisulfite	Cussans, A., McFadden, J. and L. Ostlere	2015	Sytemic sodium metabisulfite allergy. Contact Dermatitis, Contact Points, pp. 1-2. Not GLP / Published	No	Published
8.4_01 Respiratory sensitisation	Sulfur dioxide	Park, J.K. et al.	2001	Repeated exposure to low levels of sulfur dioxide (SO ₂) enhances the development of ovalbumin-induced asthmatic reactions in guinea pigs. Ann. Allergy. Asthma Immunol. 86: 62-67. Not GLP / Published	No	Published
8.4_02 Respiratory sensitisation	Sulfur dioxide	Anonymous2	1988		No	Published
8.4_03 Respiratory sensitisation	Sulfur dioxide	Anonymous3	1992		No	Published
8.4_04 Respiratory sensitisation	Sulfur dioxide	Anonymous4	1995		No	Published
8.4_05 Respiratory sensitisation	Sodium metabisulfite	Twarog, F.J., Leung D.Y.	1982	Anaphylaxis to a Component of Isoetharine (Sodium Bisulphite). JAMA, 1982; 22: 248 (16): 2030-1. Not GLP / Published	No	Published
8.4_06 Respiratory sensitisation	Sodium metabisulfite	Delohery, J. et al.	1984	The relationship of inhaled sulphur dioxide reactivity to ingested metabisulphite sensitivity in patients with asthma. Am. Rev. Respir. Dis. 130: 1027-1030 Not GLP / Published	No	Published
8.4_07 Respiratory sensitisation	Potassium metabisulfite	Schwartz, H.J., Chester, E.H.	2000	Bronchospastic responses to aerosolized metabisulphite in asthmatic subjects: Potential mechanisms and clinical implications. J Allergy Clin Immunol. 1984; 74 (4) Pt 19: 511-513. Not GLP / Published	No	Published

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8.4_08 Respiratory sensitisation	Sodium metabisulfite	Mansour, E, Ahmed, A., Cortes, A., Caplan, J., Burch, R.M., Abraham, W.M.	1992	Mechanisms of metabisulphite-induced bronchoconstriction: evidence for bradykinin B ₂ -receptor stimulation. Journal of Applied Physiology (Bethesda, Md: 1985): 1992; 72 (5): pp. 1831-1837. Not GLP / Published	No	Published
8.4_09 Respiratory sensitisation	Sodium metabisulfite	Vallon C., Sainte-Laudy, J. and Nasr, M.	1995	Allergie et exposition professionnelle aux composés soufrés: questions posées. Allerg Immunol (Paris), 27, 83-87 Not GLP / Published	No	Published
8.4_10 Respiratory sensitisation	Sodium metabisulfite	Hein, H., Kirsten, D., Jörres, R.A. and H. Magnussen	1996	Die orale Testung auf Sulfitastrhma. Pneumologie, Vol. 50, 394-398. Not GLP / Published	No	Published
8.4_11 Respiratory sensitisation	Sodium metabisulfite	Boner AL, Guarise A, Vallone G, Fornari A, Piacentini F, Sette L.	1990	Metabisulphite oral challenge: incidence of adverse responses in chronic childhood asthma and its relationship with bronchial hyperreactivity J Allergy Clin Immunol. 1990 Feb;85(2):479-83 Not GLP / Published	No	Published
8.4_12 Respiratory sensitisation	Sulfur dioxide and Sodium metabisulfite	Bush RK, Taylor SL, Holden K, Nordlee JA, Busse WW	1986	Prevalence of sensitivity to sulfiting agents in asthmatic patients Am J Med. 1986 Nov;81(5):816-20 Not GLP / Published	No	Published
8.5.1_01 Mutagenicity	Sulfur dioxide	Pool-Zobel, B.L. et al.	1990	In vitro and ex vivo effects of the air pollutants SO ₂ and NO _x on benzo(a)pyrene activating enzymes of the rat liver. Exp. Pathol. 39, 207-212. Not GLP / Published	No	Published
8.5.1_02 Mutagenicity	Sodium metabisulfite	Ishidate, M., Sofuni, T., Yoshikawa, K. et al.	1984	Primary mutagenicity screening of food additives used in Japan Food Chem. Toxicol. 22: 623-636 Not GLP / Published	No	Published
8.5.1_03 Mutagenicity	Sodium metabisulfite	Simmon, V.F. and Eckford, S.L.	1978	Microbial mutagenesis testing of substances: compound report: F76-004, sodium metabisulphite Published report: PB89-193684, SRI Project LSU-6909. Report No: FDA/CFSAN-89/83. Report date: 1978-04-01 Not GLP / Published	No	Published
8.5.1_04a Mutagenicity	Sodium metabisulfite	Simmon, V.F. and Eckford, S.L.	1978	Microbial mutagenesis testing of substances: compound report: F76-004, sodium metabisulphite Published report: PB89-193684, SRI Project LSU-6909. Report No: FDA/CFSAN-89/83. Report date: 1978-04-01 Not GLP / Published	No	Published

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8.5.1_04b Mutagenicity	Sodium metabisulfite	Prival, M.J., Simmon, V.F., Mortelmans, K.E.	1991	Bacterial mutagenicity testing of 49 food ingredients gives very few positive results. Mutat. Res. 260 (4), 321-329 Not GLP / Published	No	Published
8.5.1_05 Mutagenicity	Sodium metabisulfite	Green, S. J.	1977	Present and future uses of mutagenicity tests for assessment of the safety of food additives. Environ. Pathol. Toxicol. 1, pp. 49-54 Not GLP / Published	No	Published
8.5.1_06 Mutagenicity	Sodium metabisulfite	Green, S. J.	1977	Present and future uses of mutagenicity tests for assessment of the safety of food additives. Environ. Pathol. Toxicol. 1, pp. 49-54 Not GLP / Published	No	Published
8.5.1_07a Mutagenicity	Sodium metabisulfite	National Technical Information Service U.S. Department of Commerce (NTIS)	1972	Study of the Mutagenic Effect of Sodium Meta- Bisulphite (71-22), Report No: PB-221 825 (July 1972). Report date: 1972-07-01. Not GLP / Published	No	Published
8.5.1_07b Mutagenicity	Sodium metabisulfite	Maxwell, W.A. Newell, G.W.	1974	Screening Techniques for Environmental Mutagens. Mol. Environ. Aspects Mutagenesis, Proc. Publ., Rochester Int. Conf. Environ. Toxic. 6th, 223-252, 1974. Not GLP / Published	No	Published
8.5.1_08 Mutagenicity	Sodium sulfite	Engelhardt, G	1989	Report on the Study of Natriumsulfit wasserfrei A in the Ames test (standard plate test and preincubation test with Salmonella typhimurium). BASF Department of Toxicology, Ludwigshafen, Germany. Report No. 40M0639/884492. Report date: 1989-12-20. Not GLP / Unpublished	Yes	AFEPAS A (Micro-Pak B.V. has LoA)
8.5.1_09 Mutagenicity	Sodium bisulfite	De Giovanni-Donnelly, R.	1985	The Mutagenicity of Sodium Bisulphite on Base-Substitution Strains of Salmonella typhimurium. Teratogenesis, Carcinogenesis, and Mutagenesis 5: 195-203. Not GLP / Published	No	Published
8.5.1_10 Mutagenicity	Sodium metabisulfite	Pagano, D.A., Zeiger, E.	1987	Conditions affecting the mutagenicity of sodium bisulphite in Salmonella typhimurium. Mutation Research, 179 (1987) 159-166. Not GLP / Published	No	Published
8.5.1_11 Mutagenicity	Sulfur dioxide and Sodium metabisulfite	Shapiro R	1977	Genetic effects of bisulphite (sulphur dioxide). Mutat Res. 1977;39(2):149-75 Not GLP / Published	No	Published
8.5.1_12 Mutagenicity	Sodium metabisulfite	Hayatsu H	2008	Discovery of bisulphite-mediated cytosine conversion to uracil, the key reaction for DNA methylation analysis--a personal account.	No	Published

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				Proc Jpn Acad Ser B Phys Biol Sci. 2008;84(8):321-30 Not GLP / Published		
8.5.1_13 Mutagenicity	Sulfur dioxide and Sodium metabisulfite	Jagiello GM, Lin JS, Ducayen MB	1975	SO2 and its metabolite: effects on mammalian egg chromosomes. Environ Res. 9: 84-93 Not GLP / Published	No	Published
8.5.1_14 Mutagenicity	Sodium metabisulfite	Mukai, F Hawryluk I, Shapiro R.	1970	The mutagenic specificity of sodium bisulphite. Biochem Biophys Res Commun. 39/5: 983-988 Not GLP / Published	No	Published
8.5.2_02 Mutagenicity	Sodium metabisulfite	Green, S. J.	1977	Present and future uses of mutagenicity tests for assessment of the safety of food additives. Environ. Pathol. Toxicol. 1, pp. 49-54 Not GLP / Published	No	Published
8.5.2_03 Mutagenicity	Sulfur dioxide	Uren, N., Yuksel, S. and Onal, Y.	2014	Genotoxic effects of sulphur dioxide in human lymphocytes. Toxicol Ind Health 30(4), pp. 311-315. Not GLP / Published	No	Published
8.5.2_04a Mutagenicity	Sodium metabisulfite	National Technical Information Service U.S. Department of Commerce (NTIS)	1972	Study of the Mutagenic Effect of Sodium Meta- Bisulphite (71-22), Report No: PB-221 825 (July 1972). Report date: 1972-07-01. Not GLP / Published	No	Published
8.5.2_04b Mutagenicity	Sodium metabisulfite	Maxwell, W.A. Newell, G.W.	1974	Screening Techniques for Environmental Mutagens. Mol. Environ. Aspects Mutagenesis, Proc. Publ., Rochester Int. Conf. Environ. Toxic. 6th, 223-252, 1974. Not GLP / Published	No	Published
8.5.2_05 Mutagenicity	Potassium metabisulfite	Anonymous15	2008		No	Published
8.5.2_06 Mutagenicity	Sodium metabisulfite	Rencüzogullari, E., Basri H.I., Kayraldiz, A., Topaktas, M.	2001	Chromosome aberrations and sister chromatid exchanges in cultured human lymphocytes treated with sodium metabisulphite, a food preservative. Mutation Research 490 (2001) 107–112. Not GLP / Published	No	Published
8.5.2_07 Mutagenicity	Sodium bisulfite	Meng, Z., Zhang, L.	1992	Cytogenetic damage induced in human lymphocytes by sodium bisulphite. Mutation Research, 298 (1992) 63-69. Not GLP / Published	No	Published
8.5.2_08 Mutagenicity	Sodium bisulfite	Popescu, N.C., DiPaolo J.A.	1988	Chromosome Alterations in Syrian Hamster Cells Transformed in Vitro by Sodium Bisulphite, a Nonclastogenic Carcinogen. Cancer Research 48, 7246-7251, December	No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
				15, 1988. Not GLP / Published		
8.5.3_02 Mutagenicity	Sodium metabisulfite	Stone, V.	2010	Mutation at the hprt locus of mouse lymphoma L5178Y cells using the Microtitre fluctuation technique: Sodium metabisulphite. Report No: 8230958. Report date: 2010-12-06. GLP / Unpublished	yes	AFEPAS A (Micro-Pak B.V. has LoA)
8.5.3_02 Mutagenicity (Attachment of tables)	Sodium metabisulfite	Stone, V.	2010	Attachment of tables as contained in reference above (section 8.5.3_02). Not GLP / Unpublished	yes	AFEPAS A (Micro-Pak B.V. has LoA)
8.6_01 Mutagenicity	Sulfur dioxide and Sodium metabisulfite	Anonymous5	1978		No	Published
8.6_01a In vivo genotoxicity study	Sulfur dioxide	Anonymous6	2008		yes	AFEPAS A (Micro-Pak B.V. has LoA)
8.6_01b In vivo genotoxicity study	Sulfur dioxide	Anonymous7	2010		yes	AFEPAS A (Micro-Pak B.V. has LoA)
8.6_02 In vivo genotoxicity study	Sulfur dioxide	Anonymous8	2002		No	Published
8.6_03 In vivo genotoxicity study	Sulfur dioxide	Anonymous9	2002		No	Published
8.6_04 In vivo genotoxicity study	Sulfur dioxide	Anonymous10	2003		No	Published
8.6_05 In vivo genotoxicity study	Sulfur dioxide	Anonymous11	2005		No	Published
8.6_08a In vivo genotoxicity study	Sodium metabisulfite	National Technical Information Service U.S.	1972	Study of the Mutagenic Effect of Sodium Meta- Bisulphite (71-22), Report No: PB-221 825 (July 1972). Report date: 1972-07-01. No GLP / Published	No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
		Department of Commerce(NTIS)				
8.6_08b In vivo genotoxicity study	Sodium metabisulfite	Maxwell, W.A. Newell, G.W.	1974	Screening Techniques for Environmental Mutagens. Mol. Environ. Aspects Mutagenesis, Proc. Publ., Rochester Int. Conf. Environ. Toxic. 6th, 223-252, 1974. Not GLP / Published	No	Published
8.6_09 In vivo genotoxicity study / SCE	Sodium metabisulfite	Anonymous12	1983		No	Published
8.6_10 In vivo genotoxicity study / Chromosome aberration	Sodium metabisulfite	Anonymous12	1983		No	Published
8.6_11 In vivo genotoxicity study / Micronucleus	Sodium metabisulfite	Anonymous12	1983		No	Published
8.6_12 In vivo genotoxicity study	Sodium metabisulfite	National Technical Information Service U.S. Department of Commerce (NTIS), (1979)	1979	Study of the Mutagenic Effect of Sodium Meta-Bisulphite (76-73) by Dominant Lethal Test in Rats, Report No: PB-299 836. Report date: 1979-05-18. Not GLP / Published	No	Published
8.6_13 In vivo genotoxicity study	Sodium sulfite	Anonymous13	2008		Yes	AFEPAS A (Micro-Pak B.V. has LoA)
8.6_14a In vivo genotoxicity study	Sodium metabisulfite	National Technical Information Service U.S. Department of Commerce(NTIS)	1972	Study of the Mutagenic Effect of Sodium Meta- Bisulphite (71-22), Report No: PB-221 825 (July 1972). Report date: 1972-07-01. No GLP / Published	No	Published
8.6_14a In vivo genotoxicity study	Sodium metabisulfite	Maxwell, W.A. Newell, G.W.	1974	Screening Techniques for Environmental Mutagens. Mol. Environ. Aspects Mutagenesis, Proc. Publ., Rochester Int. Conf. Environ. Toxic. 6th, 223-252, 1974. Not GLP / Published	No	Published
8.6_15 In vivo	Sodium metabisulfite	Anonymous14	2011		No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
genotoxicity study						
8.6_16 In vivo genotoxicity study	Potassium metabisulfite	Anonymous15	2008		No	Published
8.6_17 In vivo genotoxicity study	Mixture of sodium sulfite and sodium bisulfite	Anonymous16	2004		No	Published
8.7.2_01 Acute toxicity: inhalation	Sulfur dioxide	Anonymous17	1973		No	Published
8.7.2_02 Acute toxicity: inhalation	Sulfur dioxide	Anonymous18	1988		No	Published
8.7.2_03 Acute toxicity: inhalation	Sulfur dioxide	Anonymous19	1965		No	Published
8.7.2_04 Acute toxicity: inhalation	Sulfur dioxide	Anonymous20	1989		No	Published
8.7.2_05 Acute toxicity: inhalation	Sulfur dioxide	Anonymous21	1975		No	Published
8.7.2_06 Acute toxicity: inhalation	Sulfur dioxide	Anonymous22	1972		No	Published
8.7.2_07 Acute toxicity: inhalation / rats	Sulfur dioxide	Anonymous23	1961		No	Published
8.7.2_08 Acute toxicity: inhalation / mice	Sulfur dioxide	Anonymous23	1961		No	Published
8.7.2_09 Acute toxicity: inhalation / guinea pigs	Sulfur dioxide	Anonymous23	1961		No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
8.7.2_10 Acute toxicity: inhalation	Sulfur dioxide	Anonymous24	1973		No	Published
8.7.2_11 Acute toxicity: inhalation	Sulfur dioxide	Anonymous25	1961		No	Published
8.7.2_12 Acute toxicity: inhalation	Sulfur dioxide	Anonymous26	1988		No	Published
8.7.2_15 Acute toxicity: inhalation	Sulfur dioxide	Anonymous27	1983		No	Published
8.7.2_16 Acute toxicity: inhalation	Sulfur dioxide	Anonymous28	1991		No	Published
8.7.2_17 Acute toxicity: inhalation	Sulfur dioxide	Anonymous29	1994		No	Published
8.7.2_18 Acute toxicity: inhalation	Sulfur dioxide	Anonymous30	1990		No	Published
8.7.2_19 Acute toxicity: inhalation	Sulfur dioxide	Anonymous31	2003		No	Published
8.7.2_20 Acute toxicity: inhalation	Sulfur dioxide	Anonymous32	1977		No	Published
8.7.2_21 Acute toxicity: inhalation	Sodium metabisulfite	Anonymous33	1973		No	Published
8.7.2_22 Acute toxicity: inhalation	Sodium sulfite	Anonymous34	1976		No	Published
8.7.2_23 Acute toxicity: inhalation	Sodium sulfite	Anonymous35	1980		No	Published
8.7.2_24 Acute toxicity: inhalation	Sodium sulfite	Anonymous36	1987		No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
8.8 Toxicokinetics and metabolism studies in mammals (Attachment)	Sodium metabisulfite	Chemservice S.A.	2013	Toxicokinetics, metabolism and distribution of Sodium metabisulphite Not GLP / Unpublished	Yes	Micro-Pak B.V.
8.8a Toxicokinetics and metabolism studies in mammals (Attachment - Reference for TK statement)	Sulfur species	EFSA	2008	Peer review of the pesticide risk assessment of the active substance sulphur. Question No EFSA-Q-2008-393. Issued on 19 December 2008. Not GLP / Published	No	Published
8.8b Toxicokinetics and metabolism studies in mammals (Attachment - Reference for TK statement)	Sulfur species	TGD	2003	Technical Guidance Document on Risk Assessment. European commission. Joint research centre. Part I. 2003. Not GLP / Published	No	Published
8.8c Toxicokinetics and metabolism studies in mammals (Attachment - Reference for TK statement)	Sulfur species	WHO	1986	Sulphur dioxide and sulphites (WHO Food Additives Series 21). http://www.inchem.org/documents/jecfa/jecmono/v21je15.htm . Not GLP / Published	No	Published
8.8_01 Summary of available metabolism studies in mammals	Sulfur dioxide	Chemservice S.A.	2014	Metabolism studies in mammals Not GLP / Unpublished	Yes	Micro-Pak B.V.
8.8.1_01 Further toxicokinetics and metabolism	Sulfur dioxide	Anonymous37	1971		No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
studies in mammals						
8.8.1_02 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Anonymous38	1969		No	Published
8.8.1_03 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Anonymous39	1967		No	Published
8.8.1_04 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Anonymous19	1965		No	Published
8.8.1_05 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Anonymous25	1961		No	Published
8.8.1_06 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Anonymous40	1987		No	Published
8.8.1_07 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Gunnison, A.F. and Benton, A.W.	1971	Sulphur dioxide: sulphite. Interaction with mammalian serum and plasma. Arch. Environ. Health 22: 381-388. Not GLP / Published	No	Published
8.8.1_08 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Anonymous41	1983		No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
8.8.1_09 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Anonymous42	1973		No	Published
8.8.1_10 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Tejnorová, I.	1978	Sulphite Oxidase Activity in Liver and Kidney Tissue in Five Laboratory Animals Species. Toxicology and Applied Pharmacology 44: 251-256. Not GLP / Published	No	Published
8.8.1_11 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Cohen, H.J. and Fridovich, I.	1971	Hepatic Sulphite Oxidase. The Journal of Biological Chemistry 246(2):359-366. Not GLP / Published	No	Published
8.8.1_12 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Yargicoglu, A. et al.	1999	Age-Related Alterations in Antioxidant Enzymes, Lipid Peroxide Levels, and Somatosensory-Evoked Potentials: Effect of Sulphur Dioxide. Arch. Environ. Contam. Toxicol. 37: 554-560. Not GLP / Published	No	Published
8.8.1_13 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Anonymous43	1982		No	Published
8.8.1_14 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Cabré, F. et al.	1990	Occurrence and comparison of sulphite oxidase activity in mammalian tissues. Biochem. Med. Metabol. Biol. 43: 159-162. Not GLP / Published	No	Published
8.8.1_15 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Johnson, J.L. and Rajagopalan, K.V.	1976	Human sulphite oxidase deficiency. Characterization of the molecular defect in a multicomponent system. J. Clin. Invest. 58: 551-556. Not GLP / Published	No	Published
8.8.1_16 Further toxicokinetics and metabolism	Sulfur dioxide	Anonymous44	1996		No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
studies in mammals						
8.8.1_17 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Constantin, D. et al.	1994	Alternative pathways of sulphite oxidation in human polymorphonuclear leukocytes. Pharmacol. Toxicol. 74: 136-140. Not GLP / Published	No	Published
8.8.1_18 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Anonymous45	2005		No	Published
8.8.1_19 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Anonymous46	1981		No	Published
8.8.1_20 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Anonymous47	2000		No	Published
8.8.1_21 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Anonymous48	1981		No	Published
8.8.1_22 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Anonymous49	2003		No	Published
8.8.1_23 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Anonymous50	2003		No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
8.8.1_24 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Anonymous51	2003		No	Published
8.8.1_25 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Anonymous52	2004		No	Published
8.8.1_26 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Anonymous53	2003		No	Published
8.8.1_27 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Anonymous54	1985		No	Published
8.8.1_28 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	MacLeod, R.M. et al.	1961	Purification and properties of hepatic sulphite oxidase. J. Biol. Chem. 236: 1841-1846. Not GLP / Published	No	Published
8.8.1_29 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Kilic, D.	2003	The effects of ageing and sulphur dioxide inhalation exposure on visual-evoked potentials, antioxidant enzyme systems, and lipid-peroxidation levels of the brain and eye. Neurotoxicol. Teratol. 25: 587-598. Not GLP / Published	No	Published
8.8.1_30 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Petering, D.H.	1977	Sulphur dioxide: A view of its reactions with biomolecules. Lee S (Ed.) Biochemical effects of environmental pollutants. Ann Arbor Science Publishers, p. 293-306. Not GLP / Published	No	Published
8.8.1_31 Further toxicokinetics and metabolism	Sulfur dioxide	Gunnison, A.F. and Jacobsen, D.W.	1987	Sulphite hypersensitivity. A critical review. Crit. Rev. Toxicol. 17: 185-214. Not GLP / Published	No	Published

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studies in mammals						
8.8.1_32 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Gunnison, A.F.	1981	Sulphite toxicity: a critical review of in vitro and in vivo data. Food Cosmet. Toxicol. 19: 667-682. Not GLP / Published	No	Published
8.8.1_33a Further toxicokinetics and metabolism studies in mammals	Sodium metabisulfite	Anonymous ¹²	1983	Attempts to induce cytogenetic effects with sulphite in sulphite oxidase deficient chinese Hamsters and mice. Food Chem. Toxic. 21(2), 123-127 Not GLP / Published	No	Published
8.8.1_33b Further toxicokinetics and metabolism studies in mammals	Sodium metabisulfite	OECD SIDS	2001	SIDS Initial Assessment Report for for 13th SIAM (Disodium disulphite, CAS 7681-57-4; Bern, 6-9 November 2001) Not GLP / Published	No	Published
8.8.1_34a Further toxicokinetics and metabolism studies in mammals	Sodium metabisulfite	Rost, E.	1933	Handbuch der Lebensmittelchemie Band 1, S. 993, Springer-Verlag (1993) cited in : Toxicological Evaluation of Certain Food additives and contaminants. WHO Food Additives Series 21, 1986 Not GLP / Published	No	Published
8.8.1_34b Further toxicokinetics and metabolism studies in mammals	Sodium metabisulfite	OECD	2001	SIDS Initial Assessment Report for for 13th SIAM (Disodium disulphite, CAS 7681-57-4; Bern, 6-9 November 2001) Not GLP / Published	No	Published
8.8.1_34c Further toxicokinetics and metabolism studies in mammals	Sodium metabisulfite	WHO	1987	Toxicological Evaluation of Certain Food Additives and Contaminants. WHO Food Additives Series 21, 30th Meeting of the Joint FAO/WHO Expert Committee on Food Additives, 1987. Not GLP / Published	No	Published
8.8.1_35 Further toxicokinetics and metabolism studies in mammals	Sodium metabisulfite	Gunnison, A.F., Bresnahan, C.A. and E.D. Palmes	1977	Comparative Sulphite Metabolism in the Rat, Rabbit, and Rhesus Monkey. Toxicology and Applied Pharmacology, 42, pp. 99-109. Not GLP / Published	No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
8.8.1_36 Further toxicokinetics and metabolism studies in mammals	Sodium metabisulfite	Gunnison, A.F., Palmes, E.D.	1976	A Model for the Metabolism of Sulphite in Mammal. Toxicology and Applied Pharmacology 38, 111-126 (1976). Not GLP / Published	No	Published
8.8.1_37 Further toxicokinetics and metabolism studies in mammals	Sodium metabisulfite	Anonymous55	1960		No	Published
8.8.1_38 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Anonymous56, O.J., Dybicki, J. and G.R. Meneely	1960	The dynamics of sulphur dioxide inhalation. Absorption, distribution, and retention. A.M.A. Archives of Industrial Health, Vol. 21 (June 1960), 564-569. Department of Medicine, University of Southern California, School of Medicine, Los Angeles, USA. Not GLP / Published	No	Published
8.8.1_38 Further toxicokinetics and metabolism studies in mammals (Attachment of tables)	Sulfur dioxide	Balchum, O.J., Dybicki, J. and G.R. Meneely	1960	Attachment of tables as contained in reference above for section 8.8.1_38. Not GLP / Published	No	Published
8.8.1_39 Further toxicokinetics and metabolism studies in mammals	Sodium sulphate	Cocchetto, D.M. and G. Levy	1981	Absorption of Orally Administered Sodium Sulphate in Humans. Journal of Pharmaceutical Sciences, 70, pp. 331-333. Department of Pharmaceutics, School of Pharmacy, State University of New York, Buffalo, NY, USA. Not GLP / Published	No	Published
8.8.1_40 Further toxicokinetics and metabolism studies in mammals	Sulfur	Bauer, J.H.	1976	Oral administration of radioactive sulphate to measure extracellular fluid space in man. Journal of Applied Physiology, 40, pp. 648-650. Department of Medicine, Indiana University Medical Center, Indianapolis, Indiana, USA. Not GLP / Published	No	Published
8.8.1_41 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Anonymous57	1960		No	Published

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8.8.1_41 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Balchum, O.J., Dybicki, J., Meneely, G.R.	1960	Attachment of tables as contained in reference above for section 8.8.1_41. Not GLP / Published	No	Published
8.8.1_42 Further toxicokinetics and metabolism studies in mammals	Sulphate	Florin, T., Neale, G., Gibson, G.R., Christl, S.U., Cummings, J.H.	1991	Metabolism of dietary sulphate: absorption and excretion in humans. Gut, 1991,32,766-773. Not GLP / Published	No	Published
8.8.1_42 Further toxicokinetics and metabolism studies in mammals	Sulphate	Florin, T., Neale, G., Gibson, G.R., Christl, S.U., Cummings, J.H.	1991	Attachment of tables as contained in reference above for section 8.8.1_42. Not GLP / Published	No	Published
8.8.1_43 Further toxicokinetics and metabolism studies in mammals	Sulfuric acid	Walser, M., Seldin, D.W., Grollman, A.	1953	An Evaluation of Radiosulphate for the Determination of the Volume of Extracellular Fluid in Man and Dogs. J Clin Invest; 1953; 32: 299-311. Not GLP / Published	No	Published
8.8.1_44 Further toxicokinetics and metabolism studies in mammals	Sodium sulphate	Ryan, R.J., Pascal, L.R., Inoye, T., Bernstein, L.	1956	Experiences with Radiosulphate in the Estimation of Physiologic Extracellular Water in Healthy and Abnormal Man. J Clin Invest. 1956; 35 (10): 1119-30. Not GLP / Published	No	Published
8.8.1_45 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide and Sodium metabisulfite	Beck-Speier I, Hinze H, Holzer H.	1985	Effect of sulphite on the energy metabolism of mammalian Biochim Biophys Acta. 1985 Jul 26;841(1):81-9.tissues in correlation to sulphite oxidase activity. Not GLP / Published	No	Published
8.8.1_46 Further toxicokinetics and metabolism studies in mammals	Sodium metabisulfite	Cocchetto DM, Levy G.	1981	Absorption of orally administered sodium sulphate in humans. J Pharm Sci. 1981 Mar;70(3):331-3. Not GLP / Published	No	Published
8.8.1_47 Further toxicokinetics and metabolism	Sulfur dioxide and Sodium	Constantin D, Bini A, Meletti E, Moldeus P,	1996	Age-related differences in the metabolism of sulphite to sulphate and in the identification of sulphur trioxide radical in human polymorphonuclear leukocytes. Mech Ageing Dev. 1996 Jul 5;88(1-2):95-109.	No	Published

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studies in mammals	metabisulfite	Monti D, Tomasi A.		Not GLP / Published		
8.8.1_48 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide and Sodium metabisulfite	Feng C, Tollin G, Enemark JH	2007	Sulphite oxidizing enzymes. Biochim Biophys Acta. 2007 May;1774(5):527-39 Not GLP / Published	No	Published
8.8.1_48 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide and Sodium metabisulfite	Gregory RE, Gunnison AF.	1984	Identification of plasma proteins containing sulphite-reactive disulfide bonds. Chem Biol Interact. 1984 Apr;49(1-2):55-69 Not GLP / Published	No	Published
8.9_01 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Anonymous58	1986		No	Published
8.10_01 Further toxicokinetics and metabolism studies in mammals	Sulfur dioxide	Anonymous59	2013		No	Published
8.11_01 Carcinogenicity	Sulphur dioxide	Anonymous60	1988		No	Published
8.11_02 Carcinogenicity	Sulphur dioxide	Anonymous61	1970		No	Published
8.11_04 Carcinogenicity	Sodium metabisulfite	Anonymous62	1972		No	Published
8.11_05a Carcinogenicity	Sodium metabisulfite	Anonymous63	1960		No	Published
8.11_06 Carcinogenicity	Potassium metabisulfite	Anonymous64	1979		No	Published
8.11_07 Carcinogenicity	Sulphur dioxide	Anonymous65	1967		No	Published

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8.12.1_01 Medical surveillance data on manufacturing plant personnel	Sulfur dioxide	BAuA	2011	Begründung zu Schwefeldioxid in TRGS 900. Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA). October 2011 Not GLP / Published	No	Published
8.12.1_02 Medical surveillance data on manufacturing plant personnel	Sulfur dioxide	SCOEL	2009	Recommendation from the Scientific Committee on Occupational Exposure limits for Sulphur dioxide. SCOEL/SUM/137, Updated December 2009 Not GLP / Published	No	Published
8.12.1_03 Medical surveillance data on manufacturing plant personnel	Sulfur dioxide	EPA	2008	Integrated Sciences Assessment for Sulphur Oxides – Health Criteria. United States Environmental Protection, EPA/600/R-08/047F. Not GLP / Published	No	Published
8.12.1_04 Medical surveillance data on manufacturing plant personnel	Sulfur dioxide	EPA	2010	621. Sulphur dioxide and sulphites (WHO Food Additives Series 21). Not GLP / Published	No	Published
8.12.1_05 Medical surveillance data on manufacturing plant personnel	Sulfur dioxide	IARC	1992	Occupational exposure to mists and vapours from strong inorganic acids; and other industrial chemicals – Summary of data reported and evaluation. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans vol. 54; therein Section : Sulphur dioxide and some sulphites, bisulphites and metabisulphites" (pp. 131-188), Lyon, France, ISBN 92 832 1254-1 Not GLP / Published	No	Published
8.12.1_06 Medical surveillance data on manufacturing plant personnel	Sulfur dioxide	Nordenson, I. et al.	1980	Is exposure to sulphur dioxide clstogenic? Hereditas 93: 161-164. Not GLP / Published	No	Published
8.12.1_07 Medical surveillance data on manufacturing plant personnel	Sulfur dioxide	Sorsa, M. et al.	1982	No effect of sulphur dioxide exposure, in aluminium industry, on chromosomal aberrations or sister chromatid exchanges. Hereditas 97: 159-161. Not GLP / Published	No	Published
8.12.1_08 Medical surveillance	Sulfur dioxide	Yadav, J.S. and Kaushik, V.K.	1996	Effect of sulphur dioxide exposure on humen chromosomes. Mutat. Res. 359: 25-29. Not GLP / Published	No	Published

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data on manufacturing plant personnel						
8.12.1_09 Medical surveillance data on manufacturing plant personnel	Sulfur dioxide	Meng, Z. and Zhang, L.	1990	Observation of frequencies of lymphocytes with micronuclei in human peripheral blood cultures from workers in a sulphuric acid factory. Environ. Mol. Mutagen. 15: 218-220. Not GLP / Published	No	Published
8.12.1_10 Medical surveillance data on manufacturing plant personnel	Sulfur dioxide	Meng, Z. and Zhang, L.	1990	Chromosomal aberrations and sister-chromatid exchanges in lymphocytes of workers exposed to sulphur dioxide. Mutat. Res. 241: 15-20. Not GLP / Published	No	Published
8.12.1_11 Medical surveillance data on manufacturing plant personnel	Sulfur dioxide	Henneberger, P.K. et al.	1989	Mortality among pulp and paper workers in Berlin, New Hampshire. Brit. J. Ind. Med. 46: 658-664. Not GLP / Published	No	Published
8.12.1_12 Medical surveillance data on manufacturing plant personnel	Sulfur dioxide	Jäppinen, P.	1987	A mortality study of Finnish pulp and paper workers. Brit. J. Ind. Med. 44: 580-587. Not GLP / Published	No	Published
8.12.1_13 Medical surveillance data on manufacturing plant personnel	Sulfur dioxide	Robinson, C.F. et al.	1986	Mortality among production workers in pulp and paper mills. Scand. J. Work Environ. Health 12: 552-560. Not GLP / Published	No	Published
8.12.1_14 Medical surveillance data on manufacturing plant personnel	Sodium metabisulfite	Confidential Business Information (please refer to separate reference list)				
8.12.2_01 Direct observation, e.g. clinical cases, poisoning incidents	Sulfur dioxide	Amdur, M.O. et al.	1953	Effects of inhalation of sulphur dioxide by man. The Lancet, Oct. 10, 1953: 758 Not GLP / Published	No	Published

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8.12.2_02 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Balmes, J.R. et al.	1987	Symptomatic bronchoconstriction after short-term inhalation of sulphur dioxide. Am. Rev. Respir. Dis. 136: 1117-1121 Not GLP / Published	No	Published
8.12.2_03 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Bedi, J.F. et al.	1979	Human exposure to sulphur dioxide and ozone: absence of a synergistic effect. Arch. Environ. Health 32: 233-239 Not GLP / Published	No	Published
8.12.2_04 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Hackney, J.D. et al.	1984	Time course of exercise-induced bronchoconstriction in asthmatics exposed to sulphur dioxide. Environ. Res. 34: 321-327 Not GLP / Published	No	Published
8.12.2_05 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Horstman, D. et al.	1986	Airway sensitivity of asthmatics to sulphur dioxide. Toxicol. Ind. Health 2: 289-298 Not GLP / Published	No	Published
8.12.2_06 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Horstman, D.H. et al.	1988	The relationship between exposure duration and sulphur dioxide-induced bronchoconstriction in asthmatic subjects. Am. Ind. Hyg. Assoc. J. 49: 38-47 Not GLP / Published	No	Published
8.12.2_07 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Koenig, J.Q. et al.	1983	A comparison of the pulmonary effects of 0.5 ppm versus 1.0 ppm sulphur dioxide plus sodium chloride droplets in asthmatic adolescents. J. Toxicol. Environ. Health 11: 129-139 Not GLP / Published	No	Published
8.12.2_08 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Kreisman, H. et al.	1976	Effect of low concentrations of sulphur dioxide on respiratory function in man. Lung. 154: 25-34 Not GLP / Published	No	Published

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8.12.2_09 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Lawther, P.J. and Lond, M.B.	1955	Effects of inhalation of sulphur dioxide on respiration and pulse-rate in normal subjects. The Lancet, Oct. 8, 1955: 745 Not GLP / Published	No	Published
8.12.2_10 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Lawther, P.J. et al.	1975	Pulmonary function and sulphur dioxide, some preliminary findings. Environ. Res. 10: 355-367 Not GLP / Published	No	Published
8.12.2_11 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Linn, W.S. et al.	1982	Respiratory responses of young adult asthmatics exposed to sulphur dioxide in a controlled-environment chamber. Am. Rev. Respir. Dis. 125: 151 Not GLP / Published	No	Published
8.12.2_12 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Linn, W.S. et al.	1983	Respiratory effects of sulphur dioxide in heavily exercising asthmatics. A dose-response study. Am. Rev. Respir. Dis. 127: 278-283 Not GLP / Published	No	Published
8.12.2_13 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Linn, W.S. et al.	1985	Controlled exposures of volunteers with chronic obstructive pulmonary disease to sulphur dioxide. Environ. Res. 37: 445-451 Not GLP / Published	No	Published
8.12.2_14 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Linn, W.S. et al.	1987	Replicated dose-response study of sulphur dioxide effects in normal, atopic and asthmatic volunteers. Am. Rev. Respir. Dis. 136: 1127-1134 Not GLP / Published	No	Published
8.12.2_15 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Magnussen, H. et al.	1990	Relationship between the airway response to inhaled sulphur dioxide, isocapnic hyperventilation and histamine in asthmatic subjects. Int. Arch. Occup. Environ. Health 62: 485-491 Not GLP / Published	No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
8.12.2_16 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Sandström, T. et al.	1989	Cell response in bronchoalveolar lavage fluid after sulphur dioxide exposure. Scand. J. Work Environ. Health 15: 142-146 Not GLP / Published	No	Published
8.12.2_17 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Schachter, E.N. et al.	1984	Airway effects of low concentrations of sulphur dioxide: dose response characteristics. Arch. Environ. Health 39: 34-42 Not GLP / Published	No	Published
8.12.2_18 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Sheppard, D. et al.	1981	Exercise increases sulphur dioxide-induced bronchoconstriction in asthmatic subjects. Am. Rev. Respir. Dis. 123: 486-491 Not GLP / Published	No	Published
8.12.2_19 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	van Sim, M. and Pattle, R.E.	1957	Effect of possible smog irritants on human subjects. J.A.M.A., Vol. 165, No. 15: 1908 Not GLP / Published	No	Published
8.12.2_20 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Snell, R.E. and Luchsinger, P.C.	1969	Effects of sulphur dioxide on expiratory flow rates and total respiratory resistance in normal human subjects. Arch. Environ. Health 18: 693-698 Not GLP / Published	No	Published
8.12.2_21 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Stacy, R.W. et al.	1981	Effects of 0.75 ppm sulphur dioxide on pulmonary function parameters of normal human subjects. Arch. Environ. Health 36: 172-178 Not GLP / Published	No	Published
8.12.2_22 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Andersen, I. et al.	1974	Human response to controlled levels of sulphur dioxide. Arch. Environ. Health 28: 31-39 Not GLP / Published	No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
8.12.2_23 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Andersen, I. et al.	1981	Human response to controlled levels of combinations of sulphur dioxide and inert dust. Scand J. Work Environ. Health 7: 1-7 Not GLP / Published	No	Published
8.12.2_24 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Charan, N.B. et al.	1979	Pulmonary injuries associated with acute sulphur dioxide inhalation. American Review of Respiratory Disease, Vol. 119: 555 Not GLP / Published	No	Published
8.12.2_25a Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Speizer, F.E. and Frank, N.R.	1966	Uptake and release of SO ₂ by the human nose. Arch. Environ. Health 12: 725-728 Not GLP / Published	No	Published
8.12.2_25b Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Frank, N.R. and Speizer, F.E.	1964	Uptake and release of SO ₂ by the human nose. Physiologist 7: 132 Not GLP / Published	No	Published
8.12.2_26 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Gunnison, A.F. and Palmes, E.D.	1974	S-sulphonate in human plasma following inhalation of sulphur dioxide. Am. Ind. Hyg. Assoc. J. 35: 288-291 Not GLP / Published	No	Published
8.12.2_27 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Galea, M.	1964	Case report - Fatal Sulphur Dioxide Inhalation. Canad. Med. Ass. J. , Vol. 91, p. 345-347 Not GLP / Published	No	Published
8.12.2_28 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Woodford, D.M. et al.	1979	Obstructive lung disease from acute sulphur dioxide exposure. Respiration 38: 238-245 Not GLP / Published	No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
8.12.2_29 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Sandström, T. et al.	1989	Is the short term limit value for sulphur dioxide exposure safe? Effects of controlled chamber exposure investigated with bronchoalveolar lavage. Brit. J. Ind. Med. 46: 200-203 Not GLP / Published	No	Published
8.12.2_30a Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Frank, N.R.	1964	Studies on the effects of acute exposure to sulphur dioxide in human subjects. Proc. Roy. Soc. Med. 57: 1029-1033 Not GLP / Published	No	Published
8.12.2_30b Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Frank, N.R. et al.	1962	Effects of acute controlled exposure to SO ₂ on respiratory mechanics in healthy male adults. J. Appl. Physiol. 17: 252-258 Not GLP / Published	No	Published
8.12.2_31 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Frank, N.R. et al.	1964	A comparison of the acute effects of SO ₂ administered alone or in combination with NaCl particles on the respiratory mechanisms of healthy adults. Int. J. Air. Wat. Poll. 8: 125-133 Not GLP / Published	No	Published
8.12.2_32 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Kirkpatrick, M.B. et al.	1982	Effect of oronasal breathing route on sulphur dioxide-induced bronchoconstriction in exercising asthmatic subjects. Am. Rev. Respir. Dis. 125: 627-631 Not GLP / Published	No	Published
8.12.2_33 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Islam, M.S. and Ulmer, W.T.	1979	Untersuchungen zur Schwellenkonzentration von Schwefeldioxyd bei besonders Gefährdeten (Border-line concentrations of SO ₂ for patients with oversensitivity of the bronchial system). Wiss. Umwelt 1: 41-47 Not GLP / Published	No	Published
8.12.2_34 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Sheppard, D. et al.	1980	Lower threshold and greater bronchomotor responsiveness of asthmatic subjects to sulphur dioxide. Am. Rev. Respir. Dis. 122: 873-878 Not GLP / Published	No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
8.12.2_35 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Bethel, R.A. et al.	1983	Effect of exercise rate and route of inhalation on sulphur-dioxide-induced bronchoconstriction in asthmatic subjects. Am. Rev. Respir. Dis. 128: 592-596 Not GLP / Published	No	Published
8.12.2_36 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Bedi, J.F. and Horvath, S.M.	1989	Inhalation route effects on exposure to 2.0 ppm sulphur dioxide in normal subjects. J. Air. Pollut. Control Assoc. 39: 1448-1452 Not GLP / Published	No	Published
8.12.2_37 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Kulle, T.J. et al.	1986	Pulmonary effects of sulphur dioxide and respirable carbon aerosol. SO Environm. Res. 41: 239-250 Not GLP / Published	No	Published
8.12.2_38 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Witek, T.J. and Schachter, E.N.	1985	Airway responses to sulphur dioxide and methacholine in asthmatics. J. Occup. Med. 27: 265-268 Not GLP / Published	No	Published
8.12.2_39 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Sheppard, D. et al.	1984	Magnitude of the interaction between the bronchomotor effects of sulphur dioxide and those of dry (cold) air. Am. Rev. Respir. Dis. 130: 52-55 Not GLP / Published	No	Published
8.12.2_40 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Linn, W.S. et al.	1985	Effects of heat and humidity on the responses of exercising asthmatics to sulphur dioxide exposure. Am. Rev. Respir. Dis. 131: 221-225 Not GLP / Published	No	Published
8.12.2_41 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Stacy, R.W. et al.	1983	A survey of effects of gaseous and aerosol pollutants on pulmonary function of normal males. Arch. Environ. Health 38: 104-115 Not GLP / Published	No	Published

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8.12.2_42 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Carson, J.L. et al.	1987	The appearance of compound cilia in the nasal mucosa of normal human subjects following acute, in vivo exposure to sulphur dioxide. Environ. Res. 42: 155-165 Not GLP / Published	No	Published
8.12.2_43 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Heath, K.S. et al.	1994	Effects of sulphur dioxide exposure on African-American and Caucasian asthmatics. Environ. Res. 66: 1-11 Not GLP / Published	No	Published
8.12.2_44 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Bedi, J.F. et al.	1984	Pulmonary function effects of 1.0 and 2.0 ppm sulphur dioxide exposure in active young male non-smokers. J. Air. Pollut. Control. Assoc. 34: 1117-1121 Not GLP / Published	No	Published
8.12.2_45 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Bedi, J.F. et al.	1982	Human exposure to sulphur dioxide and ozone in a high temperature-humidity environment. Am. Ind. Hyg. Assoc. J. 43: 26-30 Not GLP / Published	No	Published
8.12.2_46 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Bethel, R.A. et al.	1983	Sulphur dioxide-induced bronchoconstriction in freely breathing, exercising, asthmatic subjects. Am. Rev. Respir. Dis. 128: 987-990 Not GLP / Published	No	Published
8.12.2_47a Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Bethel, R.A. et al.	1983	Potential of sulphur dioxide-induced bronchoconstriction by airway cooling. Am. Rev. Respir. Dis. 127: A 161 Not GLP / Published	No	Published
8.12.2_47b Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Bethel, R.A. et al.	1984	Interaction of sulphur dioxide and dry cold air in causing bronchoconstriction in asthmatic subjects. J. Appl. Physiol. 57: 419-423 Not GLP / Published	No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
8.12.2_48 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Bethel, R.A. et al.	1985	Effect of 0.25 ppm sulphur dioxide on airway resistance in freely breathing, heavily exercising, asthmatic subjects. Am. Rev. Respir. Dis. 131: 659-661 Not GLP / Published	No	Published
8.12.2_49 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Burton, G.G. et al.	1969	Response of healthy men to inhaled low concentrations of gas-aerosol mixtures. Arch. Environ. Health 18: 681-692 Not GLP / Published	No	Published
8.12.2_50 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Delohery, J. et al.	1984	The relationship of inhaled sulphur dioxide reactivity to ingested metabisulphite sensitivity in patients with asthma. Am. Rev. Respir. Dis. 130: 1027-1030 Not GLP / Published	No	Published
8.12.2_51 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Folinsbee, L.J. et al.	1985	Pulmonary response to threshold levels of sulphur dioxide (1.0 ppm) and ozone (0.3 ppm). J. Appl. Physiol. 58: 1783-1787 Not GLP / Published	No	Published
8.12.2_52 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Hazucha, M. and Bates, D.V.	1975	Combined effect of ozone and sulphur dioxide on human pulmonary function. Nature 257: 50-51 Not GLP / Published	No	Published
8.12.2_53 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Islam, M.S. et al.	1992	Bronchomotoric effect of low concentration of sulphur dioxide in young healthy volunteers. Fresenius Envir. Bull. 1: 541-546 Not GLP / Published	No	Published
8.12.2_54 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Jaeger, M.J. et al.	1979	Effect of sulphur dioxide on the respiratory function of normal and asthmatic subjects. Lung 156: 119-127 Not GLP / Published	No	Published

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8.12.2_55 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Kehrl, H. et al.	1983	Pulmonary responses of young male adult asthmatics to SO ₂ with moderate exercise. Am. Rev. Respir. Dis. 127: 160 Not GLP / Published	No	Published
8.12.2_56 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Kehrl, H.R. et al.	1987	Differing response of asthmatics to sulphur dioxide exposure with continuous and intermittent exercise. Am. Rev. Respir. Dis. 135: 350-355 Not GLP / Published	No	Published
8.12.2_57 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Koenig, J.Q.	1989	Effects of inhalation of acidic compounds on pulmonary function in allergic adolescent subjects. Environ. Health Perspect. 79: 173-178 Not GLP / Published	No	Published
8.12.2_58 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Koenig, J.Q. et al.	1990	Prior exposure to ozone potentiates subsequent response to sulphur dioxide in adolescent asthmatic subjects. Am. Rev. Respir. Dis. 141: 377-380 Not GLP / Published	No	Published
8.12.2_59a Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Koenig, J.Q. et al.	1982	Effects of inhaled sulphur dioxide (SO ₂) on pulmonary function in healthy adolescents: exposure to SO ₂ alone or SO ₂ + sodium chloride droplet aerosol during rest and exercise. Arch. Environ. Health 37: 5-9 Not GLP / Published	No	Published
8.12.2_59b Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Koenig, J.Q. and Pierson, W.E.	1985	Pulmonary effects of inhaled sulphur dioxide in atopic adolescent subjects: A review. Frank R et al. (Ed.), Inhalation Toxicology of Air Pollutants: Clinical Research Considerations, ASTM STP 872, American Society for Testing and Materials, Philadelphia, p. 85-91 Not GLP / Published	No	Published
8.12.2_60 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Koenig, J.Q. et al.	1980	Acute effects of inhaled SO ₂ plus NaCl droplet aerosol on pulmonary function in asthmatic adolescents. Environ. Res. 22: 145-153 Not GLP / Published	No	Published

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8.12.2_61 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Koenig, J.Q. et al.	1981	Effects of SO ₂ plus NaCl aerosol combined with moderate exercise on pulmonary function in asthmatic adolescents. Environ. Res. 25: 340-348 Not GLP / Published	No	Published
8.12.2_62 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Koenig, J.Q. et al.	1982	Bronchoconstrictor responses to sulphur dioxide or sulphur dioxide plus sodium chloride droplets in allergic, nonasthmatic adolescents. J. Allergy. Clin. Immunol. 69: 339-344 Not GLP / Published	No	Published
8.12.2_63 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Kulle, T.J. et al.	1984	Sulphur dioxide and ammonium sulphate effects on pulmonary function and bronchial reactivity in human subjects. Am. Ind. Hyg. Assoc. J. 45: 156-161 Not GLP / Published	No	Published
8.12.2_64 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Linn, W.S. et al.	1988	Effect of metaprotenerol sulphate on mild asthmatics' response to sulphur dioxide exposure and exercise. Arch. Environ. Health. 43: 399-406 Not GLP / Published	No	Published
8.12.2_65 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Linn, W.S. et al.	1982	Respiratory responses of young adult asthmatics exposed to sulphur dioxide in a controlled-environment chamber. Am. Rev. Respir. Dis. 125: 151 Not GLP / Published	No	Published
8.12.2_66 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Linn, W.S. et al.	1984	Comparative effects of sulphur dioxide exposures at 5 °C and 22 °C in exercising asthmatics. Am. Rev. Respir. Dis. 129: 234-239 Not GLP / Published	No	Published
8.12.2_67 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Magnussen, H. et al.	1987	Relationship between the airway response to inhaled sulphur dioxide and histamine in asthmatics. Am. Rev. Respir. Dis. 135, Suppl 2: A442 Not GLP / Published	No	Published

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8.12.2_68 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Myers, D.J. et al.	1986	The inhibition of sulphur dioxide-induced bronchoconstriction in asthmatic subjects by cromolyn is dose dependent. Am. Rev. Respir. Dis. 133: 1150-1153 Not GLP / Published	No	Published
8.12.2_69 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Wolff, R.K. et al.	1975	Sulphur dioxide and tracheobronchial clearance in man. Arch. Environ. Health 30: 521-527 Not GLP / Published	No	Published
8.12.2_70 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Trenga, C.A.	1999	Sulphur dioxide sensitivity and plasma antioxidants in adult subjects with asthma. Occup. Environ. Med. 56: 544-547 Not GLP / Published	No	Published
8.12.2_71 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Speizer, F.E. and Frank, N.R.	1966	A comparison of changes in pulmonary flow resistance in healthy volunteers acutely exposed to SO ₂ by mouth and nose. Brit. J. Ind. Med. 23: 75-79 Not GLP / Published	No	Published
8.12.2_72 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Nadel, J.A. et al.	1965	Mechanism of bronchoconstriction during inhalation of sulphur dioxide. J. Appl. Physiol. 20: 164-167 Not GLP / Published	No	Published
8.12.2_73 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Newhouse, M.T. et al.	1978	Effect of TLV levels of SO ₂ and H ₂ SO ₄ on bronchial clearance in exercising man. Arch. Environ. Health 33: 24-32 Not GLP / Published	No	Published
8.12.2_74 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Sheppard, D. et al.	1983	Tolerance to sulphur dioxide-induced bronchoconstriction in subjects with asthma. Environ. Res. 30: 412-419 Not GLP / Published	No	Published

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8.12.2_75 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Nowak, D. et al.	1997	Airway responsiveness to sulphur dioxide in an adult population sample. Am. J. Respir. Crit. Care Med. 156: 1151-1156 Not GLP / Published	No	Published
8.12.2_76 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Rondinelli, R.C.A. et al.	1987	The effects of sulphur dioxide on pulmonary function in healthy nonsmoking male subjects aged 55 years and older. Am. Ind. Hyg. Assoc. J. 48: 299-303 Not GLP / Published	No	Published
8.12.2_77 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Myers, D.J. et al.	1986	Interaction of cromolyn and a muscarinic antagonist in inhibiting bronchial reactivity to sulphur dioxide and to eucapnic hyperpnea alone. Am. Rev. Respir. Dis. 133: 1154-1158 Not GLP / Published	No	Published
8.12.2_78 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Roger, L.J. et al.	1985	Bronchoconstriction in asthmatics exposed to sulphur dioxide during repeated exercise. J. Appl. Physiol. 59: 784-791 Not GLP / Published	No	Published
8.12.2_79 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Boushey, H.	1982	Asthma, sulphur dioxide and the clean air act. West. J. Med. 136: 129-135 Not GLP / Published	No	Published
8.12.2_80 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Koenig, J.Q. et al.	1985	The effects of sulphur oxides on nasal and lung function in adolescents with extrinsic asthma. J. Allergy. Clin. Immunol. 76: 813-818 Not GLP / Published	No	Published
8.12.2_81 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Linn, W.S. et al.	1984	Combined effect of sulphur dioxide and cold in exercising asthmatics. Arch. Environ. Health 39: 339-346 Not GLP / Published	No	Published

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8.12.2_82 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Härkönen, H. et al.	1983	Long-term effects of exposure to sulphur dioxide. Lung function four years after a pyrite dust explosion. Am. Rev. Respir. Dis. 128: 890-893 Not GLP / Published	No	Published
8.12.2_83 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Rabinovitch, S. et al.	1989	Clinical and laboratory features of acute sulphur dioxide inhalation poisoning: two-year follow-up. Am. Rev. Respir. Dis. 139: 556-558 Not GLP / Published	No	Published
8.12.2_84 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Sandström, T. et al.	1989	Cell response in bronchoalveolar lavage fluid after exposure to sulphur dioxide: a time-response study. Am. Rev. Respir. Dis. 140: 1828-1831 Not GLP / Published	No	Published
8.12.2_85 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Lazarus, S.C. et al.	1997	The Leukotriene Receptor Antagonist Zafirlukast Inhibits Sulphur Dioxide-induced Bronchoconstriction in Patients with Asthma. Am. J. Respir. Crit. Care. Med. 156: 1725-1730 Not GLP / Published	No	Published
8.12.2_86 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Islam, M.S. et al.	1994	Non-specific airway responsiveness to hyperventilation of low doses of sulphur dioxide and cold air of non-smoking healthy volunteers of different ages. Zbl. Hyg. 195: 556-566 Not GLP / Published	No	Published
8.12.2_87 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Melville, G.N.	1970	Changes in specific airway conductance in healthy volunteers following nasal and oral inhalation of SO ₂ . West. Indian Med. J. 19: 231-235 Not GLP / Published	No	Published
8.12.2_88 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Tunncliffe, W.S. et al.	2003	The effect of sulphurous air pollutant exposures on symptoms, lung function, exhaled nitric oxide, and nasal epithelial lining fluid antioxidant concentrations in normal and asthmatic adults. Occup. Environ. Med. 60: e15 Not GLP / Published	No	Published

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8.12.2_89 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Devalia, J.L. et al.	1994	Effect of nitrogen dioxide and sulphur dioxide on airway response of mild asthmatic patients to allergen inhalation. Lancet 344: 1668-1671 Not GLP / Published	No	Published
8.12.2_90 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Field, P.I. et al.	1996	Evidence for opioid modulation and generation of prostaglandins in sulphur dioxide (SO ₂)-induced bronchoconstriction. Thorax 51: 159-163 Not GLP / Published	No	Published
8.12.2_91 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Prügger, F.	1974	Ein Fall von sublethaler, akuter Schwefeldioxidvergiftung und deren Folgeerscheinungen auf die Lungenfunktion. (Case report of acute sulphur dioxide poisoning and its effects on lung function.) Pneumologie 150: 97-98 Not GLP / Published	No	Published
8.12.2_92 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Piirilä, P. et al.	1996	A thirteen-year follow-up of respiratory effects of acute exposure to sulphur dioxide. Scand. J. Work Environ. Health 22: 191-196 Not GLP / Published	No	Published
8.12.2_93 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Koksal, N. et al.	2003	Apricot sulphurization: an occupation that induces an asthma-like syndrome in agricultural environments. Am. J. Ind. Med. 43: 447-453 Not GLP / Published	No	Published
8.12.2_94 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Jäppinen, P.; Tola, S.	1986	Smoking among Finnish pulp and paper workers - Evaluation of its confounding effect on lung cancer and coronary heart disease. Scand. J. Work. Environ. Health 12: 619-626 Not GLP / Published	No	Published
8.12.2_95 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Mikaëlsson B. et al.	1982	The Prevalence of bronchial asthma and chronic bronchitis in an industrialized community in Northern Sweden. Scand. J. Soc. Med. 10: 11-16 Not GLP / Published	No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
8.12.2_96 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Ferris, B.G. et al.	1979	Mortality and morbidity in a pulp and paper mill in the United States: a ten-year follow-up. Brit. J. Ind. Med. 36: 127-134 Not GLP / Published	No	Published
8.12.2_97 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Stjernberg N. et al.	1985	Prevalence of bronchial asthma and chronic bronchitis in a community in northern Sweden; relation to environmental and occupational exposure to sulphur dioxide. Eur. J. Respir. Dis. 67: 41-49 Not GLP / Published	No	Published
8.12.2_98 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Savic, M. et al.	1987	Discomforts and laboratory findings in workers exposed to sulphur dioxide. Int. Arch. Occup. Environ. Health 59: 513-518 Not GLP / Published	No	Published
8.12.2_99 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Andersson, E. et al.	1998	Mortality from asthma and cancer among sulphite mill workers. Scand. J. Work Environ. Health 24: 12-17 Not GLP / Published	No	Published
8.12.2_100 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Gokirmak, M. et al.	2003	The role of oxidative stress in bronchoconstriction due to occupational sulphur dioxide exposure. Clin. Chim. Acta. 331, 119-126 Not GLP / Published	No	Published
8.12.2_101 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Andersson, E. et al.	2006	Incidence of asthma among workers exposed to sulphur dioxide and other irritant gases. Eur. Respir. J. 27, 720-725 Not GLP / Published	No	Published
8.12.2_102 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Band, P.R. et al.	1997	Cohort mortality study of pulp and paper mill workers in British Columbia, Canada. J. Exp. Anal. Environ. Epidemiol. 3: 371-382 Not GLP / Published	No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
8.12.2_103 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Band, P.R. et al.	2001	Cohort cancer incidence among pulp and paper mill workers in British Columbia. Scand. J. Work Environ. Health 27: 113-119. Am. J. Epidemiol. 146: 186-194 Not GLP / Published	No	Published
8.12.2_104 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Langseth, H.; Andersen, A.	2000	Cancer incidence among male pulp and paper workers in Norway. Scand. J. Work Environ. Health 26: 99-105 Not GLP / Published	No	Published
8.12.2_105 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Lee, W.J. et al.	2002	Mortality from lung cancer in workers exposed to sulphur dioxide in the pulp and paper industry. Environ. Health Perspect. 110: 991-995 Not GLP / Published	No	Published
8.12.2_106 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Rix, B.A. et al.	1997	Cancer incidence of sulphite pulp workers in Denmark. Scand. J. Work Environ. Health 23: 458-461 Not GLP / Published	No	Published
8.12.2_107 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Matanoski, G.M. et al.	1998	Industry-wide study of mortality of pulp and paper mill workers Am J Ind Med 33: 354-365 Not GLP / Published	No	Published
8.12.2_108 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Shih, V.E. et al.	1977	Sulphite oxidase deficiency. Biochemical and clinical investigations of a hereditary metabolic disorder in sulphur metabolism. Am. Ind. Hyg. Assoc. J. 35: 288-291 Not GLP / Published	No	Published
8.12.2_109 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Bechthold, W.E. et al.	1993	Biological markers of exposure to SO ₂ : S-sulfonates in nasal lavage. New Engl. J. Med. 329: 1022-1028 Not GLP / Published	No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
8.12.2_110 a Direct observation , e.g. clinical cases, poisoning incidents	Sodium metabisulphite	Vena, G., Foti, C. and Angelini, G.	1994	Sulphite contact allergy. Contact Dermatitis 31:172–175 Not GLP / Published	No	Published
8.12.2_110 b Direct observation , e.g. clinical cases, poisoning incidents	Sodium metabisulphite	Nair, B. and Elmore, A.R.	2003	Final Report on the Safety Assessment of Sodium Sulphite, Potassium Sulphite, Ammonium Sulphite, Sodium Bisulphite, Ammonium Bisulphite, Sodium Metabisulphite and Potassium Metabisulphite. International Journal of Toxicology 2003, Vol. 22: 63-88. Not GLP / Published	No	Published
8.12.2_111 Direct observation , e.g. clinical cases, poisoning incidents	Sodium metabisulphite	Gall, H., Boehncke, W.-H., Gietzen, K.	1996	Intolerance to sodium metabisulphite in beer. Allergy Net Not GLP / Published	No	Published
8.12.2_112 Direct observation , e.g. clinical cases, poisoning incidents	Sodium metabisulphite	Rowe, R.C., Sheykey, P.J., Quinn, M.E.	2009	Handbook of Pharmaceutical Excipients, 6. Edition, published by the Pharmaceutical Press and the American Pharmacists Association, ISBN 978 0 85369 792 3 (UK), ISBN 978 1 58212 135 2 (USA) Not GLP / Published	No	Published
8.12.2_113 Direct observation , e.g. clinical cases, poisoning incidents	Sodium metabisulphite	Sasseville, D., El-Helou, T.	2009	Occupational allergic contact dermatitis from sodium metabisulphite. Contact Dermatitis 2009: 61: 244–245 Not GLP / Published	No	Published
8.12.2_114 Direct observation , e.g. clinical cases, poisoning incidents	Sodium metabisulphite	Petersen, C and Mené, T.	1992	Consecutive patch testing with sodium sulphite in eczema patients. Contact Dermatitis 27:344–345 Not GLP / Published	No	Published
8.12.2_115 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Johns, AD.O. and Linn, W.S.	2011	A review of controlled human SO2 exposure studies contributing to the US EPA integrated science assessment for sulphur oxides. Inhalation toxicology, 2011; 23 (1-4): 33-43. Not GLP / Published	No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
8.12.2_116 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Goodman, J.E., Dodge, D.G. and Bailey, L.A.	2010	A framework for assessing causality and adverse effects in humans with a case study of sulphur dioxide. Regulatory Toxicology and Pharmacology 58: pp. 308-332. Not GLP / Published	No	Published
8.12.2_116 Direct observation , e.g. clinical cases, poisoning incidents (Attachment of tables)	Sulfur dioxide	Goodman, J.E., Dodge, D.G. and Bailey, L.A.	2010	Attachment of tables as contained in reference above (section 8.12.2_116). Not GLP / Published	No	Published
8.12.2_117 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Gong H Jr, Lachenbruch PA, Harber P, Linn WS.	1995	Comparative short-term health responses to sulphur dioxide exposure and other common stresses in a panel of asthmatics. Toxicol Ind Health. 1995 Sep-Oct;11(5):467-87. Not GLP / Published	No	Published
8.12.2_118 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Goodman JE, Dodge DG, Bailey LA.	2010	A framework for assessing causality and adverse effects in humans with a case study of sulphur dioxide. Regul Toxicol Pharmacol. 2014 Feb;68(1):8-15. Not GLP / Published	No	Published
8.12.2_119 Direct observation , e.g. clinical cases, poisoning incidents	Sulfur dioxide	Johns DO, Linn WS.	2011	A review of controlled human SO ₂ exposure studies contributing to the US EPA integrated science assessment for sulphur oxides. Inhal Toxicol. 2011 Jan;23(1):33-43 Not GLP / Published	No	Published
8.12.3_01 Health records, both from industry and any other sources	Sulfur dioxide	Kehoe, R.A. et al.	1932	On the effects of prolonged exposure to sulphur dioxide. J. Ind. Hyg. 14: 159-173 Not GLP / Published	No	Published
8.12.3_02 Health records,	Sulfur dioxide	Anderson, A.	1950	Possible long term effects of exposure to sulphur dioxide. Brit. J.Med. 7: 82-86 Not GLP / Published	No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
both from industry and any other sources						
8.12.3_03 Health records, both from industry and any other sources	Sulfur dioxide	Berges, G, et al.	1975	Einfluß der Luftfeuchtigkeit auf die Lungenfunktion bei Schwefeldioxydexposition. Arbeitsmed. Sozialmed. Präventivmed. 10: 17-19 Not GLP / Published	No	Published
8.12.3_04 Health records, both from industry and any other sources	Sulfur dioxide	Snashall, P.D. and Baldwin, C.	1982	Mechanisms of sulphur dioxide induced bronchoconstriction in normal and asthmatic man. Thorax 37: 118-123 Not GLP / Published	No	Published
8.12.3_05 Health records, both from industry and any other sources	Sulfur dioxide	Sandström, T. et al.	1988	Challenge test for sulphur dioxide - symptom and lung function measurements. Scand. J.Work Environ. Health 14 (1): 77-79 Not GLP / Published	No	Published
8.12.3_06 Health records, both from industry and any other sources	Sulfur dioxide	Andersen, I et al.	1978	Human responses to SO2 at controlled conditions. VDI-Berichte 314. 139-141 Not GLP / Published	No	Published
8.12.3_07 Health records, both from industry and any other sources	Sulfur dioxide	Stjernberg, N. et al.	1984	Long-term effects of chronic exposure to sulphuric dioxide. Bull. Int. Union Tuberc. 59: 43-45 Not GLP / Published	No	Published
8.12.3_08 Health records, both from industry and any other sources	Sulfur dioxide	Jäppinen, P. et al.	1987	Cancer incidence of workers in the Finnish pulp and paper industry. Scand. J. Environ. Health 13: 197-202 Not GLP / Published	No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
8.12.3_09 Health records, both from industry and any other sources	Sulfur dioxide	Fabri, L. et al.	1977	Alterazioni respiratorie da esposizione cronica a bassa concentrazioni di SO ₂ . - Respiratory impairment due to chronic exposure to low levels of sulphur dioxide. Med. Lav. 68: 38-50 Not GLP / Published	No	Published
8.12.3_10 Health records, both from industry and any other sources	Sulfur dioxide	Peters, J.M. et al.	1984	Pulmonary effects of exposure in silicon carbide manufacturing. Br. J. Ind. Med. 41: 109-115 Not GLP / Published	No	Published
8.12.3_11 Health records, both from industry and any other sources	Sulfur dioxide	Skalpe, I.O.	1964	Long-term effects of sulphur dioxide exposure in pulp mills. Brit. J. Ind. Med. 21: 69-73 Not GLP / Published	No	Published
8.12.3_12 Health records, both from industry and any other sources	Sulfur dioxide	Ferris, B.G. et al.	1967	Prevalence of chronic respiratory disease in a pulp mill and a paper mill in the United States. Brit. J. Ind. Med. 24: 26-37 Not GLP / Published	No	Published
8.12.3_13 Health records, both from industry and any other sources	Sulfur dioxide	Stjernberg, N. et al.	1986	Chronic bronchitis in a community in northern Sweden; relation to environmental and occupational exposure to sulphur dioxide. Eur. J. Respir. Dis. 69 (146): 153-159 Not GLP / Published	No	Published
8.12.3_14 Health records, both from industry and any other sources	Sulfur dioxide	Osterman, J.W. et al.	1989	Respiratory symptoms associated with low level sulphur dioxide exposure in silicon carbide production workers. British J. Ind. Med. 46: 629-635 Not GLP / Published	No	Published
8.12.3_15 Health records, both from industry and any other sources	Sulfur dioxide	Osterman J.W. et al.	1989	Work related decrement in pulmonary function in silicon carbide production workers. British J. Ind. Med. 46: 708-716 Not GLP / Published	No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
8.12.3_16 Health records, both from industry and any other sources	Sulfur dioxide	Kremer, A.M. et al.	1995	Airway hyperresponsiveness in workers exposed to low levels of irritants. Eur. Respir. J. 8: 53-61 Not GLP / Published	No	Published
8.12.3_17 Health records, both from industry and any other sources	Sulfur dioxide	Kremer, A.M. et al.	1994	Airway hyperresponsiveness, prevalence of chronic respiratory symptoms, and lung function in workers exposed to irritants. Occup. Environ. Med. 51: 3-13 Not GLP / Published	No	Published
8.12.3_18 Health records, both from industry and any other sources	Sulfur dioxide	Smith, T.J. et al.	1984	Respiratory exposures associated with silicon carbide production: estimation of cumulative exposures for an epidemiological study. Brit. J. Ind. Med. 41: 100-108 Not GLP / Published	No	Published
8.12.3_19 Health records, both from industry and any other sources	Not applicable	Not applicable	n.a.	Study has been deleted. To guarantee the continuous numbering of the study entries, this ESR only serves as placeholder.	No	Published
8.12.3_20 Health records, both from industry and any other sources	Sulfur dioxide	Linn, W.S. et al.	1984	Asthmatics' responses to 6-hr sulphur dioxide exposures on two successive days. Arch. Environ. Health 39: 313-319 Not GLP / Published	No	Published
8.12.3_21 Health records, both from industry and any other sources	Sulfur dioxide	Andersen, I. et al.	1977	Induced rhinovirus infection under controlled exposure to sulphur dioxide. Arch. Environ. Health 32: 120-126 Not GLP / Published	No	Published
8.12.3_22 Health records, both from industry and any other sources	Sulfur dioxide	Frank, N.R. and Speizer, F.E.	1964	Uptake and release of SO ₂ by the human nose. Physiologist 7: 132 Not GLP / Published	No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
8.12.3_23 Health records, both from industry and any other sources	Sodium metabisulphite	Kaaman, A.-C., Boman, A., Wrangsjö, K., Matura, M.	2010	Contact allergy to sodium metabisulphite: an occupational problem. Contact Dermatitis 2010; 63: 110–112 Not GLP / Published	No	Published
8.12.3_24 Health records, both from industry and any other sources	Sodium metabisulphite	Sasseville, D., El-Helou, T.	2009	Occupational allergic contact dermatitis from sodium metabisulphite. Contact Dermatitis 2009; 61: 244–245 Not GLP / Published	No	Published
8.12.3_25 Health records, both from industry and any other sources	Sodium metabisulphite	Merget, R. and Korn, M.	2005	CASE STUDY - Metabisulphite-induced occupational asthma in a radiographer. Eur Respir J 2005; 25: 386–388 Not GLP / Published	No	Published
8.12.3_26 Health records, both from industry and any other sources	Sodium metabisulphite	Pouget, R., Loddé, B., Lucas, D., Jégaden, D., Bell, S. Dewitte, J.-D.	2010	CASE STUDY - A case of occupational asthma from metabisulphite in a fisherman. Int Marit Health, 2010; 61, 3: 180–184 Not GLP / Published	No	Published
8.12.4_01 Epidemiological data	Sulfur dioxide	Raulf-Heimsoth, M.	2010	Assessment of low dose effects of acute sulphur dioxide exposure on the airways using non-invasive methods. Arch. Toxicol. 84: 121 – 127 Not GLP / Published	No	Published
8.12.4_02 Epidemiological data	Sulfur dioxide	van Thriel, C et al.	2010	Sensory and pulmonary effects of acute exposure to sulphur dioxide (SO ₂). Toxicology Letters 196: 42 – 50 Not GLP / Published	No	Published
8.12.4_03a Epidemiological data	Sodium metabisulphite	Vena, G., Foti, C. and Angelini, G.	1994	Sulphite contact allergy. Contact Dermatitis 31:172–175 Not GLP / Published	No	Published
8.12.4_03b Epidemiological data	Sodium metabisulphite	Nair, B. and Elmore, A.R.	2003	Final Report on the Safety Assessment of Sodium Sulphite, Potassium Sulphite, Ammonium Sulphite, Sodium Bisulphite, Ammonium Bisulphite, Sodium Metabisulphite and Potassium Metabisulphite. International Journal of Toxicology 2003, Vol. 22: 63-88 Not GLP / Published	No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
8.12.4_04 Epidemiological data	Sodium metabisulfite	Kaaman, A.-C., Boman, A., Wrangsjö, K., Matura, M.	2010	Contact allergy to sodium metabisulphite: an occupational problem. Contact Dermatitis 2010: 63: 110–112 Not GLP / Published	No	Published
8.12.5_02 Diagnosis of poisoning	Sodium metabisulfite	Chemservice S.A.	2014	Review of public available information - Diagnosis of Sodium metabisulphite poisoning including specific signs of poisoning and clinical tests. Chemservice S.A., Grevenmacher, Luxembourg, Report No CSL-ML-284, Not GLP / Unpublished	Yes	Micro-Pak B.V.
8.12.6_02 Contact dermatitis	Sodium metabisulfite	Sokol, W.N. and Hydick, I.B.	1990	Nasal congestion, urticaria, and angioedema, caused by IgE-mediated reaction to sodium metabisulphite. J. Allerg Clin Immunol. 65, 233-238 Not GLP / Published	No	Published
8.12.6_03 Contact dermatitis	Sodium metabisulfite	Wüthrich, B., Kagi, M.K. and Hafner, J.	1993	Disulphite-induced acute intermittent urticaria with vasculitis, Dermatology. 187, 290-292 Not GLP / Published	No	Published
8.12.6_04 Contact dermatitis	Sodium metabisulfite	Vena, G., Foti, C. and Angelini, G.	1994	Sulphite contact allergy. Contact Dermatitis 31:172–175 Not GLP / Published	No	Published
8.12.6_05 Contact dermatitis	Sodium metabisulfite	Sainte-Laudy, J., Vallon, C. and Guérin, J.-C.	1994	Mise en évidence des IgE spécifiques du groupe des sulphites chez les intolérants à ces conservateurs Allergie et immunologie 26 (4); pp. 132-134, 137-138 Not GLP / Published	No	Published
8.12.6_06 Contact dermatitis	Sodium metabisulfite	Jacobs, M.C. and Rycroft, R.J.G.	1992	Contact dermatitis and asthma from sodium metabisulphite in a photographic technician. Contact Dermatitis. 33, 65-66 Not GLP / Published	No	Published
8.12.6_07 Contact dermatitis	Sodium metabisulphitesulfite	Levanti, C., Ricciardi, L., Isola, I., Cilia, M., Guarneri, F., Purrello D'Ambrosio, F.	1996	Burning Mouth Syndrome: Hypersensitivity to Sodium Metabisulphite. Acta dermatovenereologica. 1996; 76 (2): 158-159. Not GLP / Published	No	Published
8.12.6_08 Contact dermatitis	Sodium metabisulfite	Lee, A., Nixon, R.	2001	Contact dermatitis from sodium metabisulphite in a baker. Contact Dermatitis: 2001: 44: 127 Not GLP / Published	No	Published
8.12.6_09 Contact dermatitis	Sodium metabisulfite	Nair, B. and Elmore, A.R.	2003	Final Report on the Safety Assessment of Sodium Sulphite, Potassium Sulphite, Ammonium Sulphite, Sodium Bisulphite, Ammonium Bisulphite, Sodium Metabisulphite and Potassium Metabisulfit. International Journal of Toxicology 2003,	No	Published

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				Vol. 22: 63-88. Not GLP / Published		
8.12.6_10 Contact dermatitis	Sodium metabisulfite	Riemersma, W.A., Schuttelaar, M.L.A., Coenraads, P.J.	2004	Type IV hypersensitivity to sodium metabisulphite in local anaesthetic. Contact Dermatitis 2004: 51: 148-158. Not GLP / Published	No	Published
8.12.6_11 Contact dermatitis	Sodium metabisulfite	Huang, P-Y., Ch, C-Y.	2007	Allergic contact dermatitis due to sodium metabisulphite in a bleaching cream. Contact Dermatitis, 2007: 56: 123-124. Not GLP / Published	No	Published
8.12.6_12 Contact dermatitis	Sodium metabisulfite	Madan, V., Walker, S.L., Beck, M.H.	2007	Sodium metabisulphite allergy is common but is it relevant? Contact Dermatitis: 2007: 57: pp. 173-176. Not GLP / Published	No	Published
8.12.6_13 Contact dermatitis	Sodium metabisulfite	Malik, M.M., Hegarty, M.A., Bourke, J.F.	2007	Sodium metabisulphite -a marker for cosmetic allergy? Contact Dermatitis: 2007: 56: 241-242. Not GLP / Published	No	Published
8.12.6_14 Contact dermatitis	Sodium metabisulfite	Madan, V., Beck, M.H.	2009	Sodium metabisulphite - a contact allergen? Contact Dermatitis: 2009: 61: 58 Not GLP / Published	No	Published
8.12.6_15 Contact dermatitis	Sodium metabisulfite	Rowe, R.C., Sheykey, P.J., Quinn, M.E.	2009	Handbook of Pharmaceutical Excipients, 6. Edition, published by the Pharmaceutical Press and the American Pharmacists Association, ISBN 978 0 85369 792 3 (UK), ISBN 978 1 58212 135 2 (USA) Not GLP / Published	No	Published
8.12.6_16 Contact dermatitis	Sodium metabisulfite	Sasseville, D., El-Helou, T.	2009	Occupational allergic contact dermatitis from sodium metabisulphite. Contact Dermatitis 2009: 61: 244-245 Not GLP / Published	No	Published
8.12.6_17 Contact dermatitis	Sodium metabisulfite	Aalto-Korte, K., Suuronen, K., Alanko, K.	2009	Sodium metabisulphite -a contact allergen? Contact Dermatitis: 2009; 60: 115-117. Not GLP / Published	No	Published
8.12.6_18 Contact dermatitis	Sodium metabisulfite	Kaaman, A.-C., Boman, A., Wrangsjö, K., Matura, M.	2010	Contact allergy to sodium metabisulphite: an occupational problem. Contact Dermatitis 2010: 63: 110-112 Not GLP / Published	No	Published
8.12.6_19 Contact dermatitis	Sodium metabisulfite	Davies, R.F., Johnston, G.A.	2011	New and emerging cosmetic allergens. Clinics in Dermatology (2011) 29, 311-315. Not GLP / Published	No	Published
8.12.6_20 Contact dermatitis	Sodium metabisulfite	Febriana, S.A., Jungbauer, F., Soebono, H.,	2012	Occupational allergic contact dermatitis and patch test results of leather workers at two Indonesian tanneries. Not GLP / Published	No	Published

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		Coenraads, P.J.				
8.12.6_20 Contact dermatitis (Attachment of figure)	Sodium metabisulfite	Febriana, S.A., Jungbauer, F., Soebono, H., Coenraads, P.J.	2012	Attachment of figure as contained in reference above for section 8.12.6_20. Not GLP / Published	No	Published
8.12.6_21 Contact dermatitis	Sodium metabisulfite	Garcia-Gavin, J., Parente, J., Goossens, A.	2012	Allergic contact dermatitis caused by sodium metabisulphite: a challenging allergen. A case series and literature review. Contact Dermatitis: 67, pp. 260-264; © 2012 John Wiley & Sons A/S. Not GLP / Published	No	Published
8.12.6_21 Contact dermatitis (Attachment of tables)	Sodium metabisulfite	Garcia-Gavin, J., Parente, J., Goossens, A.	2012	Attachment of tables as contained in reference above for section 8.12.6_21. Not GLP / Published	No	Published
8.12.6_22 Contact dermatitis	Sodium metabisulfite	Oliphant, T., Mitra, A., Wilkinson, M.	2012	Contact allergy to sodium sulphite and its relationship to sodium metabisulphite. Contact Dermatitis, 66, 128-130// © 2012 John Wiley & Sons A/S. Not GLP / Published	No	Published
8.12.6_23 Contact dermatitis	Sodium metabisulfite	Roberts, D.W., Basketter, D., Kimber, I., White, J., Fadden, J.Mc., White, I.R.	2012	Sodium metabisulphite as a contact allergen - an example of a rare chemical mechanism for protein modification. Contact Dermatitis, 66: 123-127. Not GLP / Published	No	Published
8.12.6_23 Contact dermatitis (Attachment of scheme)	Sodium metabisulfite	Roberts, D.W., Basketter, D., Kimber, I., White, J., Fadden, J.Mc., White, I.R.	2012	Attachment of scheme as contained in reference above for section 8.12.6_23. Not GLP / Published	No	Published
8.12.6_23 Contact dermatitis (Illustration of scheme)	Sodium metabisulfite	Roberts, D.W., Basketter, D., Kimber, I., White, J., Fadden, J.Mc., White, I.R.	2012	Attachment of illustrative scheme as contained in reference above for section 8.12.6_23. Not GLP / Published	No	Published
8.12.6_24 Respiratory	Sodium metabisulfite	Wüthrich, B. and T. Huwyler	1989	Das Disulfid-Asthma. Schweiz. Med. Wschr., 119, 1177-1188. Not GLP / Published	No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
sensitisation						
8.12.6_25 Respiratory sensitisation	Sodium metabisulphite	Wright, W., Zhang, Y.G., Salome, C.M., Woolcock, A.J.	1990	Effect of Inhaled Preservatives on Asthmatic Subjects. I Sodium metabisulphite. The American Review of Respiratory Disease: 1990; 141 (6): 1400-1404. Not GLP / Published	No	Published
8.12.6_26 Respiratory sensitisation	Sodium metabisulphite	Valero, A.L., Bescos, M., Amat, P. and Malet, A.	1993	Bronchial asthma caused by occupational sulphite exposure. Allergol. Immunopathol. (Madr). 21(6), 221-4 Not GLP / Published	No	Published
8.12.6_27 Respiratory sensitisation	Sodium metabisulphite	Field, P.I., McClean, M., Simmul, R., Berend, N.	1994	Comparison of sulphur dioxide and metabisulphite airway reactivity in subjects with asthma. Thorax 1994; 49: 250-256. Not GLP / Published	No	Published
8.12.6_28 Respiratory sensitisation	Sodium metabisulphite	Gastaminza, G., Qujrce, S., Torres, M., Tabar, A., Echechipia, S., Munoz, D., Fernandez de Corres, L.	1995	Pickled onion-induced asthma: a model of sulphite-sensitive asthma? Clinical and Experimental Allergy, 1995, Volume 25, pages 698-703. Not GLP / Published	No	Published
8.12.6_29 Respiratory sensitisation	Sodium metabisulphite	Nannini, L.J., Hofer, D.	1997	Effect of Inhaled Magnesium Sulphate on Sodium Metabisulphite-Induced Bronchoconstriction in Asthma. Chest / 111 / 4 / APRIL, 1997. Not GLP / Published	No	Published
8.12.6_30 Respiratory sensitisation	Sodium metabisulphite	Nicol, G.M., Nix, A., Chung, K.F., Barnes, P.J.	1989	Characterisation of bronchoconstrictor responses to sodium metabisulphite aerosol in atopic subjects with and without asthma. Thorax 1989;44:1009-1014. Not GLP / Published	No	Published
8.12.6_31 Respiratory sensitisation	Sodium metabisulphite	Pavord, I.D., Wisniewski, A., Tattersfield, A.E.	1994	Refractoriness to inhaled sodium metabisulphite in subjects with mild asthma. Eur Respir J, 1994, 7, 50-54. Not GLP / Published	No	Published
8.12.6_32 Respiratory sensitisation	Sodium metabisulphite	Pavord, I., Lazarowicz, H., Inchley, D., Baldwin, D., Knox, A., Tattersfiel, A.	1994	Cross refractoriness between sodium metabisulphite and exercise induced asthma. Thorax 1994; 49: 245-249. Not GLP / Published	No	Published
8.12.6_33 Respiratory sensitisation	Sodium metabisulphite	Van Schoor, J., Joos, G.F.,	2000	Indirect bronchial hyperresponsiveness in asthma: mechanisms, pharmacology and implications for clinical research. Not GLP / Published	No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
		Pauwels, R.A.				
8.12.6_34 Respiratory sensitisation	Sodium metabisulphite	Merget, R. and Korn, M.	2005	CASE STUDY - Metabisulphite-induced occupational asthma in a radiographer. Eur Respir J 2005; 25: 386–388 Not GLP / Published	No	Published
8.12.6_35 Respiratory sensitisation	Sodium metabisulphite	Steiner, M, Scaife, A., Semple, S., Hulks, G., Ayres, J.G.	2008	Sodium metabisulphite induced airways disease in the fishing and fish-processing industry. Occupational Medicine 2008; 58: 545–550. Not GLP / Published	No	Published
8.12.6_36 Respiratory sensitisation	Sodium metabisulphite	Pougnat, R., Loddé, B., Lucas, D., Jégaden, D., Bell, S. Dewitte, J.-D.	2010	CASE STUDY - A case of occupational asthma from metabisulphite in a fisherman. Int Marit Health, 2010; 61, 3: 180–184 Not GLP / Published	No	Published
8.12.6_37 Respiratory sensitisation	Sodium metabisulphite	Uriarte, S.A., Fernández-Nieto, M., Arochena, L., Sastre, J.	2015	Occupational Asthma in Seafood Manufacturing and Food Allergy to Seafood. Journal of Investigational Allergology & Clinical Immunology: 2015; Vol. 25(1): 59-60. Not GLP / Published	No	Published
8.12.6_38 Accidents and systemic action	Sodium metabisulphite	Atkinson, D.A., Sim, T.C. and J.A. Grant	1993	Sodium metabisulphite and SO ₂ release: An under-recognized hazard among shrimp fishermen. Annals of Allergy, Vol. 71 (December 1993), 563-566. Not GLP / Published	No	Published
8.12.6_39 Accidents and systemic action	Sodium metabisulphite	Kounis, N.G., Mazarakis, A., Almpanis, G., Gkouias, K., Kounis, G.N., Tsigkas, G.	2014	The more allergens an atopic patient is exposed to, the easier and quicker anaphylactic shock and Kounis syndrome appear: Clinical and therapeutic paradoxes. J Nat Sci Biol Med. 2014 Jul-Dec; 5(2): 240–244. Not GLP / Published	No	Published
8.12.7_03 Accidents	Sulfur dioxide	Delohery, J. et al.	1984	The relationship of inhaled sulphur dioxide reactivity to ingested metabisulphite sensitivity in patients with asthma. Am. Rev. Respir. Dis. 130: 1027-1030 Not GLP / Published	No	Published
8.12.7_04 Accidents	Sodium metabisulphite	Atkinson, D.A., Sim, T.C. and J.A. Grant	1993	Sodium metabisulphite and SO ₂ release: An under-recognized hazard among shrimp fishermen. Annals of Allergy, Vol. 71 (December 1993), 563-566. Not GLP / Published	No	Published

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Section No / Reference No/ ESR in IUCLID	Substance	Author(s)	Year	Title Source, Report No. GLP / (Un)Published	Data Protection Claimed (Yes/No)	Owner
8.12.7_05 Accidents	Sodium metabisulfite	Kounis, N.G., Mazarakis, A., Almpanis, G., Gkouias, K., Kounis, G.N., Tsigkas, G.	2014	The more allergens an atopic patient is exposed to, the easier and quicker anaphylactic shock and Kounis syndrome appear: Clinical and therapeutic paradoxes. J Nat Sci Biol Med. 2014 Jul-Dec; 5(2): 240–244. Not GLP / Published	No	Published
8.12.7_06 Accidents	Sodium metabisulfite	Cussans, A., McFadden, J. and L. Ostlere	2015	Systemic sodium metabisulphite allergy. Contact Dermatitis, Contact Points, pp. 1-2. Not GLP / Published	No	Published
8.13.2_1	Sulfur dioxide	Yargıçoğlu P1, Ağar A, Gümüşlü S, Bilmen S, Oğuz Y.	1999	Age-related alterations in antioxidant enzymes, lipid peroxide levels, and somatosensory-evoked potentials: effect of sulphur dioxide. Arch Environ Contam Toxicol 27:554-60 Not GLP / Published	No	Published
8.13.2_2	Sulfur dioxide	Yun Y, Yao G, Yue H, Guo L, Qin G, Li G, Sang N	2013	O(2) inhalation causes synaptic injury in rat hippocampus via its derivatives in vivo Chemosphere 93: 2426-32, Not GLP / Published	No	Published
8.13.2_3	Sulfur dioxide	Qin G, Wang J, Huo Y, Yan H, Jiang C, Zhou J, Wang X, Sang N	2012	Sulphur dioxide inhalation stimulated mitochondrial biogenesis in rat brains. Toxicology 2012 (200): 67-74 Not GLP / Published	No	Published
3.1, 10.2	-	EFSA	2012	Scientific Opinion, Guidance on Dermal Absorption, EFSA Panel on Plant Protection Products and their Residues (PPR), EFSA Journal 2012;10(4):2665, published	No	Published

12 Annex of studies on health hazards

Data relating to Table 11: Summary table of human data on respiratory sensitisation

Hein et al. 1996 Pneumologie 50/6: 394-8

39 % of patients with a history of sulfite-sensitive asthma showed significant broncho-constriction after ingestion of metabisulfite (PD₂₀ FEV₁: 34±56 mg; min: 5, max: 200 mg; n=17); specificity: 100 %, sensitivity: ca. 40 %

Onset of SMB reaction minimal 60, maximal 210 min, average 150 min.

Table 2. Age, sex distribution, atopia and smoking status, percentage of vital capacity (%FVC) and 1- second-capacity (%FEV₁) as well as PC₂₀ Histamine and PC₂₀ MBS for healthy control subjects and patients with bronchial asthma after a history of a sulfite asthma or after a response to the oral metabisulfite test.

	Control proband	Asthma bronchiale
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	No atopia	Atopia	Sulfite anamnesis		Oral metabisulfite test	
			Negative	Positive	Negative	Positive
n	4	4	27	44	27	17
Gender (female/male)	3/1	2/2	16/11	30/14	14/13	16/1
Atopia (y/n)	0/4	4/0	19/8	24/20	14/3	10/7
Smoker (y/n)	0/4	4/0	11/1	3/41	1/26	2/15
%FVC	98±7	105±5	88±13	92±20	91±24	93±13
%FEV ₁	98±7	103±6	83±18	86±18	90±17	79±19
PC ₂₀ Hist. (mg/ml)	>8	>8	1±1.1	1.3±1.8	1.7±1.9	0.3±0.2
PC ₂₀ SBM (mg)	>390	>390	>390		>390	34±56

Delohery et al. 1984 Am Rev Respir Dis; 130:1027-32

% fall after MB: Group 1: 35±14; group 2: 6±6; group 3: 5±3

Pc20 SO₂ (ppmV): group 1: 1.19±0.78 (0.5 – 2.9); group 2: 2.3±1.42; group 3: >5; Pc20 SO₂ does not correlate with MB PEFr fall. Asthmatics whose asthma is provoked by ingestion of acid MB solutions, are not supersensitive to inhaled SO₂ gas

SO₂ sensitivity does not correlate with histamine reactivity.

TABLE 1
SUBJECT DETAILS AND RESULTS

Subgroup	Group No.	Age & Sex	Baseline PEFR	% Fall PEFR			Pc20 SO ₂ ppm	Pc20 Histamine mg/ml
				Citrate	MB	Control Gas		
A	1	25 M	500	14	24	15	0.75	0.15
	2	21 M	480	4	4	13	4	0.051
	3	20 M	590	5	5	2	> 5	3.5
B	1	26 M	500	0	60	2	1	0.08
	2	24 M	390	0	1	9	1.6	0.18
	3	22 M	630	1	8	3	> 5	> 8.0
C	1	18 F	430	18	43	3	0.54	0.15
	2	22 F	290	10	7	4	2.8	0.04
	3	22 F	475	9	11	8	> 5	> 8.0
D	1	26 F	430	0	37	10	2.9	0.10
	2	31 F	390	0	18	10	2.4	0.14
	3	27 F	400	5	3	5	> 5	4.8
E	1	29 F	345	15	62	0	2	0.023
	2	33 F	395	15	14	4	1.85	0.18
	3	27 F	580	2	5.2	5	> 5	6.5
F	1	38 F	380	1	29	3	1.2	0.05
	2	40 F	240	8	8	3	0.6	0.07
	3	41 F	450	6	2	1	> 5	> 8.0
G	1	44 F	300	14	23	19	0.64	0.03
	2	40 F	270	15	2	17	0.5	0.05
	3	48 F	390	5	0	8	> 5	7.2
H	1	57 F	180	8	22	9	0.67	0.03
	2	69 F	385	14	7	1	1.75	0.5
	3	56 F	355	3	3	6	> 5	2.5
I	1	14 F	340	9	53	14	0.5	0.029
	2	22 F	190	7	0	0	1.9	0.015
	3	22 F	440	11	11	7	> 5	3.8
J	1	24 F	360	10	33	3	1.7	0.10
	2	19 F	400	7	0	3	> 5	0.7
	3	22 F	460	4	9	2	> 5	> 8.0

Definition of abbreviations: Baseline PEFR = baseline PEFR on day 1 prior to MB challenge; PEFR = peak expiratory flow rate; citrate = ingested challenge study with 30 mg control 0.5% citric acid solution; MB = ingested challenge study with 50 mg metabisulfite in 30 ml 0.5% citric acid; control gas = humidified air control gas for inhaled SO₂ gas studies.

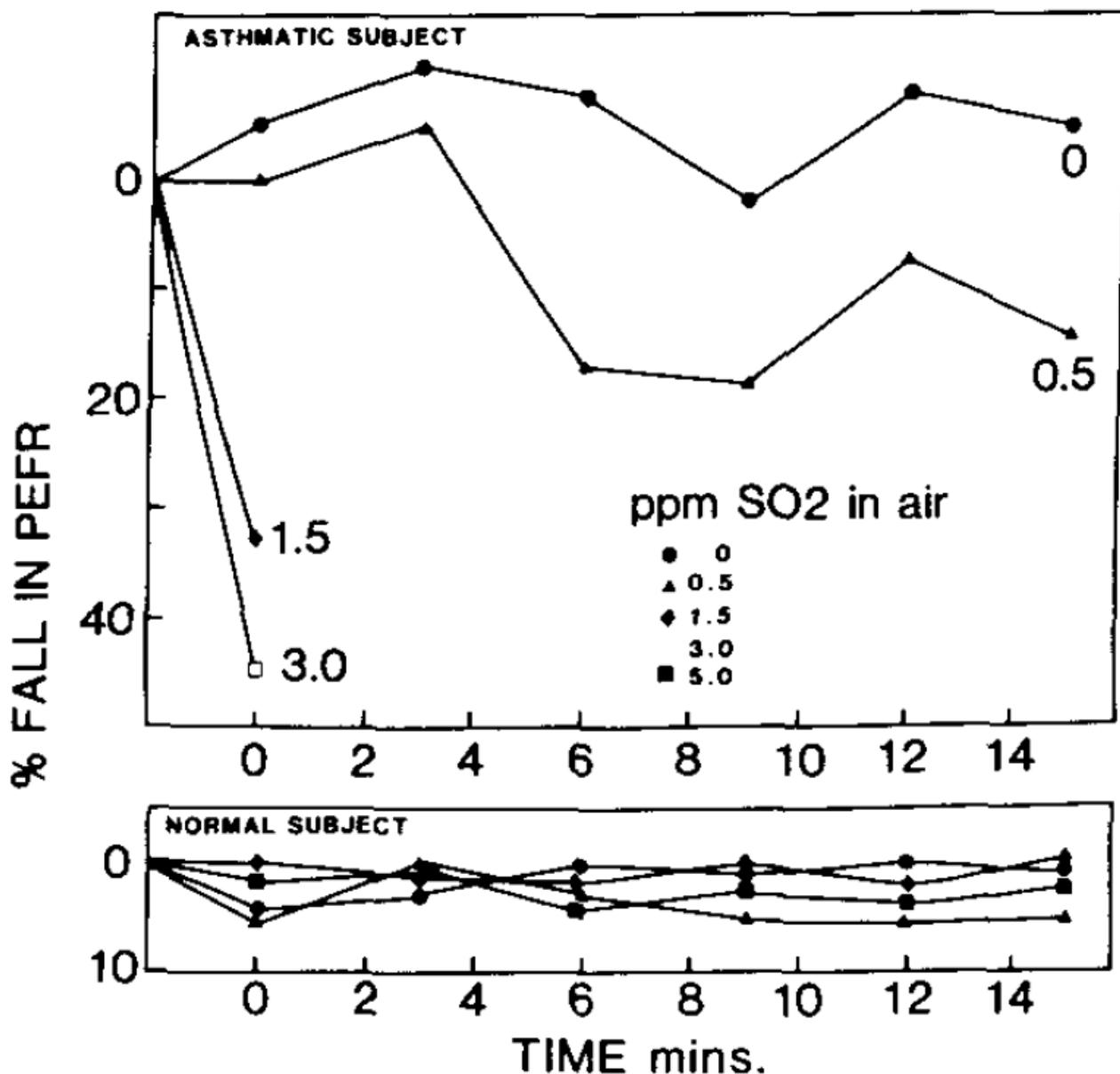


Fig. 4. Typical responses of an asthmatic subject (*upper panel*) and a normal control subject (*lower panel*) to inhalation of the SO₂ gas mixture. The asthmatic subject shows a dose-response relationship with increasing SO₂ gas concentration producing a progressive fall in PEFR.

Schwarz and Chester 1984; J Allergy Clin Immunol. 74:511-3

Bronchospastic response at 1.2 ppm

Aerosol challenge 2/8 negative; 3/8 positive at 0.5 mg/mL, and 5.0 mg/mL, respectively

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3/8 positive reactors to 0.5 mg/mL aerosol reacted at 10, 25, 50 mg oral SMB, respectively.
All patients negative in prick tests.

TABLE I. Responses of the study patients to oral metabisulfite challenge

	Dose for positive response*				Total
	5 mg	10 mg	25 mg	50 mg	
Number positive	0	2	1	3	7
Number tested	8	8	6	5	8

*A positive response is defined as having a 50% or higher change in measurement of specific airway resistance.

TABLE II. Aerosol results and characteristics of the asthmatic patients studied*

	Sex		Dose for positive responses			Atopic†	Nonatopic
	Male	Female	0.05 mg/ml	0.5 mg/ml	5.0 mg/ml		
Positive reactors	2	4	0	3	3	5	1
Negative reactors	0	2	0	0	0	1	1

*A positive response is defined as having a 50% or higher change in measurements of specific airway resistance.

†Atopy was defined as the presence of a significant history of allergic disease and immediate wheal-and-flare skin test reactions to standard inhalant allergens.

Data relating to Table 13: Summary table of human data on skin sensitisation

Garcia-Gavin et al. 2012; Contact Dermatitis 67:260-9

124 (4.5 %) positive results (77F/47M), most frequently on the face and the hands, median age: 50; 13 cases (10.5 %) occupational exposure.

Table 1. MOAHLFAs of the overall group of patients tested from 1 January 1990 to 14 October 2010 (n = 12 746), of the patients tested with sodium metabisulfite (SMS) (n = 2763), and of the sodium metabisulfite-positive patients (n = 124)

	SMS-positive patients (n = 124)	SMS-tested patients (n = 2763)	Overall sample (n = 12 746)
Male (%)	37.4	19.6	34.2
Occupational (%)	10.5	15.7	16.8
Atopy (%)	18	20	21.5
Hand (%)	24.2	29.1	38.3
Leg (%)	10.5	7.6	3.5
Face (%)	40.3	51.3	34.5
Age > 40 years (%)	61.3	54.6	47.6

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Oliphant et al. 2012 Contact Dermatitis 66/3:128-30

183 patients tested: 5.5 % (n=10) positive to sodium metabisulfite, 3.8 % (n=7) positive to sodium sulfite.

Table 1. Patients with positive patch test reactions to sodium sulfite (SS) and sodium metabisulfite (SMB)

Age (years)	Sex	Site	SMB	Relevance	Comment	SS	Relevance	Comment
25	M	Lips	+ / + +	?R	?Food preservative	?+ / +	?R	?Food preservative
45	M	Generalized	- / + +	NR	-	- / ? +	NR	-
33	M	Hands	?+ / + +	PR	Medicament	- / +	XR	-
23	F	Perioral	- / +	?R	?Food preservative	- / -	-	-
42	F	Perioral	+ / +	?R	?Food preservative	- / -	-	-
36	M	Lips	- / +	?R	?Food preservative	- / -	-	-
13	F	Face	- / +	NR	-	- / -	-	-
51	F	Hands	- / +	?R	Medicament	- / +	XR	-
92	F	Legs	+ / +	PR	Medicament	- / +	XR	-
62	M	Legs	- / +	PR	Medicament	- / +	XR	-
34	M	Scalp	- / -	-	-	+ / + +	CR	Hair dye

CR, current relevance; F, female; M, male; NR, not relevant; PR, past relevance; ?R, possible relevance; XR, cross-reaction. First/second readings according to International Contact Dermatitis Research Group criteria.

Madan, V., Walker, S.L., Beck, M.H. 2007, Contact Dermatitis; 57:173-6.

71 (4.1 %) positive reactions, interpreted as allergic. 33/71 with identifiable source (group A), 38 with unknown sources (group B). 47 cases with known sources after reanalysis (3 %).

Sensitization to sodium metabisulfite from parenteral solutions and occupational exposure from food handling may account for some of the otherwise unexplained positive patch test reactions.

Table 4. Relevant occupational/recreational exposure

Occupation	Relevant group (A) (+additional exposure)	Unexplained relevance group (B)
Baker	1 + Timodine	2
Catering	3	1
Chemical processing	1	1
Rubber manufacturing	1 + Trimovate and Timodine	0
Swimming pool	1	0
Brewer (wine)	1 + Trimovate	1
False tan	1	1
Exposure to local anaesthetic solutions (dentists, nurses, etc.)	0	5
Photographic chemical handling	0	0

Data relating to Table 14: Summary table of mutagenicity/genotoxicity tests *in vitro*

Pagano and Zeiger (1987). Mutation Research 179: 159-166

Positive – slight but dose-related increase in # of revertants – increase < 2-fold, with 60 min incubation, >2-fold after 90 or 120 min incubation)

Reproducible weak mutagenic response in *S. typhimurium* strains carrying the *his* D6610 or *his*G46 mutations.

Peak mutagenic response in G46 stains at 0.1 M and in TR3243 at 0.3 M.

Number of induced revertants per dose, the *his*D6610 site was most responsive, with **TA 97** being the most active.

Mutagenic response highest with 0.1 M sodium phosphate buffer at pH 5.0-6.0.

Base-pair substitution and frameshift mutations

Base-pair substitution (deamination of cytosine):

At higher concentrations (1 M): cytosin bisulfite adducts leading to base substitution

At lower concentrations (approx. 0.01 M) deamination of cytosine via oxidative damage assumed.

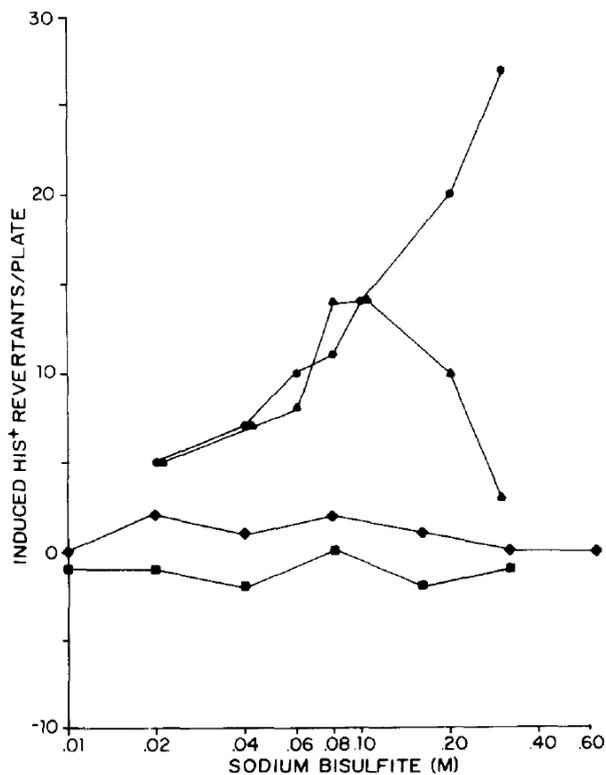


Fig. 1. The mutagenicity of bisulfite in *S. typhimurium* TR3243 (●), G46 (▲), D3052 (◆) and C3076 (■).

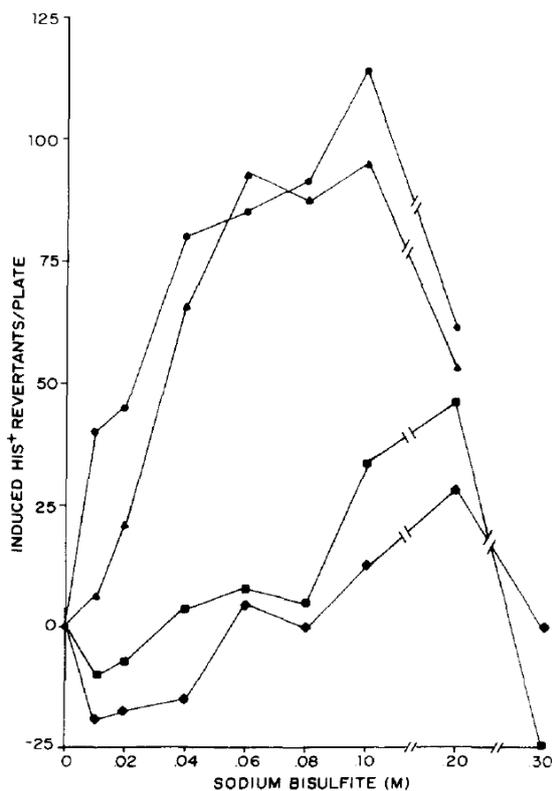


Fig. 2. The effect of pH on the mutagenicity of sodium bisulfite in *S. typhimurium* strain TA97. ●, pH 5.0; ▲, pH 6.0; ■, pH 7.0; ◆, pH 8.0.

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TABLE 2

THE MUTAGENICITY OF SODIUM BISULFITE IN DIFFERENT GENETIC BACKGROUNDS OF *Salmonella typhimurium*

(a) *hisD6610* mutation

Dose (M)	TA88	TA110	TA90	TA97
0	40 ± 3 ^a	61 ± 6	34 ± 8	132 ± 14
0.01	46 ± 4 (6)	– ^b	–	161 ± 26 (29)
0.02	61 ± 10 (21)	86 ± 10 (25)	33 ± 7 (–1)	180 ± 12 (48)
0.04	72 ± 24 (32)	101 ± 11 (40)	37 ± 6 (3)	204 ± 11 (72)
0.06	96 ± 11 (56)	108 ± 12 (47)	38 ± 2 (4)	234 ± 16 (102)
0.08	94 ± 12 (54)	123 ± 9 (62)	37 ± 8 (3)	226 ± 9 (94)
0.10	71 ± 16 (32)	110 ± 11 (49)	28 ± 5 (–6)	194 ± 14 (62)
0.20	69 ± 8 (29)	–	8 ± 4 (–26)	135 ± 8 (3)
0.30	53 ± 4 (13)	60 ± 7 (–1)	2 ± 1 (–32)	54 ± 8 (–78)

(b) *hisG46* mutation

Dose (M)	SB2802	TA92	TA1535	TA100
0	3 ± 1	25 ± 2	12 ± 2	141 ± 12
0.01	–	–	–	–
0.02	6 ± 2 (3)	34 ± 5 (9)	9 ± 3 (–3)	117 ± 7 (–24)
0.04	11 ± 4 (8)	36 ± 1 (11)	10 ± 2 (–2)	–
0.06	16 ± 5 (13)	38 ± 6 (13)	9 ± 5 (–3)	117 ± 7 (–24)
0.08	15 ± 2 (12)	41 ± 4 (16)	12 ± 2 (0)	–
0.10	15 ± 3 (12)	50 ± 5 (25)	17 ± 5 (5)	116 ± 8 (–25)
0.20	16 ± 3 (13)	51 ± 4 (26)	15 ± 3 (3)	–
0.30	16 ± 4 (13)	40 ± 2 (15)	4 ± 1 (–8)	0

^a Mean *his*⁺ revertants per plate ± S.D. (induced revertants); triplicate or quadruplicate plates.

^b Not done.

Anonymous15 2008; Environ Mol Mutagen 49: 276-281

Positive

Reduction in MI to 56 – 60 – 45 – 42 % (for concentrations: 25 – 50 – 100 – 200 µg/mL) of concurrent negative control, positive control: MI: 43 % of neg. control; OECD 473 for PBLs: MI reduction to 45 ± 5 % of controls

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TABLE I. The Structural, Numerical, Total Chromosome Aberrations (CAs), Percentage of Abnormal Cells and Mitotic Index (MI) in Cultured Human Lymphocytes Treated With PMB

Test substance	Treatment		Chromosome aberrations			Structural CA/cell ± SE	Numerical CA/cell ± SE	Total CA/Cell ± SE	Percentage of abnormal cell ± SE	MI ± SE (%)
	Period (hr)	Concentration (µg/ml)	Structural CA ^a		Numerical CA					
			B' type	B" type						
Control	—	—	9	1	0	0.025 ± 0.006	0.00	0.025 ± 0.006	2.50 ± 0.64	10.2 ± 0.90
BrdU	—	—	9	5	0	0.035 ± 0.008	0.00	0.035 ± 0.008	3.50 ± 0.86	9.00 ± 0.67
EMS	24	125	81	18	3	0.247 ± 0.038 a ₂ b ₁	0.007 ± 0.004	0.255 ± 0.033 a ₂ b ₂	20.00 ± 2.17 a ₂ b ₂	4.42 ± 0.77 a ₂ b ₂
PMB	24	25	28	14	1	0.105 ± 0.013 a ₂ b ₁ c ₂	0.002 ± 0.002	0.107 ± 0.015 a ₁ b ₁ c ₂	10.00 ± 1.41 a ₁ b ₁ c ₂	5.55 ± 0.43 a ₂ b ₂
		50	45	3	1	0.120 ± 0.007 a ₃ b ₃ c ₃	0.002 ± 0.002	0.122 ± 0.009 a ₂ b ₂ c ₃	11.00 ± 0.91 a ₂ b ₂ c ₂	6.13 ± 0.57 a ₂ b ₁
		100	41	9	3	0.125 ± 0.016 a ₂ b ₁ c ₂	0.007 ± 0.004	0.132 ± 0.018 a ₁ b ₁ c ₂	12.25 ± 0.65 a ₂ b ₁ c ₂	4.63 ± 0.42 a ₃ b ₂
		200	60	4	2	0.160 ± 0.026 a ₁ b ₁ c ₁	0.005 ± 0.002	0.165 ± 0.023 a ₂ b ₁ c ₁	14.50 ± 2.10 a ₁ b ₁	4.32 ± 0.62 a ₂ b ₂
EMS	48	125	73	18	2	0.227 ± 0.047 a ₁ b ₁	0.005 ± 0.005	0.232 ± 0.046 a ₁ b ₁	20.25 ± 3.35 a ₁ b ₁	4.54 ± 0.41 a ₃ b ₂
PMB	48	25	39	6	2	0.112 ± 0.008 a ₂ b ₂ c ₃	0.005 ± 0.002	0.117 ± 0.011 a ₂ b ₂ c ₂	11.25 ± 1.03 a ₂ b ₂ c ₂	7.18 ± 0.41 a ₂ b ₁ c ₂
		50	28	11	5	0.097 ± 0.008 a ₂ b ₂ c ₃	0.012 ± 0.009	0.110 ± 0.009 a ₂ b ₂ c ₃	10.25 ± 0.85 a ₂ b ₂ c ₃	6.78 ± 0.47 a ₂ b ₁ c ₁
		100	40	11	2	0.127 ± 0.002 a ₃ b ₃ c ₃	0.005 ± 0.002	0.132 ± 0.002 a ₃ b ₃ c ₃	12.50 ± 0.28 a ₃ b ₃ c ₃	5.58 ± 0.83 a ₁ b ₂
		200	90	9	5	0.247 ± 0.042 a ₁ b ₁	0.012 ± 0.002 a ₁ b ₁	0.260 ± 0.044 a ₁ b ₁	21.00 ± 2.91 a ₂ b ₁	3.23 ± 0.06 a ₃ b ₂ c ₃

a, significant from control; b, significant from BrdU control, c, significant from positive control (EMS); a₁b₁c₁, *P* < 0.05; a₂b₂c₂, *P* < 0.01; a₃b₃c₃, *P* < 0.001.
^aB', chromatid-type breaks; B", chromosome-type breaks.

TABLE III. The Percentage of Micronucleus (MN), the Percentage of Micronucleated Binuclear Cell and Nuclear Division Index (NDI) in Cultured Human Lymphocytes Treated With PMB

Test substance	Treatment		MN ± SE (%)	Percentage of micronucleated binuclear cell ± SE	NDI ± SE
	Periods (hr)	Concentration (µg/ml)			
Control	—	0	0.56 ± 0.02	0.55 ± 0.03	1.51 ± 0.07
EMS	24	125	1.48 ± 0.15 a ₂	1.32 ± 0.12 a ₂	1.36 ± 0.07
PMB	24	25	1.11 ± 0.20 a ₁	1.11 ± 0.11 a ₁	1.48 ± 0.09
		50	1.11 ± 0.12 a ₂	1.17 ± 0.13 a ₁	1.45 ± 0.08
		100	1.50 ± 0.14 a ₂	1.18 ± 0.09 a ₂	1.33 ± 0.08
		200	1.43 ± 0.17 a ₁	1.21 ± 0.11 a ₂	1.18 ± 0.05 a ₂ c ₁
EMS	48	125	2.41 ± 0.16 a ₂	2.22 ± 0.08 a ₃	1.37 ± 0.05
PMB	48	25	1.63 ± 0.08 a ₃ c ₂	1.33 ± 0.11 a ₂ c ₂	1.61 ± 0.10
		50	1.63 ± 0.07 a ₃ c ₂	1.46 ± 0.08 a ₂ c ₂	1.49 ± 0.09
		100	1.60 ± 0.04 a ₃ c ₃	1.46 ± 0.06 a ₃ c ₃	1.25 ± 0.06 a ₁
		200	1.71 ± 0.21 a ₁ c ₁	1.68 ± 0.04 a ₃ c ₃	1.06 ± 0.01 a ₃ c ₃

a, significant from control; c, significant from positive control (EMS); a₁c₁, *P* < 0.05; a₂c₂, *P* < 0.01; a₃c₃, *P* < 0.001.

Slightly positive: Concentration dependent significant increase in SCE but not twice as high as controls

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TABLE II. The Frequency of the Sister Chromatid Exchanges (SCE) and Replication Index (RI) in Cultured Human Lymphocytes Treated With PMB

Test substance	Treatment		Min-max SCE	SCE/cell \pm SE	M1	M2	M3 ^a	RI \pm SE
	Periods (hours)	Concentration (μ g/ml)						
BrdU Control	—	0	1–12	5.830 \pm 0.43	43	96	261	2.55 \pm 0.06
EMS	24	125	15–70	27.96 \pm 2.95 b ₂	69	147	184	2.29 \pm 0.08
PMB	24	25	3–24	8.240 \pm 0.46 b ₁ c ₃	67	99	234	2.42 \pm 0.18
		50	3–20	8.710 \pm 0.59 b ₁ c ₃	31	103	266	2.59 \pm 0.04 c ₂
		100	4–27	10.45 \pm 0.63 b ₂ c ₃	64	138	198	2.34 \pm 0.08
		200	6–30	14.19 \pm 0.74 b ₂ c ₃	103	178	119	2.04 \pm 0.12 b ₁
EMS	48	125	18–46	31.18 \pm 0.45 b ₃	79	155	166	2.22 \pm 0.08b ₁
PMB	48	25	3–19	8.790 \pm 0.56 b ₁ c ₃	50	93	257	2.52 \pm 0.02 c ₃
		50	3–28	9.540 \pm 0.32 b ₃ c ₃	57	85	258	2.50 \pm 0.05 c ₁
		100	4–24	11.09 \pm 0.27 b ₃ c ₃	52	112	236	2.46 \pm 0.06 c ₁
		200	10–32	17.65 \pm 1.13 b ₂ c ₃	180	206	14	1.59 \pm 0.02 b ₃ c ₃

b, significant from BrdU control; c, significant from positive control (EMS); b₁c₁, $P < 0.05$; b₂c₂, $P < 0.01$; b₃c₃, $P < 0.001$.

^aThe number of the cells under first mitosis (M1), second mitosis (M2), and third mitosis (M3).

Data relating to Table 15: Summary table of *in vivo* genotoxicity studies

Anonymous11 (2005) Environmental and Molecular Mutagenesis. 46 (3): 150–155

Positive

Dose-dependent increase OTM from 14 mg/m³ onwards in blood lymphocytes. Cells derived from brain, lung, liver, spleen, kidney, and intestine in both sexes and in testicles of males. No effects on food consumption and body weight

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gain; no deaths, morbidity or distinctive clinical signs.

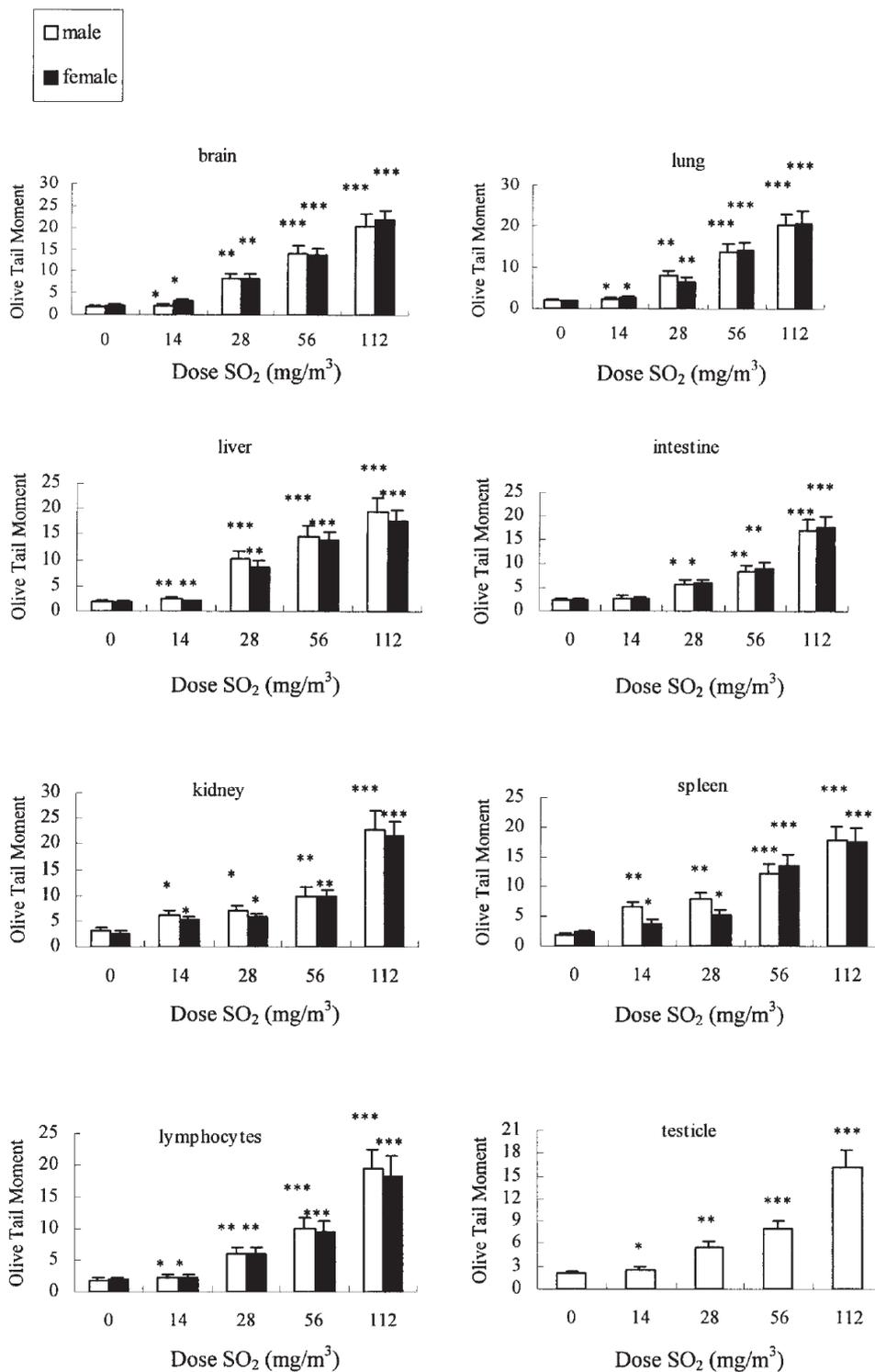


Fig. 1. DNA damage, expressed as OTM, in various organs of mice treated with SO₂ by inhalation. Untreated mice served as negative controls. Data are averages of 50 cells scored from each of six mice per group. Error bars denote SE. Treated mice different from control at **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

Anonymous6 (2008) also published as: Anonymous7, (2010) Mutation Res. 697: 38–46; reference

Negative

The number of micronuclei not increased; however not proven that the substance reached the target organ. No signs of overall toxicity.

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PCE:NCE ratio unchanged.

Table 3

Ratios of PCE:NCE and frequencies of micronucleated PCE (MNPCE) per 2000 PCE in the bone marrow of NMRI mice exposed to SO₂ or of their respective controls.

Treatment	Sex	PCE:NCE ^a	MNPCE/2000 PCE		% MNPCE ^b
			Number ^a	Range	
Clean air ^c	m	0.99 ± 0.062	2.8 ± 1.30	1-4	0.14
	f	0.90 ± 0.095	2.0 ± 0.71	1-3	0.10
CP, 60 mg/kg b.w. ^d	m	0.89 ± 0.070	70.6 ± 20.57**	43-101	3.53**
	f	0.92 ± 0.119	49.4 ± 8.41**	41-60	2.47**
SO ₂ , 1 ppm ^c	m	0.96 ± 0.049	2.3 ± 0.82	1-3	0.11
	f	0.99 ± 0.350	2.8 ± 1.94	1-6	0.14
SO ₂ , 3 ppm ^c	m	0.96 ± 0.024	2.5 ± 1.87	1-6	0.13
	f	0.90 ± 0.226	2.0 ± 1.26	1-4	0.10
SO ₂ , 10 ppm ^c	m	0.98 ± 0.022	2.7 ± 0.52	2-3	0.13
	f	0.98 ± 0.055	2.0 ± 1.26	1-4	0.10
SO ₂ , 30 ppm ^c	m	0.94 ± 0.690	3.2 ± 1.47	1-5	0.16
	f	0.95 ± 0.019	2.5 ± 1.22	1-4	0.12

CP, cyclophosphamide monohydrate; SO₂, sulfur dioxide; b.w., body weight; m, males; f, females.

^a Group mean ± standard deviation.

^b Derived from group mean.

^c Whole-body inhalation, for 4 h/day on 7 consecutive days.

^d Oral application.

** Significantly different from negative control animals (clean air), $P \leq 0.01$, *U*-test according to Mann-Whitney.

Meng et al., (2002) Inhalation Toxicity, 14: 303-309

Positive

Dose dependent increase in micronuclei in PCE, no sex differences. Increase statistically significant at 14 mg/m³ SO₂ and higher.

TABLE 1. Induction effect of SO₂ on micronuclei in the PCE of mouse bone marrow

SO ₂ (mg/m ³) ($\bar{X} \pm SD$)	Number of PCE	Female		Male		Total	
		MN (%)	PCE with MN (%)	MN (%)	PCE with MN (%)	MN (%)	PCE with MN (%)
Control	1000 × 8	0.11 ± 0.10	0.11 ± 0.10	0.13 ± 0.09	0.13 ± 0.09	0.12 ± 0.09	0.12 ± 0.09
14.0 ± 0.38	1000 × 8	0.40 ± 0.08 ^a	0.40 ± 0.08 ^a	0.39 ± 0.10 ^a	0.39 ± 0.10 ^a	0.39 ± 0.09 ^a	0.39 ± 0.09 ^a
28.0 ± 0.34	1000 × 8	0.83 ± 0.05 ^a	0.80 ± 0.06 ^a	0.83 ± 0.21 ^a	0.78 ± 0.13 ^a	0.83 ± 0.15 ^a	0.79 ± 0.10 ^a
56.0 ± 0.32	1000 × 8	1.59 ± 0.10 ^b	1.45 ± 0.12 ^b	1.38 ± 0.13 ^b	1.26 ± 0.11 ^b	1.48 ± 0.16 ^b	1.36 ± 0.15 ^b
84.0 ± 0.27	1000 × 8	1.93 ± 0.13 ^b	1.73 ± 0.10 ^b	1.73 ± 0.09 ^b	1.60 ± 0.12 ^b	1.83 ± 0.15 ^b	1.69 ± 0.14 ^b

^aSignificantly different from control without SO₂ by *t*-test at $p < .01$.

^bSignificantly different from control without SO₂ by *t*-test at $p < .001$.

TABLE 2. SO₂ and number of micronuclei per PCE of mouse bone marrow

SO ₂ (mg/m ³) ($\bar{X} \pm SD$)	Number of PCE	Female			Male		
		PCE with monoMN (%)	PCE with biMN (%)	PCE with triMN (%)	PCE with monoMN (%)	PCE with biMN (%)	PCE with triMN (%)
Control	1000 × 8	0.11 ± 0.10	0	0	0.13 ± 0.09	0	0
14.0 ± 0.38	1000 × 8	0.40 ± 0.08 ^a	0	0	0.39 ± 0.10 ^a	0	0
28.0 ± 0.34	1000 × 8	0.77 ± 0.10 ^a	0.03 ± 0.05	0	0.74 ± 0.11 ^a	0.03 ± 0.05	0.01 ± 0.03
56.0 ± 0.32	1000 × 8	1.33 ± 0.15 ^b	0.11 ± 0.06 ^a	0.01 ± 0.03	1.15 ± 0.12 ^b	0.11 ± 0.06 ^a	0
84.0 ± 0.27	1000 × 8	1.63 ± 0.15 ^b	0.15 ± 0.09 ^a	0	1.48 ± 0.19 ^b	0.13 ± 0.09 ^a	0

Note. PCE with monoMN: PCE with one MN per cell; PCE with biMN: PCE with two MN per cell; PCE with triMN: PCE with three MN per cell.

^aSignificantly different from control without SO₂ by *t*-test at $p < .01$.

^bSignificantly different from control without SO₂ by *t*-test at $p < .001$.

Anonymous10 (2003) Inhalation Toxicity, 15: 1053-58

Positive

Significant increase in micronuclei (mono-, bi, and polymicronuclei) in PCE at 28 mg/m³ compared to controls.

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TABLE 3. Defense of seabuckthorn seed oil for MNs in the PCE of mice induced by SO₂

Group	Monomiconuclei (‰)	Bimiconuclei (‰)	Polymiconuclei (‰)	Rate of micronuclei (‰)	Rate of micronuclear cells (‰)
Group A	1.6 ± 1.14	0	0	1.6 ± 1.14	1.6 ± 1.14
Group B	12.33 ± 1.75***	1.83 ± 0.75***	0.5 ± 0.55*	17.5 ± 1.87***	14.67 ± 1.51***
Group C	1.50 ± 1.64###	0.17 ± 0.41###	0 [#]	1.83 ± 2.14###	1.67 ± 1.86###
Group D	8.67 ± 1.75####	0.83 ± 1.17	0.67 ± 0.82	12.33 ± 5.57####	10.17 ± 3.19####
Group E	8.17 ± 2.93####	0.67 ± 0.52###	0 [#]	9.50 ± 3.27####	8.83 ± 3.06####
Group F	7.87 ± 2.14####	0.67 ± 0.82 [#]	0 [#]	8.83 ± 2.59####	8.50 ± 2.23####
Group G	5.50 ± 1.05####	0.67 ± 0.52###	0 [#]	6.83 ± 1.47####	6.17 ± 1.17####

Note. Group A is normal group without injection and toxicant and group B has only SO₂ inhalation. Using *t*-test and comparing with group A, significance is shown by **p* < .05; ***p* < .01; ****p* < .001. Comparing with group B, [#]*p* < .05; ^{##}*p* < .01; ^{###}*p* < .001.

Meng, Z. & Zhang, B. (2002). *Mutagenesis* 17: 215-217.

Positive

Dose and duration dependent increase in aberrant cells, dose dependent decrease of mitotic index in both sexes

Chromosome and chromatid breaks at 56 mg/m³ SO₂; at lower concentrations chromatid breaks only sign. at ≥ 14 mg/m³.

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Table I. Effects of SO₂ inhalation on mitoses and CA formation in bone marrow cells of mice

Treatment	Gap ^a	CAs per 100 cells (mean ± SD) ^b		Aberrant cells (%) (mean ± SD) ^c	Mitotic index (%) (mean ± SD) ^c
		Chromatid break	Chromosome break		
Control	5	1.61 ± 0.15	0.20 ± 0.02	1.81 ± 0.45	3.85 ± 0.78
SO ₂ (mg/m ³)					
7.00 ± 0.27	8	2.14 ± 0.28	0.20 ± 0.05	2.30 ± 0.56	3.05 ± 0.46
14.0 ± 0.38	10	3.12 ± 0.30 ^d	0.25 ± 0.06	3.28 ± 0.66 ^d	2.61 ± 0.52 ^d
28.0 ± 0.34	13	3.96 ± 0.40 ^e	0.32 ± 0.03 ^d	4.26 ± 0.44 ^f	2.48 ± 0.43 ^d
56.0 ± 0.32	14	4.68 ± 0.36 ^f	0.55 ± 0.05 ^e	4.86 ± 0.45 ^f	2.32 ± 0.44 ^d

^aTotal chromatid and chromosome gaps at each dose were recorded but not included as CAs/cell.

^bNumber of chromatid or chromosome breaks per 100 metaphase cells scored per dose group.

^cResults at each dose were compared to those of the control using Student's *t*-test. Results are from eight male and eight female animals (100 cells/animal).

^{d,e,f}Significantly different from control without SO₂ inhalation by χ^2 at ^d*P* < 0.05, ^e*P* < 0.01 and ^f*P* < 0.001.

Table II. Relationship between the relative duration of SO₂ exposure and CA formation in bone marrow cells of mice

Treatment	CAs per 100 cells (mean ± SD) ^a		Aberrant cells (%) (mean ± SD) ^b
	Chromatid break	Chromosome break	
Control	1.60 ± 0.14	0.20 ± 0.02	1.80 ± 0.16
SO ₂ (14.0 ± 0.24 mg/m ³)			
1 day	1.80 ± 0.12	0.20 ± 0.04	2.00 ± 0.10
3 days	2.00 ± 0.16	0.20 ± 0.02	2.20 ± 0.14
5 days	2.24 ± 0.24	0.20 ± 0.05	2.30 ± 0.36
7 days	3.42 ± 0.28 ^c	0.28 ± 0.04	3.58 ± 0.46 ^c

^aNumber of chromatid or chromosome breaks per 100 metaphase cells scored per dose group, significantly different from control without SO₂ inhalation by χ^2 . Results are from 10 male animals (100 cells/animal).

^bResults for each SO₂ group were compared to those of the control using Student's *t*-test.

^c*P* < 0.05.

Anonymous15 2008; Environ Mol Mutagen 49: 276-281

Positive: Dose related increase of aberrant cells

TABLE IV. The Structural, Numerical, Total Chromosome Aberrations (CAs), Percentage of Abnormal Cell and Mitotic Index (MI) in Rat Bone Marrow Cells Treated With PMB

Test substance	Treatment		Chromosome aberrations			Structural CA/cell ± SE	Numerical CA/cell ± SE	Total CA/cell ± SE	Percentage of abnormal cell ± SE	MI ± SE
	Periods (hr)	Concentration (mg/kg)	B' type	B'' type	Numerical CA					
Control	—	0	21	1	0	0.055 ± 0.006	0	0.055 ± 0.006	5.50 ± 0.64	3.60 ± 0.103
Urethane	12	400	34	6	3	0.100 ± 0.010	0.007 ± 0.004	0.107 ± 0.014	10.00 ± 1.41	3.04 ± 0.181
PMB	12	150	35	2	3	0.092 ± 0.014	0.007 ± 0.002	0.100 ± 0.012 a ₁	8.50 ± 0.50 a ₂	2.48 ± 0.262 a ₁
		300	52	2	5	0.135 ± 0.005 a ₃ c ₂	0.012 ± 0.009	0.147 ± 0.011 a ₂ c ₁	13.00 ± 1.00 a ₂	2.41 ± 0.146 a ₂ c ₁
		600	51	5	6	0.140 ± 0.016 a ₁	0.015 ± 0.005	0.155 ± 0.015 a ₂ c ₁	14.50 ± 1.32 a ₂ c ₁	1.85 ± 0.060 a ₃ c ₃
Urethane	24	400	61	9	7	0.175 ± 0.025	0.017 ± 0.004	0.192 ± 0.028	16.75 ± 1.18	1.93 ± 0.066
PMB	24	150	39	4	6	0.107 ± 0.011 a ₁ c ₂	0.015 ± 0.006	0.122 ± 0.006 a ₂ c ₂	11.25 ± 0.62 a ₂ c ₂	4.20 ± 0.416 c ₁
		300	49	5	2	0.135 ± 0.014 a ₁	0.005 ± 0.002 c ₁	0.140 ± 0.014 a ₂ c ₁	13.25 ± 1.10 a ₂ c ₁	2.90 ± 0.285 c ₁
		600	79	8	2	0.217 ± 0.030 a ₁	0.005 ± 0.002 c ₁	0.222 ± 0.029 a ₁	18.50 ± 0.86 a ₃	2.44 ± 0.276 a ₁

a, significant from control; c, significant from positive control (urethane); a₁c₁, *P* < 0.05; a₂c₂, *P* < 0.01; a₃c₃, *P* < 0.001.

B', chromatid-type breaks; B'', chromosome-type breaks.

Anonymous14 (2011) Mutat. Res. 2011 Feb 28;720(1-2):58-61

Positive

Increased frequency of micronuclei in bone marrow and peripheral blood cells at 2g/kg (limit dose); significant reduction of PCE:NCE ratio at 2 g/kg

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Table 2

Detection of micronuclei mean (\pm S.D.) in peripheral blood reticulocytes (MNRET) and in polychromatic erythrocytes (MnPCEs) of bone marrow cells of mice exposed for 24 h to sodium metabisulfite. For each group, $n=10$ (five males and five females), 2000 cells/animal.

Group	Gender	Blood		Bone marrow		Ratio (PCE:NCE) ^a
		Per gender	Per group	Per gender	Per group	
Negative control ^b	Male	2.4 \pm 0.54	2.7 \pm 0.67	2.8 \pm 0.45	3.0 \pm 0.47	1.67 \pm 0.67
	Female	3.0 \pm 0.70		3.2 \pm 0.45		
0.5 g/kg	Male	2.6 \pm 0.54	2.7 \pm 0.48	3.2 \pm 1.10	2.8 \pm 0.92	1.37 \pm 0.35
	Female	2.8 \pm 0.44		2.4 \pm 0.55		
1 g/kg	Male	4.6 \pm 1.14	4.8 \pm 1.14	4.2 \pm 1.30	4.6 \pm 1.27	1.77 \pm 0.62
	Female	5.0 \pm 1.22		5.0 \pm 1.23		
2 g/kg	Male	7.0 \pm 1.22	7.0 \pm 1.25**	7.0 \pm 1.58	6.9 \pm 1.45**	0.74 \pm 0.18**
	Female	7.0 \pm 1.41		6.8 \pm 1.48		
Positive control ^c	Male	11.8 \pm 0.84	12.5 \pm 1.18***	11.4 \pm 1.52	12.3 \pm 15.7***	0.75 \pm 0.19**
	Female	13.2 \pm 1.10		13.2 \pm 1.10		

^a PCE, polychromatic erythrocytes; NCE, normochromatic erythrocytes.

^b Water.

^c Cyclophosphamide, 25 mg/kg.

** Significant difference from negative control in the same tissue at $P < 0.01$.

*** $P < 0.001$; tested by ANOVA-Kruskal-Wallis test.

Data relating to Table 16: Summary table of human data relevant for germ cell mutagenicity

Nordenson et al (1980) *Hereditas* 93: 161-164. (published)

SO₂ group: All types of aberrations were significantly increased in comparison to the control group with $p < 0.01$ or $p < 0.001$.

Smoking was the only possible confounder recorded.

Due to lack of evaluation/ matching for possible confounders and low number of participants, no final conclusion can be drawn from the study.

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Table 3. Chromosomal aberrations in workers at a sulphite pulp factory and in controls

	Work place			Controls (Umeå)
	Boiling (SO ₂)	Bleaching (chlorine)	Paper Mill (dust)	
Number of individuals	7	6	6	15
Number of cells	1156	621	662	1500
<i>Gaps</i>				
No.	44	8	18	31
Per cell	0.038	0.013	0.027	0.021
<i>Chromatid aberrations</i>				
No.	24	4	4	9
Per cell	0.021	0.006	0.006	0.006
<i>Chromosome aberrations</i>				
No.	19	7	4	1
Per cell	0.016	0.011	0.006	0.001
<i>All aberrations</i>				
No.	87	19	26	41
Per cell	0.075	0.031	0.039	0.027

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Sorsa, M. *et al.* (1982). *Hereditas* 97: 159-161.

Frequencies of CA and SCE were similar in all groups. However, due to lack of evaluation/ matching for possible confounders and low number of participants, no final conclusion can be drawn from the study. In addition, exposure towards SO₂ was very low.

Table 1. Chromosome aberrations and SCEs of SO₂-exposed male workers and controls

Subject and occupation	Age (yr)	Employment time (yr)	Smoking habits	Cells with chromosomal aberrations			SCEs	
				No. cells analyzed	Including gaps (%)	Excluding gaps (%)	No. cells analyzed	Mean ± SD
<i>Exposed group</i>								
<i>High-exposure</i>								
1, smelter	62	39	-	100	2	1	30	8.1±3.9
2, molder	50	26	+	100	6	4	30	9.0±3.4
3, molder	32	6	-	100	2	2	30	8.6±3.0
4, castbreaker	52	5	-	100	1	1	30	10.2±3.4
5, castbreaker	62	9	+	100	4	2	30	8.9±3.9
<i>Low-exposure</i>								
6, foreman	51	30	-	45	4	4	26	7.8±3.3
7, castmaker	41	25	-	100	1	1	30	8.8±3.4
8, truckdriver	33	16	+++	100	2	1	30	10.4±4.7
n = 8	$\bar{x} = 47.9$	$\bar{x} = 19.5$		n = 745	$\bar{x} = 2.8 \pm 1.8$	$\bar{x} = 2.0 \pm 1.3$	n = 236	$\bar{x} = 8.9 \pm 0.9$
<i>Control group</i>								
9	43		-	100	4	3	30	9.1±3.5
10	52		+++	100	2	1	30	10.3±4.6
11	44		+++	100	3	2	30	10.1±4.7
12	59		-	100	4	4	30	9.0±3.4
13	59		+	100	4	3	30	6.6±3.0
14	31		(+)	100	1	0	30	9.5±3.5
15	46		-	100	2	1	30	7.0±3.5
16	37		+++	100	4	4	30	12.2±5.0
n = 8	$\bar{x} = 46.4$			800	$\bar{x} = 3.0 \pm 1.2$	$\bar{x} = 2.25 \pm 1.5$	n = 240	$\bar{x} = 9.2 \pm 1.8$

-, nonsmoker +, <10 cigarettes/day +++ , ≥20 cigarettes/day (+), recent smoker

Table 2. Chromosome aberrations and SCEs among smoking and nonsmoking subjects

No.	Smoking/exposure category		Cells with chromosomal aberrations (%)		SCEs
			Incl. gaps	Excl. gaps	Mean ± SD
<i>All smokers</i>					
16	+++	control	4	4	12.2±5.0
11	+++	control	3	2	10.1±4.7
10	+++	control	2	1	10.3±4.6
8	+++	exposed	2	1	10.4±4.7
14	(+)	control	1	0	9.5±3.5
2	+	exposed	6	4	9.0±3.4
5	+	exposed	4	2	8.9±3.9
13	+	control	4	3	6.6±3.0
n = 8			$\bar{x} = 3.3 \pm 1.6$	$\bar{x} = 2.1 \pm 1.5$	$\bar{x} = 9.6 \pm 1.6$
<i>All nonsmokers</i>					
4	-	exposed	1	1	10.2±3.4
9	-	control	4	3	9.1±3.5
12	-	control	4	4	9.0±3.4
7	-	exposed	1	1	8.8±3.4
3	-	exposed	2	2	8.6±3.0
1	-	exposed	2	1	8.1±3.9
6	-	exposed	4	4	7.8±3.3
15	-	control	2	1	7.0±3.5
n = 8			$\bar{x} = 2.5 \pm 1.3$	$\bar{x} = 2.1 \pm 1.4$	$\bar{x} = 8.6 \pm 1.0$

+++ , ≥20 cigarettes/day +, ≤10 cigarettes/day (+), recent smoker

Meng and Zhang (1989). *Mutation Research* 241:15-20 (published)

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Exposed vs. controls (p<0.001):

Lymphocytes with MN:

w/o:

0 % vs . 31 %

>0.1 %:

72.5 % vs . 16.7 %

>0.2 %:

17.5 % vs. 0 %

Higher frequency of MN in smokers in both groups, but always higher in exposed workers whether smoking or not.

Exposed vs. controls (p<0.01):

CA chromosome type:

165 vs . 25 aberrant cells

(2.1 ± 0.23 % vs. 0.3 ± 0.1 %)

CA chromatid type:

77 vs. 24 aberrant cells

(1.0 ± 0.2 % vs. 0.3 ± 0.1 %)

CA total number of cells:

242 vs. 49

(3.0 ± 0.3 % vs. 0.6 ± 0.1 %)

SCE per cell:

6.7 ± 0.2 vs. 2.7 ± 0.1

No difference of CA and SCE between smokers and non-smokers.

TABLE 8
SMOKING AND SCE IN LYMPHOCYTES

	Number of persons	Number of cells observed	SCEs/cell ($\bar{x} \pm SE$)
<i>Non-smokers</i>			
Control group	21	1 330	2.65 ± 0.13
Worker group	20	1 225	6.88 ± 0.41
<i>Smokers</i>			
Control group	21	1 330	2.80 ± 0.25
Worker group	20	1 225	6.67 ± 0.25