Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

sulfur

EC Number: 231-722-6
CAS Number: 7704-34-9

CLH-O-0000007107-77-01/F

Adopted

18 March 2022

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: Sulfur
EC number: 231-722-6
CAS number: 7704-34-9
Dossier submitter: France

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2021	Germany		MemberState	1
Comment received				
Sulfur was recently evaluated as a precursor to the biocidal active substance "Sulfur dioxide generated from sulfur by combustion in product-type 4 (disinfectants for food and feed area)" (DE CAR PT4 2021), in the context of Regulation (EU) No 528/2012. For the endpoints eye irritation and acute inhalation/respiratory irritation, the data (especially human case data) were more limited than in the RAR/CLH dossier presented here. This justifies the deviating classification. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH_Sulfur_Confidential Annex.pdf				
Dossier Submitter's Response				
Noted				
RAC's response				
Noted.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2021	Germany		MemberState	2
Comment received				
DE CA agrees with the French dossier submitter (DS) that a comparison with the CLP criteria is not possible and that classification for carcinogenicity is not warranted.				

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH_Sulfur_Confidential Annex.pdf
Dossier Submitter's Response
Thank you for your support
RAC's response
Noted.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	Germany	(i) Sulfur Working Group, (ii) Sulphur Task Force [list of SWG and STF stakeholders see public attachment]	Company-Downstream user	3

Comment received

Sulfur CLH/RAR 01, Vol. 1 - Level 2, 2.6.4.1, p. 59; Level 3, 3.1.1.4, p. 173; Level 3, 3.1.4.6, p. 183
Based on the results of the provided in vitro and in vivo data it is stated by the RMS that "overall, sulfur can be considered as void of genotoxic potential (provided that the ongoing in vitro mammalian cell gene mutation test would confirm this conclusion)."
In response to this, in the meantime an in vitro mammalian cell gene mutation test was performed according to OECD TG 476 to complete the in vitro genotoxicity testing series required by Regulation (EU) 283/2013. The test item used was Sulphur 98.5 DP (purity 98.8% sulfur). The study yielded a negative result and has been finalised and reported (Sulphur 98.5 DP – Gene Mutation Assay in Chinese Hamster V79 Cells in vitro (V79/HPRT), Report No. 1992500, 18 September 2020).
A copy of the study report (Report No. 1992500) is provided to ECHA both as a confidential attachment, together with a sanitised version as public attachment.

Sulfur CLH/RAR 01, Vol. 1 - Level 2, 2.6.4.1, p. 59; RAR 01, Vol 1 – Level 3, 3.1.9, p. 187
The Co-RMS proposed that in order to demonstrate the lack of genotoxic potential of sulfur in vivo, an in vivo genotoxicity study at site of first contact would be the most appropriate.
The applicants are of the opinion that no further in vivo studies need to be conducted for the following reasons: the only studies according to accepted test guidelines that may be conducted with a site of contact tissue would be either an in vivo alkaline comet assay (OECD 489) or an in vivo transgenic rodent and somatic cell assay (OECD 488). These assays detect DNA damage, often in response to pre-mutagenic events, or direct fixed gene mutations respectively. However, sulfur has been shown to be void of mutagenic activity in the bacterial reverse mutation assay and in vitro mammalian gene mutation assay and to lack chromosomal damage capabilities in in vitro and in vivo assays. In conclusion, it is considered that no additional in vivo studies are justified.
A corresponding expert statement (Statement on the assessment of Sulfur for genotoxicity, Report No. SWG/STF-210831-01, 31 August 2021) is provided to ECHA as public attachment.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment

Applicants(SWG_STF)_comments_on_CLH_report_sulfur_(AIR_IV)_public_attachments.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Report_1992500_Sulfur_Gene_Mutation Assay.pdf
Dossier Submitter's Response
The newly submitted *in vitro* mammalian cell gene mutation assay (V79/HPRT) has been assessed by the DS. This study was conducted in 2020 according to OECD TG 476 (2016) under GLP conditions. The test substance was Sulphur 98.5 DP, which can be used as a surrogate for technical sulfur since the minimum content of the active substance in this representative product is specified as 985 g/kg and the only co-formulant is an inert carrier. The test concentrations were chosen based on precipitation issues. The treatment period was 4 hours with and without metabolic activation. The test is considered acceptable. Under the conditions of this study, Sulphur 98.5 DP is considered to be non-mutagenic. Overall, based on the results of the genotoxicity studies available in the RAR and based on the results of the newly submitted HPRT assay, sulfur is considered unlikely to be genotoxic and further genotoxicity testing is not required.
RAC's response
RAC notes the negative results of the recently performed *in vitro* mammalian cell gene mutation assay and overall agrees that sulfur should not be classified for Germ Cell Mutagenicity.

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2021	Germany		MemberState	4
Comment received				
DE CA agrees that sulphur should NOT be classified for mutagenicity. The following studies should be taken into account to enhance the robustness of the assessment. These studies were also included in the biocides assessment report (DE CAR PT4 2021). Nagy et al. 1975 Acta microbial Acad Sci hung. 22: 309-314. Moriya et al. 1983. Mutation Research 116: 185-216. Crebelli et al. 1985. British J Industrial Med. 42: 481-487. In section 2.6.4.1 of the combined RAR/CLH dossier, it is stated "an in vitro mammalian cell gene mutation test is scheduled to complete the in vitro genotoxicity testing series required by Regulation (EU) 283/2013. The applicant informed the DS that the expected finalisation date of this study would be October 2020". It is requested that this study(s) is taken into account if available. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH_Sulfur_Confidential Annex.pdf				
Dossier Submitter's Response				
Thank you for your support. The studies available in the RAR were conducted under GLP conditions according to OECD TG in force at the time of the conduct of the respective studies. Although some limitations were noted for some of them, they are considered acceptable and sufficient to draw a conclusion on the genotoxic potential of sulfur. Overall, based on the results of the genotoxicity studies available in the RAR and based on the results of the newly submitted HPRT assay (please refer to the above comment),				

sulfur is considered unlikely to be genotoxic and further genotoxicity testing is not required. Please note that the Crebelli *et al*. 1985 paper was already included in the RAR Vol 3CAB6 and was considered not acceptable by the DS.
RAC's response
RAC notes that the *in vitro* mammalian cell gene mutation test is indeed available, with the results described by the DS in their response to comment 4. The study supports the conclusion that sulfur should not be classified for Germ Cell Mutagenicity.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2021	Germany		MemberState	5
Comment received				
DE CA agrees with the DS that a comparison with the CLP criteria is not possible and that classification for adverse effects on sexual function and fertility, developmental toxicity, and effects on or via lactation is not warranted. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH_Sulfur_Confidential Annex.pdf				
Dossier Submitter's Response				
Thank you for your support				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2021	Germany		MemberState	6
Comment received				
DE CA agrees with the DS, that classification of sulfur for acute oral, dermal or inhalation toxicity is NOT warranted as no animal or human data were identified indicating that sulphur fulfils the CLP criteria for classification for acute toxicity. The report by Gosselin et al. (1976) (or a reference to it) should be added to Table 12 (Human data on acute oral toxicity) as this study would enhance the robustness of this section. This report is currently described in section 2.6.9. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH_Sulfur_Confidential Annex.pdf				
Dossier Submitter's Response				
Thank you for your support The report by Gosselin *et al*. (1976) mentioned a man who has survived the ingestion of 60 g of sulfur over a period of 24-hour, confirming the low toxicity of sulfur. No further information is available.				

RAC's response
RAC notes the support on acute toxicity by all three routes and the additional case in humans supporting no classification for acute oral toxicity of sulfur.

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2021	Germany		MemberState	7
Comment received				
DE CA agrees with the classification of sulfur with Skin irritation Cat. 2. H315 as proposed by the DS. The skin irritation effects observed in the study by Anonymous 1 (1994) (2.6.2.4, table 20), which are supported by data in humans, warrant classification according to the CLP criteria. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH_Sulfur_Confidential Annex.pdf				
Dossier Submitter's Response				
Thank you for your support				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	Germany	(i) Sulfur Working Group, (ii) Sulphur Task Force [list of SWG and STF stakeholders see public attachment]	Company-Downstream user	8
Comment received				
Sulfur CLH/RAR 01, Vol. 1 – Level 1.1.1, p. 9; Level 2, 2.6.2.5.2 and 2.6.2.5.3, p. 43; 2.11.2.1, Table 124, p. 164 and Table 125, p. 166; RAR 01, Level 2, 2.11.3, p. 167; Level 3, 3.1.3, p. 180 The RMS proposed that "According to CLP criteria, based on a weight evidence approach considering animal and human data, classification for eye irritation Cat. 2 (H319) is warranted for sulfur" although the available eye irritation studies showed slight to moderate eye irritation with mean scores not sufficient to classify sulfur as an eye irritant. But taking into account the therapeutical use of elemental sulfur as a keratolytic as well as the recommendation of avoiding contact with the eyes, mouth, and other mucous membranes, in addition to the many cases of eye irritation collected in the occupational setting and from the incident databases after sulfur exposure, classification is considered warranted. This position is not supported by the applicants. The available human data derived from incidence databases mentioned by the RMS were evaluated by the applicants as follows: - EPA R.E.D. FACTS, 1991: Sulfur is classified in Acute toxicity Category III for eye, dermal and inhalation, which slightly toxic and irritant. No other classification for eye irritancy has been granted from EPA. - EPA assessment of US human incidence data bases: Across the databases, the relative				

number of reported incidents was low, the severity of the reported effects was low, and for most databases the dermal, ocular and respiratory symptoms/health effects were reflective of the known irritating properties of sulfur.
- OPP Incident data System (IPS): Irritation symptoms are mentioned in two of ten cases. One case in a farmer using MICROTHIOL DISPRESS is described as moderate, and the second case in 21 vineyard workers was classified as minor.
- Association of American Poison Control Center (AAPCC): The products associated with the highest number of cases are residential products, mainly a gasser product. Ocular effects are reported in 21% of the cases. The incidents were overall of low severity and most probably occurred due to sulfur gases, which could very likely be oxidized to sulfur oxides.
- California Pesticide Illness Surveillance Program: In the majority of the 63 cases submitted itchy or burning eyes were reported.
- NIOSH SENSOR Pesticides (Calvert et al., 2004): Among health effects reported, 41% involved reversible eye irritation. The exact conditions of exposure during those incidences are not known, neither the duration of the effects.
- Maddy and Edmiston 1998: Six field workers had been exposed when a helicopter applied dusting sulfur to the vineyards where they were working. The signs and symptoms experienced included eye irritation, runny noses, nausea, headache, throat irritation, cough and itching.
- French database: Acc. to the report, the powder form causes more ENT signs (oropharyngeal irritation, rhinitis/rhinorrhea, epistaxis) and eye signs (tearing, conjunctival erythema) than the wettable form.

In summary, data from human exposure have not shown that effects observed in humans during accidental exposure have been more severe or more persistent than those observed in the animal studies. No eye irritation effects have been reported in the medical surveillance report (2020) from the Syngenta site. Data in human are not considered sufficiently robust and applicant's medical data did not reveal evidence to support this classification.
In the available in vivo eye irritation studies with either sulfur technical or sulfur dust, although signs of irritation were noted in almost all animals, mean scores did not meet the criteria for classification and reversibility of the findings were observed from Day 1 to 7. In addition, in tests performed with several different sulfur formulations (Sulfur 80% SC, Sulfur 80% WG, Sulphur 80%WP and Sulfur 95%DP), effects observed were mild and reversible and did not require classification as eye irritant.
Based on the information provided, it is the applicants position that it cannot be concluded that the observed effects in humans are more severe than the effects described in the animal studies.
An expert statement on this topic was prepared by the applicants (Statement on the proposed classification of Sulfur for eye irritation, Report No. SWG/STF-210831-02, 31 August 2021) and is provided to ECHA as public attachment.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment
Applicants(SWG_STF)_comments_on_CLH_report_sulfur_(AIR_IV)_public_attachments.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Report_1992500_Sulfur_Gene_Mutation Assay.pdf

Dossier Submitter's Response

As detailed in the RAR, the DS considered that human data are indicative of eye irritant properties of sulfur and that by weight of evidence, H319 classification is warranted.

RAC's response
RAC agrees with the DS that the human data show that sulfur is an eye irritant.

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2021	Germany		MemberState	9
Comment received				
DE CA agrees with the classification of sulfur with Eye Irritation Cat. 2, H319 as proposed by the DS. With respect to the human data, signs of eye irritation were consistently observed following occupational exposure to sulfur and in incident reports/databases. Clinical signs included conjunctival irritation/erythema, corneal ulceration and lacrimation. The eye irritation effects observed in humans warrant classification according to the CLP criteria. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH_Sulfur_Confidential Annex.pdf				
Dossier Submitter's Response				
Thank you for your support				
RAC's response				
RAC agrees with the evaluation of the human data in this comment.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2021	Germany		MemberState	10
Comment received				
The DS has concluded that no reliable animal or human data are available which fulfil the CLP criteria for classification for skin sensitisation, and as such, classification of sulfur for skin sensitisation is NOT proposed. DE CA agrees that sulfur should not be classified for this endpoint. The maximisation test from 1994 and the Buehler test are considered as „acceptable with limitations" in the report. However, the positive responses after challenge are not considered reliable, because essential limitations were identified in the report. With regard to the maximisation test it is not clear whether the topical induction (25 %) was done in ethanol or vaseline, what is essential to know, because clearly more animals showed a response after challenge (25 % in vaseline) compared the induction. Furthermore, a pre-test, which determines the irritation of 25 % sulphur in vaseline, is missing in the maximisation test. However, a pre-test was done in the Buehler test and concentrations of 15 % and 25 % sulphur in vaseline revealed to be skin irritating. Thus, challenge concentrations of 15 % and 25 % in vaseline were too high. To perform a challenge with an irritating preparation is not in line with the guidance. Thus, it appears that no reliable conclusions can be drawn from these studies. A classification as „acceptable with limitations" is not justified, both studies should be downgraded. A description of the six skin sensitisation studies with the plant protection product 'Sulfur 80 % WG', mentioned in Section 2.6.2.7.1, should be provided, as these studies are used to support the non-classification of sulphur for skin sensitisation. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH_Sulfur_Confidential Annex.pdf				

Dossier Submitter's Response
Thank you for your support. As detailed in the RAR, the DS agrees that no firm conclusion on the skin sensitising potential of sulfur can be drawn from the Maximisation test (1994) and the Buehler assay (1994). Please note that description of the six skin sensitisation studies conducted on the plant protection product 'Sulfur 80% WG' is available in Vol 3CP B6 which has been made available to ECHA.
RAC's response
RAC notes the comment on the lower reliability of two studies with sulfur in animals. RAC notes that the DS included studies on a sulfur formulation as supporting evidence that the substance is not a skin sensitiser.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	Germany	(i) Sulfur Working Group, (ii) Sulphur Task Force [list of SWG and STF stakeholders see public attachment]	Company-Downstream user	11
Comment received				
Sulfur CLH/RAR 01, Vol. 1 – Level 1.1.1, p. 9; Level 2, 2.6.2.10.2 and 2.6.2.10.3, pp. 49-50;2.11.2.1, Table 124, p. 164 and Table 125, p. 166; Level 2, 2.11.3, p. 167; Level 3, 3.1.3, p. 180 The RMS proposed that "According to CLP criteria, based on a weight evidence approach considering animal and human data, classification for STOT SE Category 3 for respiratory tract irritation (H335) is considered warranted for sulfur." This is based on the effects observed in one acute inhalation toxicity study (decrease in breathing frequency, irregular breathing and choking breathing observed shortly after the start of the exposure and demonstrated to be reversible) and incidences in humans (cough, upper airway irritation, rhinitis, epistaxis, oropharyngeal irritation, runny noses, throat irritation). This is not supported by the applicants and an expert rebuttal statement was prepared by the applicant's toxicologists: - Based on the acute inhalation toxicity studies in animals presented in the MCA Section 5, sulfur is considered non-toxic by the inhalation route (LC50 for technical sulphur in rats was greater than 5430 mg/m3). No signs of respiratory irritation were observed. The studies conducted with WG and DP formulations also have similar results. - I) human incident databases: the overall conclusion from the EPA report (Sulfur. Human Health Risk Scoping Document in Support of Registration Review – Addendum, 2009) is that the risk posed to human health by sulfur appears to be low. Across the databases, the relative number of reported incidents was low, the severity of reported health effects was low, and for most databases the dermal, ocular and respiratory symptoms/health effects were reflective of the known irritating properties of sulfur. The report does not rely exclusively on the respiratory irritating effects of sulfur, as stated in the dRAR, but mainly on the known dermal and eye irritating properties of sulfur. Only in one database is respiratory tract irritation mentioned, but without any further information. Hence, it is difficult to conclude whether the symptoms were really related to respiratory tract			

irritation (RTI), as described in the Guidance or whether it was simply "irritation".
- II) in workers occasionally exposed to sulphur in California during application by helicopter (Maddy & Edmiston 1998): the symptoms described in this incidence report are very similar to the ones described in the acute inhalation toxicity studies in animals and are not indicative of respiratory tract irritation.
- III) in the French Toxicovigilance Programme: a first analysis was carried out on all 86 dossiers where either sulfur preparations (alone or in combination with other active substances) were involved on their own, or where the subject was exposed concomitantly to other PPP. The cases analysed do not allow the conclusion that sulfur was the causative agent by itself, and thus cannot be considered sufficient to warrant classification of sulfur technical as STOT-SE H335.
- A separate analysis was carried out on the 24 dossiers relating to exposure to preparations containing only sulfur. This analysis is based on very small numbers of reports and there is no mentioning of how these effects were evaluated and validated. It is not clear whether the symptoms mentioned occurred during or/and after exposure of the workers to the sulfur formulation. Respiratory effects are not described in detail, so it is not possible to distinguish between simple irritation, which should be excluded from classification, or if symptoms such as cough, pain, choking, and breathing difficulties were reported, which would be considered relevant for classification.
- Medical screening data: No cases with adverse respiratory effects have been noted despite many years of handling the technical and formulated material.
- IV) Epidemiological studies of miners (long-term exposure to sulfur dust and sulfur dioxide): whereas sulfur dioxide is a well-known and recognised respiratory irritant, no conclusion on irritating properties of sulfur technical can be made since in the reported cases there was co-exposure to other substances, (US EPA RED Sulfur 1991).
- V) Epidemiology study (Raanan 2017): the paper contains a number of confounders which draws the conclusions of the authors in doubt. It is questionable whether the study population can be seen as representative for risk assessment, because participants of the longitudinal birth cohort study belong to the poor population of the Salinas Valley. Also, the authors stated that "future studies should attempt to replicate these findings in other study populations". The predicted correlation of the use of sulfur with respiratory symptoms is questionable because no actual sulfur exposure of the participants was measured. Co-exposure to other chemicals including OPs cannot be ruled out.
- According to Guidance to Regulation (EC) No 1272/2008, classification in STOT-SE Category 3 for respiratory tract irritation is generally limited to local cytotoxic effects. However, in fact no effect such as localised redness, oedema, pruritis and/or pain have been observed in animal studies with sulfur, and such effects have also not been mentioned in the incident reports analysed above.
- Ambiguous reports simply of 'irritation' should be excluded from classification, since this term is commonly used indiscriminately 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 tract irritation.
- A solid substance which causes RTI primarily because of physical/mechanical irritation when inhaled as a dust should also not be classified.

Therefore, it is concluded that considering all available information and data, the position of the applicants is that sulfur technical classification as "STOT-SE Category 3: May cause respiratory tract irritation" is not warranted, because the criteria for classification are not met.
A corresponding expert statement (Statement on the proposal of Sulfur classification as STOT SE Cat 3, Report No. SWG/STF-210831-03, 31 August 2021) is provided to ECHA as public attachment.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Applicants(SWG_STF)_comments_on_CLH_report_sulfur_(AIR_IV)_public_attachments.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Report_1992500_Sulfur_Gene_Mutation Assay.pdf

Dossier Submitter's Response

As detailed in the RAR, the DS considered that human and animal data are indicative of respiratory tract irritant properties of sulfur and that by weight of evidence, H335 classification is warranted.

RAC's response

RAC notes the human cases of respiratory tract effects from exposure to sulfur from American and French databases. However, the reports include few details on the severity of the effects. Considering the extensive use of sulfur through several decades, the number of cases reported are low while the severity of the effects on the respiratory tract are considered outside the scope of classification for respiratory irritation. RAC agrees with the commenter that the human data showing respiratory tract irritation should not lead to classification as STOT SE 3; H335.

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2021	Germany		MemberState	12

Comment received

DE CA agrees with the classification of sulfur with STOT SE Category 3 for respiratory tract irritation (H335) as proposed by the DS (FR).
Justification: In the combined RAR/CLH dossier provided by the DS (FR), an animal study ((Anonymous 2 (1994) (see 2.6.2.3., table 17) and several human case reports were described. Several relevant clinical signs were noted in rats exposed to 5.43 mg/L. Specifically, a decrease in breathing frequency was noted in all rats starting from the second hour of exposure. Irregular breathing was observed in all rats during the last two hours of exposure. In the first hour after exposure, all rats showed choked breathing and the eyes were partly closed. With respect to the human data, signs of respiratory tract irritation were observed following occupational exposure to sulfur and in incident reports/databases. Clinical signs included cough, upper airway irritation, rhinitis, epistaxis and oropharyngeal irritation. The transient respiratory tract irritation effects observed in rats and humans warrant classification according to the CLP criteria.

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH_Sulfur_Confidential Annex.pdf

Dossier Submitter's Response

Thank you for your support

RAC's response

Noted.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	Germany	(i) Sulfur Working Group, (ii) Sulphur Task Force [list of SWG and STF stakeholders see public attachment]	Company-Downstream user	13

Comment received

Sulfur CLH/RAR 01, Vol. 1 - Level 2; 2.6.3.1.1, p. 55; Vol.1 - Level 3, 3.1.8, p.187
The RMS proposed to discuss the need for a subchronic toxicity study by the inhalation route between Member States during the expert meeting. The major concern arises from the epidemiological study conducted in California (Raanan et al., 2017). The epidemiological study was considered a justification for conducting a repeat dose inhalation study with sulfur by the RMS. Poorer lung function (spirometry measurements) and higher odds of reported respiratory symptoms and asthma medication use were found in 7-year old children living within 0.5 km and 1 km of elemental sulfur applications during the previous week, month and year. However, the study authors already stated that further studies would be beneficial in order to confirm or infirm these results in other (more relevant) study populations.

The performance of a subchronic inhalation toxicity study is not supported by the applicants, based on the conclusions of an expert statement as follows:
• Some adverse effects occurring after long-term inhalation exposure were reported in humans (please refer to B.6.9). Nevertheless, chronic findings were only reported when sulfur was not the only active substance used and/or in cases of high acute exposure (accidents);
• Based on screening data in companies manufacturing sulfur or sulfur formulations provided in the confidential parts of the dossier (please refer to Vol 4), the occupational medical surveillance of factory workers revealed no evidence of any adverse findings, except cases of eye and/or skin irritations;
• Short-term toxicity studies via the inhalation route shall be considered where the vapour pressure exceeds 10-2 Pascals, which is not the case for sulfur (vapour pressure 9.8 × 10-5 Pa at 20 °C). Therefore, a short-term inhalation toxicity study has not been conducted with sulfur;
• Two acute inhalation toxicity studies in rodents are available and from these studies, sulfur is not considered toxic by the inhalation route; no classification for acute toxicity by inhalation is warranted according to the CLP regulation;
• The paper from Raanan has been discussed in detail in the MCA Section 5 and contains a number of confounders which draws the conclusions of the authors in doubt (see our comment and further explanations to Medical data and information, No. 1);

Thus, the applicants do not agree that the publication provides sufficient evidence to support the need for an additional animal study.
A corresponding expert statement (Statement on the assessment of Sulfur for inhalation toxicity, Report No. SWG/STF-210831-04, 31 August 2021) is provided to ECHA as public attachment.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment

Applicants(SWG_STF)_comments_on_CLH_report_sulfur_(AIR_IV)_public_attachments.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Report_1992500_Sulfur_Gene_Mutation Assay.pdf
Dossier Submitter's Response
A conclusion on STOT RE classification should be taken based on the available information. Based on the available data, no classification as STOT RE is warranted for sulfur for the oral and dermal route. Regarding inhalation route, in the absence of appropriate animal studies investigating this endpoint, the data are considered insufficient to conclude on STOT RE classification for this route of exposure.
RAC's response
RAC considers that although a concern for serious chronic effect to the lung function is raised in the Raanan *et al.* (2017) paper, the study is not sufficiently robust to base classification as STOT RE upon. RAC emphasises that requirements for further testing are not relevant under CLP.

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2021	Germany		MemberState	14
Comment received				
As no animal or human data were identified indicating that sulphur fulfils the CLP criteria for classification for STOT RE, classification of sulfur for STOT RE is NOT proposed by the DS. DE CA agrees that sulfur should not be classified for this endpoint. However, it is noted that this proposal is based on oral and dermal repeat dose studies only. The reports by Blum and Coe (1977) and Greengard and Woolley (1940) (or a reference to them) should be taken into account, providing human data on repeat dose toxicity and thus enhancing the robustness of the conclusion. These reports are currently described in section 2.6.9. The DS has indicated that a repeat dose inhalation study conducted with sulfur should be requested. The DS quote an epidemiological study conducted in California (Raanan et al., 2017) as the basis for this request. In this study the authors reported that poorer lung function (spirometry measurements), and higher odds of respiratory symptoms and asthma medication use were found in 7-year old children living within 0.5 km and 1 km of elemental sulfur applications during the previous week, month and year. For reasons described below, under the heading Justification, DE CA has concerns regarding the request for a repeat dose inhalation study: a) In accordance with the data requirements for active substances (Commission Regulation (EU) No 283/2013), short-term toxicity studies via the inhalation route shall be considered where the vapour pressure exceeds 10-2 Pascals. This is not the case for sulfur (vapour pressure 9.8 × 10-5 Pa at 20 °C). b) Section 3.9 of the CLP Guidance document (2017) states: "Where the same target organ toxicity of similar severity is observed after single and repeated exposure to a similar dose, it may be concluded that the toxicity is essentially an acute (i.e. single exposure) effect with no accumulation or exacerbation of the toxicity with repeated exposure. In such a case classification with STOT-SE only would be appropriate". As such, any respiratory tract irritation observed in the proposed repeat dose inhalation study is likely to be covered by the STOT-SE classification proposed above. c) Animal welfare considerations d) Section 3.9.2.1 of the CLP Guidance document (2017) states: "CLP does not require				

testing of substances and mixtures for classification purposes. The assessment is based on the respective criteria and consideration of all available adequate and reliable information". As such, new data, such as that proposed her, should not be generated for solely for classification purposes. e) Epidemiological studies conducted on other target populations could be used to confirm or infirm the findings of Raanan et al. (2017). A conclusion on STOT RE should be taken on the available information. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH_Sulfur_Confidential Annex.pdf
Dossier Submitter's Response
The DS agrees that a conclusion on STOT RE should be taken on the available information. Based on the available data, no classification as STOT RE is warranted for sulfur for the oral and dermal route. Regarding inhalation route, in the absence of appropriate animal studies, the data are considered insufficient to conclude on STOT RE classification for this route of exposure.
RAC's response
RAC notes the support for not classifying sulfur for STOT RE by either route and the listing of evidence on repeated dose toxicity by the inhalation route.

PUBLIC ATTACHMENTS
1.
Applicants(SWG_STF)_comments_on_CLH_report_sulfur_(AIR_IV)_public_attachments.zip [Please refer to comment No. 3, 8, 11, 13]

CONFIDENTIAL ATTACHMENTS
1. Report_1992500_Sulfur_Gene_Mutation Assay.pdf [Please refer to comment No. 3, 8, 11, 13]2. CLH_Sulfur_Confidential Annex.pdf [Please refer to comment No. 1, 2, 4, 5, 6, 7, 9, 10, 12, 14]