COMPILED COMMENTS ON CLH CONSULTATION

Comments provided during consultation are made available in the table below as submitted through the web form. Please note that the comments displayed below may have been accompanied by attachments which are listed in this table and included in a zip file if non-confidential. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Last data extracted on 22.04.2024

Substance name: sulcotrione (ISO); 2-[2-chloro-4-(methylsulfonyl)benzoyl]cyclohexane-1,3-dione
CAS number: 99105-77-8
EC number: -
Dossier submitter: Germany

HEALTH HAZARDS – Acute toxicity

Date	Country	Organisation	Type of Organisation	Comment number
11.04.2024	Belgium		MemberState	1
Comment received				
Acute Toxicity – Oral Based on the available information (LD50 >2000 mg/kg bw in an acceptable study as well as >5000 mg/kg bw in a supplementary study), BE CA agrees with the conclusion that Sulcotrione does not fulfil the criteria to classify for acute toxicity via oral route. Acute Toxicity – dermal Based on the available data (LD50 >2000 mg/kg bw in an acceptable study and >4000 mg/kg bw in a supplementary study), BE CA supports the conclusion that Sulcotrione does not fulfil the criteria to classify for acute toxicity via dermal route. Acute Toxicity – Inhalation We have some comments about the inhalational toxicity study, the regulatory limit concentration could not be achieved in study TOX9401305. The highest attainable stable concentration 1.4 mg/L didn't show mortality after a nose-only exposure for 4 hours. Water was used as vehicle to produce aerosol. The AED <2.5 µm 42.02%, MMAD was not mentioned. A second attempt/study with a different vehicle is not present. (Sulcotrione_ vapor pressure 0.01Pa) Do you still have data in your possession that indicates that it is indeed impossible to form an aerosol of sulcotrione with a MMAD <4µm. Based on the available information (LC50 >1.63 mg/L in an acceptable study, mentioned as the maximum achievable concentration), BE CA can support the conclusion that no classification for Sulcotrione is warranted.				

HEALTH HAZARDS – Skin corrosion/irritation

Date	Country	Organisation	Type of Organisation	Comment number
11.04.2024	Belgium		MemberState	2
Comment received				
Based on the available information, no signs of erythema or edema were observed in two studies. BE CA agrees that no classification is warranted for Skin Corrosion/Irritation.				

HEALTH HAZARDS – Serious eye damage / eye irritation

Date	Country	Organisation	Type of Organisation	Comment number
11.04.2024	Belgium		MemberState	3
Comment received				
Based on the available information (mild eye irritation and chemosis, however below the mean score relevant to classify), BE CA supports the conclusion that no classification is warranted for eye damage/eye irritation.				

HEALTH HAZARDS – Respiratory sensitisation

Date	Country	Organisation	Type of Organisation	Comment number
11.04.2024	Belgium		MemberState	4
Comment received				
BE CA support the conclusion that a classification cannot be drawn as no data is available. The reason for no classification mentioned in Table 2.11-7 is “data inconclusive”. BE CA is of the opinion that the reason for no classification is “data lacking”.				

HEALTH HAZARDS – Skin sensitisation

Date	Country	Organisation	Type of Organisation	Comment number
11.04.2024	Belgium		MemberState	5
Comment received				
Based on the available information, BE CA agrees with the current harmonized classification as Skin Sens. 1A.				

HEALTH HAZARDS – Germ cell mutagenicity

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2024	Netherlands		Individual	6
Comment received				
The DS/RMS states that a reliable conclusion based on in vitro and in vivo studies can not be drawn based on the available studies. Most gene mutation and clastogenicity studies in vitro and in vivo were negative, the positive study in mice had a high dosing concentration. The NL-CA agrees there is insufficient support for classification as mutagenic.				

Date	Country	Organisation	Type of Organisation	Comment number
11.04.2024	Belgium		MemberState	7
Comment received				
In Table 2.11-7, it states that the reason for no classification for germ cell mutagenicity is “Data conclusive but not sufficient for classification”. Based on the available information and as mentioned in the CLH dossier, further information is required for this endpoint. Indeed, positive results are observed in in vitro gene mutation tests which rise an indication of mutagenic potential. BE CA is then of the opinion that a classification for germ cell mutagenicity is not warranted due to data lacking.				

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2024	Spain	<confidential>	Company-Manufacturer	8

Comment received
As the genotoxicity potential of sulcotrione could not be excluded, further argumentation and data is proposed in the submitted attachment "Sulcotrione_CLH_report_comments_2024" ECHA note – An attachment was submitted with the comment above. Refer to public attachment Sulcotrione_CLH_report_comments_2024.pdf

HEALTH HAZARDS – Carcinogenicity

Date	Country	Organisation	Type of Organisation	Comment number
11.04.2024	Belgium		MemberState	9
Comment received				
Limited evidence of carcinogenic potential is observed in 18-month dietary mouse oncogenicity study. Statistically significant increase of primary malignant mammary tumours was noted and was outside HCD. However, HCD is limited (only 5 studies available), then must be taken with caution. Just one observation of malignant mammary tumors in mice at a dose of 409mg/kg bw/d, without metastases and lacking other neoplastic findings in additional studies. Then based on the available results, BE CA is not entirely convinced to classify in category 2.				

Date	Country	Organisation	Type of Organisation	Comment number
18.04.2024	Netherlands		Individual	10
Comment received				
The DS/RMS proposes category 2 for carcinogenicity based on tumor formation found in two species, rat and mice, both in one sex. No additional studies for carcinogenicity were performed compared to 2011. However, in the previous assessment the Leydig cell tumor formation was not reported. Therefore, there is reason to reconsider the previously proposed classification even though there is no new data. Previously, RAC concluded the mammary adenocarcinomas in a single sex in mice insufficient for classification as there were strong doubts about the relevance of the findings also considering the late stage at which the tumors occurred and potential excessive doses in the female mice. In short, there was too much uncertainty and therefore no classification was proposed. In the current proposal, the DS/RMS mentions they do not consider the mid-dose group of 3000 ppm excessive and the DS/RMS supports this with comparing mortality of this dose group to the low dose group which is not significantly different. Following the compilation of factors (Table 2.6-49 and 50), classification for carcinogenicity cat. 2 could be proposed based on this alone (malignant carcinoma in single sex/species). In addition, Leydig cell tumors are reported in rats in one of the other studies. Apart from the interesting fact these were not reported previously, the Leydig cell tumors are of benign nature and do not follow a clear dose response. Both the adversity and relevance for humans are somewhat uncertain. This evidence seems at best supportive for classification. Overall, there are indications sulcotrione could be carcinogenic to humans but uncertainties are clearly still present. Category 2 classification exists for this situation and therefore the NL-CA can support the proposal for classification as Carc. 2.				

HEALTH HAZARDS – Reproductive toxicity

Date	Country	Organisation	Type of Organisation	Comment number
11.04.2024	Belgium		MemberState	11
Comment received				

Could you please provide us with more detailed data regarding Table B.6.6-30 (TOX9401330) specifically focusing on “dams with resorption (1000 mg/kg bw/d)” with 7 occurrences vs 17 in the control group and “post implantation loss (1000 mg/kg bw/d)” with 4.3 occurrences vs 12.2 in the control group”? Is any information known about fertility indices?
In Tox2004-2853, significant severe fetal toxicity was noted at doses of 355mg/kg bw/d. Mild parental toxicity was significant from this dose onwards.
In TOX9401328, a trend of increased fetal toxicity was noted at doses of 225ppm. Mild parental toxicity was first noted at a dose of 10ppm. Other fetal observations made were abnormal functional growth and delayed eye opening.
Fetal toxicity and parental toxicity are seen at the same dose level, but the severity of toxic effects (fetal mortality) can not been fully attributed to the observed mild parental toxicity. Developmental effects are considered evidence of developmental toxicity. BE CA recommends classification as a repro 1B, H360D.
With the currently available information regarding fertility, can we align ourselves with the RMS on the subject of fertility.

HEALTH HAZARDS – Specific target organ toxicity - single exposure

Date	Country	Organisation	Type of Organisation	Comment number
11.04.2024	Belgium		MemberState	12
Comment received				
Based on the available information, BE CA supports the conclusion that no classification is warranted for STOT SE.				

HEALTH HAZARDS – Specific target organ toxicity - repeated exposure

Date	Country	Organisation	Type of Organisation	Comment number
11.04.2024	Belgium		MemberState	13
Comment received				
Regarding classification for eyes: Based on the available studies, ocular lesions are clearly demonstrated in several studies and in different species (rat and dog). Furthermore, the lesions occurred at very low doses in male rats (already at 1.4 mg/kg bw/d and 3.3 mg/kg bw/d). Based on the CLP criteria “Annex 1: 3.9.2.1 Substances are classified as specific target organ toxicants following repeated exposure by the use of expert judgement (see 1.1.1), on the basis of the weight of all evidence available, including the use of recommended guidance values which take into account the duration of exposure and the dose/concentration which produced the effect(s), (see 3.9.2.9), and are placed in one of two categories, depending upon the nature and severity of the effect(s) observed (Table 3.9.1). Category 1: 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 repeated exposure. Substances are classified in Category 1 for target organ toxicity (repeat exposure) on the basis of: reliable and good quality evidence from human cases or epidemiological studies; or 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 (see 3.9.2.9), to be used as part of a weight-of- evidence evaluation.” And based on the Table 3.9.2, the guidance values to assist in Category 1 classification is ≤10 mg/kg bw/d in rat via the oral route. While the criteria to classify in Category 2 is “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 repeated exposure. Substances are classified in category 2 for target organ toxicity (repeat 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 (see 3.9.2.9) in order to help in classification. In exceptional cases human evidence can also be used to place a substance in Category 2 (see 3.9.2.6).".
Based on the available data, BE CA is of the opinion that the criteria are fulfil to classify in Category 1 as the ocular lesin are observed at low exposure concentrations.
Moreover, in the Guidance on the Application of the CLP criteria (Version 6.0, Jan 2024), it states that "Annex I : 3.9.2.8.1. It is recognised that effects may be seen in humans and/or animals that do not justify classification. Such effects include, but are not limited to:
(e) substance-induced species-specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification.".
BE CA is of the opinion that this point is not fulfilled. Many case report demonstrate ocular lesions with NTBC, another HPPD inhibitor. Indeed, there are no studies with sulcotrione in humans, however there is no prove that sulcotrione, a HPPD inhibitor, did not leading ocular effects.
Taken together, BE CA is of the opinion that ocular lesions are sufficient basis for classification. Overall data (human evidence and observations below the guidance value from acceptable experimental animal studies) warrant a classification as STOT RE 1.

Kidneys:
BE CA agrees to retain the current classification for kidneys.

Liver:
Based on the available information, BE CA supports the conclusion that a classification for liver is not warranted.

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2024	Spain	<confidential>	Company-Manufacturer	14
Comment received				
Applicant disagree in considering certain organs as target organs on a series of studies. Detailed information and background of justification is provided in the attachment "Sulcotrione_CLH_report_comments_2024" ECHA note – An attachment was submitted with the comment above. Refer to public attachment Sulcotrione_CLH_report_comments_2024.pdf				

ENVIRONMENTAL HAZARDS – Hazardous to the aquatic environment

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2024	Sweden		MemberState	15
Comment received				
Aquatic environmental hazard classification: SE CA supports the aquatic environmental hazard classification of sulcotrione (Cas No 99105-77-8) as specified in the proposal. SE CA agrees with the proposal to classify sulcotrione as Aquatic acute 1 with an acute M-factor of 10 and Aquatic Chronic 1 with a chronic M-factor of 100. Toxicity data are available for all three trophic levels and the lowest endpoints, for both acute and chronic assessment, are for aquatic plants (Lemna gibba).				

SE CA noticed that the chronic endpoint for fish (Pimephales promelas) is reported as NOEC <0.38 mg/L. “Less-than-toxicity data” is not possible to compare with the criteria. In the study summary report for this study (available on p. 111-119 in “Sulcotrione_RAR_11_Volume_3CA_B-9_2023-12-14” the RMS concludes that the NOEC (33d, body weight) <0.38 mg/L and that the LOEC (33d, body weight) = 0.38 mg/L. Additionally, according to p. 11 in “Guidance on information requirements and chemical safety assessment, Chapter R.10: Characterisation of dose (concentration)-response for environment (ECHA, 2008)”, a NOEC can be calculated as LOEC/2 (if LOEC > 10 and < 20% effect). In this study, the LOEC of 0.38 mg/L has 10.2% inhibition of wet weight and 12.8% inhibition of dry weight compared to the control. Consequently, the NOEC could be calculated to be 0.38/2 = 0.19 mg/L, which can be compared with the criteria. This re-calculation of the NOEC for fish, does however not affect the conclusion of the classification proposal.

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2024	United Kingdom	Health and Safety Executive	National Authority	16

Comment received

The DS considers that the key chronic endpoint is the 2020a Lemna gibba 7-day NOErC(dry weight) of 0.000745 mg/L (nominal - recalculated by the RMS/DS). The 7-day ErC10s (frond number or dry weight) from this study were not considered reliable by the DS for hazard classification based on statistical re-evaluation under PPP regulations. Recognising the specific technical assessment and protection goal for PPPs are different to hazard classification, we consider that the ErC10s endpoints are relevant and reliable for hazard classification. The ErC10s (recalculated by the DS and based on nominal concentrations) from this L. gibba study were:
7-day ErC10(dry weight): 0.00215 mg/L (95% CI 0.00123 – 0.00308 mg/L)
7-day ErC10(frond number): 0.0024 mg/L (95% CI 0.00092 – 0.00398 mg/L).

These values support a chronic M-factor of 10 for a non-rapidly degradable substance. The PPP assessment noted that the ErC10 values were subject to NW (Normalised Width of Confident Interval) values that indicated ‘poor’ quality endpoints. Considering the data further, this appears to be a function of a steep dose-response – whilst the treatment spacing was adequate in terms of reflecting the test guideline, this is likely due to the herbicidal MoA of the substance. The NW values are a statistical indicator of the width of the endpoint CIs - endpoints have rarely been subject to such assessment for CLH previously. In this instance, the NW values may indicate relatively wide CIs but we note that the CIs are either within the same 0.001-0.01 mg/L hazard classification or slightly below for the frond number endpoint. On this basis, we consider the ErC10 values are sufficiently reliable to describe the dose-response effect of 10% and should not be superseded by a NOErC given that substantial wider data* also support long-term hazard classification endpoints in the 0.001-0.01 mg/L range.

* Additional endpoints in the 0.001 – 0.01 mg/L range that are reliable and relevant for hazard classification which also support the Aquatic Chronic 1 classification with an M-factor of 10:
• Anon 2009b Lemna gibba study endpoints (nominal - verified):
7-day ErC10 = 0.0044 mg/L (95% CI 0.0033 – 0.0052) based on frond number
7-day ErC10 = 0.0046 mg/L (95% CI 0.0037 – 0.0053) based on dry weight
• Anon 2016 Myriophyllum spicatum study endpoints (nominal – verified):
14-day ErC10 = 0.0086 mg/L (95% CI: 0.00518 – 0.0125) based on total shoot length

14-day ErC10 = 0.00284 mg/L (95% CI 0.00133 – 0.00478) based on fresh weight
14-day ErC10 = 0.00136 mg/L (95% CI 0.000696 – 0.00221) based on dry weight
14-day NOErC = 0.00191 mg/L based on dry weight and fresh weight
• Anon 2011a Lemna minor study endpoints:
7d NOErC = 0.00316 mg/L (nominal - verified) based on frond number, frond area and dry weight
A reliable ErC10 is not available for this study.
• Anon 2002a Lemna gibba study endpoints:
7d NOErC = 0.0062 mg/L (mean measured)
This endpoint was not considered reliable for PPP assessment because test concentrations were not maintained within 80-120% of the nominal, reaching below the LOQ in two samples by the end of the study. However, we note that mean measured endpoints calculated using the half LOQ for measured concentrations below the LOQ is acceptable for CLP so it would be useful if such an endpoint could be determined.
No EC10 values were reported for this study.

Date	Country	Organisation	Type of Organisation	Comment number
11.04.2024	Belgium		MemberState	17
Comment received				
Based on the results of the aquatic toxicity test on the most sensitive species (aquatic plants (Lemna gibba) with a 7d ErC50 = 0.018 mg/L (nom – dry weight) and 7d NOErC = 0.000745 mg/L (nom – dry weight)), the fact that the substance is not rapidly degradable it is justified to classify, following the classification criteria of regulation 1272/2008, as aquatic Acute 1, H400 and Aquatic Chronic 1, H410 . In view of the proposed classification and toxicity band for acute toxicity between 0.01 mg/l and 0.1 mg/l, an M-factor for acute toxicity of 10 could be assigned and an M-factor for chronic toxicity of 100 (not rapidly degradable substance and NOEC between 0.0001 and 0.001 mg/L) In conclusion : we support the proposed environmental classification.				

Date	Country	Organisation	Type of Organisation	Comment number
17.04.2024	France		MemberState	18
Comment received				
FR agrees with the conclusion on classification and labelling for environmental hazards: Sulcotrione is classified in acute aquatic hazard Cat 1 - H400: Very toxic to aquatic life with M-factor = 10 based on L.gibba 7d-ErC50 = 0.018 mg a.s/Lnom and long-term aquatic hazard Cat 1 - H410: Very Toxic to aquatic life with long lasting effects with M-factor = 100 based on L. gibba 7d-NOErC = 0.000745 mg a.s/Lnom and considering the substance as non-rapidly degradable.				

ADDITIONAL HAZARDS – Hazardous for the ozone layer

Date	Country	Organisation	Type of Organisation	Comment number
11.04.2024	Belgium		MemberState	19
Comment received				

Based on the low vapour pressure and henry's law constant and the short half life of the substance in air, we agree that no classification is warranted as hazardous for the ozone layer.

PUBLIC ATTACHMENTS

1. Sulcotrione_CLH_report_comments_2024.pdf [Please refer to comment No. 8, 14]