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 08.07.2024

Substance name: 1,3-dichloropropene [1]; (*Z*)-1,3-dichloropropene [2]; (*E*)-1,3-dichloropropene [3]
CAS number: 542-75-6 [1] 10061-01-5 [2] 10061-02-6 [3]
EC number: 208-826-5 [1] 233-195-8 [2] 431-460-4 [3]
Dossier submitter: Poland

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2024	United States of America	Dow Europe GmbH	Company-Manufacturer	1
Comment received				
Dow Europe GmbH (Dow) has been a manufacturer of 1,3-Dichloropropene for over sixty-years. Numerous manufacturing process improvements have been undertaken over the years to improve the product quality, resulting in reduction in both the number and levels of impurities. It is also important to note that epichlorohydrin, previously added as a stabilizer, was replaced with epoxidized soybean oil in 1983. It is believed that certain findings in toxicity studies conducted prior to 1983, most notably in mutagenicity and carcinogenicity studies, were due to the presence of epichlorohydrin. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 1,3-D.zip				

Date	Country	Organisation	Type of Organisation	Comment number
03.07.2024	Germany	Kanesho Soil Treatment SRL/BV	Company-Manufacturer	2
Comment received				
The commenting party has included comments on the CLH Report and the proposed classification of 1,3-dichloropropene as follows: For each individual section, either agreement to the proposal is claimed or comments are compliled in the enclosed .pdf document referring to respective parts of the CLH Report. Reference in the text boxes in the online template is made where reasonable. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 12. Public Attachment.docx				

Date	Country	Organisation	Type of Organisation	Comment number
02.07.2024	Germany		MemberState	3

Comment received
The CLH dossier proposes to classify the substance as Acute Tox. 3, H331, but without specifying an ATE value (inhalation) for this classification. According to Annex VI Part 1 No. 1.1.2.3 paragraph 1 last sentence of Regulation (EC) No. 1272/2008 (CLP Regulation), in the absence of harmonised ATE values for acute toxicity, the classifier must use the correct value based on available data. The CLH dossier does not specify an ATE value, but only lists a data range that is used to classify the substance, but is not sufficient to correctly classify mixtures containing this substance. It is therefore strongly suggested that a harmonized ATE value for classification as acute toxic by inhalation is specified in the CLH dossier, which can then be included in Annex VI Part 3 Table 3 of the CLP Regulation. Similar to the determination of the ATE value for oral toxicity for nicotine, the conversion value of acute toxicity for category 3 (vapours) from Table 3.1.2 of the CLP Regulation could also be recommended as a harmonised ATE value (inhalation) for 1,3-dichloropropene. Only with a harmonized ATE value a mixture formulator will be able to classify mixtures in accordance with the regulation with regard to the acute inhalation toxicity hazard class. Moreover, compared to the pesticidal active substance approval procedure performed at EU level for 1,3-dichloropropene, this CLH dossier takes into account additional studies that were not previously available to the DE CA, other MS and EFSA. As a result, several studies were not evaluated at EU level and full documentation including study reports is not available to the MS. Therefore, not all information/conclusions provided are sufficiently transparent. In particular, the DE CA believes that the assessment of germ cell mutagenicity requires additional consideration and attention. The newly available genotoxicity studies appear to have limited reliability and may not be sufficient to conclude on non-classification for mutagenicity. Regarding carcinogenicity, the DE CA would like to point out the recent EFSA conclusion on 1,3-dichloroporpene proposed classification as Carc. 2, which is in contrast to the assessment in the CLH report.

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2024	Spain		MemberState	4
Comment received				
The Spanish CA agrees with the DS proposal for harmonized classification and labelling.				

PHYSICAL HAZARDS

Date	Country	Organisation	Type of Organisation	Comment number
03.07.2024	Germany	Kanesho Soil Treatment SRL/BV	Company-Manufacturer	5
Comment received				
Comments are made to chapter 8.15.3 on "corrosive to metals". For this, please refer to the enclosed .pdf document. The commenting party agrees to the proposed classification.				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 12. Public Attachment.docx

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2024	Spain		MemberState	6
Comment received				
No comments.				

HEALTH HAZARDS – Acute toxicity

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2024	France		MemberState	7
Comment received				
Oral FR agrees with the classification of 1,3-D (mix of isomers), (Z)-1,3-D (cis-isomer) and (E)-1,3-D (trans-isomer) as Acute Oral Toxicity Category 3, H301, Toxic if swallowed with ATE value = 85 mg/kg bw. Dermal FR agrees with the overall classification of the group of substances as Acute toxicity Category 3, H311, Toxic in contact with skin with an ATE value of 330 mg/kg bw. Inhalation FR agrees with the classification 1,3-D (mix of isomers), (Z)-1,3-D (cis isomer) and (E)-1,3-D (trans isomer) as Acute toxicity Category 3, H331, Toxic if inhaled. No harmonised ATE-value is proposed.				

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2024	United Kingdom	Health and Safety Executive	National Authority	8
Comment received				
We note that an ATE value has not been set for the Acute Inhalation Toxicity 3 classification. Would the DS please provide justification for this conclusion.				

Date	Country	Organisation	Type of Organisation	Comment number
03.07.2024	Germany	Kanesho Soil Treatment SRL/BV	Company-Manufacturer	9
Comment received				
References are made to Chapter 10.1.2, 10.2.3, 10.3.3 referring to acute toxicity. The commenting party agrees to the proposed classification. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 12. Public Attachment.docx				

Date	Country	Organisation	Type of Organisation	Comment number

02.07.2024	Germany		MemberState	10
Comment received				
Acute toxicity – inhalation: The DE CA agrees with the dossier submitter's proposal to classify 1,3-dichloropropene as acutely toxic (inhalation), category 3 (H331). However, the dossier does not justify why no ATE value is proposed. According to the latest evaluation at EU level [EFSA Journal 2018;16(11):5464], the lowest LC50 is 2.7 mg/L/4 h, which should be used as the ATE. Additional studies in the CLH dossier for this endpoint did not show lower LC50 values. Acute toxicity – dermal: The DE CA supports the dossier submitter's proposal to retain the existing classification in category 3 (H311). The dermal ATE of 330 mg/kg bw is supported as well. Acute Toxicity – oral: The DE CA supports the dossier submitter's proposal to retain the existing classification into category 3 (H301). However, more justification is needed for the proposed ATE value for combined sexes of 85 mg/kg bw for this classification. Females appear to be slightly more sensitive than males, but it is not clear whether the difference compared to males is statistically significant. If so, an ATE of 78 mg/kg bw may be more appropriate.				

Date	Country	Organisation	Type of Organisation	Comment number
02.07.2024	Belgium		MemberState	11
Comment received				
Acute oral toxicity BE CA agrees with Acute tox. 3, H301 classification. However, in general, classification is based on the lowest ATE value available i.e. the lowest ATE in the most sensitive appropriate species tested. Out of anonymous 23 (1989) BE CA proposes an ATE (oral) 78mg/kg bw, observed in female rats. Acute dermal toxicity BE CA supports the classification proposal: Acute tox. 3, H311. ATE (dermal) 330 mg/kg bw. Acute inhalational toxicity BE CA agrees with Acute tox. 3, H331 classification. However, BE CA is of the opinion that an ATE could be chosen and, based on the study Anonymous 20 (1990), BE CA proposes an ATE (vapour) of 3.0 mg/L.				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2024	Spain		MemberState	12
Comment received				
The Spanish MSCA agrees with the Dossier Submitter in the whole assessment of acute inhalation toxicity and ES supports the classification proposal for Acute Tox. 3 (H331).				

HEALTH HAZARDS – Skin corrosion/irritation

Date	Country	Organisation	Type of Organisation	Comment number
02.07.2024	Belgium		MemberState	13
Comment received				
BE CA supports the classification proposal of the DS: skin irritation Category 2, H315.				

Date	Country	Organisation	Type of Organisation	Comment number
03.07.2024	Germany	Kanesho Soil Treatment SRL/BV	Company-Manufacturer	14
Comment received				
Reference is made to Chapter 10.4.3 referring to skin corrosion/irritation. The commenting party agrees to the proposed classification. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 12. Public Attachment.docx				

Date	Country	Organisation	Type of Organisation	Comment number
02.07.2024	Germany		MemberState	15
Comment received				
The DE CA supports the dossier submitter's proposal of retaining the existing classification as "irritating to the skin", category 2, H315. This classification was also proposed in the latest EFSA conclusion on 1,3-dichloropropene [EFSA Journal 2018;16(11):5464].				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2024	Spain		MemberState	16
Comment received				
The Spanish MSCA agrees with the Dossier Submitter proposal				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2024	France		MemberState	17
Comment received				
FR agrees with the classification of 1,3-D (mix of isomers), (Z)-1,3-D (cis isomer) and (E)--1,3-D (trans isomer) as: Skin Irritation Category 2, H315, Causes skin irritation.				

HEALTH HAZARDS – Serious eye damage/eye irritation

Date	Country	Organisation	Type of Organisation	Comment number
02.07.2024	Belgium		MemberState	18
Comment received				
The isolated rabbit eye (IRE) test, performed under GLP-guidelines (anonymous 23, 1989) using cis-1,3-dichloropropene with a purity of 96.9%, indicates serious eye damage that is not fully reversible within 21days. However, an in vivo study on rabbits for the isomer mixture (anonymous 15, 1987) (52.63% cis, 44.91% trans) performed under GLP guidelines, shows only mild eye irritation. In this study, conjunctival redness ≥2 in 4:6 rabbits was observed, but this irritation was fully reversed within 14 days after exposure. Upon instillation of the test material a moderate discomfort was observed in the first animal. To minimize discomfort, the eyes of the remaining animals were anaesthetized. Another in vivo study on rabbits for the trans-isomer with a purity of 96.7% (anonymous 18, 1988) shows signs of irritation within the first 24hours, but complete resolution was				

observed 14 days after the initial exposure. The initial administration of the test material caused a severe pain response.

Considering the tiered approach proposed in the guidance on the application of the CLP criteria (v5-2017), classification as category 1 seems more appropriate. This conclusion is based on inconclusive in vivo animal data regarding serious eye damage/ eye irritation (1 positive and 1 negative for classification as an irritative), combined with positive ex vivo eye data for serious eye damage.

Date	Country	Organisation	Type of Organisation	Comment number
03.07.2024	Germany	Kanesho Soil Treatment SRL/BV	Company-Manufacturer	19
Comment received				
Reference is made to Chapter 10.5.3 referring to serious eye damage/eye irritation. The commenting party agrees to the proposed classification. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 12. Public Attachment.docx				

Date	Country	Organisation	Type of Organisation	Comment number
02.07.2024	Germany		MemberState	20
Comment received				
The DE CA supports the dossier submitter's proposal of retaining the existing classification as "irritating to eyes", category 2, H319. This is in agreement with the latest EFSA conclusion on 1,3-dichloropropene [EFSA Journal 2018;16(11):5464].				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2024	Spain		MemberState	21
Comment received				
The Spanish MSCA agrees with the Dossier Submitter proposal.				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2024	France		MemberState	22
Comment received				
FR agrees with the classification of 1,3-D (mix of isomers), (Z)-1,3-D (cis isomer) and (E)--1,3-D (trans isomer) as Eye Irritation Category 2, H319, Causes serious eye irritation.				

HEALTH HAZARDS – Skin sensitisation

Date	Country	Organisation	Type of Organisation	Comment number
02.07.2024	Belgium		MemberState	23
Comment received				
BE CA agrees with DS.				

Date	Country	Organisation	Type of Organisation	Comment number
03.07.2024	Germany	Kanesho Soil	Company-Manufacturer	24

		Treatment SRL/BV		
Comment received				
Reference is made to Chapter 10.7.3 referring to Skin sensitization. The commenting party agrees to the proposed classification. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 12. Public Attachment.docx				

Date	Country	Organisation	Type of Organisation	Comment number
02.07.2024	Germany		MemberState	25
Comment received				
Based on the results of the Buehler test and two guinea pig maximisation tests according to Magnusson and Kligman, classification as Skin Sens. 1A is supported. This classification was also proposed in the latest EFSA conclusion on 1,3-dichloropropene [EFSA Journal 2018;16(11):5464].				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2024	Spain		MemberState	26
Comment received				
The Spanish MSCA agrees with the Dossier Submitter in the whole assessment of skin sensitisation and ES supports the classification proposal for Skin Sens. 1A (H317).				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2024	France		MemberState	27
Comment received				
FR agrees with the classification of 1,3-D (mix of isomers), (Z)-1,3-D (cis isomer) and (E)--1,3-D (trans isomer) as classification in Skin Sensitisation Category 1A (H317) "May cause an allergic reaction.				

HEALTH HAZARDS – Germ cell mutagenicity

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2024	France		MemberState	28
Comment received				
FR agrees with the absence of classification of 1,3-D (mix of isomers), (Z)-1,3-D (cis isomer) and (E)--1,3-D (trans isomer) as mutagenic, based on negative in vivo mutations studies.				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2024	Greece	Benaki Phytopathological Institute (BPI)	National Authority	29
Comment received				
Background information on 1,3-D (EFSA's Journal 2018;16(11):5464): Regarding genotoxicity only three studies were considered acceptable (Ames test - positive, in vitro mammalian chromosome aberration test - positive and in vivo mammalian chromosome aberration test – negative). The other studies had limited acceptability or were				

unacceptable due to methodological deficiencies or use of batches of unknown purity or not compliant with the new technical specification.
Considering these indications of a genotoxic potential in vitro and pending a complete data set of genotoxicity studies performed with batches well characterised and representative of the current production of (EZ)-1,3-dichloropropene (data gap), the classification Mutagen Cat 2 is proposed.

Current CLH report of 1,3-D
In the current CLH: No classification is warranted for Genotoxicity.
EL-BPI proposes the following points for consideration:

I. On the reliability of the following In vitro genotoxicity tests:
General comment: Regarding the low solubility of the tested substance, the solvent should be mentioned in all studies. Purity of the a.s., positive controls chosen, cytotoxicity levels should be also mentioned in the summarized Table 30.
(a) In vitro chromosome aberration assay (Anonymous 38; 1988; Table 30, n. 13): It remains unclear why this study was considered as "supplementary" and not "accepted". In this study, 1,3-dichloropropene induced dose dependent and statistically significant increase in structural chromosome aberrations (with or without S9) and numerical chromosome aberrations (without S9). 5 doses were selected based on preliminary cytotoxicity test (17.34-277.5 µg/ml) with DMSO as solvent with the highest dose only to exceed the max limit of cytotoxicity based on the guideline. The purity is known, but batch analysis not available. pH and osmolarity changes are not mentioned and the number of cells is insufficient based on the guideline. Although a limited number of metaphases was scored, considering that positive results are obtained in all the doses tested (and not only at the highest cytotoxic dose) the study should be considered acceptable and positive.
(b) SCEs test in human lymphocytes in vitro (Kevekordes et al. 1996, Table 30, n. 14): Considering the positive outcomes the study could be considered as acceptable with limitations. The limitations observed do not affect significantly the reliability of the results.
(c) in vitro mammalian chromosome aberration in CHO cells (Anonymous 45, 1991; Table 30, n.17): From the available data in the CLH, it remains unclear why this study was considered as "supplementary" and not "accepted". This study gave positive results with metabolic activation and no deviations were noted. The underlying mechanism of chromosomal damage may involve (but not limited to) production of ROS as indicated by the reduction in number of chromosome aberrations in the presence of glutathione.
(d) in vitro chromosome studies (Anonymous 46, 1989; Table 30, n.18): It remains unclear why this study was considered as "supplementary" and not "accepted". This study gave positive results with metabolic activation and no deviations were noted.

EL-BPI conclusion: Considering the above, 1,3-D is considered an in vitro clastogen. Appropriate in vivo follow up is needed to investigate in vivo clastogenic potential.

II. Commenting on the role of Glutathione (GSH) and the underlying genotoxicity mechanism:
The comment by the applicant that "Scattered positives in in vitro (Ames and chromosome damage assays) were completely mitigated by addition of antioxidants (glutathione). The in vitro effects were driven entirely by reactive oxygen species (ROS).", should be interpreted carefully. Indeed, there is evidence – mainly from studies considered as supplementary- that the presence of glutathione (GSH) can decrease the incidence of in vitro mutations (i.e. Ames test; Table 30, study n. 2, n.3, n.7, n. 9, n.11) and in vitro chromosomal damage (Table 30, study n. 17). However, the outcomes do not support the notion that the addition of GSH can eliminate chromosome damage or that the damage did not occur. In fact, ROS production is considered as a well-known and widely accepted mechanism of genotoxicity, as well as an initiating event of tumorigenesis and other conditions including

neurodegenerative diseases, inflammation, and age-related defects. Therefore, the information obtained from in vitro studies that the levels of GSH affect the genotoxic outcome, is an indication of the underlying genotoxic mechanism.

The observed underlying mechanism of in vitro genotoxicity mainly mediated through the production of ROS urges the need for a careful design of in vivo studies. Considering that the levels of GSH could affect the level of expressed DNA and chromosomal damage and that the levels of GSH varies within the tissues, tissue specificity is expected. Open literature data support that GSH levels vary significantly between different tissues from 1 to 10 mM (particularly concentrated in the liver) and it is present at high levels in the brain, with a total GSH content of 0.5–3.4 μmol/g (with the highest concentration of GSH found in the glial cells of the cortex) [2], kidney [3], and lungs (GSH in epithelial cells 100-300 μM, up to 1mM under conditions of stress) [4], while low GSH levels are observed in the bone marrow (that varies from 1.94 to 3.27 nmol/mg) [5].
Considering that GSH levels affect the observed genotoxic damage induced by the tested active substance, testing of tissues with high levels of glutathione is expected to limit the sensitivity of the test, and underestimate its genotoxic risk. Therefore, in transgenic rodent assay, tissues with naturally lower glutathione levels should be chosen, such as brain or muscle. In the newly submitted transgenic rodent assay, the tissues tested are liver, lungs, and kidney, which are considered among the most abundant glutathione tissues, limiting thus the sensitivity of the test.

Furthermore, while GSH plays a significant role in protecting against DNA damage caused by ROS, its presence doesn't guarantee complete protection from the DNA damaging effects of all chemicals. Specifically, GSH is only one of the cells antioxidant's system including catalase, superoxide dismutase and the enzymes of the DNA repair machinery. Besides the cell's antioxidants and DNA repair enzymes the cell cycle regulation and kinetics (e.g. chromatin condensation-decondensation, cell cycle checkpoints) play a major role in the conversion of DNA damage into chromosomal abnormalities that determines the intrinsic cell sensitivity to DNA damage, leading to uncontrolled proliferation, a hallmark of cancer. The significance of cell cycle kinetics justifies why slower dividing cells with long life span (e.g. some types of brain cells) show increased susceptibility to genotoxic agents (including ionizing radiation), since they have more time to repair errors before dividing. Also, in mitotically quiescent cells that remain in G0-phase cells (i.e., they do not divide to create new cells), any potential damage does not pass to the next generation of cells. In addition, slow-growing tissues generally have lower metabolic rate, produce fewer ROS and less susceptible to oxidative stress. On the other hand, rapidly dividing cells (e.g. bone marrow or gut lining cells) have a high metabolic rate, produce more ROS and are more susceptible to oxidative stress, and more susceptible to accumulating DNA damage.
Considering cell cycle kinetics, rapidly developing tissues (e.g., bone marrow, glandular stomach or duodenum) would be more suitable in genotoxicity testing, including the transgenic rodent assay. In the two new transgenic rodent assays submitted, liver, kidney (oral administration test), and lung (inhalation test) are used. Liver and kidney are considered slow developing tissues, with kidney cells being mitotically quiescent in the G0, while lung cells have both slow and fast turnover rate cells and no details are given in the study summary.

EL-BPI conclusion: Based on the above, the suitability of the tested tissues in the transgenic rodent assay is questionable since (a) no rapidly dividing tissues such as bone marrow, glandular stomach or duodenum were tested, and (b) only tissues with high levels of GSH are tested limiting the sensitivity of the assays.

III. Limitations and issues for consideration in in vivo genotoxicity tests in somatic cells (Table 31):

(a) General comments: Regarding the low solubility of the tested substance, the solvent should be mentioned in all studies. Also, the purity of the a.s., route of administration, positive controls chosen, tissue selected should be provided in the summarized Table (Table 31).
Although the testing strategy followed is in line with regulatory approaches, e.g. the EFSA opinion on genotoxicity testing strategies (EFSA Journal 2011;9(9):2379), to our opinion an in vivo Comet Assay would facilitate the elucidation of 1,3-D genotoxic profile.

(b) Limitations in in vivo Gene Mutation Assays:

Study 1 (Anonymous 24, 2018): Gene Mutation Assay at the cII Locus in Male Big Blue Transgenic F344 Rats (oral exposure; liver and kidney tested):
1. The purity of the tested substance is very low (33%; a mixture of the cis and trans Isomers) due to microencapsulation of 1.3-D in 80% starch and 20% sucrose. Doses administered should be corrected for 1,3-D content.
2. Stability of the tested chemical is not mentioned.
3. Solvent/vehicle used are not mentioned.
4. No signs of toxicity were observed in the treated animals. No preliminary toxicity is mentioned and no justification is provided for the selection of doses (max dose tested: 50 mg/kg bw/day). No dose ranging finding study is provided.
5. The suitability of the tested tissues in the transgenic rodent assay is questionable since (a) no rapidly dividing tissues such as bone marrow, glandular stomach or duodenum were tested, and (b) only tissues with high levels of GSH are tested limiting the sensitivity of the assays. Therefore, in transgenic rodent assay, tissues with naturally lower GSH levels should be chosen, such as brain or muscle (see comment II, above).
6. Sampling time is very critical: The administration was for 28 consecutive days. However, termination occurred on day 31; while in the guideline a period of 28 days after final treatment is suggested, especially for the slowly proliferating tissues used in the test.
7. One positive control is used in the test while a minimum of two positive controls is recommended by the OECD TG 488 (2022) guideline.
8. The negative control should be specified.
9. Historical control data should be presented.
10. No information is given on the transfection process, plating method, number of colony forming units per tissues, the determination of mutants, scoring etc.

Study 2 (Anonymous 25, 1997): Gene mutation assay at the lacI target gene of transgenic Big Blue B6C3F1 male mice (inhalation; lung and liver tested):
1. The exposure to test substance was only 2 weeks (6 h/day, 5 days/week) instead of the daily treatment for a period of 28-days administration recommended in the current OECD Guideline 488 (July 2013 and June 2022), to produce a sufficient accumulation of mutation and detect mutation in slowly proliferating organs. Considering that the tested tissues are kidney and liver (no rapidly developing tissues), this limitation affects the reliability of the study.
2. The metabolism of the tested substance in rodents and humans is extremely rapid. The principal route of excretion of radioactivity was the urine (83.1%), almost all of which 80.7% of the administered dose occurred in the first 24 hours. Available rat ADME data confirm extensive tissue distribution occurs following oral exposure to 1,3-D, thus it is considered that the target tissue has been adequately exposed to 1,3-D and/or its metabolites. However, no clear data on administration in the target organs exists after inhalation.
3. The selection of tissues is questionable since rapidly dividing tissues with low abundance of GSH should be selected (see comment b5, and cII, above)
4. No historical control data are presented.

EL-BPI conclusion: Due to the deficiencies observed in both in vivo gene mutation assays, the in vivo mutagenicity is not considered sufficiently investigated.

(c) Limitations in in vivo chromosome aberration assays and MN assays:

Study 8 In MN test in polychromatic erythrocytes of trans-D mice (inhalation, 135-535 ppm) (Anonymous 47, 1999).
1. The exposure to positive controls (mitomycin-C) was via intraperitoneal exposure, whereas test animals were exposed by inhalation.
2. According to the relevant OECD TG 474 two positive controls are required, here only mitomycin-C used.
3. Details on particle size (MMAD) of test material should be clearly presented in the CLH dossier to allow assessment of adequate animal exposure.
4. Historical control data not presented.

References
1. Zitka O., Skalickova S., Gumulec J., Masarik M., Adam V., Hubalek J., Trnkova L., Kruseova J., Eckschlager T., Kizek R. Redox status expressed as GSH:GSSG ratio as a marker for oxidative stress in paediatric tumour patients. Oncol. Lett. 2012;4:1247–1253. doi: 10.3892/ol.2012.931.
2. Guo N., McIntosh C., Shaw C. Glutathione: New candidate neuropeptide in the central nervous system. Neuroscience. 1992;51:835–842. doi: 10.1016/0306-4522(92)90524-6.
3. Eunyong Ahn , Jueun Lee1 , Jisu Han , Seung-Min Lee , Ki-Sun Kwon , Geum-Sook Hwang. Glutathione is an aging-related metabolic signature in the mouse kidney. Research Paper Volume 13, Issue 17 pp 21009—21028.
4. Neal S. Gould and Brian J Day (2011) "Targeting maladaptive glutathione responses in lung disease" Biochem Pharmacol. Jan 15; 81(2): 187–193. doi: 10.1016/j.bcp.2010.10.001; PMCID: PMC3039114.
5. Smaaland R, Svardal A M, Lote K, Ueland M, Laerum O D (1991) Glutathione content in human bone marrow and circadian stage relation to DNA synthesis. J Natl Cancer Inst. 1991 Aug 7;83(15):1092-8. doi: 10.1093/jnci/83.15.1092.

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2024	United States of America	Dow Europe GmbH	Company-Manufacturer	30

Comment received

1,3-D has been evaluated in many in vitro and in vivo studies. While several were initiated pre-OECD guidelines or tested to older versions, the studies are well conducted and have concurrent positive and negative controls. Many older studies do not use historical control data (HCD) or score the current recommended number of cells. A weight of evidence (WOE) approach was therefore utilized to assess data holistically.
In Vitro: The in vitro studies include: eight Ames assays, a single mammalian gene mutation assay at the HPRT locus, three in vitro chromosome aberration assays and an unscheduled DNA synthesis (UDS) assay (ex vivo). 1,3-D was Ames positive in majority of studies, exclusively TA100 and TA1535 - these strains detect base pair substitution mutations (amongst others), typical of damage induced by reactive oxygen species (ROS). Effects in the in vitro studies were mitigated by addition of exogenous glutathione (GSH) further defining a role for ROS in the mutagenicity of 1,3-D. The single HPRT study (CHO cells) was negative and only showed evidence of increases in mutations at unacceptably high levels of toxicity. 1,3-D was positive for chromosome damage in rodent cell lines in the

presence and absence of S-9 although not always in the same study. Addition of exogenous GSH also reduced chromosome damage effects to background levels. An ex vivo UDS test in rat hepatocytes was negative. In summary, 1,3-D treatment resulted in positive responses in bacterial mutation assays and in vitro chromosome damage assays but not in a mammalian cell mutation assay or UDS. Effects are mitigated using glutathione and therefore the observed positive responses are via an indirect mechanism which is not biologically relevant in vivo. An in vitro DNA binding study (GLP compliant, but no OECD guideline is available) was negative concluding that 1,3-D does not bind to naked calf thymus DNA in the presence and absence of metabolic activation and, as such, the in vitro positives are not generated by direct interaction of 1,3-D with DNA (Anonymous 40).
In Vivo: The in vivo studies include: an unscheduled DNA synthesis assay, two transgenic gene mutation assays in rodents (TGR), two alkaline elution (AE) assays and five chromosome damage assays (micronucleus (MN) tests). Of the five chromosome damage assays, only two show increases in MN, the single dose study of 1993 in mice (Shelby et al), was inconsistent, negative at 24 hours but positive 48 via i.p. dosing. The 1996 publication (Kevekordes et al) showed positive effects in female animals only. A recent, higher quality (GLP and OECD 474 compliant) MN study in mice (Anonymous 145) (p.o. dosed) was negative at all doses in both male and female mice testing at similar doses to the other studies. The in vivo UDS study was negative. The UDS is no longer in routine use because it only detects a single type of DNA damage, that which is repaired by base excision repair (BER). If there were large amounts of ROS being induced and causing DNA damage, this should be repaired via BER and the UDS could in principle be expected to pick this up. Positive effects were noted in tissues from alkaline elution assays (gastric mucosa, liver, kidney); however, alkaline elution is an indicator test and does not evaluate single cells, apoptotic and necrotic cells can easily skew data. In follow up TGR assays (GLP and OECD 488 compliant), dosed via p.o.. and inhalation, there is no evidence of any mutational effects.
Published ADME data show that there is plasma exposure to 1,3-D after oral dosing thereby confirming exposure to the target tissues of the in vivo assays described.
In summary, 1,3-D is positive in mutation and chromosome damaging assays in vitro but these effects (MN/Cab's and Ames) are mediated by GSH. Addition of epichlorohydrin in older studies as a stabiliser (pre-1983) may have been the reason for positive responses in older Ames tests. All in vitro data point towards ROS as a driver for observed effects as GSH addition reduces mutations and chromosome damage to background levels. GSH depletion is also observed in vivo. 1,3-D is negative for clastogenicity in vivo with high quality studies (most recently 2023). 1,3-D induced DNA strand breakage/fragmentation in AE assays however when TGR assays were performed there were no mutational increases in the liver, kidney or lung of treated animals. 1,3-D exposure neither induces clastogenicity nor mutation in vivo in well conducted OECD guideline compliant studies. The in vitro positives are explained by a mechanism involving glutathione which has high constitutive levels in vivo. These data do not support classification of 1,3-D for mutagenicity.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 1,3-D.zip

Date	Country	Organisation	Type of Organisation	Comment number
03.07.2024	Germany	Kanesho Soil Treatment SRL/BV	Company-Manufacturer	31
Comment received				
Reference is made to Chapter 10.8.3 referring to Mutagenicity. The commenting party agrees to the proposed classification.				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 12. Public Attachment.docx

Date	Country	Organisation	Type of Organisation	Comment number
02.07.2024	Germany		MemberState	32

Comment received

During the active substance approval at EU level, the classification as Muta. 2 was proposed. This proposal was based on a small number of acceptable genotoxicity tests (one positive Ames test, one positive in vitro mammalian chromosome aberration test and one negative in vivo mammalian chromosome aberration test in germinal cells). However, it was also concluded that a complete package of genotoxicity studies with well-characterised batches that are representative of the current technical material of 1,3-dichloropropene is needed. In the present CLH dossier, two new in vivo studies are identified that are considered as suitable follow-up studies for positive in vitro chromosome damage and mutagenicity studies, respectively:
- in vivo micronucleus assay of 1,3-dichloropropene by oral gavage in CD1-mice (2023)
- gene mutation assay at the cII locus in male Big Blue® transgenic F344 Rats (2018)

According to the brief description provided in the CLH dossier, the DS regards both tests as negative and acceptable. However, it should be noted that these new studies have not been evaluated at EU level.

Only the full study report on the TGR test is available to the DE CA. Contrary to the assessment provided in the CLH report, this study shows TG deviations. For example, the test substance was administered to male animals in the diet for 28 consecutive days with the highest dose being 50 mg/kg bw/d. However, according to the study report, there was no evidence of toxicity, only palatability issues leading to reduced food consumption associated with reduced body weight gain in a previous 13-week study. According to OECD TG 488 (2013), the highest dose should be set at the MTD to ensure sufficient sensitivity of the test. It appears that this criterion is not met in the TGR study and it remains unclear whether application by gavage was considered to address known palatability issues.

No increase in mutation frequency was observed in the liver and kidneys after treatment with 1,3-dichloropropene. A rapidly dividing tissue such as glandular stomach or duodenum was not included in the examination, although recommended by OECD TG 488.

Finally, the purity of 1,3-dichloropropene used in the TGR was low at 33.7 %.

The in vivo micronucleus assay in mice did not show an increase in micronucleated reticulocytes. However, it is questionable whether the test provides evidence of sufficient bone marrow exposure. According to the CLH dossier, a decreasing nonmonotonic trend in the percentage of reticulocytes in males and females is indicative of systemic availability. From a mechanistic point of view, it seems unlikely that the toxicity to reticulocytes is non-monotonic. Therefore, the DE CA proposes including further evidence of systemic toxicity [EFSA Journal 2017;15(12):5113].

Taking into account the following facts, that
I. positive in vitro tests are available,
II. the substance contains structural features associated with genotoxicity,
III. an epoxide can be formed as a minor metabolite,
IV. some positive in vivo studies are available (although of limited reliability),

V. 1,3-dichloropropene is a skin sensitiser showing clearly a reactive potential and
VI. carcinogenic effects were observed,
full TG-compliant and therefore acceptable follow-up studies would be required to finalise the classification on genotoxicity/mutagenicity before non-classification can be ruled out.

Date	Country	Organisation	Type of Organisation	Comment number
02.07.2024	Belgium		MemberState	33

Comment received

Positive results were observed in in vitro bacterial gene mutation assays with, and without, metabolic activation. There is a difference in mutagenic potential between the cis- and trans-isomers. Subsequent investigations included in vivo gene mutation testing on male Big Blue F344-rats (28d, 0-12.5-25-50mg/kg bw, gavage, cII gene, liver and kidney tissue) and male Big Blue B6C3F1 mice (14d, 0-10-60-150ppm, inhalation, lacI gene , liver and lung tissues), which were previously reported in DAR (October 2003_v.3). Both in vivo tests were negative. However, BE CA has some remarks.

In a previous short-term toxicity study, evaluated in DAR (October 2003_v.3) (Haut et al, 1992) dose levels were fixed at 0-10-25-50-100mg/kg bw (F344-rats) without causing excessive systemic toxicity. The test doses used in the transgenic Big Blue rodent models were not as high.

Histopathological findings from carcinogenicity studies highlighted observations in the forestomach, liver, nasal and olfactory epithelium, urinary bladder, and lungs. In B6C3F1 mice bronchioalveolar adenomas were observed after exposure to 60ppm by inhalation for 2 years. In F344 rats hepatocellular adenomas were observed after administration of 25mg/kg bw/d in the diet for 2 years.

The mice received 10 days of exposure over a 2-week period, instead of the recommended 28days.

In repeated inhalational toxicity studies, alterations in the upper respiratory tract, nasal tissue, and histopathological findings in liver, kidney and urinary bladder were observed. As the stomach was mentioned as a target organ out of repeated oral toxicity studies and the site of first contact in F344-rats study was the stomach, another choice of tissues would be more convincing to the BE CA. Additionally, the stomach is a rapidly dividing tissue.

Chromosomal effects were investigated in six in vivo micronucleus studies. In vivo chromosome aberration tests are not mentioned in this dossier.

One key micronucleus study, performed in mice (bone marrow) (unknown strain) (anonymous 47, 1999), concluded negative for trans 1,3-dichloropropene after a 4-hour inhalational exposure.

Another key study performed in mice (peripheral blood) (unknown strain) (anonymous 145, 2023) was not fully reported by the DS but stated as fully compliant with OECD TG 474. The performed range-finding study determined a MTC of 250mg/kg bw/day. However, in the definitive study, doses up to 325mg/kg bw/day (in males) and 350mg/kg bw/day (in females) were used. Two males and one female did not survive until sampling time. Regarding the MTC obtained in the range-finding study, the highest dose level in the definitive phase seems to be too high. However, DS reports in the summary of in vivo somatic cell data (page 80): "In the range finder 500 mg/kg/day resulted in lethality and as such the MTD was determined as 325 mg/kg in males and 350 mg/kg in female mice…

There were no adverse clinical signs in the main study;…" This is not in line with the description made on page 77: under "range-finding phase" and "definitive phase" as mentioned above. Can DS clarify this issue? The remaining dose-levels in males were 81.25 and 162.5 mg/kg bw/day, and in females 87.5-175 mg/kg bw/day. No significant increase in RET% was observed upon mid dose levels.

The four other in vivo micronucleus studies are not conclusive due to unacceptable deviations in the study protocol, or lack of confirmation that exposure of the bone marrow occurred.

1,3-dichloropropene have been studied in both in vitro and in vivo assays. Mixed results in mammalian in vitro and in vivo genotoxicity studies were noted. The short-term studies suggests that 1,3-dichloropropene can be mutagenic, but the relevance is uncertain.

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2024	Spain		MemberState	34
Comment received				
The Spanish MSCA agrees with the Dossier Submitter in the whole assessment of genotoxicity and supports the no classification for this hazard class. It is noted that the purity of the active substance in the TGR oral study (Anonymous 24; 2018) is stated as 33.7%. For clarification, please state the purity of the technical 1,3-dichloropropene used prior to the formulation with starch and sugar and also clarify whether the dose has been corrected taking this percentage into account. The in vivo micronucleus study (Shelby et al, 1993) gave an equivocal result using the intraperitoneal route. The study is deemed as supplementary and ES agrees this route of administration is not recommended by guidance. The metabolism of the active substance via this route of administration may differ to the oral route, for which most data are available, i.e. primarily the formation of glutathione conjugates.				

HEALTH HAZARDS – Carcinogenicity

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2024	France		MemberState	35
Comment received				
FR agrees with the absence of classification of 1,3-D (mix of isomers), (Z)-1,3-D (cis isomer) and (E)--1,3-D (trans isomer) as carcinogenic based on limitations in the 3 key carcinogenic studies taken into account for weight of evidence. However, despite deviation from carcinogenic study protocol in NTP (1985) studies in rats and mice (treatment 3 times/week), benign tumours in several organs were reported (liver and stomach for rats, bladder and lung for mice). Stomach tumours in the rat study are considered to be induced by the presence of epichlorohydrin (1%) in the mixture. Please, clarify (if data are available) the potential carcinogenic effects of epichlorohydrin on liver and bladder. This is of particular concern because tumours in these tissues are found in other studies (Anonymous 54 (1995) in rats: liver; Anonymous 52, 1997 in mice: bladder). Moreover, potential involvement of epichlorohydrin in the apparition of tumours in the mice study is not discussed. Of note, the chronic irritation, cytotoxicity, hyperplasia, hypertrophy (and increased relative organs weight as a result) found in several cancerogenicity studies in rats and mice could be the signs of a cancerogenic process. Please note that table p.95 on organ weights is not discussed despite significant results. FR wonders if different composition between Telone II and DD-92 could influence 1,3-D				

effects in carcinogenicity studies.

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2024	Greece	Benaki Phytopathological Institute (BPI)	National Authority	36

Comment received

Background information on 1,3-D (EFSA's Journal 2018;16(11):5464):
Taking into account the long-term studies with rats and mice, where a statistically increased incidence in tumors was observed in both species (not within historical control data) together with preneoplastic lesions and a structural similarity to known carcinogens, (EZ)-1,3-dichloropropene is proposed to be classified as Carc. Cat. 2.

Current CLH report of 1,3-D
In the current CLH: No classification is warranted for Carcinogenicity.

EL-BPI considers that the concerns raised in previous EFSA assessment (i.e. increased tumour incidences above historical control range, preneoplastic lesions and a structural similarity to known carcinogens, (EZ)-1,3-dichloropropene) should be further elaborated in the CLH dossier in the context of Carc. 2 classification or not.

It is noted that gender differences in oxidative stress in relation to cancer susceptibility and survival are reported by the pubic literature [1], with females exhibiting a more proficient antioxidant defense, lower accumulation of ROS-induced damage over time, and longer lifespan and males showing a more pronounced susceptibility to ROS. The dossier submitter is kindly requested to further elaborate on sex differences observed noting also that a postulated genotoxic mode of action for 1,3-D involves ROS production.

Please also note that the isomeric content of the test material "Telone soil fumigant" is not included in the CLH dossier and it is not clear if it is the same as "Telone II". Please clarify the identity of "Telone soil fumigant".

EL-BPI proposes to consider the above points on potential classification and labelling of 1,3-D for carcinogenesis or not.
References
1. Allegra, A.; Caserta, S.; Genovese, S.; Pioggia, G.; Gangemi, S. Gender Differences in Oxidative Stress in Relation to Cancer Susceptibility and Survival. Antioxidants 2023, 12, 1255. https://doi.org/10.3390/antiox12061255.

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2024	United States of America	Dow Europe GmbH	Company-Manufacturer	37

Comment received

Oral: The results from four well-designed oral rodent cancer bioassays utilizing test material representative of current manufactured product indicates that prolonged treatment with 1,3-D causes increased incidence of benign hepatocellular adenomas in high-dose male Fischer 344 rats only, at levels which caused significant reduction in body weight and gain and exceeded the maximum tolerated dose (MTD). (Anonymous 54) There was no increase in hepatocellular adenomas in female Fischer 344 rats, male or female CD rats, or in either sex of B6C3F1 or CD-1 mice.

Inhalation: Prolonged inhalation exposure of male B6C3F1 mice to a high concentration (60 ppm) of 1,3-D is associated with an increased incidence of benign bronchioloalveolar lung adenomas, a commonly occurring spontaneous tumor type in this strain. (Anonymous 147) The increase in lung tumors is a portal-of-entry effect as lung toxicity was not observed in any of the four cancer bioassays via the oral route. There was no increase of bronchiololalveolar adenomas in female B6C3F1 mice or either sex of Fischer 344 rats.
A slight increase in benign urinary bladder tumours (submucosal mesenchymal) in female CD-1 mice lacked statistical significance and were considered to be a secondary response to chronic irritation. (Anonymous 52) There was no increase in male CD-1 mice, male or female B6C3F1 mice or Fischer 344 rats. No benign tumors of any kind from oral or inhalation studies progressed to malignancy.
In mice, 30 ppm should be considered as a kinetically derived maximum dose (KMD) for repeated exposures of 1,3-D. Concentrations above this KMD would not be considered relevant to human hazard assessment. Inhalation pharmacokinetics of 1,3-D in rats, showed that uptake of 1,3-D did not increase proportionately with increasing exposure concentration due to an exposure level-related decrease in the respiratory ventilatory frequency of rats exposed to 90 ppm or greater and the saturation of elimination of 1,3-D by rats exposed to 300 ppm or greater. A comprehensive weight-of-evidence (WOE) review of the four oral and two inhalation cancer bioassays that have been conducted on 1,3-D has been published (Yan et al., 2020) along with an independent panel review (Hays et al., 2021) of that WOE that considered updated toxicokinetic, genotoxicity, and carcinogenicity data. These papers are included as attachments to Dow comments.
Analysis of rat and mouse urine revealed no unchanged parent compound and two major 1,3-D metabolites, which are formed via glutathione conjugation are mercapturic acid of 1,3-D and its corresponding sulfoxide (or sulfone), indicating that conjugation with glutathione appears to play an important role in the metabolism of 1,3-D by rodents. In rats, at high oral dose levels of 50 mg/kg, metabolite profiles suggested that oxidation route from mercapturic acid to its sulfoxide was saturated.
Oral administration of 1,3-D (50 mg/kg bw) produced significant alterations in non-protein sulfhydryl content in the liver, kidney, forestomach and glandular stomach of male rats; GSH conjugation is an important pathway for depression of forestomach, glandular stomach, liver and kidney non-protein sulfhydryl content observed, suggesting that the ability of the rat to detoxify 1,3-D may be compromised at an oral dosage level of ≥50 mg/kg.
In summary, across four oral cancer bioassays in rodents, benign liver tumors (adenomas) were only increased in high-dose male F344 rats at a level which exceeded the maximum tolerated dose. The tumors did not progress to malignancy and slightly exceeded the historical control incidence for such tumors. Liver adenomas were not observed in female F344 rats, CD rats, or in B6C3F1 or CD-1 mice. Following long-term inhalation exposure, benign lung tumors (bronchioloalveolar adenomas) were increased in male B6C3F1 mice at a level which exceeded the kinetically-derived maximum dose. These tumors did not progress to malignancy and the increase was within the historical control incidence for such tumors. Finally, these tumors were not observed in female B6C3F1 mice or in either sex of Fischer 344 rats. A weight of evidence evaluation across all 6 cancer bioassays (involving multiple strains in both rats and mice) following exposure to 1,3-D does not support classification for carcinogenicity.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 1,3-D.zip

Date	Country	Organisation	Type of Organisation	Comment number
03.07.2024	Germany	Kanesho Soil	Company-Manufacturer	38

		Treatment SRL/BV		
Comment received				
References are made to Chapters 10.9, 10.9.2 referring to Carcinogenicity. The commenting party agrees to the proposed classification. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 12. Public Attachment.docx				

Date	Country	Organisation	Type of Organisation	Comment number
02.07.2024	Germany		MemberState	39
Comment received				
During evaluation of 1,3-dichloropropene as pesticidal active substance, the EFSA expert meeting concluded that classification as Carc. 2 would be justified. This proposal was based on a statistically increased incidence of tumours in mice and rats associated with the presence of preneoplastic lesions and was supported by structural similarity to known carcinogens. In contrast to this conclusion, the dossier submitter does not propose a classification for carcinogenicity. However, except for a toxicokinetic study after repeated inhalation exposure in mice, there are no relevant new data. The DS discusses excessive toxicity as the cause of tumour formation in liver (rats) and the exceedance of the kinetically derived maximum dose in the lung (mice). In rats, significant reductions in body weight and body weight gain were observed at the highest dose level. Consistent with the reduced body weight and body-weight gain, food consumption was reduced, presumably due to palatability issues as discussed in other studies. Therefore, the DE CA does not support the conclusion that the decreased body-weight and body weight gain were the result of excessive toxicity. In B6C3F1 mice, a statistically significant increased incidence of benign lung tumours (bronchioloalveolar adenomas) was observed at 60 ppm in males, with an incidence of 22/50 versus 9/50 in controls after repeated inhalation exposure. According to the CLH dossier, the kinetically derived maximum dose in mice would be 30 ppm, as suggested by the newly available toxicokinetic study, with saturation of clearance capacity above this concentration. Therefore, as stated in the dossier, concentrations above 30 ppm were not considered as relevant for human hazard assessment by the DS. However, the DE CA regards the systemic clearance/availability investigated in this study as of limited relevance to the local effect observed in the lung and therefore is of the opinion that it does not justify disregarding local tumours. In CD-1 mice, benign submucosal mesenchymal tumours were also observed in the urinary bladder following oral exposure at 25 mg/kg bw/d. The CLH report suggested that these tumours were probably a secondary response to chronic irritation. This conclusion is supported by the presence of preneoplastic lesions such as transitional cell hyperplasia, hyaline change of the lamina propria, and chronic active inflammation. However, even though the incidences of bladder tumours are low (3/65 at 25 mg/kg bw/d vs. 0/65 in controls), they should be taken into account in the classification decision for carcinogenicity. Human relevance cannot be excluded. In the opinion of the DE CA, a treatment-related tumour response could not be ruled out in rats and mice. Therefore, the classification of 1,3-dichloropropene as Carc. 2 should be considered.				

Date	Country	Organisation	Type of Organisation	Comment

				number
02.07.2024	Belgium		MemberState	40
Comment received				
Besides proliferative processes, we see in rats and mice, in both sexes, an increased incidence of benign tumours (at the level of the urinary bladder; only in mice, liver: only in rats, lung: only in mice) in the terminal life stage. Progression to malignancy was not detected. Based on these data, there is not sufficient evidence of carcinogenicity.				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2024	Spain		MemberState	41
Comment received				
The Spanish MSCA agrees with the DS proposal for carcinogenicity. We agree with the lack of relevance for carcinogenicity for the bronchioloalveolar adenomas in B6C3F1 mice (inhalation exposure) and the urinary bladder tumours in the same strain of mice (oral). With respect to liver tumours in rats, the incidence of benign liver tumours (hepatocellular adenomas) in the carcinogenicity study in Fischer 344 rats (Anonymous 54) was statistically significant at the highest tested dose level of 25 mg/kg bw/day in both sexes by a trend test but only pairwise significant in males. This incidence in males was slightly above HCD provided. However, there are no indications of the occurrence of preneoplastic lesions in the liver, no evidence of progression to malignancy and no reduction of latency. The tumours were seen at a dose level with clear toxicity and occurring at later stages of the study. Besides 1,3-D is not genotoxic and liver tumours were not seen in the other available oral carcinogenicity study in Sprague Dawley rats, in two oral carcinogenicity studies in mice and in other oncogenicity studies after inhalation exposure. In conclusion, the Spanish MSCA is of the opinion that these benign liver tumours are not sufficient evidence for the carcinogenicity of 1,3-D according to CLP criteria. However, for completeness, we recommend providing further details on HCD to confirm their validity. Besides the HCD range given in the report, it could be provided the number of studies performed in the same laboratory in the 5-year period around the study index, the tumour incidence in each study and other details concerning the conditions of the study such as the route of exposure, the study duration or the strain of rat. Besides, for the confirmation of the lack of reduced latency, it would be valuable to provide individual data for the time of death (terminal sacrifice or unscheduled deaths) of those animals with hepatocellular adenomas to confirm the occurrence at later stages of the study.				

HEALTH HAZARDS – Specific target organ toxicity - single exposure

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2024	United Kingdom	Health and Safety Executive	National Authority	42
Comment received				
The DS has proposed to retain the classification of STOT SE 3 (H335) for narcotic effects. We note that narcotic effects in animals coincide with similar doses to those which cause mortality. The substance is already classified for acute toxicity. Therefore, we request that the DS/RAC discuss whether this is a double classification for the same effect. Furthermore, the relevance of the human data to support this classification should be further scrutinised.				

Date	Country	Organisation	Type of Organisation	Comment number

03.07.2024	Germany	Kanesho Soil Treatment SRL/BV	Company-Manufacturer	43
Comment received				
References are made to Chapters 10.11.3, 10.12.2 referring to STOT SE and Stot RE. The commenting party agrees to the proposed classification. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 12. Public Attachment.docx				

Date	Country	Organisation	Type of Organisation	Comment number
02.07.2024	Germany		MemberState	44
Comment received				
The DE CA supports the dossier submitter's proposal to retain the existing classification for specific organ toxicity after single exposure in category 3. This classification was also proposed in the recent EFSA conclusion on 1,3-dichloropropene [EFSA Journal 2018;16(11):5464].				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2024	Spain		MemberState	45
Comment received				
The Spanish MSCA agrees with the Dossier Submitter proposal.				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2024	France		MemberState	46
Comment received				
FR agrees with the classification of 1,3-D (mix of isomers), (Z)-1,3-D (cis isomer) and (E)--1,3-D (trans isomer) for STOT SE in category 3 (STOT SE 3) with statement H335 "May cause respiratory irritation" and H336: 'May cause drowsiness or dizziness' is justified. It was based on evidence in inhalation rats studies (labored breathing, changes in the respiratory and olfactory epithelium: moderate hyperplasia and degeneration), respiratory irritation in animal studies and in epidemiological data, respiratory health effects with various symptoms in epidemiological data of workers and pulmonary clinical signs in acute oral/inhalation studies				

HEALTH HAZARDS – Specific target organ toxicity - repeated exposure

Date	Country	Organisation	Type of Organisation	Comment number
04.07.2024	United Kingdom	Health and Safety Executive	National Authority	47
Comment received				
A classification for STOT RE 2 has been proposed for the stomach, based on histopathological findings consistent with minor local irritation of the forestomach. As noted on Page 383 for the Guidance on the Application of the CLP Criteria, the forestomach is not present in humans, yet they do have a comparable squamous epithelial tissues in the oral cavity and the upper 2/3 of the oesophagus. It is uncertain whether findings of local irritation in the rodent forestomach should be used to support classification with STOT RE. Therefore, we request that the relevance of these findings in an equivalent human tissue is discussed. Furthermore, the severity of the hyperplasia/hyperkeratosis should be further considered against the CLP criteria, which requires a significant/severe effect for				

classification purposes.

Date	Country	Organisation	Type of Organisation	Comment number
03.07.2024	Germany	Kanesho Soil Treatment SRL/BV	Company-Manufacturer	48
Comment received				
References are made to Chapters 10.11.3, 10.12.2 referring to STOT SE and Stot RE. The commenting party agrees to the proposed classification. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 12. Public Attachment.docx				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2024	Spain		MemberState	49
Comment received				
The Spanish MSCA agrees with the Dossier Submitter proposal.				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2024	France		MemberState	50
Comment received				
FR agrees with the classification of 1,3-D (mix of isomers), (Z)-1,3-D (cis isomer) and (E)--1,3-D (trans isomer) for oral STOT RE category 2 – H373: 'May cause damage to organs through prolonged or repeated exposure with the stomach as the target organ. It was based on repeated oral studies in rats (mice studies excluded) that showed stomach hyperkeratosis and hyperplasia in both sexes. FR agrees that classification for inhalation STOT RE is not considered to be applicable. The two nose-only inhalation studies (exclusion of inhalation studies of whole-body exposure) did not show a significant increase in hazard or dose-sensitivity compared to acute exposure. Systemic effects are limited to a single species (mouse) and these studies are limited because they used whole-body exposure.				

ENVIRONMENTAL HAZARDS – Hazardous to the aquatic environment

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2024	United Kingdom	Health and Safety Executive	National Authority	51
Comment received				
We agree with the aquatic chronic hazard classification for 1,3-dichloropropene proposed by the DS based on the Pimephales promelas 33d EC10 of 0.02 mg/L and NOEC of 0.015 mg/L. As the DS refers to both the EC10 and NOEC for the chronic aquatic hazard classification in sections 11.7.2 and 11.8 of the CLH report, please can the DS clarify if either of these is the key endpoint for hazard classification, or if they are both considered relevant to determine the hazard classification band. We note that they both support the same classification of Aquatic Chronic 1 with an M-factor of 1. We also note that the surrogate approach is relevant for chronic classification given there are no long-term data for the most acutely sensitive fish and invertebrates species. This also results in Aquatic Chronic 1 with an M-factor of 1 and supports the DS proposal.				

Date	Country	Organisation	Type of Organisation	Comment number
03.07.2024	Germany	Kanesho Soil Treatment SRL/BV	Company-Manufacturer	52
Comment received				
Reference are made to Chapters 11.1, 11.1.3, 11.1.4.3 (all referring to environmental fate), 11.4.1 (bioaccumulation potential), 11.5, Table 92 and 11.7.1 (all referring to aquatic hazards). The commenting party agrees to the proposed classification. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 12. Public Attachment.docx				

Date	Country	Organisation	Type of Organisation	Comment number
02.07.2024	Belgium		MemberState	53
Comment received				
BE CA supports the proposal of the dossier submitter. Degradation : The substance 1,3-dichlorpropene is not readily biodegradable (4.9% degradation within 28 days). Although 1,3-dichlorpropene hydrolyses quickly (half life <16 days) it should be noted that its hydrolysis product Chloroallyl Alcohol is hydrolytically stable. Furthermore, the degradation products Chloroallyl Alcohol and 3-chloroacrylic acid fulfil the criteria as hazardous to the aquatic environment and therefore 1,3-dichlorpropene is to be considered not rapidly degradable. Based on the results of the aquatic toxicity test on the most sensitive species (fish (Cyprinodon variegatus) with 96hEC50 = 0.290 mg/L and fish (Pimephales promelas) with 33d EC10 = 0.020 mg/L), the fact that the substance is not rapidly degradable, it is justified to classify 1,3-dichloropropen as Aquatic Acute 1, H400 and Aquatic Chronic 1, H410. Based on the available log Kow's <4, the substance shows no potential to bioaccumulate. In view of the proposed classification and toxicity band for acute toxicity between 0.1 mg/L and 1mg/L, the proposed M-factor for acute toxicity of 1 is supported. Also the proposed M-factor for chronic toxicity of 1, based on not rapidly degradable substance and NOEC between 0.01 and 0.1 mg/L, is supported.				

Date	Country	Organisation	Type of Organisation	Comment number
05.07.2024	France		MemberState	54
Comment received				
1. In section 11.1.1, FR agrees with the non-ready biodegradability of 1,3-dichloropropene based on an OECD 301D that showed the substance did not easily degrade in water. 2. FR agrees with the conclusion on the rapid hydrolysis of the cis and trans isomers that was not pH-dependent (two OECD TG 111 studies). FR agrees with the stability of the degradation product 3-chloroallyl alcohol (cis/trans 3-chloro-1-hydroxypropene) in water. 3. Additional simulation studies (degradation in water, water/sediment, and soil) were presented in the CLH dossier (Section 11.1.4.3). The results indicated rapid dissipation of 3-chloro-1-hydroxypropene (Dt<16 days), with degradation products identified as 3-chloroallyl alcohol and 3-chloroacrylic acid. These degradation products also dissipated				

rapidly, with a Dt50 of 0.2 days for 3-chloroallyl alcohol and 6.0 to 19.9 days for 3-chloroacrylic acid.
Based on the various elements presented in section 11.1, and according to the CLP guidance decision scheme (part II.4), 1,3-dichloropropene (with its isomers) could be considered as a rapidly degradable substance. In the CLH document, DS reported that "The full mineralisation condition is not achieved in the aforementioned environmental fate studies therefore, 1,3-dichloropropene should be assessed as not rapidly degradable". According to table 83 (section 11.1 of the CLH document), the study conducted in water/sediment system (Anonymous 80, 1999) showed that 42.5% of 1,3-dichloropropene dissipated as CO2. FR agrees with this argument (i.e. the incomplete mineralisation of the substance) when considering the results of this study (Anonymous 80, 1999). However, FR wonders if the production of CO2 in the soil simulation study (Anonymous 81, 2002), was also evaluated to confirm the incomplete mineralisation of the substance, which supports the non-rapid degradation of the substance. This information is important because it could influence the conclusion on the chronic toxicity of the substance (see comment 6).
4. Regarding bioaccumulation (Section 11.4), the results demonstrated, through a Log KOW <4, a low potential for bioaccumulation in aquatic organisms. FR agrees that bioconcentration and subsequent bioaccumulation through the food chain are not expected. However, for bioaccumulation assessment (section 11.4.1), DS presented results from various regulatory studies reported in Table 84 as estimated data. FR suggests to transfer information from this section to section 11.4.2 (Measured partition coefficient and bioaccumulation test data), as bioaccumulation estimates should be based on valid QSAR data rather than measured data).
5. FR agrees with the classification of 1,3-dichloropropene as Acute Toxic 1 with an M-factor of 1 based on the lowest LC50 reported (0.29 mg/L) with (E)-1,3-dichloropropene (Trans isomer) from the acute sheepshead minnow study (LC50= 0.29 mg/L).
6. FR agrees with the classification of 1,3-dichloropropene as Aquatic Chronic 1 with a multiplication factor of 1 based on NOEC of 0.015 mg/L in Pimephales promelas study (Anonymous 90, 2015). However, as mentioned in comment 3, FR suggests to verify the incomplete mineralization of the in the soil simulation study to ensure the non-rapid degradation of 1,3-dichloropropene. This information could change the substance's chronic toxicity category, depending on whether it is considered as rapidly or non-rapidly degradable.

ADDITIONAL HAZARDS – Hazardous for the ozone layer

Date	Country	Organisation	Type of Organisation	Comment number
03.07.2024	Germany	Kanesho Soil Treatment SRL/BV	Company-Manufacturer	55

Comment received

The commenting party agrees to the proposed classification.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 12. Public Attachment.docx

PUBLIC ATTACHMENTS
1. 12. Public Attachment.docx [Please refer to comment No. 2, 5, 9, 14, 19, 24, 31, 38, 43, 48, 52, 55]

CONFIDENTIAL ATTACHMENTS
2. 1,3-D.zip [Please refer to comment No. 1, 30, 37]
3. Gender Differences in Oxidative Stress in Relation to Cancer