Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

captan (ISO); 1,2,3,6-tetrahydro-*N*-(trichloromethylthio)phthalimide

EC Number: 205-087-0
CAS Number: 133-06-2

CLH-O-0000007361-79-01/F

Adopted

14 September 2023

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ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON CAPTAN (ISO); 1,2,3,6-TETRAHYDRO-N-(TRICHLOROMETHYLTHIO)PHTHALIMIDE

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: captan (ISO); 1,2,3,6-tetrahydro-N-(trichloromethylthio)phthalimide
EC number: 205-087-0
CAS number: 133-06-2
Dossier submitter: Austria

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
06.10.2022	France	ADAMA MAKHTESHIM ltd	Company-Manufacturer	1
Comment received				
The dataset of Captan and the presentation of it within this dossier clearly establishes local acute irritation as Captan's only intrinsic hazard property. There is no convincing evidence for any systemic, non-local or non-acute effects in the dataset; all effects are of primary acute aetiology. Such a clear hazard profile is rare for fungicides and should be appropriately captured in the hazard classification. It should be discussed whether a proposed classification for four hazard categories for the same underlying toxicity (in situ membrane reactivity □cytotoxicity / irritation) represents an extreme case of "double classification", as discouraged by CLP guidance. Based on the data, Captan can be robustly classified for acute inhalation toxicity, eye irritation and skin sensitization. Other classifications are inappropriate (STOT RE 1), redundant (STOT RE 1) or irrelevant for humans (STOT RE 1, carcinogenicity) and inappropriately communicate Captan's hazard for humans. Captan's mechanism of action (MoA) is well understood, and the data are concordant with what is predicted based on this known MoA. Due to a similar mode of action, the data of Folpet may also be informative for the assessment of Captan, however, the compounds differ in solubility and thus in situ efficiency at the site of first contact, which is relevant for contact irritation (Captan has a higher water solubility than Folpet). NB: All studies listed in the hazard classes comments are available upon request. Studies could not be attached due to the zip file size limitation.				

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Submitted docs.zip
Dossier Submitter's Response
We agree that Captan exhibits irritating properties. However, in our understanding similar MoAs can lead to classification for different hazard classes (e.g. eye damage and carcinogenicity). For specific comments please refer to the respective section, i.e. carcinogenicity: Comment number 5, STOT-RE: Comment number 27.
RAC's response
RAC concurs with the DS comments.

Date	Country	Organisation	Type of Organisation	Comment number
05.10.2022	Germany		MemberState	2
Comment received				
DE-CA agrees with the update of the entries in Annex VI of the CLP regulation for Skin Sens. Into category 1A (H317) as well as the addition of STOT RE 1 (H372). This is in line with our recent assessment in the EU pesticide peer review process for captan (01/2020). However, we do not completely agree with the classification for the environmental hazards.				
Dossier Submitter's Response				
Thank you for your agreement. Please refer to comment number 29 for the environmental hazards.				
RAC's response				
RAC agrees with the MS to propose updating of the entries in Annex VI of the CLP regulation for Skin Sens. into category 1A (H317). RAC also agrees with the DS regarding classification for STOT RE 1.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
07.10.2022	Denmark		MemberState	3
Comment received				
DK agrees that a classification for carcinogenicity based on findings in the duodenum in mice studies is warranted. The mechanism behind the effect in the duodenum is well supported empirically and is likely an irritant effect and not a genotoxic MoA. This is supported by in vivo genotoxicity tests that do not support a genotoxic potential and the very rapid metabolism of captan in vivo. Please take into consideration the effects in the lungs observed in the 90 day inhalation study in rats. Non-reversible squamous hyperplasia and metaplasia was observed and consideration should be given to whether these effects could be pre-neoplastic lesions and support the evaluation of carcinogenicity of captan.				
Dossier Submitter's Response				
According to the "Guidance on the Application of the CLP Criteria" epithelial hyperplasia and metaplasia in the rat larynx may be adaptive responses to inhalation of irritants. Squamous metaplasia was observed in the ventral part of the larynx in the region of the arytenoid projections in males and females exposed to 12.98 or 5.06 µg/L. In some rats metaplasia was associated with keratinisation and/or ulceration on the arytenoid projections (please refer to the table below for additional larynx findings).				

Therefore, in our opinion hyperplasia and metaplasia observed in the larynx should be considered rather as response to an irritant effect than as pre-neoplastic lesion.

Removal reason / sex	Additional larynx findings	0 µg/L	0.13 µg/L	0.60 µg/L	5.06 µg/L	12.98 µg/L
Intercurrent males	Examined	0	0	0	0	5
	Ulceration (total)	0	0	0	0	2
	- Slight	0	0	0	0	1
	- Moderate	0	0	0	0	1
	Parakeratosis (total)	0	0	0	0	3
	- Minimal	0	0	0	0	1
	- Slight	0	0	0	0	2
Terminal / females	Examined	0	1	0	1	1
	Ulceration (total)	0	0	0	0	1
Terminal / females	- Moderate	0	0	0	0	1
Terminal / males	Examined	10	10	10	10	6
	Ulceration (total)	0	0	0	0	1
	- Slight	0	0	0	0	1
	Parakeratosis (total)	0	0	0	2	2
	- Minimal	0	0	0	2	2
	Vacuolar degeneration squamous epithelium (total)	0	0	0	3	4
	- Minimal	0	0	0	3	4
Terminal / females	Examined	10	9	10	9	9
	Ulceration (total)	0	0	0	3	1
	- Minimal	0	0	0	3	0
	- Slight	0	0	0	0	1
	Parakeratosis (total)	0	0	0	2	3
	- Minimal	0	0	0	2	3
	Vacuolar degeneration squamous epithelium (total)	0	0	0	4	7
	Minimal	0	0	0	4	7
Recovery / males	Examined	10	0	0	0	9
	Vacuolar degeneration squamous epithelium (total)	0	-	-	-	1
	- Minimal	0	-	-	-	1
Recovery / females	Examined	10	0	0	0	10
	Vacuolar degeneration squamous epithelium (total)	0	-	-	-	2
	- Minimal	0	-	-	-	2

RAC's response

RAC agrees with the classification for carcinogenicity and further supports the comments by the DS regarding the effects of hyperplasia and metaplasia observed in the larynx. The effects noted in the DS response are considered to be more inline with subchronic irritation rather than indicative of preneoplastic potential.

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2022	Netherlands		MemberState	4

Comment received

The dossier submitter proposes to keep Carc. 2 classification for Captan. Two well performed GLP mice studies showed increased level of carcinogenicity in both sexes in the small intestine, without marked general toxicity upon chronic Captan exposure. This is normally considered sufficient to classify Captan as Carc 1B. The proposed mode of action of Captan induced small intestine carcinogenicity is via irritation (sustained crypt cell proliferation/hyperplasia resulting in mutation/transformation). It is agreed this mode of

action is plausible and a threshold mechanism is likely. In the dossier it is suggested in the comparison with the classification criteria, using an AOP (Bhat et al. 2020), that levels of exposure needed for irritation to result in cancer are not reached in humans. However, classification and labelling criteria are based on the presence of a hazard. The exposure scenario is thus irrelevant for classification. Simultaneously the DS notes the KEs are qualitatively plausible in humans as well.

Since this was the main argument to limit the classification to category 2 instead of 1B, the NL-CA disagrees with the proposed classification. Instead, classification as a carcinogen in category 1B is warranted based on tumour findings in a single species, but both sexes and two well performed/reliable independent studies.

Dossier Submitter's Response

We agree that normally reproducible tumours observed in one species would be sufficient for classification as Carc. 1B.
However, the MoA for Captan was established as non-genotoxic, but irritation-driven with reversibility of early and mid key events.
According to the ECHA "Guidance on the Application of the CLP Criteria", the existence of a secondary mechanism of action with the implication of a practical threshold above a certain dose level (e.g. chronic stimulation of cell proliferation) may lead to a downgrading of a Category 1 to Category 2 classification.
A clear threshold for tumour-development in mice GI-tract can be established.
Furthermore in the case of Captan, differences in GI-tract and glutathione-conjugation seem to result in different susceptibility of species [please refer to comment number 5 (2)].
Thiophosgene, formed by hydrolysis of Captan, readily reacts with cellular thiols, which likely results in cytotoxicity. It is detoxified by conjugation with glutathione (GSH).
The mouse, more than the rat, relies on glutathione for the detoxification, therefore glutathione supply in the mouse may be inadequate to deal with high doses.
In conclusion, regarding the specific threshold-MoA (cytotoxicity and regenerative cell proliferation by continuous irritation) of Captan, we propose classification as Carc. 2.

RAC's response

The comment by the MS is well noted by RAC, however the interpretation of the application of CLP criteria for classification outlined by the DS is supported, i.e., a downgrading of a Carc. Category 1 to Carc. Category 2 classification in this case is supported.

Date	Country	Organisation	Type of Organisation	Comment number
06.10.2022	France	ADAMA MAKHTESHIM ltd	Company-Manufacturer	5

Comment received

Captan induces gastrointestinal tumours in mice due to a well-understood mode of action initiated by continuous life-long direct contact of the gastrointestinal epithelium with diet containing high cytotoxic concentrations of Captan. Non-irritating concentrations in the diet do not induce tumours in mice. An adverse outcome pathway (AOP) was established by Bhat et al. 2020, i.e., duodenal tumours in mice occur secondary to chronic villous enterocyte cytotoxicity and regenerative repair-driven proliferation. The authors consider the AOP useful for regulatory applications including hazard identification because human exposures are orders of magnitude below those associated with key events in this AOP.
Overall, Captan's inherent hazard property is acute irritation and not carcinogenicity.
However, there are further lines of evidence that support a non-classification of Captan

for carcinogenicity for hazard communication purposes.
1) The effect is restricted to the exposure scenario in the study because mice, and all other investigated vertebrate species, avoid diet enriched with Captan. Since Captan has a distinct chemical smell, this manifests as reduced palatability; however, gastrointestinal irritation at continued high doses also reduces feed intake, as observed in dogs. The animals only resort to feeding upon body weight decrease/hunger and the absence of alternative feed sources. When exposure is stopped, gastrointestinal lesions in mice recede, i.e., the effect is reversible and thus directly linked to the artificial continuous exposure scenario.
2) The effect is species-specific to mice. There are no gastrointestinal tumours in the other species, even if gastrointestinal irritation is observed (specifically tumours are not present in rat but there is also no similar histopathological progression in dog 1 year studies). This may be related to a relatively high dietary consumption of diet/kg bw for mice as compared to other species, including human, and a relatively narrow duodenal lumen in mice as compared to other species, including human, which increases the likelihood of Captan to interact with epithelia before degradation in mice. Further, mice have much less water available in the small intestine compared with rats and also less than humans (McConnell et al. 2008, doi:10.1211/jpp.60.1.0008), which may decrease degradation of Captan and thus increase the likelihood of membrane interaction in mice (Note: McConnell et al. normalize water content between species also by body weight, which skews the assessment, while it makes more sense to normalize by diameter here, which better explains the observed physical damage presented. For mouse, rat and human small intestine, the water content can be estimated for diameters of 1.5, 3 and 50 mm, respectively, to 0.6, 2.6 and 3.7 mL water/mm. The length seems less relevant as irritation decreases from the proximal to the distal end in the carcinogenicity studies.).
3) There is no exposure scenario for humans that results in life-long, or even short-term, irritating concentrations of Captan via the diet.
3a) The use as a plant protection product in Europe does not result in irritating concentrations of Captan in diet and cannot achieve cytotoxic concentrations, as required by the adverse outcome pathway. Accordingly, authorities in Europe (EFSA), the United States of America (EPA) and Canada (PRMA) consider the observed gastrointestinal tumours in mice to be not relevant for human dietary exposure, in the respective regulatory documents (EFSA Conclusion 2020/Expert Consulation 2.2; USEPA, 2004, Amendment to the 1999 Captan RED; PMRA 2018, Re-evaluation Decision RVD2018-12, Captan and Its Associated End-use Products), and all base risk assessment on doses that do not induce gastrointestinal irritation in laboratory animals.
3b) It is highly unlikely that irritating concentrations of Captan could be practically achieved even by artificial means in a diet that would be edible for humans. Captan reacts rapidly with thiols present in diet (and gastrointestinal tract) and is only present at sufficient levels to induce irritation in dietary experiments in the laboratory due to very high doses in combination with a low moisture content; neither is relevant for human dietary exposure. It has been clearly established by data, that the trichloromethylthio-moiety is associated with primary irritation in the intestine and this moiety has been shown to react rapidly with proteins and thiols.
3c) Captan's primary degradation product tetrahydrophthalimide lacks the trichloromethylthio-moiety and is not irritating. Therefore, tetrahydrophthalimide , which is more relevant for human dietary exposure following Captan degradation in human diet, cannot induce gastrointestinal irritation.
3d) Non-dietary exposure scenarios are irrelevant for this local effect because Captan does not reach the intestinal epithelia via non-dietary routes following repeated, chronic exposure, and its systemic metabolites are not irritating.
Based on this weight of evidence listed above, a carcinogenicity hazard classification does not appropriately communicate hazard associated with Captan exposure for humans,

as there is no exposure scenario that can induce gastrointestinal irritation, cytotoxicity and thus carcinogenicity in humans. In primary exposure scenarios, e.g., users of Captan products, first responders, bystanders etc, it is not reasonable to assume life-long dietary exposure and, as stated above, non-dietary routes are not relevant. Captan is appropriately classified as an irritant (eye irritation, acute inhalation toxicity) based on the underlying toxicity of acute contact irritation, which appropriately communicates its inherent hazard property. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Submitted docs.zip
Dossier Submitter's Response
We agree to the AOP developed by Bhat et al. 2020 concluding that, the KEs become quantitively implausible in humans after accounting for background levels of human exposure. Nevertheless, the authors also concluded that the KEs are qualitatively plausible in humans. Classification is hazard based, therefore considerations about exposure and risk are not relevant. Furthermore, we would like to clarify that the metabolites/ degradation products were not assessed for irritating properties. Considering the specific MoA and the differences in the GI tract between rodents and humans we propose classification as Carc. 2. Please also refer to comment number 4.
RAC's response
RAC supports the DS' approach. This is a hazard based assessment and exposure considerations are risk based. RAC agrees with the proposal for Carc. 2.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
07.10.2022	Denmark		MemberState	6
Comment received				
DK agrees. No classification is warranted.				
Dossier Submitter's Response				
Thank you for your agreement.				
RAC's response				
RAC agrees with the MS, no classification is warranted.				

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2022	Netherlands		MemberState	7
Comment received				
No classification proposed by Dossier Submitter. NL-CA agrees no classification for mutagenicity is required. Positive results in microbial and in vitro mammalian systems were greatly diminished or eliminated by addition of thiol containing compounds or addition of metabolic activation. In vivo studies generally show negative results. As half-life in human blood was determined to be <1 second, it is plausible that the substance is rapidly metabolized in vivo to a non-genotoxic compound. Therefore classification as germ cell mutagen is not warranted.				
Dossier Submitter's Response				
Thank you for your agreement.				

RAC's response
RAC agrees with the MS, no classification is warranted.

Date	Country	Organisation	Type of Organisation	Comment number
06.10.2022	France	ADAMA MAKHTESHIM ltd	Company-Manufacturer	8
Comment received				
We agree with the conclusion in the CLH report. Captan is not genotoxic in vivo, due to Captan's inability to penetrate into the systemic compartment and Captan's rapid reaction with thiol groups/proteins in the gastrointestinal tract. This is supported by the in vitro data that shows that GSH and S9 abolish or reduce Captan's in vitro genotoxicity potency. Together, the artificial thiol-poor environment of the in vitro experiments seems to be limiting an effective prediction of Captan effects in complex biological systems, including human Captan exposure scenarios. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Submitted docs.zip				
Dossier Submitter's Response				
Thank you for your agreement.				
RAC's response				
RAC agrees with the company comment, no classification is warranted.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
07.10.2022	Denmark		MemberState	9
Comment received				
DK agrees. No classification is warranted.				
Dossier Submitter's Response				
Thank you for your agreement.				
RAC's response				
RAC notes in the rat 3-Gen study there were substantial reductions in pup body weights, dose related and consistent across generations on PND0 and PND21, with weight reduction maintained into adulthood indicating a general retardation of growth and a developmental delay. There was no investigation into effects on sexual maturation in the multigeneration study. In both the male and female rat pubertal development studies, there is also clear evidence for adverse effects on pubertal development, but it is acknowledged that these effects may partially be secondary to the moderate reductions in body weight due to treatment noted in the multigeneration study. Overall, Repr. 2 for fertility is considered warranted based on effects noted in the pubertal and thyroid developmental studies on male and female rats.				

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2022	Netherlands		MemberState	10
Comment received				
No classification proposed by Dossier Submitter. NL-CA agrees no classification is required. Effects on body weight and food intake were observed in some in vivo studies upon Captan exposure. Fetal malformations were observed in four prenatal				

developmental toxicity studies in rabbits. No consistent evidence of a dose-response relationship was observed and malformations were considered to be spontaneous in origin.
Dossier Submitter's Response
Thank you for your agreement.
RAC's response
See response to comment 9.

Date	Country	Organisation	Type of Organisation	Comment number
06.10.2022	France	ADAMA MAKHTESHIM ltd	Company-Manufacturer	11
Comment received				
We agree with the conclusion in the CLH report. Captan and its systemic metabolites are not toxic for reproduction or development. Rabbits seem to be a poor model to predict potential human developmental effects for the contact irritant Captan, due to their known sensitivity towards gastrointestinal disturbance and their reliance on caecotrophy. Captan's systemic metabolite, which is relevant for human exposure scenarios, does not affect the gastrointestinal tract of rabbits and is also clearly not toxic for rabbit development. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Submitted docs.zip				
Dossier Submitter's Response				
Thank you for your agreement. However, we would like to point out for RAC discussion that Captan's metabolite THPI has a structure similar to thalidomide which is a known teratogenic substance in the rabbit. In a developmental study (Study 8), the metabolite THPI was tested clearly below the MTD, therefore effects at higher dose, capturing maternal toxicity, cannot be excluded based on this study.				
RAC's response				
See response to comment 9. There is no evidence to suggest that THPI may act in a similar way to thalidomide which is a known teratogenic substance in the rabbit.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
03.10.2022	Belgium	Arysta LifeScience SAS (part of UPL group)	Company-Manufacturer	12
Comment received				
Comments related to the acute inhalation toxicity - section 9.3 Acute toxicity - inhalation route, page 21-25 of the CLH report: We want to thank the dossier submitter for their work in drafting the CLH proposal for captan (ECHA CLH, 2022). However, we respectfully disagree with the dossier submitter's proposal to upgrade the current harmonised classification for acute inhalation toxicity of captan (Index No. 613-044-00-6). Currently, captan has a harmonised classification for acute inhalation toxicity: Acute Tox Category 3 – H331 "Toxic if inhaled". In the newly published CLH proposal, Austria, as the dossier submitter, propose to modify the existing				

Annex VI entry of captan to change the acute inhalation classification to Acute Tox Category 2 H330 "Fatal if inhaled" with an associated ATE of 0.22 mg/L (dusts and mists). The dossier submitter's proposal to modify the existing harmonised classification of Acute Tox Category 3 (H331) to Acute Tox Category 2 (H330) is based solely on the findings (milled test material) from Study 4 (2000). The paper in attachment details the scientific reasoning for retaining the current harmonised classification entry for acute inhalation (Acute Tox Category 3). ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Captan CLH Proposal - Position Paper - Final.pdf
Dossier Submitter's Response
The studies with the most appropriate test material regarding MMAD (between 2-4 µm, as required in OECD TG 403) are Study 2 and 4 (milled part). The LC50 (both sexes) for Study 2 was 0.78 mg/L with a confidence interval of 0.49-1.13 mg/L, while LC50 of Study 4 (milled part) was 0.272 mg/L (both sexes) with a 95th confidence limits of 0.159-0.466 mg/L. In the position paper of Arysta the reliability of Study 4 was questioned due to dose spacing (i.e. 9- fold difference between the low-dose and mid-dose groups while there is a 3.5-fold difference between the mid to high-dose groups) potentially leading to substantial variation in the LC50 results, as demonstrated by the confidence interval. We agree that the confidence interval for males (i.e. 0.084-0.579 mg/L) is higher than in other studies. However, this effect diminishes when both sexes are combined. Furthermore, it was pointed out in the position paper that a non-representative physical form of the test material (i.e. milled) was used. In our view only the milled part of this study meets the requirements for MMAD as outlined in OECD TG 403. In our understanding, the lowest LC50 value from a fully reliable study should be used for classification, which leads to our classification proposal as Acute Tox 2 (H330).
RAC's response
RAC agrees with the DS, the lowest ATE may be derived from a well conducted study where the test material adheres to test guidelines regarding an aerosol containing a primary proportion of respirable particles (MMAD 1-4µm). For captan, the milled test material from Anonymous (2000) complies with these requirements as does the Anonymous (1991) study. The criteria outlined in OECD TG 403 are quite specific, and require rodents to be exposed to an aerosol comprised of mostly respirable particles to ensure hazard driven testing irrespective of the form of the technical material available to market. A difficulty arises with the interpretation of the guidance on application of CLP criteria (ECHA, 2017) (CLP guidance) for regulatory purposes. It can be argued that testing is performed under artificial conditions that do not occur within the marketed technical material or under conditions of reasonable use. The CLP guidance makes reference to a number of articles under the CLP Regulation whereby consideration is given to the physical forms of a substance but it is sadly lacking in advice in how to tackle such conumdrums when they occur. Instead there is a greater focus on testing respirable fractions. Under section 1.2.3.2 of the CLP guidance, "*the assumption is made that the testing conditions of valid animal assays reflect the hazards to man and these data must be used for classification*". However, some margin for the pragmatic evaluation of effects of particulate materials is allowed for when considering "*any limitations due to the fact that the specific form of the tested substance or mixture does not or not perfectly represent that to which human exposure may occur during intended, known, or reasonably expected use*". Within the CLP guidance there is also a brief reference to the paper by Pauluhn (2008) which tries to address these regulatory challenges through consideration of the EU split-entry concept. However, RAC considers that while there are some indications that toxicity could be particle size dependent, overall there is insufficient testing on this point to support such a concept. In addition, there is no information on how to incorporate this concept on the CLP guidance document which brings into question

the consideration of such a concept to begin with. One of the main tennets for split-entry consideration (according to Pauluhn, 2008) is that toxicity is confined only to the gas exchange region of the lungs. Study #2 (1991) necropsy results indicate other organs are also affected, noting both liver and GIT involvement. Study #3, though not ideal also, shows that a low LC_{50} value can be attained with particle sizes of 5-5.8 µm, thus illustrating that toxicity is not only confined to a size distribution ≤ 4 µm for particles from the tested substance. On the basis that the CLP guidance document stresses the importance of hazard driven testing (see also section 3.1.2.3.2 dealing with "Special considerations concerning aerosols (dusts and mists)"), RAC concurs with the DS that there is sufficient data from the well conducted study #4 and its milled material to derive a lowest value ATE for inhalation (i.e. 0.22 mg/L), such that a classification proposal of Acute Tox. 2 (H330) is supported. Also of note is that the individual LC_{50} values for both males and females from study #4 support category 2.

Date	Country	Organisation	Type of Organisation	Comment number
07.10.2022	Denmark		MemberState	13

Comment received

For acute oral toxicity in mice, the LD50 was calculated as a combined value for the two sexes. However, since the resulting LD50 is close to the cut-off value for cat. 4 of 2000 mg/kg bw/day and considering that there is a difference in sensitivity between the sexes (higher mortality in males), the LD50 should be calculated for the sexes separately and especially for the most sensitive sex. The LD50 in males should then be compared with the limit of 2000 mg/kg bw/day and the conclusion on classification be based on this.
DK agrees that no classification for acute dermal toxicity is warranted.
DK agrees that a classification for acute inhalation toxicity in cat. 2 is warranted based on the study with the lowest LC50-value (study 4).

Dossier Submitter's Response

Thank you for your agreement (inhalation and dermal).

We agree that the most sensitive sex should be used for acute oral classification. Unfortunately, LD50 in the acute oral mouse study (Study 4) is not reported separately per sex. Details for mortalities in this study can be found in Annex 1_Human health in Table 3.1.1.4-1.

RAC's response

The original mouse study summarised the combined data for oral toxicity only, however, the appendix to the original study report tabulated the data for each sex and confirms the greater sensitivity of males. Using simple non-linear regression, the resulting dose-response curve gives estimates of the LD_{50} above 2000 mg/kg bw for both sexes independently and the original proposal by the DS is supported by RAC.

Individual summary data:
Males – 0/5; 1/5; 4/5; 5/5 for 1500; 1890; 2380; and 3000 mg/kg bw (LD_{50} = 2121 mg/kg bw)
Females – 0/5; 1/5; 3/5; and 5/5 for the same doses (LD_{50} = 2245 mg/kg bw).
Combined – 0/10; 2/10; 7/10; 10/10 (LD_{50} = 2179 mg/kg bw).

RAC agrees with the DS, no classification for acute oral toxicity.
RAC agrees with the DS, no classification for acute dermal toxicity.
RAC agrees with the MS and DS, acute inhalation toxicity in Cat. 2, see response to comment 12.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON CAPTAN (ISO); 1,2,3,6-TETRAHYDRO-N-(TRICHLOROMETHYLTHIO)PHTHALIMIDE

Date	Country	Organisation	Type of Organisation	Comment number
05.10.2022	Germany		MemberState	14
Comment received				
We support the change to Acute Tox. 2 (H330) as proposed, based on the lowest LC50 of 0.22 mg/L obtained with the milled substance in Study 4. According to Annex I, 3.1.2.3.2, inhaled particles with an MMAD of between 1 and 4 micrometers will deposit in all regions of the rat respiratory tract and are thus recommended for testing. Study 4 shows that the required MMAD is not reached for the non-milled substance same as in study 1. The MMAD of 3-6 micrometers reported for study 3 indicates less well-suited test material. Study 2 with a reported MMAD of 1.6-1.8 µm yielded a LC50 (both sexes) of 0.78 mg/L with a confidence interval of 0.49-1.13 mg/L spanning across both the upper and the lower guidance value (0.5 and 1.0) for Acute Tox. 3. A rounding of the ATE to 0.2 mg/L, which is better reflecting experimental variability reported as 95 % confidence interval in section 9.3.1, could be discussed.				
Dossier Submitter's Response				
Thank you for your agreement. The most reliable studies for acute inhalation toxicity are Study 2 and 4 (milled part). LC50 values of these studies lead to different categories for acute inhalation properties. Therefore, we are slightly more in favour of not rounding the ATE.				
RAC's response				
RAC agrees with the acute inhalation toxicity classification proposal by the MS and supports the DS conclusion.				

Date	Country	Organisation	Type of Organisation	Comment number
06.10.2022	France	ADAMA MAKHTESHIM ltd	Company-Manufacturer	15
Comment received				
We agree in principle with the conclusion in the CLH report. It should be noted that the wealth of acute inhalation toxicity data allows an assessment of the appropriateness for a STOT RE 1 (respiratory tract) classification for the same target organ and toxicity (irritation) observed throughout the study package, independent of the target organ. It may be informative to add that Captan formally qualifies for the "split-entry approach" proposed by Pauluhn, 2008, and referenced in CLP guidance (the same applies for Folpet), which is relevant for irritant particles as generated by Captan. Toxicity from irritant particles is dependent on exposure time and dose but is also dependent on particle size. Therefore, a refined hazard assessment approach may be suitable for Captan products containing larger particle sizes, in the form they are placed on the market, rather than those tested in the generic studies here. Such an approach can be followed either by dedicated testing or, preferably, by other new approach methods which consider particle size in the hazard characterisation. Split-entry approach criteria for irritant particles (Pauluhn, 2008) are listed below, and compared with findings observed for Captan: - Non-inhalation route (acute) (low toxicity): LD50 (oral, dermal) >2000 mg/kg bw - MMAD in the relevant acute inhalation toxicity studies (< ~4 µm): < 4 µm - Irritation/Inflammation (yes): Yes, at all sites of first contact, independent of exposure route				

- Lethality dependent on particle size (yes): Yes, studies with various particle size material are available.
- Onset of lethality (immediate - up to day 7): hours - 1-2 days
- Respiratory distress (yes): During exposure: reduced respiratory rate and exaggerated respiratory movement, wet fur, struggling movements. After exposure: piloerection, hunched posture, red/brown/pigmented stain around the snout, hypothermia, reduced respiratory rate, exaggerated respiratory movements, noisy respiration, gasping, rales
- Evidence of severe non-respiratory tract toxicity (no): Not in the inhalation studies. The compounds show irritative effects at all sites of first exposure.
- Necropsy findings in succumbed rats (Hepatization, lung enlarged, edema): Applies
- Supportive, increase in BAL protein (yes): No data available
- Supportive histopathology (major lesions restricted to lower respiratory tract): Repeated inhalation exposure studies show squamous metaplasia in the nasal turbinate and larynx along with degeneration, influx of inflammatory cells and increased lung weights
- Severe extrapulmonary organ damage (no): Not in the inhalation studies. The compounds show irritation effects at all sites of first exposure.

In summary, Captan clearly meets these criteria, confirming its contact irritation properties as an irritative particle with a clear acute inhalation toxicity profile, according to the criteria of Pauluhn, 2008. Thus Captan is best described by acute classifications.
Reference mentioned:
Pauluhn J (2008) Inhalation toxicology: Methodological and regulatory challenges. Exp Toxicol Pathol 60(2):111-124 doi:https://doi.org/10.1016/j.etp.2008.01.013

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Submitted docs.zip

Dossier Submitter's Response

We would like to point out that Captan is used per spraying, where nozzles could have an impact on particle size.
Furthermore, some uncertainties regarding the split entry concept include:

- Captan is not irritating to all local site of contacts (i.e. skin).
- There are uncertainties regarding acute oral classification with a study conducted in mice (please refer to comment number 13).
- Additionally, some effects at necropsy were observed outside the respiratory tract:
  - In Study 2, two animals in the 0.94 mg/L group that died showed dark liver and haemorrhage as well as reddening or congestion of the small intestine.
  - In Study 3 the eyes, in several of the rats that died at the 0.71 and 1.39 mg/L exposure levels during observation period, were cloudy-white.

Therefore, we disagree to a split-entry.

RAC's response

RAC disagrees with the split entry concept in this case and supports the proposal by the DS. Please see the response to comment 12.

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
06.10.2022	France	ADAMA MAKHTESHIM ltd	Company-Manufacturer	16

Comment received

We agree with the conclusion in the CLH report, Captan is not a skin irritant in the appropriate acute irritation studies.
Please note that there is novel and recently published data, i.e., in vitro studies modelling

human skin that show that Captan does not induce irritation in models with human-like epithelia. Those studies support a no-classification proposal, similar to the rabbit studies. Please refer to Kluxen et al., 2022 ("Characterizing local acute irritation properties of Captan and Folpet with new approach methods", Applied In Vitro Toxicology, 8(9): 83-101, doi: 10.1089/aivt.2022.0004) and the associated study reports (reports 20273734 and 20273736) uploaded along with this comment. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Submitted docs.zip
Dossier Submitter's Response
Thank you for your agreement.
RAC's response
RAC agrees, no classification is warranted. Industry supplied two new *in vitro* dermal corrosion/irritancy tests for captan, these were also negative and provide further supportive data for no classification.

Date	Country	Organisation	Type of Organisation	Comment number
07.10.2022	Denmark		MemberState	17
Comment received				
DK agrees. No classification is warranted.				
Dossier Submitter's Response				
Thank you for your agreement.				
RAC's response				
RAC agrees, no classification is warranted.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
06.10.2022	France	ADAMA MAKHTESHIM ltd	Company-Manufacturer	18
Comment received				
We principally agree with this assessment based on the available vertebrate studies. However, please be aware that there is novel and relevant in vitro data available modelling human tissue. The studies support a classification for Category 2. The in vitro studies may indicate a lower sensitivity of human tissue against Captan-induced irritation, which is biologically plausible as human cornea has a different morphology than rabbit cornea. Please refer to Kluxen et al., 2022 ("Characterizing local acute irritation properties of Captan and Folpet with new approach methods", Applied In Vitro Toxicology, 8(9): 83-101, doi: 10.1089/aivt.2022.0004) and the associated study reports (reports 20273725 and 20273728) uploaded along with this comment. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Submitted docs.zip				
Dossier Submitter's Response				
The application of in vitro methods should be based on lacking in vivo data. The absence of in vitro effects should not be used to overrule positive in vivo data unless the in vivo data is unreliable.				

The classification proposal for Category 1 is based on the irreversibility of effects until the end of the study in 1 out of 2 studies. Study 1 conducted in only one female rabbit was terminated due to the severity of effects after 5 hours (haemorrhage of the nictitating and conjunctival membrane), while in Study 2 persisting effects until Day 21 were observed in 4/6 animals. These effects included conjunctival bleeding, roughed cornea and pannus formation in the cornea. In our opinion, these effects cannot be captured by in vitro systems. Most of the effects reported in the in vivo assay, are outside the applicability domain of the proposed in vitro assays (Both in vitro assays have corneal opacity as endpoint). According to the OECD Test Guideline No 467, using the combination of both assays is used for the defined approaches 1 (DAL-1) for eye hazard identification (based on physicochemical properties and in vitro data). However, this approach is only applicable to neat non-surfactant liquids (solid suspensions or solids are outside the applicability domain). Furthermore, we would like to point out that Captan was applied as solid in the in the first run of the BCOP test, while in the second run it was added pure on the top of the corneas (± 300 mg to completely cover the cornea) and physiological saline was added to have a 20% w/v concentration of the test item on the cornea (cf. page 272 of clh_CONF_comments_captan_attachments_en). This concentration is exceeding the water solubility of Captan. Effects were more pronounced when Captan was applied with physiological saline, an application form also strongly recommended by OECD TG 437. We would like to question, if by applying first Captan and than physiological saline a homogenous suspension with equal distribution in the corneal area can be reached or if the test results might be impacted by irregular distribution of Captan over the cornea.
RAC's response
The current approved reference model (gold standard) for ocular irritation testing is the *in vivo* Draize test. The data available from the two animal tests support Eye Dam. 1 classification. The BCOP assay results are inconclusive, while the results from the study utilising the EpiOcular Cornea Epithelial Model suggests captan is irritant and/or corrosive. There is clear information from the *in vivo* tests and the weight of evidence from these studies is sufficient to propose retaining the Eye Dam. 1 classification.

Date	Country	Organisation	Type of Organisation	Comment number
07.10.2022	Denmark		MemberState	19
Comment received				
DK agrees. Captan should be classified as eye damaging cat. 1.				
Dossier Submitter's Response				
Thank you for your agreement.				
RAC's response				
RAC agrees with both the DS and MSCA.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
06.10.2022	France	ADAMA MAKHTESHIM ltd	Company-Manufacturer	20
Comment received				
We principally agree with the assessment based on the available vertebrate studies. Please be aware that there is novel and relevant in vitro data available modelling human tissue. The studies support also a classification for skin sensitization. Please refer to				

Kluxen et al., 2022 ("Characterizing local acute irritation properties of Captan and Folpet with new approach methods", Applied In Vitro Toxicology, 8(9): 83-101, doi: 10.1089/aivt.2022.0004) and the associated study reports (20273730, and 20273732) uploaded along with this comment.
We do not agree with classifying Captan as an extreme skin sensitizer as the underlying in vivo studies are not designed to identify potency. However, Kluxen et al. 2022 also describes the results of a GARD assay (report 1063-2022). The GARD assay method allows a post hoc assessment of potency by deriving a LLNA EC3 estimate based on cytotoxicity data and simulation studies, please see the study report (report 1063-2022 potency prediction). While this is less robust than a dose-response GARD assay, it allows an approximation of sensitization potential. For Captan, an LLNA EC3 of 4.09% can be estimated, which indicates only moderate sensitizing potential. This claim is supported with high statistical confidence, the 95% confidence interval is [2.19%, 7.62%], i.e., the confidence interval lies completely within the ECETOC category for moderate sensitizers and exceeds the category for moderate sensitizers of the CLP guidance- note to achieve a 5% alpha per comparison to the different categories, the confidence interval must be shrunk to <95% (for example, the 90% confidence interval is [2.45%, 6.82%]).

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Submitted docs.zip

Dossier Submitter's Response

Substances, where ≥ 60 % of the animals are responding at > 0,1 % to ≤ 1 % intradermal induction dose in a guinea pig maximisation test shall be classified as Cat. 1A skin sensitizers. This is the case for Captan, where a sensitisation rate of 100% was observed, after an intradermal induction dose of 0.1% (Study 1). A SCL of 0.001% is proposed.

In our opinion, the new in vitro data provided are not appropriate to allow potency considerations.
According to OECD No. 497 "Guideline on Defined Approaches for Skin Sensitisation", for potency considerations quantitative results from the h-CLAT (Human Cell Line Activation test) and the DPRA (Direct Peptide Reactivity Assay) in combination witheither Derek Nexus (ITSv1 DA) or OECD QSAR TB (ITSv2 DA) are needed for potency predictions. Within the 2 out of 3 approach (which includes hCLAT, KeratinoSens and DPRA) only predictions on the Hazard is possible. It is noted that the DPRA of Captan was terminated owing to unsuitable solvents for the test item. No h-CLAT or in silico predictions are available, but potency extrapolations are based on the GARDskin assay, which provides binary hazard identification of skin sensitizers (i.e. UN GHS Category 1 versus non-sensitizers) only, according to OECD TG 442E.
Potency extrapolation of GARDskin assay are therefore not validated.
In the extrapolation of the GARDskin assay, RV90 concentration (i.e. concentration for 90% relative viability) was used as cDV_0 (i.e. lowest concentration expected to induce a positive response in the GARD assay), resulting in a confidence interval of 2.19-7.62% for LLNA EC3 value prediction. It is noted that the lower bound of the confidence interval is close to 2%. Potency values are inversely correlated to skin sensitisation potency (i.e. lower cDV_0 mean higher relative sensitising potency).
Limitations in the extrapolation are outlined in the discussion section of the "Report/GARDskin in silico potency predictions", where it is stated that "the test item was classified as skin sensitizer in the GARDskin assay with a mean DV of moderate magnitude (mean DV of 5.59), indicating that the cDV_0 concentration will be strictly lower than the RV90 concentration" and that a more precise estimation of potency (i.e. cDV_0) would be needed for a conclusion (page 13 of

clh_CONF_comments_captan_attachments_en). In our opinion the results of the extrapolation show that Captan is at least a moderate skin sensitizer, but do neither allow a conclusion regarding Cat. 1A classification nor setting of SCLs.
RAC's response
RAC agrees with the DS comments. We have an acceptable guinea pig maximisation test and there is no reason to disregard its results or place a higher relevance on the results from the in vitro tests. RAC supports the proposal for Cat. 1A with an SCL of 0.001%.

Date	Country	Organisation	Type of Organisation	Comment number
07.10.2022	Denmark		MemberState	21
Comment received				
DK agrees that a classification for skin sensitisation in cat. 1A is warranted along with an SCL of 0.001 % as 100 % of test animals exhibit a positive response in the maximisation test corresponding to captan being an extreme sensitiser.				
Dossier Submitter's Response				
Thank you for your agreement.				
RAC's response				
RAC agrees with both the DS and MSCA.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
07.10.2022	Denmark		MemberState	22
Comment received				
DK agrees that a classification for STOT SE is not warranted. Most acute effects observed were in acute inhalation toxicity studies and occurred mainly at doses that caused mortality. The acute effects are here most likely linked to the mortality and are already covered by the classification for acute inhalation toxicity.				
Dossier Submitter's Response				
Thank you for your agreement.				
RAC's response				
RAC agrees with both the DS and MSCA.				

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2022	Netherlands		MemberState	23
Comment received				
STOT SE. P 75. "Furthermore, irritation effects in the respiratory tract are sufficiently characterized by the Acute inhalation toxicity category 3 classification proposal." It is noted, in the dossier category 2 is proposed H330: fatal if inhaled, not category 3. Some of the statements that have led to the conclusion of the DS are either insufficiently clear or incorrect in the view of the NL-CA: - It could be considered that acute inhalation 2 results in sufficient protection but this does not automatically mean STOT SE classification becomes irrelevant. In this case the guidance on the application of CLP criteria suggests both STOT SE and acute toxicity should not be applied if the classification is a result from the same type of effects. In this case respiratory irritation. Therefore the NL-CA can agree with a no classification in this				

particular case. - The respiratory tract can and should be viewed as a specific target organ as opposed to the DS statements at the end of the conclusion.
Dossier Submitter's Response
Thank you for your agreement. We apologize for the mistake on page 75, it should be "Acute inhalation toxicity category 2 classification proposal".
RAC's response
RAC agrees with the comment by the MSCA.

Date	Country	Organisation	Type of Organisation	Comment number
06.10.2022	France	ADAMA MAKHTESHIM ltd	Company-Manufacturer	24
Comment received				
There is no specific target organ or specific target organ toxicity for Captan. Hence, any STOT classification per se miscommunicates hazard associated with Captan exposure. Captan's lead toxicity and inherent hazard property is acute irritation. If a STOT classification would nevertheless be considered relevant for Captan, due to its effects on the respiratory system and associated mortality, then a STOT SE 3 classification, i.e., Respiratory tract irritation, would at least communicate the associated hazard appropriately. However, this would result in double classification for the same underlying hazard as Acute Inhalation Toxicity. The effects in the repeated exposure study are the result of multiple subsequent acute irritation events. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Submitted docs.zip				
Dossier Submitter's Response				
Thank you for your agreement. Effects relevant for STOT-SE 3 (H335) classification occurred mainly in acute inhalation toxicity studies at doses, which caused mortalities. Therefore, in our opinion no further classification as STOT-SE 3 is warranted. For STOT-RE please refer to comment number 27.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
07.10.2022	Denmark		MemberState	25
Comment received				
DK agrees with the classification for STOT RE cat. 1 with inhalation as route of exposure and the respiratory tract as target organ. In a subchronic inhalation toxicity study, a variety of effects were observed in the lungs, larynx and nasal cavity not observed after a single exposure in the acute inhalation toxicity studies. Furthermore, the effects in the subchronic study occurred at dose levels well below the dose levels causing clinical signs				

in the acute inhalation toxicity studies, thus indicating that clinical signs were related to the repeated exposure.
Dossier Submitter's Response
Thank you for your agreement.
RAC's response
RAC agrees and takes note of the comment.

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2022	Netherlands		MemberState	26
Comment received				
STOT RE. P 84 "Captan is proposed to be classified for STOT-RE Category 1." NL-CA agrees STOT-RE Cat 1 classification is required, due to inhalation toxicity observed at low doses (0.13 µg/L) and treatment related mortalities at higher doses (12.98 µg/L) in a well performed GLP sub chronic inhalation study performed in both sexes in one species. These doses are below the limit set by CLP criteria for category 1 classification (0.02 mg/L).				
Dossier Submitter's Response				
Thank you for your agreement.				
RAC's response				
RAC agrees and takes note of the comment.				

Date	Country	Organisation	Type of Organisation	Comment number
06.10.2022	France	ADAMA MAKHTESHIM ltd	Company-Manufacturer	27
Comment received				
We strongly disagree with the conclusion in the CLH report. There is no specific target organ or specific target organ toxicity for Captan. Hence, any STOT classification per se miscommunicates hazard associated with Captan exposure. Captan's lead toxicity and inherent hazard property is acute irritation. If a STOT classification would nevertheless be considered relevant for Captan, due to its effects on the respiratory system, then a STOT SE 3 classification, i.e., Respiratory tract irritation, would at least communicate the associated hazard appropriately. However, this would result in double classification for the same underlying hazard as Acute Inhalation Toxicity. The effects in the repeated exposure study are the result of multiple subsequent acute irritation events. Captan's mode of toxic action is well established as acute in situ membrane reactivity, cytotoxicity and irritation; it is highly unlikely that the effects in the repeated exposure studies are the result of toxicity other than repeated acute contact irritation. Novel evidence, not considered in the CLH report, comes from available in vitro data conducted with Folpet and Captan. Please refer to Kluxen et al., 2022 ("Characterizing local acute irritation properties of Captan and Folpet with new approach methods", Applied In Vitro Toxicology, 8(9): 83-101, doi: 10.1089/aivt.2022.0004) and the associated study report (report 787149) uploaded along with this comment. Overall, the in vitro data clearly support acute cytotoxicity/irritation as the driver of Captan's inhalation toxicity, which corroborates the acute aetiology of the effects observed in the repeated exposure inhalation studies.				

Further lines of evidence against a classification for STOT RE are given in the following.
1) Captan is classified for effects on the respiratory tract and mortality by the acute inhalation toxicity classification. A STOT classification double classifies for the same underlying toxicity in the same organ and is thus redundant and inappropriate.
2) Modelling rat tissue using the rat EpiAirway assay (see the earlier referred Kluxen et al. 2022 publication) demonstrates that Captan induces histopathological changes already after 1 day of treatment, i.e., a single exposure results in a higher incidence and severity of degenerative type changes (squamous differentiation or intercellular separation), compared to controls. Subsequent treatments exacerbate this effect. The data are concurrent with what one would assume to observe for an irritant particle.
3) Various in vitro assays show that Captan (and Folpet) are cytotoxic upon direct contact. Ritter et al. 2019 show that Captan has the same irritative effect as the known irritant sodium dodecyl sulphate (SDS) in an isolated perfused lung model (37th AAAR Annual Conference, https://docisolation-eu.prod.fire.glass/?guid=fc8562c5-4a16-4f47-69ef-c6f4a9fd11f6). Canal-Raffin et al. (Toxicology, 249 (2008): 160–166) show that Folpet induces cytotoxicity in a human bronchial epithelial cell line (16HBE14o-). The genotoxicity assays conducted with mammalian cells indicate a very high cytotoxicity potential of Captan. Considering a molar mass of about 300 g/mol for Captan, a 0.004 mM solution relates to a concentration of 1.2 mg/L that reduces cell survival to only 18% in the HPRT assay (CLH report page 34, Study 11, 2018a).
4) The wealth of acute inhalation toxicity data further allows an assessment of the relevance for STOT RE 1 classification. While brought forward in the CLH report, it is rephrased for clarity in the following. One approach to estimate whether the observations in a repeated exposure study come from acute toxicity, is to compare tested concentrations. However, this ignores exposure duration/Haber's rule because the exposure durations in repeated exposure studies are 50% longer per day and repeated. This should be taken into account rather than focussing on a daily exposure concentration in isolation. The data shows that histopathological pathological changes in the respiratory tract, which are typical for irritant particles, and mortality occur close to concentrations with significant toxicity due to irritation in acute studies. This demonstrates that the effects observed in repeated inhalation exposure studies have an acute aetiology.
4a) Mortality, proposed to trigger STOT RE 1, occurs after 65 repeated treatments with 12.98 µg/L for 6 hours/day, i.e., 0.013 mg/L. Acute Inhalation Study 4 (2000, CLH report page 22) shows that mortality occurs already after 4 hours treatment with 0.072 mg/L, which can be extrapolated by Haber's rule to 0.048 mg/L for 6 hours. Hence, significant toxicity, i.e., 10% mortality, due to irritation, occurs already at 3.7-times the daily concentration, at a single exposure event. While it cannot be shown in the acute studies whether there were irritation-induced events present at a lower concentration after a single exposure (no lower doses were tested), it is highly likely that such would be observed at a single lower concentration exposure, due to the established mode of action, the concordant reactions throughout the dataset and the presence of significant toxicity (mortality) already at 0.048mg/L (extrapolated) (NB: the in vitro EpiAirway studies, comment 2 above, demonstrate that histopathological changes occur after single exposure events and are thus of acute aetiology). Based on this, one may question why there is not a higher mortality in the repeated exposure studies? If one assumes that the full pulmonary dose is available for toxicity in the repeated inhalation exposure study at the highest tested concentration, the rats receive a single exposure equivalent concentration of (65 * 1.5 * 0.013=) 1.3 mg/L, i.e., significantly higher (~6 times) than the LC50 for classification (0.22 mg/L) but with only 50% mortality. Due to the known rapid reaction capacity of Captan with GSH and protein, and the known presence of such in mucus/surfactant in the respiratory system, it is very likely that only a fraction of inhaled Captan particles is available for toxicity at the respiratory epithelia. Hence, repeated exposure of small concentrations is associated with relatively less respiratory

toxicity than a single exposure of the same respiratory dose, i.e., less than predicted by Haber's rule. Accordingly, the hazard is best described as being acute.

Other comments:
Page 82: Please note the Kluxen and Koenig publication, as referenced in the CLP report, was an accepted manuscript but not a manuscript accepted for publication. It was suggested by the editor to be revised and split into several manuscripts. The first of those is published (Kluxen et al., 2022, "Characterizing local acute irritation properties of Captan and Folpet with new approach methods", Applied In Vitro Toxicology, 8(9): 83-101, doi: 10.1089/aivt.2022.0004)) but it does not contain the dosimetry calculations, which are presented in another manuscript.

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Submitted docs.zip

Dossier Submitter's Response

Ad 1) In our understanding similar MoAs can lead to classification for different hazard classes. For STOT-RE the question is, if the resulting effect is an adaptive change (e.g. in the larynx) or if it leads to an adverse (e.g. irreversible) effect.
Ad 2) Microscopic findings in the EpiAirway assay are considered to be of limited reliability, because only two samples per group were assessed (non-GLP). It is further noted, that squamous differentiation of the positive control (Formaldehyde) is in the range of the negative controls for 24 hour exposure, while no positive control was included for 72 hour exposure. Please refer to page 422 ff of document "clh_CONF_comments_captan_attachments_en". Cytotoxic effects of Captan were observed at 250 µg/ml (LDH-release and TEER).
Ad 3) Please note, that the publication of Canal-Raffin was conducted with a plant protection product containing Folpet (Folpan 80 WG). The poster of Ritter did not report essential parameters of methodology (e.g. number of replicants, solvent) and cannot be considered reliable.
Ad 4) Considering the rapid degradation of Captan mainly by hydrolysis ($T_{1/2}$ in vitro human blood: 0.97 seconds), we assume that no steady-state condition was achieved for repeated inhalative exposure, resulting in exceptions to Haber's rule e.g. by effective dose changing with time. Furthermore, linear dose and time relationship can be confounded by local irritative properties. Therefore, we would like to question applicability of Haber's rule for extrapolating Captan's acute and repeated-dose inhalative toxicity.

In the 90-day inhalation study mortalities occurred. In the same study squamous hyperplasia and squamous hyperplasia in the larynx persisted in the recovery period. Therefore, classification as STOT-RE1 seems appropriate.

RAC's response

RAC agrees with the DS. Though the CLP guidance does indicate that one approach to distinguish between acute and repeated dose toxicity is by way of dose comparison, it must be pointed out that this is in respect of severe toxicological effects due to corrosivity. Captan acts by way of cytotoxicity and is presumed to result from the chemical reactivity with free sulphydryl groups on extracellular and transmembrane macromolecules. It is not classified as corrosive though it is recognised to be highly irritating, especially to mucous membranes. It is acknowledged that the only study to support classification is the 90-day rat inhalation study but the effects are severe (death, associated with lung histopathology) and occur after a prolonged period of time (weeks 5-13) with some effects, though minor, indicative of tissue change in the larynx that were not reversed following a 4-week recovery period.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
07.10.2022	Denmark		MemberState	28
Comment received				
Not considered.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
05.10.2022	Germany		MemberState	29
Comment received				
DE-CA does not completely agree with the classification. Captan is not readily biodegradable according to the biological degradation study (see 10.1.1.) and therefore not rapidly degradable. This is correctly given in Table 53. The results of the simulation studies do not change this. The DegT50 in the whole water sediment system for the active substance captan and its metabolites THPI and THPAM is < 16 days; however, this means only primary degradation, not ultimate degradation. According to Table 53 mineralization in the water/sediment study is only 49-53% on day 90 after application. This means that a DT50 considering mineralization is about 90 days. Captan is therefore not ultimately degraded with a half-life of < 16 days. Rapid hydrolysis is only because of transformation. There is no mineralisation of > 70 % within 28 days (point II.4 b. of, Guidance on the Application of the CLP Criteria, Version 5.0 – July 2017). In conclusion, captan is not rapidly degradable. This allows classification based on the scheme proposed in Annex I, Section 4.1, Table 4.1.0. (iii), according to which acute toxicity data should be used for chronic classification, if appropriate chronic data are missing and the substance is not rapidly degradable. The lowest LC50 is 0.0147 mg/L, which is below 1 mg/L and leads to classification as aquatic chronic 1. This is the same classification as proposed by the dossier submitter, but obtained through another approach. We agree to the classification as aquatic acute 1 (M=10).				
Dossier Submitter's Response				
Degradation: According to Guidance on the Application of the CLP Criteria, Version 5.0 – July 2017 (p.498-499) "A substance is considered to be not rapidly degradable unless at least one of the following is fulfilled: c. The substance is demonstrated to be primarily degraded biotically or abiotically e.g. via hydroysis, in the aquatic environment with a half-life <16 days (corresponding to a degradation of >70 % within 28 days), and it can be demonstrated that the degradation products do not fulfill the criteria for classification as hazardous to the aquatic environment." Captan is degraded in water/sediment with DT50<16 d an its degradation products THPI and THPAM do not fulfill the criteria for classification as hazardous to the aquatic environment. Therefore, captan is classified as rapidly degradable.				

The metabolite THPAI doesnot exceed the trigger values (2 x > 5 %, > 10 %, max at end of study) in water or in sediment separately and therefore, was not included in the residue definition and not considered further in risk assessment. The metabolite THCY was not detected in an aerob water/sediment study; the metabolite THCY was only detected under anaerobic conditions in soil and water/sediment studies and in systems with (assumed) low oxygen concentrations. Under aerobic conditions THCY was quickly degraded in soil. Therefore, the metabolite was not included in the residue definition and not considered further in risk assessment.

RAC's response

Overall, all degradation studies (hydrolysis, aerobic mineralisation, water/sediment) showed a rapid degradation of captan in water to several degradation products. Nevertheless, ultimate biodegradation (i.e., full mineralisation) has not been achieved at the required level. The higher amounts of CO_2 occurred only in the water/sediment study at 60 and 90 days. The ready biodegradability test with a CO_2 Evolution Test indicates that 60 % level was not reached in the 10-days window and within 28 days. In addition, it cannot be excluded that the hydrolysis products fulfil the criteria for classification as hazardous to the aquatic environment.
Therefore, RAC considers that, despite rapidly hydrolysis and indications of very fast primary degradation, captan is not ultimately degraded to > 70 % within 28 days (equivalent to a half-life < 16 days) and it cannot be demonstrated that all degradation products do not fulfil the criteria for classification as hazardous to the aquatic environment. Therefore, RAC considers captan as not rapidly degradable according to the CLP criteria.
RAC indicate that adequate chronic toxicity data are not available for all trophic group. In addition, there are no reliable chronic toxicity data on most sensitive species comparing with acute toxicity. Hence, according to CLP criteria classification shall be assessed according to the criteria given in Table 4.1.0(b)(i) and if for the other trophic level adequate acute toxicity data are available according to the criteria given in Table 4.1.0(b)(iii) and should be based on the most stringent outcome.
Overall, RAC disagrees with the DS and concludes that captan warrants classification as Aquatic Chronic 1 with M factor of 10 based on most stringent outcome and supported by additional studies and read-across assessment with Folpet.

Date	Country	Organisation	Type of Organisation	Comment number
06.10.2022	United Kingdom	Health and Safety Executive	National Authority	30

Comment received

Captan (CAS: 133-06-2)
Degradation

The CLH DS concluded that captan is rapidly degradable based on the simulation study water/water-sediment DT50 values for captan itself and its major degradation products THPI and THPAM being <16 days. Table 53 in the CLH report, on the information on rapid degradability, also states that the "degradation products do not meet the criteria for classification as hazardous to the aquatic environment". Whilst we agree that the available ecotoxicity information indicates that the classification criteria for aquatic hazards are not met for the major degradation products THPI and THPAM, we note that there is no information on the chronic toxicity of the degradants to fish and aquatic invertebrates.

In addition to THPAM and THPI, THCY and THPAI were other identified major degradation products. THPC was another major degradation product but was noted to be formed rapidly and degraded rapidly so was considered only a transient degradant. No aquatic ecotoxicity data are available for these other degradation products that exceeded 10% AR.

Therefore, we are unclear whether there is sufficient information to demonstrate that the degradants do not meet the criteria for classification as hazardous to the aquatic environment and to support the rapid degradation conclusion. Overall, the degradation studies do not demonstrate that >70% of the substance is ultimately degraded within 28 days under environmental conditions. In particular, the surface water and water-sediment simulation studies were conducted around pH 8 which favours the hydrolysis of THPI, whereas the hydrolysis DT50s for THPI are considerably greater (≥16 days) under more acidic or neutral environmental conditions at pH 4 and 7 than at pH 9. We note that there are implications on the Aquatic Chronic M-factor if captan is considered not rapidly degradable. Read-across A CLH proposal for folpet, which has been used for read-across in this CLH proposal for captan, has been subject to public consultation and is currently awaiting RAC discussion. The public consultation comments and RAC Opinion should ideally be finalised before a conclusion on read-across is accepted as there could be an impact on the rapid degradability of folpet which could further impact the rapid degradability conclusion for captan. Active substance versus formulation studies Generally, studies with the active substance are preferred over formulation studies for the purpose of hazard classification due to the potential effects of co-formulants on the toxicity and behaviour of the active substance. As formulation studies have been used as key studies in the current CLH proposal and the information on the composition of the formulations is in a confidential annex, please could the DS and RAC consider whether it is appropriate in this instance to use these formulation studies? The most sensitive acute endpoints for both captan and the formulations are within the 0.01 – 0.1 mg/L range. The CLH DS considered that the two acute Salmo trutta endpoints for the active substance in this range (Anonymous, 2002b; 2016a) were not reliable and relevant to CLP because exposure was not maintained throughout the study period and analytical measurements were not available at the end of the tests. However, we note that analysis of test/stock solutions at 0 h in these two studies indicated correct dosing with measured concentrations within 80-120% of the nominal. Rapid primary degradation of captan is expected over acute exposure periods, and available data for the degradants indicate that these are much less ecotoxic, with endpoints not meeting the classification criteria for hazardous to the aquatic environment. This suggests that captan is driving the ecotoxicity observed in the studies with the parent substance. In the absence of more reliable data, acute toxicity endpoints for captan based on nominal or initial measured concentrations could be relevant for CLP, despite the lack of chemical analysis over the whole exposure duration. Other test validity criteria were met in both acute toxicity to Salmo trutta studies. If captan is considered not rapidly degradable, the surrogate approach with acute toxicity data for Salmo trutta and the active substance should be considered in the absence of chronic toxicity data for this species.
Dossier Submitter's Response
Degradation:

We agree that there are no chronic toxicity data with the degradation products THPAM and THPI; however, the submission of chronic toxicity data is not triggered and is also not required for the renewal of the active substance captan.
The degradation products THCY and THPAI were not considered relevant for further assessment; hence, no aquatic toxicity studies were submitted by the applicant.
According to the e-fate experts degradation product relevant for the assessment are THPI and THPAM. The metabolite THPAI does not exceed the trigger values (2 x > 5 %, > 10 %, max at end of study) in water or in sediment separately and therefore, was not included in the residue definition and not considered further in risk assessment. The metabolite THCY was not detected in an aerob water/sediment study; the metabolite THCY was only detected under anaerobic conditions in soil and water/sediment studies and in systems with (assumed) low oxygen concentrations. Under aerobic conditions THCY was quickly degraded in soil. Therefore, the metabolite was not included in the residue definition and not considered further in risk assessment.

Furthermore, according to Guidance on the Application of the CLP Criteria, Version 5.0 – July 2017 (p.498-499) "A substance is considered to be not rapidly degradable unless at least one of the following is fulfilled:
c. The substance is demonstrated to be primarily degraded biotically or abiotically e.g. via hydroysis, in the aquatic environment with a half-life <16 days (corresponding to a degradation of >70 % within 28 days), and it can be demonstrated that the degradation products do not fulfill the criteria for classification as hazardous to the aquatic environment."
Captan is degraded in water/sediment with DT50<16 d an its degradation products THPI and THPAM do not fulfill the criteria for classification as hazardous to the aquatic environment. Therefore, captan is classified as rapidly degradable.

Active substance versus formulation studies:
The studies conducted with formulations were also used for the risk assessment and therefore are considered acceptable by the DS to be used for classification purposes. The formulations mainly consists of the active substance (~ 80%) and the co-formulants used are not considered to significantly increase the toxicity of the formulation.

The DS does not agree with the comment regarding the use of not reliable endpoints for classification puposes. According to the OECD test guidelines the test organisms should be exposed to the test substance throughout the test duration. If the measured concentrations are below 80% of nominal the endpoints should be expressed as mean measured concentrations. Especially for rapidly degradable substances the endpoints may differ greatly depending on whether they are expressed in terms of nominal/initial measured or mean measured concentrations. Therfore, the DS is of the opinion that this should be considered for classification. The use of endpoints expressed in terms of nominal or initial measured concentrations might be acceptable in the risk assessment (refined exposure studies) considering more realistic exposure profiles taking into account the rapid degradation of captan but not for classification.

Regarding the use of the surrogate approach for chronic classification see comment by DE.

RAC's response

Degradation
Overall, all degradation studies (hydrolysis, aerobic mineralisation, water/sediment) showed a rapid degradation of captan in water to several degradation products. Nevertheless, ultimate biodegradation (i.e., full mineralisation) has not been achieved at the required level. The higher amounts of CO_2 occurred only in the water/sediment study at 60 and 90 days. The ready biodegradability test with a CO_2 Evolution Test indicates that 60 % level was not reached in the 10-

days window and within 28 days. In addition, it cannot be excluded that the hydrolysis products fulfil the criteria for classification as hazardous to the aquatic environment.
Therefore, RAC considers that, despite rapidly hydrolysis and indications of very fast primary degradation, captan is not ultimately degraded to > 70 % within 28 days (equivalent to a half-life < 16 days) and it cannot be demonstrated that all degradation products do not fulfil the criteria for classification as hazardous to the aquatic environment. Therefore, RAC considers captan as not rapidly degradable according to the CLP criteria.
Read-across
RAC evaluation of the CLH proposal for Folpet concluded that Folpet is not readily degradable, has a low bioaccumulation potential and proposes classification as Aquatic Acute 1 with an M-factor of 10 based on 96-hour LC50 of 0.015 mg/L for Oncorhynchus mykiss and Aquatic Chronic 1 with an M-factor of 10 based on 33-day NOEC of 0.00881 mg/L for Pimephales promelas.
Overall, RAC is of opinion that use of read – across assessment between captan and Folpet is principally acceptable. RAC acknowledge that read – across assessment between Captan and Folpet would lead to classification of Aquatic Chronic 1 with M factor of 10 based on 33-day NOEC of 0.00881 mg/L for Pimephales promelas (folpet being not rapidly degradable). However, RAC notes that due to the availability of long-term toxicity data for P. promelas using captan a read-across to folpet is not required to classify captan, although it is included as suportive information and to indicate that outcome is the same as the approach proposed by RAC.
Active substance versus formulation studies
RAC acknowledges that formulations (80 WDG and 83% WP) used in acute and chronic toxicity testing mainly consist of active substance captan (>80%). Although the are no aquatic toxicity data with used co-formulants, RAC note that co-formulants are not classified as toxic to aquatic environment and unlikely to significantly increase the toxicity of the formulation.

RAC concludes that reliable acute toxicity data are available for fish, invertebrates, and algae. Regarding aquatic acute toxicity to fish, RAC notes that when measured concentrations do not remain within 80-120 % of the nominal concentrations, the effect concentrations cannot be based on nominal concentrations and should be expressed as mean measured concentrations. Therefore, RAC assumes that the 24-h LC50 value of 0.025 mg a.s./L for Salmo trutta determined based on predicted mean measured concentrations based on the degradation observed in one test concentration could be used as only supportive information.
Overall, RAC consider that reliable and valid Aquatic Acute endpoint is 72-hour LC50 of 0.0147 mg/L (mean measured) for Oncorhynchus mykiss conducted with an 83% WP formulation, resulting in classification as Aquatic Acute 1, M = 10.

RAC indicate that adequate chronic toxicity data are not available for all trophic group. In addition, there are no reliable chronic toxicity data on most sensitive species comparing with acute toxicity. Hence, according to CLP criteria classification shall be assessed according to the criteria given in Table 4.1.0(b)(i) and if for the other trophic level adequate acute toxicity data are available according to the criteria given in Table 4.1.0(b)(iii) and should be based on the most stringent outcome.
Overall, RAC disagrees with the DS and concludes that captan warrants classification as Aquatic Chronic 1 with M factor of 10 based on most stringent outcome and supported by additional studies and read-across assessment with Folpet.

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2022	Netherlands		MemberState	31
Comment received				
The dossier submitter intended to add Aquatic Chronic 1 (H410), M=1 for classification of captan. This addition is not based on chronic toxicity data of captan. Instead, it used a precautionary chronic classification approach by reading across with another substance folpet. Based on a valid and reliable fish early life stage study on folpet (NOEC = 0.00881 mg folpet/L), rapidly degradable captan was proposed to classify as Aquatic Chronic 1 (H410), M=1. This read across approach was applied because the dossier submitter did not provide valid chronic fish toxicity tests. In contrast to the dossier's statement that no reliable chronic toxicity data with the most sensitive species are available, we notice that				

many chronic fish toxicity test data are available (see following details). We therefore suggest that classification should be based on the available chronic toxicity data for captan.

In detail:
P100, In section 10.6.1, only one fish chronic experiment was provided. The description of this study was not clear and difficult to follow. For example, age of animals exposed, sampling time/date for fish, concentrations tested, endpoints studied, etc, were not provided. The DS is requested to provide more details on this study.
Additionally, more chronic fish toxicity test results should be included in this section. For example, the Annex VI report does not include three chronic fish studies described in the RIVM report published in 2008 (https://www.rivm.nl/bibliotheek/rapporten/601716004.pdf, please note that this report is largely based on the DAR from 2005). Especially the study from Hermanutz et al. (1973) cited in the RIVM report seems to provide relevant data for the classification of captan. Additionally, a Fish Short-term Reproduction Assay (TG229) is available in the US EPA EDSP which can be found in the website: Status of Endocrine Disruptor Screening Program Tier 1 Screening Results and Data Evaluation Records | US EPA. The NOEC values of some of these studies are lower than the provided NOEC values of fish, daphnia and algae for captan described in this report. These studies should be used for the classification purpose.

Furthermore, a 21-day daphnia study is listed in the above RIVM report. Although it is not reliable, it is suggested to be included for completeness.

P100, section 10.6.3. In this section, it has stated that "The lowest endpoint for algae of 0.077 mg a.s./L (72 h NOErC) was derived from a study with the 83% WP formulation (Anonymous, 1994)". The DS is requested to explain why this value is not considered for the classification purpose as the concentration of the AI in the formulation seems sufficiently high to draw conclusions on the toxicity of the AI.

P101, in section 10.6.4 chronic toxicity to other aquatic organisms, it stated that "no toxicity data are available on other groups of aquatic organisms". This is not true. For example, an amphibian metamorphosis assay (AMA, TG 231, given in the US EPA ADSP) and a chronic development study with cancer magister (according to the CLH guidance, freshwater and marine data should be considered equivalent) from 1977 resulting in a NOEC of 3.1 ug/L (cited in the RIVM report) are also available. The results from these test should be considered for the classification proposal.

Dossier Submitter's Response

All detailed information on the studies are provided in the RAR of captan. The chronic studies with fish and aquatic invertebrates were not considered for classification as the studies are refined pulsed exposure studies which are not considered relevant for classification purposes.

For the chronic classification all data submitted by applicant were included in the assessment. The applicant submitted also prolonged toxicity studies with the active substance and the product (according OECD 204); however, these studies were not considered because the test guideline is no longer supported and therefore, the studies were not evaluated by the RMS or considered in the risk assessment.
The study by Hermanutz *et al*. (1973) was not submitted by the applicant and was also not mentioned in the literature search provided for the re-newal of the active substance.

Hence, the study was not evaluated by the RMS. This is also the case for the mentioned chronic developmental study with cancer magister from 1977.

However, we agree that the short-term reproduction assay (FSTRA) might be useful to consider for the chronic classification. In the study (Anonymous, 2012) a NOEC of 0.01 µg a.s./L can be determined. Further, the AMA might be considered as additional information; however, considering that most of the endpoints determined in the AMA are ED-specific endpoints the relevance of the AMA is questionable. Taking into account fresh weight and developmental stage a NOEC of 0.0073 mg a.s./L can be determined.

Regarding on the use of not reliable studies, the DS is of the opinion that only reliable studies should be included in the CLH report.

The algae study might be considered as additional information; however, considering that fish is the most sensitive species, the DS was of the opinion that the use of the algae study would result in a less conservative classification. However, the NOEC of 0.077 mg a.s./L might be considered as additional information.

Overall, the DS acknowleged that there might be further chronic studies which might be relevant for classification. However, these studies were not submitted by the applicant or were considered not relevant during the re-newal of the active substance captan.

RAC's response

RAC took note on additionally provided information regarding toxicity studies.
Regarding information from the RIVM report "Environmental risk limits for captan" (2008) (which is largely based on Draft Assessment Report (DAR, 2005) for captan) no robust summaries of the studies provided, therefore, RAC was not able to evaluate acceptability and reliability of these studies. RAC is also not in a position to clarify why studies available in the Draft Assessment Report (DAR, 2005) was not considered in the Draft Renewal Assessment Report (DRAR, 2012). As RAC do not have access to the full RAR or DRAR of active substance captan, evaluation of these studies can only rely on available information in the RVIM report.
Overall, the chronic development toxicity with Cancer magister study indicates 69 d-NOEC of 0.0031 mg/L for molting. Although given reliability of this study is score 1, RAC concedes that is not standard test and not standard species used in classification process. Without robust summary of the study, RAC cannot evaluate and confirm that obtained NOEC is acceptable and reliable from classification perspective according to CLP criteria.
Overall, fish early life stage test with Pimephales promelas is a common test which are frequently used in classification process. Although Klimisch score of the study is 2 without further information RAC is not in the position to assess reliability and acceptability of the obtained 30 d-NOEC (growth) of 0.017 mg/L. As such, these studies can only be used as supporting information.

Regarding information which are available in the US EPA Endocrine Disruptor Screening Program (US EPA EDSP) RAC acknowledge that 21-day short-term reproduction assay (MRID 48669501) of captan with fathead minnow (*Pimephales promelas*) was conducted under flow-through conditions. Mean-measured concentrations were <0.000014 (<LOQ; controls), 0.00011, 0.00099, and 0.010 mg a.s./L. The test system was maintained at 24 to 26°C and a pH of 7.0 to 7.7. Overall survival in the negative (clean water) and solvent controls was 88 and 96%, respectively. Overall survival was 100% in all captan treatment groups and was not significantly different from the negative control. Significant increases in male body weight at the high treatment level and in male body length at the mid and high treatment levels were observed relative to the negative control. There were no treatment-related effects on secondary sex characteristics or clinical signs. In the negative and solvent controls, spawning occurred at least every 4 days in three out of four replicates in the negative control and two out of four replicates in the solvent control. Fecundity and fertilization success was not significantly different in any treatment group relative to the negative control. Plasma vitellogenin (VTG) was significantly increased in males at the mid and high treatment levels relative

to the negative control. However, the increase was not concentration responsive. No EC_{10} or NOEC was obtained.
Overall, no reliable EC_{10} or NOEC can be derived from available information. However, RAC assume that significant increases in male body weight at the high treatment level and in male body length at the mid and high treatment levels suggest 21 d-NOEC of ≥ 0.01 mg/L.
The 21-day assay (MRID 49136701) of captan on Amphibian Metamorphosis (AMA) of African clawed frog (*Xenopus laevis*) was conducted under flow-through conditions. Mean-measured concentrations were <0.0000091 (<LOQ; controls), 0.000064, 0.00077, and 0.0073 mg a.i./L. Reviewer-calculated time-weighted average (TWA) measured concentrations were <0.0000091 (<LOQ; controls), 0.000060, 0.00074, and 0.0072 mg a.i./L. The test system was maintained at 21 to 23°C and a pH of 6.9 to 7.8. There were no significant differences between the negative control and solvent control. Throughout the 21-day exposure period, mortality did not exceed 3% in any treatment group. There were no significant effects of treatment on body weight or snout-vent length. As indicated in the study after 96 hours of exposure, the LC_{50}/EC_{50} values (based on sublethal effects) were 0.0774 mg/L. No EC_{10} or NOEC was obtained.
Overall, the AMA study result is related to endocrine disruptors specific endpoints and usually are not standard test used for classification purposes. Nevertheless, in the past RAC has classified based on ED endpoints. From available information no reliable EC_{10} or NOEC can be derived. At the highest treatment level no significant effects was observed. Therefore, RAC assume that 21 d-NOEC of >0.0072 mg/L could be obtained. However, might be used only as supportive information in the classification process.

Regarding information which is available in both sources (RIVM report (2008) and US EPA EDSP RAC acknowledge that Fish early life stage (ELS) study for 45 weeks by Hermanutz et al. (1973) are presented in both sources. The only difference is the rounded NOEC (growth) value.
Groups of 9-day old of Fathead minnow (*Pimephales promelas*) embryos (25 embryos/aquaria; 2 aquaria/dose group) were exposed to captan (88.4% purity) at nominal concentrations of 0 (negative control), 12.5-15.6, 25-31.3, 50-62.5, 100-125, or 200-250 µg/L under flow-through conditions for 45 weeks. Surfactant (Triton X-100) added at 6.7x10-6% vol/vol. Concentrations were measured daily and test results are based on mean measured concentrations. For the chronic exposure of Fathead minnows, survival of parental fish was decreased in the mean-measured 63.5 µg/L treatment group (↓98%). The parental fish length and the F_1 fish survival and length were also decreased in the mean-measured 39.5 µg/L treatment group. At the medium and medium-high concentrations (16.8 and 39.5 µg/L), the mean number of spawnings/female were decreased by 82 and 96%, respectively, compared to the control, and the mean number of eggs spawned/female were decreased, by 77 and 98%, respectively. The mean number of eggs/spawning was also decreased at the medium-high concentration by 42%, compared to the control. Percent hatchability of embryos from unexposed parents incubated at 63.5 µg/L captan was similar to that of control embryos, but all larvae died 5-8 days after hatching. There was 100% mortality of 1-day-old larvae from unexposed parents incubated at 63.5 µg/L captan within 24 hours. Survival of 3-day-old hatchlings in the medium-high concentration group was decreased approximately 50%. Overall, the LOAEC of 39.5 µg/L based on decreased growth and survival, and the NOEC of 16.8 µg/L was derived.
Overall, fish early life stage test with *Pimephales promelas* is a common test which are frequently used in classification process. The reliability score of the study by Klimisch is 2 and based on provided short summary in the US EPA EDSP the study seems to be acceptable and valid. Therefore, RAC concludes that 45 w-NOEC (growth) = 0.0168 mg/L is valid, acceptable, and reliable, and can be used in classification process according to CLP criteria.

Date	Country	Organisation	Type of Organisation	Comment number
05.10.2022	France		MemberState	32
Comment received				
FR globally agrees with the assessment and the approach performed by AT to reach the following hazard class and category for Captan: Acute Hazard Category 1, M-factor = 10; Chronic Hazard Category 1, M-factor = 1. 10.7.2 Long-term aquatic hazard (including bioaccumulation potential and degradation)				

page 101:
Could you, please, clarify the second paragraph of point 10.7.2?. Indeed, at the beginning of this paragraph it is written that captan 'is also not rapidly degradable based on the aerobic mineralisation in the surface water (DT50 < 1 h) and the results derived from the water sediment studies', which is not totally in line with the table 53 pages 84-86.
Then, at the end of the same paragraph, it is stated that captan is considered as being rapidly degradable in the aquatic environment.

10.7.2 Long-term aquatic hazard (including bioaccumulation potential and degradation) pages 102 to 105:
We acknowledge the read-across assessment conducted using the OECD QSAR Toolbox. However, for such complex prediction tool more details would had been appreciated in the CLH report.

Dossier Submitter's Response

Degradation:
Captan is not readily biodegradable but rapidly degradable in the water-sediment system. The sentence on aerobic mineralisation in the surface water is wrong. It should read "is also rapidly degradable based on the aerobic mineralisation….".

We acknowledge your comment on the read-across assessment. Further guidance on which information to include in the CLH report would be helpful for such kind of assessments.

RAC's response

RAC considers that, despite rapidly hydrolysis and indications of very fast primary degradation, captan is not ultimately degraded to > 70 % within 28 days (equivalent to a half-life < 16 days) and it cannot be demonstrated that all degradation products do not fulfil the criteria for classification as hazardous to the aquatic environment. Therefore, RAC considers captan as not rapidly degradable according to the CLP criteria.
RAC consider that reliable and valid Aquatic Acute endpoint is 72-hour LC_{50} of 0.0147 mg/L (mean measured) for *Oncorhynchus mykiss* conducted with an 83% WP formulation, resulting in classification as Aquatic Acute 1, M = 10.
RAC indicated that adequate chronic toxicity data are not available for all trophic group. In addition, there are no reliable chronic toxicity data on most sensitive species comparing with acute toxicity. Hence, according to CLP criteria classification shall be assessed according to the criteria given in Table 4.1.0(b)(i) and if for the other trophic level adequate acute toxicity data are available according to the criteria given in Table 4.1.0(b)(iii) and should be based on the most stringent outcome.
Overall, RAC disagrees with the DS and concludes that captan warrants classification as Aquatic Chronic 1 with M factor of **10** based on most stringent outcome and supported by additional studies and read-across assessment with Folpet.

CONFIDENTIAL ATTACHMENTS
1. Submitted docs.zip [Please refer to comment No. 1, 5, 8, 11, 15, 16, 18, 20, 24, 27]
2. Captan CLH Proposal - Position Paper - Final.pdf [Please refer to comment No. 12]