Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

folpet (ISO); *N*-(trichloromethylthio)phthalimide

EC Number: 205-088-6
CAS Number: 133-07-3

CLH-O-0000007326-73-01/F

Adopted

8 June 2023

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON FOLPET (ISO); 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: folpet (ISO); N-(trichloromethylthio)phthalimide
EC number: 205-088-6
CAS number: 133-07-3
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 Folpet and the presentation of it within this dossier clearly establishes local acute irritation as Folpet'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 five 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, Folpet can be robustly classified for acute inhalation toxicity, eye irritation and skin sensitization. Other classifications are inappropriate (STOT RE 1 and skin irritation), redundant (STOT RE 1) or irrelevant for humans (STOT RE 1, skin irritation, carcinogenicity) and inappropriately communicate Folpet's hazard for humans. Folpet'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 Captan may also be informative for the assessment of Folpet, 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. They could not be attached due to 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 Folpet 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 3, STOT-RE: Comment number 15.
RAC's response
RAC agrees with the DS that classification for different hazard classes can be triggered by folpet known cytotoxicity/irritation properties. A "double classification" is avoided by not proposing STOT SE 3; H335 since folpet is already classified for acute inhalation toxicity.

Date	Country	Organisation	Type of Organisation	Comment number
05.10.2022	Germany		MemberState	2
Comment received				
Based on our assessment under the recent pesticide peer review process for folpet (01/2020), DE-CA agrees with the update of the entries in Annex VI of CLP Regulation for Acute Tox. 2 (H330), Skin Sens. 1A (H317) as well as the addition of STOT RE 1 (H372) and Eye Dam. 1 (H318). We also agree with the proposal Aquatic Acute 1 (H400), M=10 and Aquatic Chronic 1 (H410), M=1. We would question, however, the proposed classification as Skin Irrit. 2 (H315). Please refer to our specific comment below.				
Dossier Submitter's Response				
Thank you for your agreement to our classification proposal for Acute Tox. 2 (H330), Skin Sens. 1A (H317), STOT RE 1 (H372), Eye Dam. 1 (H318), Aquatic Acute 1 (H400), M=10 and Aquatic Chronic 1 (H410), M=1. Regarding Skin Irrit. 2 (H315), please refer to comment number 11.				
RAC's response				
Noted.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
06.10.2022	France	ADAMA Makhteshim Ltd	Company-Manufacturer	3
Comment received				
Folpet 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 Folpet. 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, Folpet's inherent hazard property is acute irritation and not carcinogenicity. However, there are further lines of evidence that support a non-classification of Folpet 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 Folpet. Since Folpet 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 Folpet 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 Folpet 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 Folpet via the diet. US EPA states in their assessment report (US EPA 2022 "Folpet Proposed Interim Registration Review Decision Case Number 0630", Docket Number EPA-HQ-OPP-2012-0859) "Qualitatively, exposures to folpet are not expected to reach doses which would elicit an irritation response in the mucosal epithelium, and therefore exposures to folpet are not likely to induce carcinogenesis." (Note: this is a qualitative and not a quantitative argument)
3a) The use as a plant protection product in Europe does not result in irritating concentrations of Folpet 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.
3b) It is highly unlikely that irritating concentrations of Folpet could be practically achieved even by artificial means in a diet that would be edible for humans. Folpet 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) Folpet's primary degradation product phthalimide lacks the trichloromethylthio-moiety and is not irritating. Therefore, phthalimide, which is more relevant for human dietary exposure following Folpet degradation in human diet, cannot induce gastrointestinal irritation.
3d) Non-dietary exposure scenarios are irrelevant for this local effect because Folpet does not reach the intestinal epithelia via non-dietary routes following repeated, chronic exposure, and its systemic metabolites are not irritating.
A carcinogenicity hazard classification does not appropriately communicate hazard

associated with Folpet 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 Folpet 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.
Folpet 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.

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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 agrees with the DS arguments. Classification is hazard based. The available data provides sufficient evidence of carcinogenicity according to CLP criteria since folpet induces benign and malignant neoplasms in the gastrointestinal tracts in three independent, well-conducted studies in mice. While the underpinning mode of action is considered qualitatively relevant for human, RAC acknowledges that a clear threshold for tumour-development in mice is established and sustained irritating concentrations are necessary to trigger the downstream key events, which supports Category 2 classification.

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 Folpet. Three independent mice studies (with deviations from guidelines) showed increased level of carcinogenicity in both sexes in a single target tissue (duodenum), without marked general toxicity upon chronic Folpet exposure. This is normally considered sufficient to classify Folpet as Carc 1B. The proposed underlying mode of action of Folpet induced duodenum cancer is local irritation at the first site of contact. In the dossier it is suggested that continuous doses of Folpet are required for tumor formation. NL-CA agrees that this mode of action is plausible and a threshold mechanism is likely. The Dossier Submitter suggests, using an AOP developed by Bhat et al. (2020) that the levels of exposure needed for irritation to result in carcinogenicity are not reached in humans. However, classification and labelling criteria are based on the presence of a hazard, thus an unlikely human exposure scenario is irrelevant for classification. The Dossier Submitter also notes that the KEs are qualitatively plausible in humans (p 70).

As there is no evidence that the proposed mode of action of Folpet is not relevant for humans and the exposure scenario was the main argument to limit classification of Folpet to category 2 instead of 1B, the NL-CA disagrees with the proposed classification and considers classification as a carcinogen in category 1B would be warranted.
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 Folpet 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 Folpet, differences in GI-tract and glutathione-conjugation seem to result in different susceptibility of species [please refer to comment number 3 (2)]. Thiophosgene, formed by hydrolysis of Folpet, 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 Folpet, we propose classification as Carc. 2.
RAC's response
RAC agrees that classification and labelling criteria are based on the presence of a hazard. While the carcinogenicity studies in mice provide sufficient evidence to trigger Category 1B, RAC proposes to keep Category 2 taking into consideration the following factors decreasing the level of concern for human carcinogenicity: - Tumours are limited to one tissue (small intestine). - There is sufficient evidence that folpet is not mutagenic *in vivo*. Especially, no DNA damage in duodenal was noted in two independent comet assays in mice. - Based on a weight of evidence analysis, RAC considers that the proposed mode of action driven by enterocyte cytotoxicity with subsequent regenerative proliferation is sufficiently substantiated in mice. While this mode of action is considered qualitatively relevant for human, RAC acknowledges that a clear threshold for tumour-development in mice is established and sustained irritating concentrations are necessary to trigger the downstream key events.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
06.10.2022	France	ADAMA Makhteshim Ltd	Company-Manufacturer	5
Comment received				
We agree with the conclusion on classification in the CLH report. Folpet is not genotoxic in vivo, due to Folpet's inability to penetrate into the systemic compartment and Folpet'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 Folpet's in vitro genotoxicity potency. Together, the artificial thiol-poor environment of the in vitro experiments seems to be limiting an effective prediction of Folpet effects in complex biological systems, including human Folpet exposure scenarios.				

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Dossier Submitter's Response
Thank you for your agreement.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2022	Netherlands		MemberState	6
Comment received				
No Classification proposed by Dossier Submitter. NL-CA agrees no classification for mutagenicity is required. In vitro studies are consistently positive. However, in vivo studies are consistently negative and it is unlikely that Folpet is systemically available due to its short half-life. Metabolites show negative results in in vitro studies. Therefore classification as germ cell mutagen is not warranted.				
Dossier Submitter's Response				
Thank you for your agreement.				
RAC's response				
Noted.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
06.10.2022	France	ADAMA Makhteshim Ltd	Company-Manufacturer	7
Comment received				
We agree with the conclusion on classification in the CLH report. Folpet 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 Folpet, due to their known sensitivity towards gastrointestinal disturbance and their reliance on caecotrophy. Folpet'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 Folpet's metabolite phthalimide has a structure similar to thalidomide which is a known teratogenic substance in the rabbit. In a developmental study (Study 15), the metabolite phthalimide was tested clearly below the MTD, therefore effects at higher dose, capturing maternal toxicity, cannot be excluded based on this study.				
RAC's response				
RAC agrees with the DS that the dose tested in study 15 was too low to adequately investigate the developmental toxicity potential of phthalimide. Nevertheless, no				

teratogenic potential was demonstrated up to 30 mg/kg bw/day (molecular equivalent dose of folpet 60 mg/kg bw/day).

Furthermore, while of limited reliability (old studies with poor reporting, low number of animals, limited exposure duration), publications from open literature are consistently negative in rabbits up to 100 mg/kg bw/days in rabbits (Kennedy, 1966; Febro, 1966), and up to 1000 mg/kg bw (single dose) in Hamster (Robens, 1970). In all these publications thalidomide was also tested and was teratogenic.

From ECHA dissemination site (2023): Toxicity for reproduction of phthalimide was investigated in a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (1999). While this study is not dedicated to investigate structural abnormality, no pups were found with any malformation and body weight at birth was not affected up to 1000 mg/kg bw/d.

Folpet's PNDTS in rats (up to 2000 mg/kg bw/day corresponding to a molar equivalent dose of 1333 mg/kg bw/day) provide also some indirect evidence that phthalimide is not teratogenic in rats.

Overall, RAC acknowledges that some uncertainties remain due to the low dose level tested in the available GLP-compliant PNDTS in rabbits and the poor reliability of the supplementary data. However, none of these data provide evidence for embryonic/fetal lethality or teratogenicity of phthalimide. Therefore, phthalimide is not considered as toxic for the development based on inconclusive dataset.

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2022	Netherlands		MemberState	8
Comment received				
No Classification proposed by Dossier Submitter. NL-CA agrees no classification for reproductive toxicity is required.				
Dossier Submitter's Response				
Thank you for your agreement.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
06.10.2022	France	ADAMA Makhteshim Ltd	Company-Manufacturer	9
Comment received				
We agree with the conclusion on classification 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 Folpet formally qualifies for the "split-entry approach" proposed by Pauluhn, 2008, and referenced in CLP guidance (the same applies for Captan), which is relevant for irritant particles as generated by Folpet. 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 Folpet 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 Folpet:
- 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, for Folpet please refer to Figure 3 (page 25) in the CLH report
- 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): Hepatization of the lungs, incomplete lung collapse when trachea was cut, Haemorrhagic, swollen lungs, filled with liquid, trachea and thoracic cavity also filled with liquid/edema
- 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, Folpet 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, Folpet 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 Folpet is used per spraying, where nozzles could have an impact on particle size.
Furthermore, some uncertainties regarding the split entry concept include:

- Folpet might not be acutely irritating to all local site of contacts (i.e. skin). (Please refer to comment numbers 10-11)
- There are uncertainties regarding acute oral classification of the sibling Captan with a study conducted in mice (please refer to comment number 13 in the RCOM for Captan). Higher acute oral toxicity was observed in mouse- compared to rat-studies for Captan. No acute oral toxicity study in mice is available for Folpet.
- Additionally some effects at necropsy were observed outside the respiratory tract:
  - In Study 1 indirect macroscopic (liver discolouration) and microscopic changes in the liver were observed. Histopathological effects included vacuolar changes and necrosis, both centrilobular. However, the vacuolar changes were considered to be a result of anoxia, associated with congestion and vascular stasis, while the

necrosis was considered as an extention of the anoxic lesion, by the study author.
- In Study 2 most of the animals which died had either gelatinous material or gas in the stomach, small and large intestines, caecum and colon.
- In Study 3 several animals exposed to 4.35 mg/L showed haemorrhage of the small intestine with isolated signs of congestion and general reddening and one showed haemorrhage of the large intestine. One female, which was killed in extremis, also showed patchy pallor of the liver and kidneys and test material was present in the stomach. In two animals exposed to 1.06 mg/L, congestion of the small intestine was noted and one showed haemorrhage of the small intestine. Three animals that died at 0.14 mg/L exposure showed congestion and haemorrhage in the intestinal tract and patchy pallor of the liver.
- In Study 5 necropsy examination revealed a high incidence of dark mandibular lymph nodes particularly among the males. However, it was unclear if this finding was substance-related.

Therefore, we disagree to a split-entry.

RAC's response

RAC acknowledges that based on the available acute inhalation toxicity studies, lethality seems to be associated with differences in achieved particle sizes as illustrated in Figure 3 of the CLH report and some criteria of the split-entry are fulfilled for folpet. However, some uncertainties as listed by the DS remain and some criteria (Bal protein, histopathology after acute inhalation) were not examined.

CLP is a hazard-based regulation and Annex VI is dedicated to substances classification and not to formulated products. For acute inhalation toxicity of dusts and mists, testing with MMAD in the range of 1.0 to 4.0 is explicitly required to ensure comprehensive respiratory tract exposure in order to appropriately address inhalation hazard of the substance and subsequent labelling to communicate recommended measures. While, not all forms in formulated products and life cycle according different uses can be anticipated, the works from Canal-Raffin *et al.* (2007) provide one example not supporting the split-entry approach.

Indeed, Canal-Raffin *et al.* showed that the majority (>75%) of the particles of two commercial forms of folpet Folpan 80WG® and Myco 500® had a size under 5 µm under their typical application conditions.

In their commercial forms, while Myco 500® (a suspension concentrate) had particles size of 1–3 µm, Folpan 80WG® (a wettable granules formulation) had a mean particles size of 233.7 ± 6.01 µm. However, under their typical in-use conditions (working concentration of 1 g/l aqueous suspension), the proportion of Folpet's particles smaller than 5 µm was 76% and 84% for Folpan 80WG® and Myco 500®, respectively. After spraying, more than 80% of folpet particles were found to be under 5 µm in size for both commercial forms. This work showed that both the workers and the general population are indeed exposed predominantly to respirable particles of folpet whatever the granulometry of the formulated product is, which does not support a split-entry approach.

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
06.10.2022	France	ADAMA Makhteshim Ltd	Company-Manufacturer	10

Comment received

We disagree with the conclusion on classification in the CLH report.
While Folpet exposure is associated with skin irritation in rodent studies, the effect is not

considered to be relevant for human hazard communication:
- The effect only occurs with relevant potency in studies with repeated exposure. However, the classification criterion considers single exposure.
- The appropriate rabbit acute irritation studies with single exposure show no skin irritation relevant for classification. Note, Captan, which has the same underlying toxic mode of action, also shows no relevant skin irritation in the appropriate acute irritation assays.
- Skin irritation is a hazard observed in rodents but is probably driven by species differences due to different skin morphology/stratum corneum thickness. The data shows that rodents seem to be especially sensitive towards Folpet-induced irritation. Since rabbits show no irritation, and humans have an even thicker stratum corneum than rabbits, a classification for skin irritation is not considered relevant for humans.
- Critically, there is novel and recently published data, i.e., in vitro studies modelling human skin that show that Folpet 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 the publication 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 20273726 and 20273724) uploaded along with this comment.

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Dossier Submitter's Response

Please refer to comment number 11.

RAC's response

In a weight of evidence approach, giving more weight to reliable studies dedicated to answer to the CLP criteria, RAC considers that no classification is warranted for skin acute irritation.

Date	Country	Organisation	Type of Organisation	Comment number
05.10.2022	Germany		MemberState	11

Comment received

As stated in the CLH report, no classification for skin corrosion/irritation for folpet is triggered by the acute skin corrosion/irritation studies. In fact, study 1 and study 2 were both negative without any indications for skin irritation potential and mean scores of 0 - 0.3 in all animals. In contrast, erythema, oedema, scab formation, sloughing and lacerations were observed in one dermal subacute rat study with moderate effects from day 2 and in chronic oral mice studies.

According to the definition of the CLP Regulation, skin irritation/corrosion relates to damage to the skin following the application of a test substance for up to 4 hours. It remains questionable whether the effects observed in a repeated dose dermal toxicity study starting after 2 days of 6-h treatments in male rats can be extrapolated to a single 4-h dermal exposure scenario. An understanding of the mechanism leading to local skin effects observed with folpet in the repeated dose studies would be helpful to support such extrapolation.

In an overall WoE approach, we would currently conclude that there is not sufficient evidence for skin damage following up to 4-hour exposures.

Please note that we do not question the skin effects reported for the repeated dose studies and that labelling with EUH066 was considered as an alternative to classification during the pesticide peer review process for folpet (09/2019).
Dossier Submitter's Response
In the light of the new in vitro studies, we agree to the arguments provided by ADAMA (comment number 10) and Germany. Therefore, we would like to revise our proposal: Labelling with EUH066, based on erythema/oedema observed from Day 2 onwards in a 4-week dermal rat study, might be more appropriate than classification as skin irritant. We confirm that the recommendation from the pesticide peer review was "RMS to provide a CLH report to ECHA indicating that criteria for labelling for Folpet EUH066 might be met."
RAC's response
In order to signal the skin effects reported in the repeated dose studies, RAC concurs with DS's proposal to supplementary label folpet with EUH066.

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
06.10.2022	France	ADAMA Makhteshim Ltd	Company-Manufacturer	12
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 Folpet-induced irritation, which is biologically plausible as human cornea has a different morphology than rabbit cornea. Please refer to the publication 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 20273729 and 20273731) 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 2 out of 4 studies. Study 1 was terminated after 7 days due to irreversibility of changes (pannus formation associated with areas of severe opacity in the cornea) in 2/3 animals. In Study 4 vascularisation of the cornea and/or petechial haemorrhage of the nictitating membrane in conjunctiva persisted in animals until Day 14. Overall 3/6 animals were affected in this study by persisting effects. 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 Folpet 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 243 of clh_CONF_comments_folpet_attachments_en). This concentration is exceeding the water solubility of Folpet. Effects were more pronounced when Folpet was applied with physiological saline, an application form also strongly recommended by OECD TG 437. We would like to question, if by applying first Folpet 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 Folpet over the cornea.

RAC's response

The inconclusive results obtained in the *in vitro* assays do not challenge the positive results obtained in the reliable *in vivo* studies.
Based on the irreversibility of the effects, in accordance with the CLP criteria, RAC supports the DS's proposal to classify folpet for Serious Eye Damage Category 1 (H318; Causes serious eye damage).

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
06.10.2022	France	ADAMA Makhteshim Ltd	Company-Manufacturer	13

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 the publication 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 20273737 and 20273733) uploaded along with this comment.

We do not agree with classifying Folpet 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 (please refer to study report 1063-2003). 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 refer to study report 1063-2003 – potency prediction). While this is less robust than a dose-response GARD assay, it allows an approximation of sensitization potential. For Folpet, an LLNA EC3 of 3.27% can be estimated, which indicates only moderate sensitizing potential. This claim is supported with high statistical confidence, the 95% confidence interval is [1.75%, 6.16%], i.e., the confidence interval lies completely within the ECETOC category for moderate sensitizers and almost completely 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 [1.95%, 5.48%]).
The result of the GARD assay aligns with the unconvincing evidence for sensitization in exposed humans.

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 Study 1 of Folpet, where a sensitisation rate of 68% was observed, after an intradermal induction dose of 0.1% (Note in Study 2: 10% induction dose was used, allowing no potency discrimination). 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 Folpet 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 1.75-6.13% for LLNA EC3 value prediction. It is noted that the lower bound of the confidence interval is below 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 5.41), 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 24 of clh_CONF_comments_folpet_attachments_en). In our opinion the results of the extrapolation show that Folpet 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 concurs with the DS's proposal to classify folpet for Skin Sensitization Category 1A with a SCL of 0.001% based on a reliable GPMT. Sensitizing potential is further supported by human data. While not numerous, all diagnostic clinical studies among dermatitis patients report cases with positive results from patch testing with folpet 0.1% with relatively high frequency of occurrence. The *in vitro* tests also demonstrate that folpet is a skin sensitizer. Regarding potency discrimination, the GARDskin Dose-Response response assay being not validated as mentioned by the study author (disclaimer) and not cited in the OECD TG 497 dedicated to Defined Approaches for Skin Sensitisation, the estimated LLNA EC3 value is considered of lower reliability for subcategorization than available reliable GPMT.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
06.10.2022	France	ADAMA Makhteshim Ltd	Company-Manufacturer	14

Comment received

We disagree with the conclusion on classification in the CLH report.
There is no specific target organ or specific target organ toxicity for Folpet. Hence, any STOT classification per se miscommunicates hazard associated with Folpet exposure. Folpet's lead toxicity and inherent hazard property is acute irritation.
If a STOT classification would nevertheless be considered relevant for Folpet, 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.

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 15.

RAC's response

The acute inhalation toxicity studies clearly indicate respiratory irritant relevant for STOT-SE 3 (H335). However, the doses tested caused lethality. Folpet is already proposed to be classified for Acute Inhalation Toxicity Category 2 which takes precedence over STOT SE.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
06.10.2022	France	ADAMA Makhteshim Ltd	Company-Manufacturer	15

Comment received

We disagree with the conclusion on classification in the CLH report.
There is no specific target organ or specific target organ toxicity for Folpet. Hence, any STOT classification per se miscommunicates hazard associated with Folpet exposure. Folpet's lead toxicity and inherent hazard property is acute irritation.
If a STOT classification would nevertheless be considered relevant for Folpet, 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.
Folpet'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 the publication 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 787154) uploaded along with this comment.
Overall, the in vitro data clearly support acute cytotoxicity/irritation as the driver of Folpet'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) Folpet is classified for effects on the respiratory tract 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 Folpet 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 Folpet (and Captan) 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 Folpet. Considering a molar mass of about 300 g/mol for Folpet, a 0.0003 mM solution relates to a concentration of 0.09 mg/L that reduces cell survival to only 58% in the HPRT assay (CLH report page 44, Study 12, 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, 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) Laryngeal squamous metaplasia, proposed to trigger STOT RE 1, occurs after 20 repeated treatments with 25 µg/L for 6 hours/day, i.e., 0.025 mg/L. Acute Inhalation Study 3 (1991, CLH report page 26) shows that mortality occurs already after 4 hours treatment with 0.14 mg/L, which can be extrapolated by Haber's rule to 0.09 mg/L for 6 hours. Hence, significant toxicity, i.e., mortality, due to irritation, occurs already at 3.6-times the daily concentration, at a single exposure event, whereas laryngeal effects were observed after 20 (!) daily exposure events. 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 0.09 mg/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).

4b) An acute inhalation toxicity study for Captan resulted in 10% mortality after a single 4-hour treatment with only 0.072 mg/L, which can be extrapolated to 0.048 mg/L for 6 hours and which is less than twice the concentration that induces laryngeal effects. Since the toxic mode of action regarding irritation-induced acute inhalation toxicity is similar between the substances, the data indicates that irritative effects can be observed for such substances, at nominal concentrations similar to those inducing histopathological changes in the larynx in the repeated exposure study.
4c) The following discusses that the observed mortality in the repeated inhalation exposure is underpredicted by Haber's rule, which may serve as another line of evidence against the classification for STOT RE but may conversely support a STOT SE classification (while this double classifies for acute inhalation toxicity): The highest exposure concentration in the Folpet repeated inhalation exposure study was 0.1 mg/L (100 µg/L, nominal), which is a similar concentration resulting in 10% mortality in acute studies (see above). Indeed, in the repeated inhalation exposure study, 20% mortality is observed at the highest treatment concentration in males with 10% mortality averaged over males and females. Hence, comparable concentrations result in comparable mortality. However, considering that Folpet rapidly reacts with proteins and biomembranes, the apical effects in the repeated exposure studies can be described as the result of subsequent daily acute contact irritation events that have individually the same outcome but a lower potency according to Haber's law. 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 (20 * 1.5 * 0.1=) 3 mg/L (nominal, measured 2.91 mg/L), i.e., significantly higher (~7 times) than the LC50 for classification (0.43 mg/L) and with only 10% mortality. Due to the known rapid reaction capacity of Folpet 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 Folpet 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.

Additional comments:

Page 114, last line of Table 49: 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.

Page 117 (2nd paragraph): Regarding the CLH report assessment that there are no repeated dose inhalation ADME studies that would support accumulation of Folpet dose in the respiratory tract, and thus creates uncertainty regarding exposure cumulation: There may be a misunderstanding. It is rather unlikely that Folpet can cumulate in any biological system. However, the membrane reactivity -induced effects cumulate with subsequent exposure events, rather than accumulating an actual deposited dose. Any Folpet at the site of first exposure will react with the present proteins (within mucus or biomembranes) and degrade to its reaction products. As explained in previous sections in the CLH report, Folpet rapidly reacts and degrades but is continuously replenished for hours in inhalation studies due to the exposure scenario in the study design. It is not reasonable to assume that Folpet's MoA changes in the respiratory tract. Please also refer

to the available in vitro data and acute inhalation toxicity data that show that Folpet induces toxicity acutely.

Page 117 (last paragraph before 9.12.2):
- Regarding the CLH report assessment that there is a factor >25 between the dose causing adverse effects in the larynx and the dose concentration causing clinical signs in acute inhalation studies: The difference is rather 3.6 based on Acute Inhalation Study 3 which observes significant toxicity (mortality) at 0.14 mg/L or 0.09 mg/L (extrapolated for 6 hour exposure time). The difference is <2, based on a study conducted with Captan observing mortality at 0.072 mg/L, or 0.048 mg/L (extrapolated for 6 hour exposure time). Overall, it is suggested to base an assessment on the available weight-of-evidence and not on a single numeric comparison.
- Regarding the CLH report assessment that no histopathological evaluations of the respiratory system were performed after single exposure, making a direct comparison of effects difficult: There is novel in vitro data available (Kluxen et al. 2022) that clearly demonstrates that histopathological changes are induced after a single exposure event. Further, the effects observed in the study package are consistent and concordant with respect to the proposed MoA. Single exposure irritation is seen in the eye irritation studies and the acute inhalation toxicity studies. It is not reasonable to assume that Folpet's MoA changes in the respiratory tract or that a histopathological evaluation would add novel information - the adverse outcomes of eye irritation and mortality due to emphysema are known to be based on irritation and associated underlying histopathological effects. The assessment should be based on the weight of evidence from the available study package and not a single histopathological evaluation within one specific study.

Page 118 (table with CLP criteria) on assessment on larynx:
- It should be noted that the effects in larynx are typical for irritant particles in rat studies and are not considered relevant for humans, as extensively published and as appropriately referenced in the CLH report (see page 116). Hence, the currently proposed classification is based on effects that do not appropriately communicate human relevant hazard.
- Regarding the read-across to Captan, it should be considered that also the effects for Captan clearly occur due to acute aetiology. The effects (mortality) in the repeated inhalation exposure study are also less pronounced than predicted by Haber’s rule (compare comment 4c above), similar to the observation for Folpet, which again demonstrates that the compounds are best described as acute irritants.
- Regarding the read-across to Captan, while the underlying toxic mode of action is similar, it is unclear how laryngeal changes in the respiratory tract for Folpet are considered to be of similar toxic relevance and potency and thus classification as the mortality observed for Captan, also considering that the laryngeal changes are typical in rat studies with irritant particles and not relevant for humans due to morphological differences. It is very likely that the respiratory tract irritation is affected by solubility and thus in situ efficiency. Folpet is 5-10 times less soluble than Captan in water and thus obviously elicits its effects less efficiently on the cell surface in the respiratory tract, i.e., it is demonstrably less toxic after inhalation exposure than Captan (compare also Figure 1 in Kluxen et al., 2022 showing that Folpet has on average also higher LC50 values in acute inhalation toxicity studies than Captan).

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 107 ff of document "clh_CONF_comments_folpet_attachments_en". Cytotoxic effects of Folpet were observed at 400 µg/ml (LDH-release). 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 Folpet mainly by hydrolysis ($T_{1/2}$ in vitro human blood: 4.9 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 Folpet's acute and repeated-dose inhalative toxicity. Histopathological effects of Folpet were not only observed in larynx but also in nasal turbinates, trachea and lung. Furthermore, in a 90-day inhalation study of the sibling Captan 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 acknowledges that Folpet's mode of toxic action is well established as acute in situ membrane reactivity, cytotoxicity and irritation. However, RAC concurs with the DS 's arguments and considers that the effects observed in the 28-day inhalation toxicity study fulfil classification criteria for STOT RE since - quite severe laryngeal effects are observed from the lowest concertation and other effects in the olfactory epithelium tract, nasal cavity and trachea are also observed from the mid-concentration - an indirect line of evidence of irreversibility of laryngeal effects is provided by the results obtained in a 90-day inhalation toxicity study carried out with the sibling Captan. Atrophy of the olfactory epithelium is not considered to be reversible - considering the lowest tested concentration in the acute inhalation toxicity studies i.e. 0.14 mg/L for 4-hour treatment (equivalent 0.09 mg/L for 6 hours) where animals showed clinical signs and one out of five males died, a factor of 18 between the lowest concentration causing effects in the larynx in the 28-day study and the lowest concentration causing clinical signs in the acute inhalation toxicity study considering a 6-hour treatment. While the EpiAirway test has some limitations, histopathological changes seem more pronounced with repeated treatments (3-day exposure) compared to single exposure.

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2022	Netherlands		MemberState	16
Comment received				
Folpet 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 (5 µg/L), below the limit set by CLP criteria for category 1 classification (0.06 mg/L, adapted for exposure time).				
Dossier Submitter's Response				
Thank you for your agreement.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
05.10.2022	Germany		MemberState	17
Comment received				
DE-CA thanks the RMS for the assessment. We agree to the proposed classification as "Aquatic Acute 1" (M=10) and "Aquatic Chronic 1" (M=1). However, we have one additional remark concerning the report. • 10.1.1 Ready biodegradability To: Comments (RMS AT): As already noted, results in Anonymous (1998) are not fully in line with result obtained in Anonymous (1994) for unknown reasons Please also be aware that in study 1 (Anonymous (1994)) the used concentration of folpet was more than 30 times higher than the aqueous solubility limit. Study 2 (Anonymous (1998)) was conducted with a lower concentration of folpet. In the test report of study 2 it was considered that the biodegradation in study 1 may have been influenced by its rate of dissolution in the test medium.				
Dossier Submitter's Response				
Classification: Thank you for your agreement. We agree with Germany that the test concentration in Anonymous (1994) (10 mg C/L or 27.5 mg folpet/L) was about 30 times higher than the water solubility of folpet (0.8 mg/L). As mentioned by Germany this fact was already highlighted in Anonymous (1998) repeating the ready biodegradability study at significantly lower test concentration (1.0 mg folpet/L) for that reason ("… *it was considered that the observed rate of biodegradation* [in Anonymous, 1994] *may have been influenced by its rate of dissolution in the test medium.*" As the test concentration in Anonymous (1998) was set to the water solubility of folpet, results from Anonymous (1998) are considered more reliable then results from Anonymous (1994), even if the folpet test concetration was clearly below the test concetration of 10 – 20 mg C/L recommended in OECD 301. On overall, considering rapid degradation/dissipation in other aquatic systems (OECD 308, OECD 309 and OECD 111), we are of the opinion that folpet should be considered readily biodegradable.				
RAC's response				
Noted. RAC is of the opinion that Anon. (1998) test is not reliable for assessing ready biodegradability because of the unknown effect of lowering the test concentration so far from the general condition of the test. More details available in the RAC Opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
06.10.2022	France		MemberState	18
Comment received				
We agree with the aquatic acute and chronic toxicity classifications proposed, and with their respective M factors.				
Dossier Submitter's Response				
Thank you for your agreement.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
06.10.2022	United Kingdom	Health and Safety Executive	National Authority	19
Comment received				
Folpet (CAS: 133-07-3) If folpet is not considered rapidly degradable for hazard classification, we note the surrogate approach should be considered for aquatic chronic classification. This should consider the most sensitive fish species and invertebrate data. In an OECD TG301B study (Anon., 1994), significant mineralisation was observed but folpet did not meet the CLP criteria to be considered rapidly degradable. This study employed folpet at 27.5 mg/L equating to 10 C/L as per the relevant test validity criterion of 10-20 mg DOC/l. In a second OECD TG301B study (Anon., 1998), folpet was considered to meet the CLP criteria as rapidly biodegradable on the basis that it was considered readily biodegradable. The CLH report notes that this study employed a 'nominal [14C]-folpet concentration of 1 mg/L (10 mg/L of total folpet)'. This appears to be below the OECD TG301B test conditions of 10-20 mg DOC/L which may have been more favourable to rapid biodegradation. If the test item concentration was below the test conditions, the OECD TG 301 validity criterion (para 26) appears not to be met. On this basis, please can you confirm if the test item concentration met the test conditions and therefore relevant validity criterion. If the test item concentration was below OECD TG301B test criterion, we are unclear if this positive result should take precedent over the earlier reliable OECD TG301B standard study (Anon., 1994). We note that degradants do not fulfil the Aquatic Acute hazard classification criterion, but that chronic toxicity data do not appear to be available to consider if they meet Aquatic Chronic hazard classification criteria. If folpet is not considered rapidly degradable for hazard classification, we note the surrogate approach should be considered for aquatic chronic classification. This should consider the most sensitive fish species and invertebrate data.				
Dossier Submitter's Response				
Classification: According to the e-fate expert folpet is considered readily biodegradable and rapidly degradable in the water/sediment system. We agree that there are no chronic toxicity data with the degradation; however, the submission of chronic toxicity data is not triggered and is also not required for the renewal of the active substance folpet. Please also refer to comment 17. Be aware that the test concentration in Anonymous (1998) was actually 1 mg folpet/L (radiolabelled + unlabelled folpet) and not "10 mg of total folpet/L" as indicated in the comment above. Folpet tested in Anonymous (1998)				

comprised 10 % radiolabelled and 90 % unlabelled folpet, so 0.1 mg labelled and 0.9 mg unlabelled folpet per litre.
RAC's response
RAC agrees with the NA comments. RAC does not consider Anon. (1998) reliable based on the low test substance concentration. RAC also recognises the need for chronic toxicity data and use of the surrogate approach. More details available in the RAC Opinion.

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2022	Netherlands		MemberState	20
Comment received				
The dossier submitter intended to add Aquatic Chronic 1 (H410), M=1 for classification of folpet. This addition is based on a valid and reliable fish early life stage study on folpet (NOEC = 0.00881 mg folpet/L) for rapidly degradable folpet. We agree with this addition. Any other hazard classes or endpoints In the public domain more data on ecotoxicity of folpet is available than currently used in the report. In detail: P147, in section 10.6.1, ELS studies have been included. However, a fish reproduction test with Pimephales promelas is also available and should be included too. The details of this reproduction test can be found in the US EPA EDSP. P147, 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) performed with Xenopus is also available in the US EPA EDSP. These data can be found at (Status of Endocrine Disruptor Screening Program Tier 1 Screening Results and Data Evaluation Records | US EPA) and should be considered for the classification purpose too.				
Dossier Submitter's Response				
Regarding the data on chronic toxicity to fish all studies submitted by the applicant and considered valid and reliable were included in the CLH report. For the ED assessment of the active substance two fish short-term reproduction assays (Anonymous, 2012 and 2021) and an amphibian metamorphosis assay (Anonymous, 2013) were submitted as well. We agree that the fish short-term reproduction assays should have been included in the CLH report as well. However, the endpoints determined from these studies (NOEC = 0.0086 mg a.s./L (Anonymous, 2021) and 0.00627 mg a.s./L (Anonymous, 2021)) do not have an impact on the porposed classification. The use of the AMA for classification purposes is questionable considering that most of the key endpoints determined in these kind of studies are specific for ED, e.g. snout-vent legth. However, taking into account the paramters developmental stage and wet weight the NOEC derived from the AMA (NOEC = 0.0096 mg a.s./L, Anonymous, 2013) would also not change the proposed classification for folpet. Overall, we agree that the mentioned studies should have been included in the CLH report; however, the endpoints derived from these studies do not have an impact on the proposed classification of folpet.				
RAC's response				
Noted. RAC agrees with the DS.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON FOLPET (ISO); N-(TRICHLOROMETHYLTHIO)PHTHALIMIDE

Date	Country	Organisation	Type of Organisation	Comment number
06.10.2022	France	ADAMA Makhteshim Ltd	Company-Manufacturer	21
Comment received				
There are no further comments on acute and long-term aquatic hazard for classification and labelling. On OECD 301 B (Ready biodegradability): slight difference between the non-labelled (inherently degradable) and the phenyl labelled study (ready degradable); applicant supports RMS AT conclusion that the low dose radio-labelled study is more reliable as the non-labelled study. This approach is proven by the very fast degradation/dissipation rates of Folpet in water-sediment systems (OECD 308), in open water (OECD 309) and aqueous buffer solutions (OECD 111). ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Submitted docs.zip				
Dossier Submitter's Response				
We agree with France that Anonymous (1998) (low dose radio-labelled) is more reliable than Anonymous (1994) (high dose non-labelled) and that folpet should therefore be considered readily biodegradable. Please also refer to comment 17.				
RAC's response				
RAC disagrees with this comment and considers Anon. (1998) not reliable due to the very low test substance concentration (0.1 mg/L [U-phenyl-14C]-folpet + 0.9 mg/L) in the screening test where the general condition is to use 10-20 mg/DOC/L concentration.				

CONFIDENTIAL ATTACHMENTS
1. Submitted docs.zip [Please refer to comment No. 1, 3, 5, 7, 9, 10, 12, 13, 14, 15, 21]