COMPILED COMMENTS ON CLH CONSULTATION

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

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Last data extracted on 28.05.2024

Substance name: propyl [3-(dimethylamino)propyl]carbamate monohydrochloride; propamocarb hydrochloride
CAS number: 25606-41-1
EC number: 247-125-9
Dossier submitter: Portugal

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	Germany	Bayer AG	Industry or trade association	1
Comment received				
For convinience, the comments on the hazard classes are compiled in the document M-855327-01-1. Additionally, an Annex to the comments on the hazard classes is provided where the inconsistencies observed in the CLH report are summarized (M-855328-01-3). ECHA note – An attachment was submitted with the comment above. Refer to public attachment M-855328-01-3_Annex_redacted.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Propamocarb_ECHA consultation.zip				

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	United Kingdom	Health and Safety Executive (HSE)	National Authority	2
Comment received				
The CLH report states ‘Annex I is attached as a separate document.’ It would be useful to have this ‘annex’ available for the overall assessment.				

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	Belgium		MemberState	3
Comment received				
The BE CA would like to highlight that the reported data for some hazard classes are insufficient for a conclusive decision.				

PHYSICAL HAZARDS

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	Germany	Bayer AG	Industry or trade	4

			association	
Comment received				
We agree to the conclusion that no classification is warranted based on the data suitable for classification or labelling as: explosive (8.1.3), flammable liquids (8.5.3), self-reactive substances (8.7.2), pyrophoric liquids (8.8.3), self-heating substances (8.10.3), oxidising liquids (8.12.3), corrosive to metals (8.15.3). ECHA note – An attachment was submitted with the comment above. Refer to public attachment M-855328-01-3_Annex_redacted.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Propamocarb_ECHA consultation.zip				

HEALTH HAZARDS – Acute toxicity

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	Germany	Bayer AG	Industry or trade association	5
Comment received				
We agree with the conclusion that an acute oral, dermal and inhalation toxicity classification is not warranted under 10.1.3/10.2.3/10.3.3 "Conclusion on classification and labelling for acute oral/dermal/inhalation toxicity": The available toxicity studies with acute oral, dermal and inhalative administration demonstrate a low acute toxic potential of propamocarb with LD50 and LC50 values above the classification criteria. All studies are conclusive, but not sufficient to warrant an acute toxicity classification." Furthermore, we have the following comments: Table: 25 • One study on acute oral toxicity in rat from 2001 (M-205214-01-1) is not mentioned in the CLH report: The study supports the conclusion that no acute oral toxicity classification is warranted. • The last study (Acute oral toxicity study in mice) has the wrong reference. M-164833-01-1 is correct, instead of M-157621-01-1. Table 28: The last study (acute dermal LD50) has the wrong reference. M-205218-01-1 is correct, instead of M-205222-01-1. 10.2.1: • The described findings "…except erythema on the skin of 1 male and 2 female rats in one of the studies but all treated skin sites had returned to normal within 2 to 7 days after application." are not mentioned in the respective study (M-310341-01-1) 10.3.1: • "The principal clinical signs seen in the studies were wet fur, hunched posture and piloerection, but all animals were normal two to four days post-exposure." --> Animals were normal one to four days post exposure ECHA note – An attachment was submitted with the comment above. Refer to public				

attachment M-855328-01-3_Annex_redacted.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Propamocarb_ECHA consultation.zip

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	Belgium		MemberState	6

Comment received

Acute Toxicity – Oral
The preferred test species for evaluation of acute toxicity by the oral route is the rat. In general, classification is based on the lowest ATE value available i.e. the lowest ATE in the most sensitive appropriate species tested. The toxicokinetic profile didn't reveal any gender differences, neither species differences.
Out of anonymous_1982, a LD50 2000mg/kg bw is noted in females (mortality was observed from 1739mg/kg onwards and occurred on the day of dosing). This LD50 is borderline to classify in Category 4. Can DS provide us more data (number of tested animals? mortality at each dose?). Could you give us also these data for the other acute toxicity studies?
According to the criteria in CLP Annex I, 3.1.2 to 3.1.3.4, when the test substance have an oral LD50 >300 but ≤2000mg/kg bw, category 4 is required as an acute toxicity classification, harmful if swallowed (H302), a classification could be considered.

Acute Toxicity – Dermal
Based on the available data, BE CA can agree with the RMS, no classification is required.

Acute Toxicity – Inhalation
Based on the available data, BE CA can support the conclusion of the RMS, no classification is required.

HEALTH HAZARDS – Skin corrosion/irritation

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	Germany	Bayer AG	Industry or trade association	7

Comment received

We agree with the conclusion that skin corrosion/irritation classification is not warranted under 10.4.2 "Conclusion on classification and labelling for skin corrosion/irritation":

The available toxicity studies demonstrate no or mild effects on the skin which were completely reversible. Therefore, the criteria for classification are not met.

All studies are conclusive, but not sufficient to warrant a skin corrosion/irritation classification.

Furthermore, we have the following comments:
4. Text
• "In a primary dermal irritation study, each of 6 young adult NZW rabbits (3/sex) were exposed via the dermal route to 0.5 mL Previcur N
(68.7% propamocarb hydrochloride)."
--> 6 female animals were used.

• "However, all reactions had resolved by 24 hours apart from one animal in which the skin was normal by 48 hours"

-->According to the study, all reactions were resolved after 24 h.

• "In another primary dermal irritation study, each of 6 young adult NZW rabbits were exposed via the dermal route to 0.5 mL Proplant
(propamocarb hydrochloride722 g/L SL)."
--> 3 instead of 6 animals were used.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment M-855328-01-3_Annex_redacted.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Propamocarb_ECHA consultation.zip

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	Belgium		MemberState	8
Comment received				
Based on the available results, we can agree with the conclusion that no classification is warranted.				

HEALTH HAZARDS – Serious eye damage/eye irritation

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	Germany	Bayer AG	Industry or trade association	9
Comment received				
We agree with the conclusion that eye damage/irritation classification is not warranted under 10.5.3 "Conclusion on classification and labelling for eye damage/eye irritation": One study demonstrates slight and reversible eye irritating effects while the other study shows no irritating effects. In both studies the criteria for classification are not met. All studies are conclusive, but not sufficient to warrant an eye damage/eye irritation classification." Furthermore, we have the following comments: Table 37: • One study on acute eye irritation in rabbit from 1983 (M-157614-01-1) is not mentioned in the CLH report: The study supports the conclusion that no eye damage/eye irritation classification is warranted. ECHA note – An attachment was submitted with the comment above. Refer to public attachment M-855328-01-3_Annex_redacted.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Propamocarb_ECHA consultation.zip				

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	Belgium		MemberState	10
Comment received				
Based on the available results, we can agree with the conclusion that no classification is				

warranted.

HEALTH HAZARDS – Respiratory sensitisation

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	Germany	Bayer AG	Industry or trade association	11
Comment received				
We agree with the conclusion that a classification for respiratory tract irritation is not warranted under 10.6.3 "Conclusion on classification and labelling for respiratory sensitization": Since in the animal studies with propamocarb hydrochloride, no evidence of respiratory tract irritation was obvious, the data are conclusive but not sufficient to warrant a respiratory sensitisation classification. Furthermore, we have the following comments: Table 40: • "The NOEL for immunotoxic potential is expressed as propamocarb hydrochloride is 1065 ppm corresponding to 807.7 mg/kg bw/day." --> Here the NOEL is wrong, the correct NOEL for immunotoxic potential is 10605 ppm. ECHA note – An attachment was submitted with the comment above. Refer to public attachment M-855328-01-3_Annex_redacted.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Propamocarb_ECHA consultation.zip				

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	Belgium		MemberState	12
Comment received				
BE CA agrees that no classification is warranted.				

HEALTH HAZARDS – Skin sensitisation

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	Germany	Bayer AG	Industry or trade association	13
Comment received				
We agree with the conclusion that a classification as weak skin sensitizer (Category 1B) is warranted under 10.7.3 "Conclusion on classification and labelling for skin sensitisation": Weak evidence of skin sensitisation was observed in a Magnusson and Kligman test (M-184379-01-1) and in a local lymph node assay with Propamocarb hydrochloride SL 722 (M-252483-01-1). This classifies Propamocarb hydrochloride as a weak sensitizer (Cat. 1B). All studies are conclusive, and sufficient to warrant a classification for skin sensitization. Furthermore, we have the following comments: 10.7.1: • "In the positive control group given p-Benzoquinone, a SI value of 3 was noted which				

demonstrated the validity of this assay using the
specific test formulation, with a positive response to treatment with p-Benzoquinone."
--> correct is: …a SI value of >3…

ECHA note – An attachment was submitted with the comment above. Refer to public attachment M-855328-01-3_Annex_redacted.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Propamocarb_ECHA consultation.zip

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	United Kingdom	Health and Safety Executive (HSE)	National Authority	14
Comment received				
Section 10.7. We note that the DS has proposed a classification of Skin. Sens 1B for propamocarb hydrochloride primarily based on the findings from the OECD TG 429 study (LLNA). However, an agrochemical formulation has been employed to dose the animals. Would the DS be able to clarify what the co-formulants were and any harmonised or self-classifications?				

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	Belgium		MemberState	15
Comment received				
Based on the available results, we support the proposal to classify in category 1B.				

Date	Country	Organisation	Type of Organisation	Comment number
22.05.2024	Germany		MemberState	16
Comment received				
Subclassification in category 1B is supported.				

HEALTH HAZARDS – Germ cell mutagenicity

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	Germany	Bayer AG	Industry or trade association	17
Comment received				
We agree with the conclusion that classification for germ cell mutagenicity is not warranted under 10.8.3 "Conclusion on classification and labelling for germ cell mutagenicity": The available in vitro and in vivo mutagenicity/genotoxicity studies (4 tests for bacterial mutation, 2 tests for chromosome aberration, 2 tests for mammalian cell mutation, 2 in vivo MNT studies and 1 in vivo dominant lethal mutation test) are all negative and demonstrate that propamocarb hydrochloride does not fulfil the criteria for classification. All studies are conclusive, but not sufficient to warrant classification for mutagenicity. Furthermore, we have the following comments: Table 46: Study Nr. 4 (M-310449-01-1):				

The tested concentration range is given as "69 – 5000 µg/plate (with and without S-9 mix)"; however, it should be 7 – 5000 µg/plate

Study Nr. 5 (M-157641-01-1):
"Technical propamocarb hydrochloride did not significantly increase the incidence of chromosomal aberrations…".
However, according to the study, the highest concentration in the absence of S9 mix lead to a very small increase. This was only significant if compared to solvent control (not if compared to untreated control) and was within HCD of the laboratory.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment M-855328-01-3_Annex_redacted.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Propamocarb_ECHA consultation.zip

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	Belgium		MemberState	18
Comment received				
No in vivo mutagenicity/genotoxicity was observed; BE CA agrees with RMS. However, noteworthy is the disturbance of erythropoiesis during an in vivo micronucleus test in CD-1 mice.				

HEALTH HAZARDS – Carcinogenicity

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	Germany	Bayer AG	Industry or trade association	19
Comment received				
We agree to the conclusion of the absence of a carcinogenic potential: In the conclusion part '10.9.2 Comparison with the CLP criteria', the CLH report states: "The discussed mononuclear cell leukaemias in the female haemolymphoreticular system and kidney neoplasms in male rats at a dose beyond MTD are within historical control ranges and not treatment-related, therefore, no evidence of a tumorigenic or carcinogenic potential was evident in these studies with propamocarb hydrochloride." We also agree to their conclusion about the mortality results in the long-term mouse studies, which led in the RAR to a reduction of the NOAEL for the setting of the ADI since interestingly, the published CLH draft report supports our conclusion that in the three mouse long-term studies no treatment-related effect on mortality occurred so that the establishment of the NOAEL of 6.8 mg/kg bw/day for establishment of the ADI is not justified. Text in CLH report: "In a 104-week mouse oncogenicity study, there were no treatment-related clinical signs of toxicity, mortalities, gross pathological findings, histopathological findings or effects on body weight, body weight gain, food consumption and food efficiency." In the CLH report a NOAEL of 36.5 mg/g bw/day is set, which we concluded from this mouse study for setting the ADI.				

For the other mouse long-term studies also no effects on mortality are claimed.

Text in the CLH report: "In a 18-month mouse oncogenicity study, no treatment-related clinical signs of toxicity, mortalities, ocular effects or effects on food consumption, haematology, organ weight, gross pathological or histopathological findings were noted."

For a third mouse long-term study only body weight effects at the highest dose were the reason for using the next lower dose of 106 mg/kg bw/day (males) as NOAEL. Mortality is not mentioned in the text.

In the conclusion part '10.9.2 Comparison with the CLP criteria', the CLH report states: "In mice only body weight and food intake effects were observed. In these studies, no compound-related deaths, major functional changes in the central or peripheral nervous system or in other organs, consistent changes in clinical biochemistry, hematology or urinalysis parameters that indicate severe organ dysfunction or severe organ damage noted in microscopic examination following autopsy were seen."

We agree to their conclusion with regard to the finding choroid plexus cellular vacuolation, especially not to classify it under STOT-RE.

Text in CLH report: "A re-evaluation of choroid plexus cellular vacuolation led to the conclusion that this phenomenon could be due to either phospholipidosis or a direct localised effect on fluid homeostasis. However, staining of the choroid plexus for neutral fat (Sudan Black) or lipoprotein (Periodic Schiff) were negative in samples from control and high dose males while staining with Toluidine Blue did not indicate the presence of material within the ependymal cells. Vacuolation was not recorded in other tissues and no other histopathological findings were documented in the central nervous tissue or the ciliary body of the eye which is related to the choroid plexus. Since phospholipidosis stains strongly positive with Periodic Schiff stain, it was concluded that the observed vacuolation was likely the result of a species-specific localised effect on fluid homeostasis, i.e. accumulation of excess intracellular fluid."

No conclusion of a relevance of this finding for humans is made, see also STOT-RE chapter 10.12.1.

Text in CLH report: "Therefore, the available toxicity studies do not show significant or severe toxic effects at dose levels requiring classification as STOT-RE. Especially, the lowest doses at which first signs of choroid plexus vacuolization were seen were rather high with an isolated finding in one of the subacute rat studies at 200 mg/kg bw in 1 animal per sex only and with only minimal severity. It was clearly above the STOTRE criteria with approximately more than 400 mg/kg bw/day in the more relevant subchronic toxicity and subchronic neurotoxicity studies in rats"

In Table 49 (Summary table of animal studies on carcinogenicity) on page 48 they say "This is a pre-guideline study and consequently a number of significant deviations from current guidelines were identified. Most notably, the mortality rate exceeded 50% by 24-months ranging from 43 – 70% (mean 58%) which invalidates the conclusions drawn in the study with respect to the negative toxicological effects of the test material." It could e added that the highe mortality occurred in all groups, including the control and thus was not treatment-related.

On page57, a sentence is interrupted, see text part in CLH report:
"An increased incidence of icterus was recorded in females found dead or prematurely

sacrificed which reflects the clinical signs of jaundice recorded. Body fat depletion in high-dose males may be a consequence of the decrease in -- body weight while the incidence of 'thin and watery blood' was not corroborated by any haematological findings."

Page 51:
In Table 49 the NOAEL carcinogenicity should be the highest dose of 1098 (males)/1195 (females) mg/kg bw/day since no carcinogenic effect occurred.

Page 54:
In Table 49 for the 2nd mouse study no doses given: 0, 120, 840, 6000 ppm (equivalent to 0, 15, 106, 790 (m)/0, 19, 136, 1014 (f) mg/kg
bw/day.

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Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	Belgium		MemberState	20

Comment received

In the report, the DS mentions 4 combined chronic toxicity and oncogenicity studies conducted in rats (across 4 different strains) and 3 studies in CD-1 mice. Notably, neoplastic findings were observed in one study involving F-344 rats. Specifically, a statistically significant positive dose-response for fatal/possibly fatal mononuclear cell leukemias in the females was noted, with significant results when pooling the data across prevalence and death-rate analyses. The DS mentions that the study's incidence of 38 % fall within the range of historical control rates (Haseman et al., 1998) leading to no attributed toxicological significance to the statistical difference in leukemia incidence in female rats. Historically it is known that leukemias in female F-344 rats are common, with a mean incidence of 28 % and a range up to 52 %. In the same study the incidence of kidney neoplasms in males exceeded historical control data for kidney carcinoma and adenoma.
In another study using SD-rats, the incidence of mammary gland fibro-adenoma in terminal sacrifice females was increased at the mid and high doses compared to controls, although the frequencies are mentioned to stay within the normal range for SD female rats.
Could you please provide us with more details about these two studies? Without having more details it's difficult to draw a meaningful conclusion.
It's true that a high spontaneous tumor incidence is observed in female SD rats in terms of mammary gland tumors (adenomas and carcinomas) (NTP, 2005). The same is true for mononuclear cell leukemia in F344 rats (NTP, 2007a; RIVM, 2005). However, this is not the case for the observed kidney neoplasms.
In table 52 'Haseman et al., 1998' is mentioned as a reference for the kidney data, although in the text above, this publication was used as a reference for HCD for mononuclear cell leukemia. Is there a typo here? A statistically significant positive dose-response trend was identified when all treated groups were compared to the control group (p=0.03), but pair-wise comparisons were not statistically significant when adenomas and carcinomas were analyze separately.
However, when compared to historical control incidences, the incidences of kidney carcinoma (2 %) and adenoma (4 %) in males exceeded the historical control incidences of 1/90 animals and 1/175 animals, respectively.
Despite these ambiguities, we do agree that neoplasm findings were only seen in one species, one sex at doses exceeding the MTD, which leads to greater doubt about the

potential for carcinogenicity in humans. We note the lack of genotoxicity. We observe bone marrow toxicity in a subacute systemic tolerance study, without any organ damage. Any consistent changes which could be predictive for severe organ dysfunctions or organ damage are not noted in studies with propamocarb. Therefore, classification does not appear to be necessary at this time, out of these mentioned studies.
While screening the literature, we found another mention to another chronic exposure and carcinogenicity study conducted on Sprague-Dawley CD rats (dietary administration of propamocarb hydrochloride as a 70 % aqueous formulation at 0-40-200-1000 ppm during 104 weeks). In this study evaluation of the neoplastic changes demonstrated an increase in occurrence in males of subcutaneous fibrosarcoma in the treated groups. Incidence of the tumor was 0/58 in controls, 5/56 (8.9 %) at 40 ppm, 2/58 (3.5 %) at 200 ppm and 7/55 (12.7 %) at 1000 ppm (the denominator denoted the number of survivors from both main and satellite groups at each dosage level at the end of 51 weeks when the first subcutaneous fibrosarcoma was detected in the males). The difference from concurrent controls was statistically significant at 40 ppm and 1000 ppm. Data on background incidence of subcutaneous fibrosarcoma in the particular strain of rats employed in the study were not available in the report. Over 80 % of the concurrent controls (both sexes) had tumors, with pituitary adenoma (both sexes), mammary tumors (females) and subcutaneous fibroma and lipoma (males), the most prevalent tumors. There were no other neoplastic differences between treated and control groups.
WHO/FAO; Joint Meeting on Pesticide Residues; Pesticide Residues in Food: Propamocarb (1984). Available from, as of July 31, 2018: https://www.inchem.org/pages/jmpr.html

HEALTH HAZARDS – Reproductive toxicity

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	Germany	Bayer AG	Industry or trade association	21

Comment received

Text in CLH report (page 62): "In another two-generation reproduction study Sprague-Dawley rats were administered doses of 0, 50, 200 and 1000 mg/kg bw/day by gavage. Reduced body weight gains and food consumption, reduced survival, clinical signs and vacuolar changes in the epithelial cells of the choroid plexus were seen at ≥ 200 mg/kg bw. Only at the highest dose of 1000 mg/kg bw/day, changes in sperm parameters and decreased survival in F1 pups during lactation were noted. At this dose also a slightly decreased copulation index for F1 females was seen, with slight effects on this parameter also at 200 mg/kg bw.

Therefore, the parental NOAEL was 50 mg/kg bw/day, equivalent to 37.5 mg active ingredient/kg bw/day. The reproductive NOAEL was 200 mg/kg bw/day, equivalent to 150.1 mg active/ ingredient/kg bw/day. The developmental NOAEL was 200 mg/kg bw/day, equivalent to 150.1 mg active ingredient/kg bw/day based on decreased pup viability at 1000 mg/kg bw/day.

This is discussed in detail in a position paper M-256378-01-1).

The changes in sperm parameters occurred only at the highest dose of 1000 mg/kg bw which caused severe clinical signs and distinct body weight and feed intake effects. Therefore, the sperm parameter changes are clearly the consequence of the general parental toxicity. Most importantly, the relevant reproduction parameters, like mating, female and male fertility index, did not show any impairment in any generation, even not at the highest dose. This shows that an evaluation of isolated sperm parameters is not reasonable, but that the male reproductive parameters have to be interpreted collectively,

and ECETOC (EPA, 1996 cited by ECETOC, 2002). Furthermore, the 2nd reproduction toxicity study did not confirm these sperm findings. Therefore, overall, based on the results of the two reproduction studies together, a classification is not justified. Furthermore, no evidence of an effect of sperm parameters, testicular weight changes or other changes which are indicative of an effect on the male endocrine system were noted in the short- and long-term studies."

We agree to this conclusion since they accepted our position that the changes of sperm parameters at the highest dose of 1000 mg/kg bw are clearly the consequence of the general parental toxicity and not a direct endocrine-mediated effect. They also agree to our proposal that an evaluation of isolated sperm parameters is not reasonable, but that the male reproductive parameters have to be interpreted collectively, using a weight of evidence approach as recommended by USEPA and ECETOC (EPA, 1996 cited by ECETOC, 2002). They accepted also all our other arguments to support that this sperm finding is not an ED effect, therefore, we agree that a classification is not warranted.

Page 60:
In Table 53, NOAEL in Rat dietary two-generation study: parental: 200 ppm, offspring: 1250 ppm.

Page 61:
for 2nd study, NOAELs: reproductive: 50 mg/kg bw, offspring: 200 mg/kg bw

We agree with the conclusion that no classification for reproductive and development toxicity is warranted.

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

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	Belgium		MemberState	22

Comment received

The DS reports several effects (maternal, fertility or developmental), without providing further available data. However, these data are essential to conclude on the reproductive toxicity. Can DS provide more data:
In the Rat Dietary Two-generation Reproductive Toxicity Study (Anonymous, 1998), an increase duration of gestation length and modification in offspring are mentioned in the Table 53. Could you give us the data about these. NOAEL for parental toxicity and developmental toxicity mentioned in the section 10.10.2 is 1250 ppm. Additional data regarding maternal toxicity are needed to correctly conclude if the developmental effects are secondary or not to maternal toxicity.
In the second Two-generation Reproductive Toxicity Study in Rats (Anonymous, 2002), Table 53 also mention several effects without providing more information. Could you please develop the data regarding maternal toxicity (mortality, clinical signs, body weight and food consumption) as well as sperm parameters and offspring data (mean number of pups, viability and body weight).
Concerning the study Embryotoxicity including Teratogenicity in rats (Anonymous, 1990), the provided information does not allow us to conclude. In Table 56, a NOAEL for developmental toxicity of 68 mg/kg bw/d and 204 mg/kg bw/d for maternal toxicity are mentioned while in the section 10.10.5 it is states "The NOAEL for maternal and

developmental toxicity was 204 mg/kg bw/day of Propamocarb hydrochloride.". Could you please clarify which is the correct NOAEL. Furthermore, the report give us the incidences (in %) for additional 14th ribs. Have you got also the data regarding incidence of resorptions, the number of live foetus as well as dead foetus, mean fetal weight and incidence of variations (retarded skeletal ossification).

Date	Country	Organisation	Type of Organisation	Comment number
22.05.2024	Germany		MemberState	23
Comment received				
At a previous pesticides peer review meeting (April 2019), developmental toxicity was already discussed controversially. Here, the DS states that "effects on foetuses were observed at dose levels which caused also maternal toxicity". However, from the documentation available, it is difficult to conclude whether the extent of maternal toxicity was sufficient to conclude on a causal relationship between maternal and embryo-/fetotoxicity. A systematic comparison of maternal and offspring toxicity for the dose levels investigated and, if available, an analysis of the correlation based on individual animal/litter data would be helpful to draw a final conclusion. More information is needed on the extent/significance of the maternal toxicity.				

HEALTH HAZARDS – Specific target organ toxicity - single exposure

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	Germany	Bayer AG	Industry or trade association	24
Comment received				
We agree with the conclusion that a STOT-SE classification is not warranted under 10.11.3 "Conclusion on classification and labelling for STOT SE": The available toxicity studies with acute oral, dermal and inhalative administration demonstrate a low acute toxic potential of propamocarb with LD50 and LC50 values above the classification criteria. Furthermore, the acute neurotoxicity studies do not show significant or severe toxic effects at dose levels requiring classification. All studies are conclusive, but not sufficient to warrant a STOT-SE classification. ECHA note – An attachment was submitted with the comment above. Refer to public attachment M-855328-01-3_Annex_redacted.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Propamocarb_ECHA consultation.zip				

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	Belgium		MemberState	25
Comment received				
Reversible neurotoxic adversity was observed after a single oral exposure in SD rats at doses greater than 2000 mg/kg bw. In another study conducted on Wistar rats, no neurotoxicity was observed even at the highest dose level of 2000 mg/kg bw. In a micronucleus test conducted in CD-1 mice, a single dose of 2500 mg/kg bw produced evidence of bone marrow toxicity. Based on these available results no classification is required, and BE CA agrees with the DS.				

HEALTH HAZARDS – Specific target organ toxicity - repeated exposure

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	Germany	Bayer AG	Industry or trade association	26
Comment received				
We agree to the conclusion that a STOT-RE classification is not warranted under "10.12.3 Conclusion on classification and labelling for STOT RE : The available toxicity studies with repeated oral, dermal and inhalative administration do not show significant or severe toxic effects at dose levels requiring classification, thus they are conclusive, but not sufficient to warrant a STOT-RE classification." ECHA note – An attachment was submitted with the comment above. Refer to public attachment M-855328-01-3_Annex_redacted.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Propamocarb_ECHA consultation.zip				

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	Belgium		MemberState	27
Comment received				
Based on the available information, indication of toxicity in the choroid plexus of the brain was noted in rats (in the 28 days and 90 days studies), however these effects were observed at doses which don't trigger classification. We support the conclusion that no classification is warranted as no significant toxic effect was noted in the range to classify as STOT RE.				

ENVIRONMENTAL HAZARDS – Hazardous to the aquatic environment

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	Germany	Bayer AG	Industry or trade association	28
Comment received				
We agree to the conclusion that no classification is warranted based on the data suitable for aquatic hazard classification (acute and longterm), bioaccumulation potential and degradation. Furthermore, following comments that are compiled in a separate document M-855328-01-3. ECHA note – An attachment was submitted with the comment above. Refer to public attachment M-855328-01-3_Annex_redacted.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Propamocarb_ECHA consultation.zip				

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2024	United Kingdom	Environment Agency	National Authority	29
Comment received				
Propamocarb hydrochloride (CAS: 25606-41-1)				

Rapid degradability (section 11.1 - Rapid degradability of organic substances)

Whilst it will not impact the classification, we are unclear if the substance meets the CLP criteria for rapid degradation.

In the comparison for the CLP criteria section (11.7) of the CLH report, the DS considered the substance was rapidly degradable based on a water/sediment DT50 of 8.7 days and a soil DT50 of 6.5 days. We are unclear of the basis of this DT50 of 8.7 days as it is not referred to in body of the CLH report – please could the DS clarify? We also note that aquatic simulation degradation data are available so should be used in preference to soil degradation data for CLP purposes.

Total system DT50 values of 15.5 and 15.9 days have been reported for the water-sediment degradation simulation study by De Vries (1997). Although these values are below the hazard classification criterion of <16 days for rapid degradability, they do not demonstrate ultimate degradation by >70% over 28 days as CO2 accounted for only 30.6% AR after 28 days (propamocarb DAR, 2005). The DAR (2005) also notes that the DT50 values are a function of dissipation as well as degradation. Minor degradation products were detected in the study but not identified. Therefore, it is not possible to demonstrate that the degradation products do not meet the criteria for classification as hazardous to the aquatic environment. Overall, it appears that this study does not support the substance being rapidly degradable.

Although the pass level was reached in the two ready biodegradation studies, no significant degradation was observed in some of the test vessels in the study by Desmares-Koopmans (1990) and the 10-day window, although borderline, was not met in the study by Weyers (2008). The nitrification correction carried out for the study by Weyers (2008) follows OECD TG 301 recommendations which is based on 28-day measurements of nitrite and nitrate, as opposed to measurements throughout the study duration. We therefore believe it is appropriate that these corrected BOD values have been used to assess the 10-day window as per OECD TG 301F, and support that the substance is not readily biodegradable.

Chemical forms

We note the pesticide RAR (2017) for propamocarb mentions both 'propamocarb (base)' and 'propamocarb hydrochloride (variant; salt)' as 'the active substances'. With a pKa of 9.6 at 20°C, propamocarb hydrochloride dissociates in water. Is this CLH proposal intended to cover both the propamocarb 'base' (CAS: 24579-73-5, EC: 607-406-2) and hydrochloride (CAS: 25606-41-1, EC: 247-125-90) variants of the substance? The ECHA database appears to include another variant, 1,1,2,2,3,3,3-heptadeuteriopropyl N-[3-(dimethylamino)propyl]carbamate (CAS: 1398065-89-8, EC: 975-390-7). Would it be appropriate to also cover this substance under the same CLH proposal since it presumably dissociates into the same active molecule, and consider any additional hazard data for this form too?

PUBLIC ATTACHMENTS
1. M-855328-01-3_Annex_redacted.pdf [Please refer to comment No. 1, 4, 5, 7, 9, 11, 13, 17, 19, 21, 24, 26, 28]

CONFIDENTIAL ATTACHMENTS
1. Propamocarb_ECHA consultation.zip [Please refer to comment No. 1, 4, 5, 7, 9, 11, 13, 17, 19, 21, 24, 26, 28]