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 24.07.2023

Substance name: dimethachlor (ISO); 2-chloro-N-(2,6-dimethylphenyl)-N-(2-methoxyethyl)acetamide
CAS number: 50563-36-5
EC number: 256-625-6
Dossier submitter: Croatia

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
19.07.2023	United Kingdom	Health and Safety Executive	National Authority	1
Comment received				
Carcinogenicity We note comments from the RMS about histopathological findings in the nasal cavity for acetochlor, alachlor and butachlor. To further understand the carcinogenic potential of dimethachlor it would be useful to include any detailed histopathological findings for the nasal passage from the available repeated dose toxicity studies for dimethachlor. We note there are some uncertainties about the nasalpharanygeal adenoma in rodents and their relevance to humans. We think it may be important to provide some comment on the known difference in enterohepatic circulation cut-offs in rodents and humans and the relative bioavailability's of the critical sulfur containing metabolites.				

Date	Country	Organisation	Type of Organisation	Comment number
21.07.2023	United Kingdom	Syngenta	Company-Manufacturer	2
Comment received				
The Applicant considers that classification of dimethachlor as Carc. Cat. 2 is not justified. As explained in the detailed expert statement, "Dimethachlor Mechanism of Formation and Human Non-Relevance of Nasal Turbinate Tumours in Rat", provided separately, the weak carcinogenic effect observed with dimethachlor in the nasal tissue of the high dose male rats in the long-term rat toxicity study is not relevant for humans. As mentioned in the expert statement, two in vitro metabolism studies have been conducted with dimethachlor, in order to support the mode of action for nasal tumour formation. As one of the previously submitted reports has been amended to correct information on the material used, and the second, GLP report has not been included in the submitted dossier, OECD summaries of both studies are provided. Study reports can be provided on request. These studies are considered key information with regard to dimethachlor metabolism and mode of action.				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment dimethachlor.zip

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2023	Germany		MemberState	3

Comment received

The classification as Carc. 2 is supported. However, the following aspects should be taken into consideration:

a) Despite the results of the newer study (K-CA 5.1.1/04), an N-dealkylated metabolite MET 11U was detected in the study by <confidential> (K-CA 5.1.1/02), albeit at low levels (U7 in Table B.6.1.1-14). N-dealkylation of the alpha-carbon atom is a key step resulting in protein adduct formation.

b) S-metolachlor was wholly excluded from the argument; however, the DE CA opines it should also be included because it is structurally more similar at a key position, namely the beta rather than the alpha carbon, which as mentioned above is the crux of the argument. In the recent RAC Opinion for S-metolachlor (CLH-O-0000007145-77-01/F), the RAC stated that the "nasal olphactory tumours induced by acetochlor were determined to be secondary to local cytotoxicity due to the formation of quinone imine. These tumours were considered relevant to humans, although rats appeared to be more sensitive than humans." The increased incidences of nasal turbinate adenocarcinomas in male rats were deemed to be of concern as it is a rare tumour type. For S-metolachlor the incidence was 2/69, compared to 3/60 at 4000 ppm dimethachlor.

c) The DE CA notes that there is an increase in kidney lipoma: 0,1,1,2 in the males. The last of these values lie just outside/at the high end the HCD range given in Table B.6.5.1-15. According to one publication (10.1002/jat.2550130207), the incidence in SD rats is 0.37% and another study (10.1177/0192623310373777) puts the incidence in SD rats at 0.42%, both about 10-fold lower than the incidence seen in this study. Given that the kidney is also affected by dimethachlor, some more information and/or a discussion of the kidney lipoma would be appreciated.

Furthermore, we would appreciate if the RMS could answer the following questions:

1) In the mechanistic study by Knowles et al. (2020), nasal microsomes from rats and humans were used. Do you know from which epithelium these microsomes originated, from the respiratory epithelium or from the olfactory epithelium?

2) Nasopharyngal ademonas were detected in 3/60 high dose male Tif:RAIf rats. Do you know in which animals these tumours were detected: in animals surviving until the end of the study or/and in animals dying before study termination? In light of the considerably lower survival rate of male control animals (48% vs. 72% in the high dose group), information on the age of tumour-bearing animals could supply another valuable piece for the interpretation of nasopharyngeal adenomas in top dose males.

3) In the DRAR/CLH report, it is stated on page 97: "In contrast to top dose and control group, only limited number of tissue samples was examined in animals in the low and intermediate dose carcinogenicity sub-groups (lung, liver, kidney, testis, epididymidis, muzzle, and all gross lesions). This approach can create problems in the statistical analysis of dose-response trends and cannot be recommended if dose-response characterization is an objective of a study (OECD 2012). Namely, the actual number of tumours in low and

mid-dose groups may be higher than the observed values. […]”

On page 98, by contrast, it is stated in footnote 7: “Trend test is considered justified, since the nasal tissues from all groups were analysed.”

We think that there is a contradiction between these two statements. Even though nasal (muzzle) tissues were analysed from all groups, it seems that analyses were not conducted from nasal (muzzle) tissues from all animals. Consequently, a trend test should not be applied for nasopharyngal adenomas according to the first statement. Is this correct? If not, could you please clarify?

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2023	Germany		MemberState	4
Comment received				
We notice that e.g. in Tables 91 and 95, multiple studies per taxonomic group are indicated as key studies. Generally, only studies yielding the lowest reliable toxicity endpoint per taxonomic group should be marked as key study. We recommend to change the tables accordingly. However, as in Tables 98 and 99 only the actual key studies are given and used for classification, our remark does not influence the overall conclusion. As the tables in the aquatic section provide data on the active substance as well as formulated product, we recommend to add an indication clarifying whether the endpoints for the formulated product are given as mg a.s./L or mg product/L. We agree with the classification as aquatic acute 1 (M= 10) and aquatic chronic 1 (M=10).				

Date	Country	Organisation	Type of Organisation	Comment number
20.07.2023	France		MemberState	5
Comment received				
FR agrees the conclusion on classification and labelling for environmental hazards, i.e Dimethachlor is classified in acute aquatic hazard Cat 1 - H400 : Very toxic to aquatic life with M-factor = 10 based on L.gibba 7d-ErC50 = 0.0658 mg a.s/Lnom and long-term aquatic hazard Cat 1 - H410 : Very Toxic to aquatic life with long lasting effects with M-factor = 10 based on L. gibba 7d-NOErC = 0.005 mg a.s/Lnom and considering the substance as non-rapidly degradable.				

PUBLIC ATTACHMENTS
1. dimethachlor.zip [Please refer to comment No. 2]