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 15.03.2023

Substance name: metyltetraprole (ISO); 1-[2-({[1-(4-chlorophenyl)-1H-pyrazol-3-yl]oxy}methyl)-3-methylphenyl]-4-methyl-1,4-dihydro-5H-tetrazol-5-one;
CAS number: 1472649-01-6
EC number: -
Dossier submitter: Spain

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
10.03.2023	France	Sumitomo Chemical Agro Europe S.A.S.	Company-Manufacturer	1

Comment received

It has been proposed that the classification Carc Cat 2 H351 is warranted (CLH report page 286, point 2.11.2.1 Proposed harmonised classification and labelling according to the CLP criteria).

The applicant does not agree with this proposed classification and conducted additional histopathological examination on intermediate groups of carcinogenicity studies and statistical analysis to evaluate carcinogenic potential of metyltetraprole more precisely. Then, a third-party peer review was performed, and the Expert Panel consisting of multiple worldwide expert pathologists concludes that all tumors of ANSES concern are not treatment-related.

The reports of the additional histopathological examinations and of the external peer-review are under finalization and will be available in May 2023:
- Additional histopathology of mouse carcinogenicity study
- Additional histopathology of rat carcinogenicity study
- Statistical analysis of mouse carcinogenicity data
- Statistical analysis of rat carcinogenicity data
- Peer-review of mouse carcinogenicity data
- Peer-review of rat carcinogenicity data
- Expert panel report

In addition, an updated position paper "Metyltetraprole (S-2367): Position Paper on Harmonised C&L (CLH) Proposal for Carcinogenicity Classification" is under preparation and will be available in May 2023, clearly detailing the weight of evidence demonstrating that there were no treatment related tumours meriting carcinogenicity classification in accordance with the CLP criteria and taking into account the CLP Annex I: 3.6.2.2.6. which lists some important factors which may be taken into consideration, when assessing the overall level of concern for classification.

A summary of the evidences not supporting a treatment-related carcinogenic effect is provided below:

Biological plausibility (paragraph 3.6.2.3.1)
- Lack of statistical significance in the PETO trend and pair-wise tests
- Lack of dose-response relationship
- All tumours were within the HCD range, except for one tumor attributed to high background incidence of the animals used in the study
- None of tumour pathogeneses are supported by the fact that the test substance does not have any hormonal effects and genotoxicity, and any AOPs published
- No higher distribution and accumulation to the sites where tumours were observed than the other tissues, i.e., uterus for malignant schwannoma, and uterus and other sites for histiocytic sarcoma
- The uterus and liver where the malignant schwannoma and/or histiocytic sarcoma were observed, common tissues where they occur spontaneously as well
- Mammary gland tumours were common spontaneous tumours which occurred in association with spontaneous pituitary proliferative lesions in female rat
- Malignant lymphomas were common spontaneous tumours in rats and mice

Comparison with CLP criteria (paragraph 3.6.2.3.2)
(a) Tumor type and background incidence: Some types of tumour were noted, but almost within the HCD range.
(b) Multi-site responses: No clear evidences of multi-site responses.
(c) Progression of lesions to malignancy: No evidences of progression of lesions to malignancy
(d) Reduced tumor latency: Reduced tumour latency was not observed.
(e) Whether responses are in single or both sexes: No clear evidence that the responses were observed in any sexes.
(f) Whether responses are in a single species or several species: No clear evidence that the responses were observed in any species.
(g) Structural similarity to a substance(s) for which there is good evidence of carcinogenicity: Not structurally similar to substances that have carcinogenic potential.
(h) Routes of exposure: Oral route (dietary administration), which is relevant to consumer dietary risk assessment.
(i) Comparison of ADME between test animals and humans: Suggestive of the similarity between experimental animals and humans
(j) The possibility of a confounding effect of excessive toxicity at test doses: No evidence of a confounding effect of excessive toxicity.
(k) Mode of action and its relevance for humans, such as cytotoxicity with growth stimulation, mitogenesis, immunosuppression, mutagenicity: No toxicity data supporting particular MOAs for carcinogenicity.

The updated position paper TST-0100 on Historical Control Data is provided in support of this response.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment TST-0100 revised February 2023 (final)_Redacted.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment TST-0100 revised February 2023 (final).pdf

Date	Country	Organisation	Type of Organisation	Comment number
09.03.2023	United Kingdom	<confidential>	National Authority	2

Comment received
Carcinogenicity Page 56 of the CLH report states: 'the RMS considered that the HCD provided by the applicant are not fully relevant as a period of 5 years around the study was not used and also, studies conducted by several routes of administration have been included in the HCD. As the study was conducted in 2015-2017, HCD from studies conducted before 2010 should be disregarded. In addition, only HCD from studies conducted by dietary administration should be considered'. Some of the discarded HCD could be informative for the assessment of carcinogenicity (i.e., the data from other routes of administration). Would it be possible to see the full HCD set? We note reference to a position paper 'TST-0100' in the DAR which appears to contain this information.

Date	Country	Organisation	Type of Organisation	Comment number
09.03.2023	Germany		MemberState	3
Comment received				
Prior to the discussion on classification for carcinogenicity, further statistical analysis is required. As shown below on one example, classification in category 1B, H350 may be more appropriate. Justification: The statistical analysis of tumour incidences presented in the dossier does not meet current OECD recommendations. A trend test can be performed despite the smaller number of animals at low and medium doses. Tumour findings should be reconsidered based on appropriate statistical analysis. We have carried out a few analyses as examples: • The trend test (Cochran-Armitage test for trend one-sided (one-tailed)) was significant (alpha = 0.05) for the endpoints mammary adenocarcinoma (female rats) (p-value: 0.049) and mammary adenoma and carcinoma (female rats) (p-value 0.0098). For the endpoint mammary adenomas female rats, the p-value was 0.0594 for the trend test. • For the endpoint malignant lymphoma (both male and female mice), both the lower (m: 82.2 mg/kg bw/d; f: 103.4 mg/kg bw/d) (p-value males = 0.044; p-value females = 0.0086) as well as the second highest dose group (m: 225 mg/kg bw/d; f: 291 mg/kg bw/d) (p-value males= 0.002; p-value females = 0.0004) were statistically significant according to the Fisher's exact test. Lack of statistical significance at the top dose remains to be discussed in the context of systemic toxicity. According to OECD GD 116 (2012), paragraph 345, "A trend test is more powerful than the pair-wise test. A complication is that a trend test may fail to detect curvi-linear responses such as might arise from non-linear effects such as complications from saturation. In such situations the pair-wise tests may give more appropriate results". For pair wise comparisons, "Fisher's exact test is now preferred […] (paragraph 342)."				

Date	Country	Organisation	Type of Organisation	Comment number
23.02.2023	Netherlands		MemberState	4

Comment received
The RMS proposes a Carc. Cat 2 (H351) classification based on a weight of evidence approach described on pages 64 to 66. Based on the available evidence most factors seem to favor a Cat 1B classification (same type of tumors in both sexes and in both species, malignant tumors, multisite response/other tumors in different organs (in female rats), MoA unknown and no evidence of a confounding effect of excessive toxicity). The classification seems to have been downgraded to a Cat 2 based on the arguments that 1) the tumor incidences are relatively low and not suggestive of a clear effect and 2) that statistical significance was not reached. However, a firm justification should be added. The statement on the relatively low tumor incidence seems rather subjective and this should be further elaborated. A low tumor incidence is normally considered relevant/sufficient for classification when the background incidence is low or the tumor type is relatively rare. Obtaining statistical significance is sometimes not possible with low tumor incidences even though they are relevant. In this case it seems the difference with the HCD should be considered more important. In addition, we propose to more extensively discuss the weight of evidence specified for tumor type (i.e. 1) malignant lymphomas observed in male and female rats and male mice, 2) uterine schwannomas in rat, 3) mammary gland tumors in rat and 4) histiocytic sarcomas in female mice) as these tumors occurred in different organs, have different cells of origin and different natural background incidences. Based on the current argumentation the NL-CA leans more towards supporting a classification as Carc. 1B H350, but this may be changed with a better justification for downgrading to category 2.

Date	Country	Organisation	Type of Organisation	Comment number
10.03.2023	France	Générations Futures	National NGO	5
Comment received				
this substance is proposed by the RMS to be classified as suspected carcinogen (category 2). However, there are much more factors in favor of a classification in category 1B than in category 2: - Several types of malignant tumors were observed at several sites in both sexes and both species following metyltetraprole administration. - The incidences of tumours were slightly but above the range of HCD. - The MoA underlying these neoplastic lesions were unknown and therefore human relevance cannot be excluded. - There is no evidence of confounding effect of excessive toxicity. Indeed, although the tumours were generally observed at high dose levels, the systemic toxicity at these doses remain low. The only element in favor of a classification in category 2 is the slight incidence of tumors reported when compared to controls or HCD. However, according to the guidance on the application of the CLP criteria (p.383/647) , "if a substance causes tumours at multiple sites and/or in more than one species then this usually provides strong evidence of carcinogenicity. Typically such a tumour profile would lead to a classification in category 1B." Metyltetraprole should therefore be classified in category 1B. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Générations Futures_metyltetraprole.pdf				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
09.03.2023	Germany		MemberState	6
Comment received				
We agree with the DS that based on the available data, no classification for mutagenicity is warranted for metyltetraprole. Nevertheless, we noted that the in vitro chromosome aberration assay is not designed to measure aneugenic effects and an in vitro micronucleus assay may have been more informative. However, taking into account the available in vivo micronucleus test, the data is considered conclusive.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
09.03.2023	Germany		MemberState	7
Comment received				
Adverse effects on sexual function and fertility: We agree with the DS that based on the available data from a 2-generation study in rats (Anonymous, 2017), the effects are not sufficient for classification of metyltetraprole as toxic for sexual function and fertility. Adverse effects on development: Overall, we could support non-classification for developmental toxicity. However, skeletal findings in the rat were observed at a dose without maternal effects and although incidences were low, they exceeded the HCD. According to the DevTox database, these findings are considered grey zone. The following information might support the proposed conclusion that the observed findings are not sufficient for a classification for developmental toxicity, and could be provided by the DS: • Was a statistical analysis performed to calculate possible significances? • Considering the different skeletal findings, were there always different fetuses affected, or were there fetuses with multiple findings? • Were the historical control data appropriately reported?				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
09.03.2023	Germany		MemberState	8
Comment received				
DE-CA supports the proposal that classification for acute toxicity (oral, dermal and inhalation) is not required for metyltetraprole.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
09.03.2023	Germany		MemberState	9
Comment received				
DE-CA supports the proposal that classification for skin corrosion/irritation is not required for metyltetraprole.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment

				number
09.03.2023	Germany		MemberState	10
Comment received				
DE-CA supports the proposal that classification for skin sensitisation is not required for metyltetraprole. Although the LLNA was not conducted, the available GPMT is acceptable.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
09.03.2023	Germany		MemberState	11
Comment received				
DE-CA supports the proposal that specific target organ toxicity after single exposure relevant for classification of metyltetraprole was not observed. However, neurobehavioural and neuropathological findings observed in the acute neurotoxicity study as well as in the second 90-d study in rats require further consideration. In Vol. 1, section 2.6.2.10.1 (STOT SE), only FOB findings observed in the acute neurotoxicity study are presented. Based on histopathologic examinations of the peripheral nerves of females at the highest dose, minor effects were observed although in some cases the findings are within the range of reported HCD. An overall discussion of other studies should be provided, especially the second 90-d study in rats.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
09.03.2023	Germany		MemberState	12
Comment received				
Classification for specific target organ toxicity after repeated exposure is not indicated for metyltetraprole.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
09.03.2023	United Kingdom	<confidential>	National Authority	13
Comment received				
Metyltetraprole (ISO) (EC: -; CAS: 1472649-01-6 Relevant bioaccumulation information is presented in the CLH report. However, it is currently unclear if the substance meets the bioaccumulation criteria for hazard classification under CLP. While this does not impact the classification proposal, it would be useful for the DS/RAC to present a conclusion. We note that an OECD TG 229 Fish Short Term Reproduction Assay (Pimephales promelas) study is available resulting in a 21-day NOEC of 0.0092 mg a.s./L (mm) based on mean eggs per female per reproductive day. The study endpoint is considered reliable and we consider it potentially relevant to hazard classification given the endpoint reflect population effects. This endpoint leads to a more stringent hazard classification of Aquatic Chronic 1 with a Chronic M-factor of 10. Additional information is also available for amphibians although this does not appear to impact the hazard classification proposal.				

We note that chronic data are not available for the most acutely sensitive fish species (Oncorhynchus mykiss). Using the surrogate approach would also result in Aquatic Chronic 1 with an M-factor of 10.

Finally, while we recognise it will not impact the hazard classification, we are unclear why the algal growth inhibition study with metyltetraprole is not considered reliable.

Please can the DS provide further information to clarify.

PUBLIC ATTACHMENTS
1. Générations Futures_metyltetraprole.pdf [Please refer to comment No. 5]
2. TST-0100 revised February 2023 (final)_Redacted.pdf [Please refer to comment No. 1]

CONFIDENTIAL ATTACHMENTS
1. TST-0100 revised February 2023 (final).pdf [Please refer to comment No. 1]