Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

***S*-metolachlor (ISO); 2-chloro-*N*-(2-ethyl-6-methylphenyl)-*N*-[(2*S*)-1-methoxypropan-2-yl]acetamide; (R_aS_a)-2-chloro-*N*-(6-ethyl-*o*-tolyl)-*N*-[(1*S*)-2-methoxy-1-methylethyl]acetamide**

[contains 80-100% 2-chloro-*N*-(2-ethyl-6-methylphenyl)-*N*-[(2*S*)-1-methoxypropan-2-yl]acetamide and 0-20% 2-chloro-*N*-(2-ethyl-6-methylphenyl)-*N*-[(2*R*)-1-methoxypropan-2-yl]acetamide]

EC Number: -
CAS Number: 87392-12-9

CLH-O-0000007145-77-01/F

Adopted

2 June 2022

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON *S*-metolachlor (ISO); 2-chloro-*N*-(2-ethyl-6-methylphenyl)-*N*-[(2*S*)-1-methoxypropan-2-yl]acetamide; (R_aS_a)-2-chloro-*N*-(6-ethyl-*o*-tolyl)-*N*-[(1*S*)-2-methoxy-1-methylethyl]acetamide [contains 80-100% 2-chloro-*N*-(2-ethyl-6-methylphenyl)-*N*-[(2*S*)-1-methoxypropan-2-yl]acetamide and 0-20% 2-chloro-*N*-(2-ethyl-6-methylphenyl)-*N*-[(2*R*)-1-methoxypropan-2-yl]acetamide]

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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_S_-metolachlor (ISO); 2-chloro-_N_-(2-ethyl-6-methylphenyl)-_N_-[(2_S_)-1-methoxypropan-2-yl]acetamide; (R_aS_a)-2-chloro-_N_-(6-ethyl-_o_-tolyl)-_N_-[(1_S_)-2-methoxy-1-methylethyl]acetamide

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EC number: -
CAS number: 87392-12-9
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	Netherlands		MemberState	1
Comment received				
The NL-CA can support the read-across with Metolachlor. However, it needs to be noted that the S-isomer, which is the main isomer in S-Metolachlor, is considered more active as a herbicide than the R-isomer. Further consideration on this differences would be appreciated.				
Dossier Submitter's Response				
Thank you for the comment. The DS agrees that the two isomers differ with regard to their herbicidal activity. According to the applicant, the S-isomer is by 10-15 times more active than the R-isomer. However, in acute toxicity as well as in 28- and 90-day repeated dose studies, in genotoxicity assays and developmental toxicity studies, it was demonstrated that the toxicological properties of S-metolachlor and metolachlor were similar. Therefore, it was concluded that bridging between S-metolachlor and metolachlor with regard to their toxicological evaluation is scientifically justified. In particular, studies with metolachlor can be used for those endpoints such as long-term toxicity and carcinogenicity for which no separate studies with the S-isomer have been performed. There is no indication that the results of these studies would underestimate the toxicity of S-metolachlor.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON *S*-metolachlor (ISO); 2-chloro-*N*-(2-ethyl-6-methylphenyl)-*N*-[(2*S*)-1-methoxypropan-2-yl]acetamide; (R_aS_a)-2-chloro-*N*-(6-ethyl-*o*-tolyl)-*N*-[(1*S*)-2-methoxy-1-methylethyl]acetamide [contains 80-100% 2-chloro-*N*-(2-ethyl-6-methylphenyl)-*N*-[(2*S*)-1-methoxypropan-2-yl]acetamide and 0-20% 2-chloro-*N*-(2-ethyl-6-methylphenyl)-*N*-[(2*R*)-1-methoxypropan-2-yl]acetamide]

RAC's response
Thank you for your comment. RAC agrees with DS's response.

Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	France		MemberState	2

Comment received

FR: Please add purity of test item used for determination of physicochemical properties. Specify the S-isomer and R-isomer content in tested substance to show/prove that S-metolachlor tested was as defined (80-100% S-isomer and 0-20% R-isomer).

Dossier Submitter's Response

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	at 25 °C : clear extremely pale-yellow liquid	Das (1995)	Visual assessment Purity (%) AMS 757/101 99.8 (S+R) 88.4 (S)
Melting/freezing point	freezing temp. (glass transition temp) = - 61.1 °C	Geoffroy (1995)	Measured EC A 1 (DSC) Purity (%) AMS 757/101 99.8 (S+R) 88.4 (S)
Boiling point	boiling temp. = approx. 334 °C (could not be properly determined due to thermal decomposition at a temperature lower than that of the boiling point)	Das (1995)	measured EC A 2 (Siwoloboff-method with photocell detection) Purity (%) AMS 757/101 99.8 (S+R) 88.4 (S)
Relative density	density at 20 °C = 1117 kg/m^3	Das (1995)	Measured EC A 3 (oscillating density meter) Purity (%) AMS 757/101 99.8 (S+R) 88.4 (S)
Vapour pressure	vapour pressure at 25 °C = 3.7 x 10^{-3} Pa (extrapolated) Measurement between 40 °C am 90 °C	Widmer (1995)	Measured EC A 4 (atomized gas saturation method with online GC-detection) Purity (%) AMS 757/101 99.8 (S+R) 88.4 (S)

Surface tension	54.3 mN/m - 54.5 mN/m (90 % saturated aqueous solution; 22 °C) The substance is considered surface active.	O'Connor (2013)	Measured OECD 115 EC A 5 Purity (%) AMS 757/3 99.6 (S+R) 89.3 (S)
Water solubility	solubility at 25 °C in water (pH 7.3) = 480 mg/L The a.s. has no dissociation constant in an accessible pH range (see also B.2.8), which means the pH has no effect on the water solubility of the compound in the pH range 4 - 10.	Stulz (1995)	Measured EC A 6 (flask method + HPLC-analysis) Purity (%) AMS 757/101 99.8 (S+R) 88.4 (S)

	at 25 °C : log Pow = 3.05 ± 0.02 (pH of aqueous phase = 7)	Stulz (1995)	EC A 8 (shake-flask method + HPLC analysis) Purity (%) AMS 757/101 99.8 (S+R) 88.4 (S)
	Calculated partition coefficients (logpow) of metabolites: CGA35743 : 0.63 CGA51202 : 2.73 CGA40172 : 2.15 NOA436611 (SYN546829) : 1.88 CGA37735 : 0.50 CGA41507 (NOA407127) : 2.48 CGA217498 : 1.50 CGA41638 : 2.33 SYN542489: 0.97 SYN542490: -0.56 SYN542607: -1.13 SYN547969: 1.97 SYN542491: 0.60 SYN542492: 3.25 SYN542488: 0.97 SYN547977: 1.90	Document M (2019 2017)	Calculation Solstice cLogP v4.95 Purity (%) (-)
Partition coefficient n-octanol/water			
	CGA 368208: log Po/w = -2.1 (25 °C; pH 7.0)	Das (2002)	OECD 107, EC A.8 (Shake-flask-method) Purity (%): 98
	CGA 50720: log Po/w = -1.3 (25 °C; pH 4.9) log Po/w = -1.8 (25 °C; pH 6.7) log Po/w = -1.8 (25 °C; pH 8.9)	Das (2002)	OECD 107, EC A.8 (Shake-flask-method) Purity (%): 99
	CGA 357704: log Po/w = -1.8 (25 °C; pH 4.8) At pH 6.5 and 8.8 CGA 357704 could only be found in the aqueous phase and could not be detected in the octanol phase.	Das (2002)	OECD 107, EC A.8 (Shake-flask-method) Purity (%): 96
	CGA 351916: log Po/w = -0.80 (25 °C; pH 5.0) log Po/w = -1.5 (25 °C; pH 6.8) log Po/w = -1.6 (25 °C; pH	Das (2002)	OECD 107, EC A.8 (Shake-flask-method) Purity (%): 100

	8.9) CGA 50267: log Po/w = 1.2 (25 °C; pH 5.0) log Po/w = -0.23 (25 °C; pH 6.8) log Po/w = -1.3 (25 °C; pH 8.9) NOA 413173: log Po/w = -3.2 (25 °C; pH 7.0)	Das (2002) Das (2002)	OECD 107, EC A.8 (Shake-flask-method) Purity (%): 95 OECD 107, EC A.8 (Shake-flask-method) Purity (%): 89
Flash point	flash point (1013 mbar) = 190 °C	Schürch (1995)	Measured EC A 9 DIN 51758 Purity (%) P.501001 98.5 (S+R) 87.4 (S)
	<u>Statement on study for flash point (Schürch (1995)) with respect to data requirements of Reg. 1272/2008:</u> EC Test A.9 does not define a method for flash point measurement, but merely lists acceptable national and international standards (e.g. ASTM, BS, DIN, ISO, NM). This is also the case in Section 32 of the UN Manual of Tests and Criteria, which covers the testing of flammable liquids as required for UN transport and UN GHS classification. For S-metolachlor, the flash point was originally determined according to the German DIN 51758 standard for closed-cup Pensky-Martens flash point testing. The original German standard has since been withdrawn but now exists in the form of DIN ISO 2719, which is the same as ISO 2719, the international standard for Pensky-Martens closed-cup testing. ISO 2719 is listed as an acceptable method for flash point in both EC Test A.9 and the UN MoTC. Therefore the original flash point is still valid and meets Reg (EU) 1272/2008 requirements.	Document M (2017)	Statement Purity (%) (-)

Flammability	Not applicable (a.s. is a liquid with flash point > 55 °C)	DAR	Statement Purity (%) (-)
Explosive properties	- no thermal sensitivity (effect of a flame) - no mechanical sensitivity (shock) friction testing method is not applicable for liquids => S-metolachlor is not considered an explosive	Schürch (1995)	Measured EC A 14 Purity (%) P.501001 98.5 (S+R) 87.4 (S)
	An examination of the structures of S-metolachlor indicates that there are no bond groupings associated with explosive properties. Conclusions: (i) On the basis of this assessment, the substance is not an explosive. (ii) An experimental determination of the explosive properties, in accordance with UN Test Series 2, is therefore considered unnecessary and has not been carried out on this substance.	Document M (2017)	Statement Purity (%) (-)
Self-ignition temperature	auto-ignition temperature = 430 °C	Schürch (1995)	Measured EC A 15 DIN 51794 Purity (%) P.501001 98.5 (S+R) 87.4 (S)
	Statement on study for self-heating (Schürch (1995)) with respect to data requirements of Reg. 1272/2008:	Document M (2017)	Statement Purity (%) (-)

	EC Test A.15 does not define a method for AIT measurement, but merely lists acceptable national and international standards (e.g. BS, DIN, IEC, NM). For S-metolachlor, the AIT was originally determined according to the DIN 51794 standard, which is still a valid national standard today. The apparatus defined in DIN 51794 is also covered by IEC 60079-20-1 Section 7, "Method of Test for Auto-Ignition Temperature", which is a currently accepted international standard for AIT measurement. Therefore, the original AIT measurement is still valid. (Note: neither the UN transport recommendations nor the UN GHS address auto-ignition temperatures).		
Oxidising properties	S-metolachlor technical is not an oxidising substance.	Jackson (2013)	Measured EC A 21 Purity (%) CAB2H12058 98.8 (S+R) 87.4 (S)
	<u>Statement on study for oxidising properties (Jackson (2013)) with respect to data requirements of Reg. 1272/2008:</u> The original test for oxidizing properties was carried out in accordance with EC Test A.21, which is identical to UN Test O.2 for substances testing negative, as was the case here. The result reported in the study is therefore considered to be still valid for use when classifying the material for UN transport or in accordance with the UN GHS, and therefore the requirements of Reg (EU) 1272/2008.	Document M (2017)	Statement Purity (%) (-)
Stability in organic solvents and identity of relevant degradation products	solubility at 25 °C in n-hexane : completely miscible toluene : completely miscible dichloromethane : completely miscible	Stulz (1995)	Measured SOP 209/5 (essentially an adaptation of CIPAC MT 157.3) Purity (%) P.501001 98.5 (S+R) 87.4 (S)

	methanol : completely miscible n-octanol : completely miscible acetone : completely miscible ethyl acetate: completely miscible tested in the range from 5% to 95% (v/v)		
Dissociation constant	*consideration of structural formula :* no dissociation expected within pH-range 2-12 *experimental confirmation :* UV/VIS-absorption spectra (210-400 nm) recorded in neutral, acidic and basic solution are identical => no dissociation constant (pKa) in an accessible pH-range	Stulz (1995)	Measured OECD 112 (UV/VIS-absorption spectra) Purity (%) AMS 757/101 99.8 (S+R) 88.4 (S)

RAC's response

Thank you for your comment. Noted.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	France		MemberState	3

Comment received

FR:
Epidemiological studies:
Regarding epidemiological studies there are a number significant outcomes that may be considered to show human evidence of association with cancer, although some other epidemiological findings do not show an association. For most studies, data are from cohort and RR were adjusted for almost all of them. The significant findings are:
1. AHS prospective study Iowa and North Carolina 1993—2002 (Rusiecki et al., 2006): Lung cancer: statistically significant findings (trend test p = 0.03) along the tertiles of lifetime exposure-days. There is an exposure duration – cancer response relationship and the RR is close to statistical significance for T3U tertile. Prostate and all cancers no such significant findings;
2. AHS prospective study Iowa and North Carolina 1993—2010 (North Carolina)/2011 (Iowa) (Silver et al., 2015): Significant findings for liver cancers and follicular cell lymphoma. For both cancers there is clear exposure duration – cancer response relationship, both p-trend values are significant, and both RR are statistically significant;
3. AHS prospective study of pesticide applicators in Iowa and North Caroline 1993—2001 (Alavanja et al., 2004): Statistically significant OR for highest lifetime exposure days for lung cancer;
4. AHS prospective study of pesticide applicators in Iowa and North Caroline 1993—2005 (Andreotti et al., 2010): Statistically significant increase of HR for colon cancer when BMI

≥ 30 showing that BMI is an interaction factor; 5. AHS prospective study of pesticide applicators in Iowa and North Caroline 1993—2003 (Koutros et al., 2010): Statistically significant OR increase for persons with 8q24 variants genetic risk factor for prostate cancer for high exposure group to metolachlor 6. Data from the Maryland Cancer registry for bone and brain cancer, leukemia and lymphomas (Thorpe and Shirmohammadi, 2005): Significant crude OR for brain cancer Animal studies: − In rats, different tumour types were observed in the liver, the pituitary, the nasal turbinates and the thyroid. These tumours are considered treatment-related based on statistical and biological significances (e.g. incidences exceeding the historical control data, dose-relationship, statistical significance by pairwise comparison and/or trend analysis). Compared to CLP criteria, a multi-site response was therefore noted, progression to malignancy was evident for several tumours, both sexes were affected, no excessive toxicity was observed. − Human relevance of these tumour types are not excluded since modes of action were not clarified. − Nasal tumours were also observed with a structurally similar compound, i.e. alachlor. − Tumours were not reported in mice, nevertheless the carcinogenicity study in mice is considered unacceptable. Overall, based on the epidemiological findings and depending on the weight attributed to the human evidence in combination with the aforementioned animal findings, a detailed strength of evidence discussion should be held at the RAC level to more formally establish whether a Category 1B or Category 2 classification is warranted.
Dossier Submitter's Response
Thank you for the comment and the excellent summary of relevant results from epidemiological studies and animal studies. The DS strongly agrees. Even if the original proposal of the DS had been Category 2, the overall evidence might in fact point to a need for Category 1B, in line with the recommendation of EFSA's 2020 expert meeting. It must be emphasised that animal data is coming only from a study in one species since the long-term study in mice was downgraded to "not acceptable". Accordingly, an important source of information is missing that is normally available for a pesticide active ingredient. The argument that no evidence of carcinogenicity had been observed in the mouse, as put forward in the past, cannot be considered valid any longer.
RAC's response
Thank you for your comment. RAC agrees that the human data, and more specifically the association between metolachlor and liver tumours, observed in large prospective cohort study, hint to an increased concern and warrants follow-up. However, the data are insufficient for classification as potential confounding factors cannot be excluded (e.g. drinking water consumption, co-exposure with other pesticides). As to the classification, RAC agrees with the dossier submitter's proposal to classify *S*-metolachlor as Carc. 2. (H351). RAC acknowledges the limitations in the mice carcinogenicity study. However, although the presence in tumours in both sexes in rats could justify classification in Category 1B, several specific factors decrease the concern, as described in the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2021	United Kingdom	Syngenta	Company-Manufacturer	4

Comment received

Syngenta disagree with the dossier submitters proposal for H351 classification and believe that no classification for carcinogenicity is most appropriate for S-metolachlor. For carcinogenicity, all findings are considered to be incidental and not related to treatment with S-metolachlor. The pre-neoplastic nodules in the liver have been demonstrated to be non-human relevant and therefore not relevant for classification.
Please see the detailed document attached - "S-metolachlor Syngenta Carcinogenicity Position Statement.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Syngenta S-metolachlor PC.zip

Dossier Submitter's Response

The DS is still convinced that classification of S-metolachlor for carcinogenicity is needed anyway whereas it is indeed more challenging to make a decision on the appropriate category. In his comment, only findings in the long-term study on rats are addressed in detail by the applicant. The very brief paragraph on epidemiological data is simply the recommendation to disregard them all because of the fact that operators were exposed not only to one pesticide but also to various plant protection products. This may be true but then, logically, epidemiological studies could not be used for hazard assessment of any pesticide. It should be doubted to perform epidemiological studies at all since any positive result could be easily contravened by taking the same approach. In contrast, however, epidemiology is given increasing weight in the toxicological evaluation of agrochemicals, provided that study quality and reliability is sufficient. In case of S-metolachlor, the proposal to classify for carcinogenicity is based on both, animal findings and epidemiological evidence which is, with regard to liver tumours at least, partly overlapping.

With regard to the neoplastic liver findings in the long-term study on rats, an increase in neoplastic nodules and carcinoma was observed at the top dose level. This combined increase was statistically significant in a test for trend in males and in the group-wise comparison as well as in the trend test in females. In females, in addition, a positive trend was detected for carcinoma alone. These findings from the original study were virtually confirmed in a re-evaluation one year later. The historical control range was exceeded but the HCD itself is small and its contribution to overall assessment very limited. The arguments for human non-relevance as put forward by the applicant had not been accepted by the DS and by EFSA's expert meeting in 2020 mainly because of insufficient data to exclude other mechanisms than CAR activation, limitations of the available studies (missing positive controls, no increase of PROD in human hepatocytes, no studies using humanised-CAR animals or CAR-knockout hepatocytes) and effects that were not always comparable to phenobarbital. The DS still keeps this position that is further supported by the epidemiological evidence (see French comment (3) above).

Nasal tumours were of particular interest since the structural related alachlor is infamous for this tumour type. A decision if also metolachlor might produce such a kind of

neoplasia is very difficult. Clearly, its potency is less strong than that of alachlor. Precisely, adenocarcinoma of the nasal turbinates in male rats was of concern. Its incidence was very low (1 or 2 out of 59 or 69 animals depending on the pathological examination) and confined to the maximum dose level. However, it seems above the limited HCD for this very rare tumour. A precautionary approach is recommended. This high-dose finding might be not relevant for risk assessment but should be taken into account for hazard assessment when it comes down to carcinogenicity of metolachlor in general.

In female rats, there was a significant increase in pituitary adenoma (test for trend and group-wise comparison) and carcinoma (trend test) at the highest dose level. Adenoma is not addressed in the applicant's position paper and the figures given for carcinoma are difficult to understand. It seems that statistical significance has now disappeared or was not accepted as such by the applicant as relevant if "only" a positive trend had been found. The top dose incidence was at the upper edge of HCD. The DS still thinks that the increase in pituitary tumours might also point to a carcinogenic potential of metolachlor in the rat.

On balance, the DS thinks that the findings in rats, despite the multisite response, rather support Carc 2 than Carc 1B, just because of the low incidences at least of the liver and nasal tumours and the fact that apparently long-lasting exposure to a high dose is needed to cause a higher tumour frequency. However, since there is also evidence of carcinogenicity in humans, the DS feels that Carc 1B might be indeed more appropriate in this case.

RAC's response

Thank you for your comment and thanks for the DS's response. RAC agrees that the MoA for liver may be plausible but that uncertainties remain. The increase in pituitary adenoma and carcinoma is of concern and may be relevant for classification. Although very low incidences of nasal turbinates tumour in male rats were noted, the presence of this type of tumour is also of concern and provides supporting evidence for classification. RAC agrees with the DS that the findings in rats support classification as Carc. 2 for *S*-metolachlor. The available evidence in humans need further follow-up to confirm a causal link between *S*-metolachlor and liver tumours.

Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	Netherlands		MemberState	5

Comment received

The NL-CA can support the proposed Carc. 2 classification for carcinogenicity, as summarized on p54-55. Although a more detailed summary of the weight of evidence would be appreciated in favor of carc 1B. or carc. 2.

In short, the NL-CA considers the arguments in favor of classification as carc. 1B are:

- Multisite response
- Malignant tumours
- Support from multiple epidemiology studies

Uncertainty of the findings and therefore arguments in favor for classification in category 2 would be:

- Single species
- Single sex for more severe carcinogenic (carcinoma) effects.

- Multisite response in humans and rats do not clearly overlap except liver tumors
- Rat corona virus outbreak
- Other minor study deficits (feed measurements etc.)
- Effects limited to the highest dose

Overall, classification as a category 2 carcinogen seems more appropriate based on the date available.

Dossier Submitter's Response

Thank you for the comment and the general support for the proposal to classify S-metolachlor for carcinogenicity. The DS agrees with the arguments as highlighted by the NL authority in favour of Carc. 1B. The counterarguments which would support rather Carc. 2, do not appear equally valid.

- Evidence can come only from one species since the long-term study in mice is meanwhile considered not acceptable. In particular the low survival in this study precludes a reliable assessment of carcinogenicity in a second species. Accordingly, the mouse study cannot be used neither to support or contravene a need for classification in general and is of no use for the decision which category would be the most appropriate.
- Many pathologies including tumours display a sex-specific pattern even if the same number of male and female animals is theoretically at risk to develop them. In humans, sex differences in the incidence, in symptoms, course, prognosis etc. of disease, including neoplasia which may affect both sexes, as well as sex-related differences in the response to medical drugs are common experience. This knowledge has come more and more now into the focus of clinicians and scientists and has made its way into public perception as well. More frequent occurrence of a certain tumour type in only one sex of a rodent species than in the control group was an often used argument in the past to weaken the evidence of carcinogenicity but, taking into account the impact of sex on the manifestation of disease, does not make things any better. One ought protect women and men as well. Furthermore, in this case, an increase in total nodules + carcinoma in rats was observed in both sexes even though, it was statistically significant in a group-wise comparison "only" in females.
- It is true that epidemiology points to a clear "match" of tumours in humans to those in rodents only for liver cancer. However, a carcinogenic effect in general appears likely since a multisite response was observed in the rat and similar evidence was obtained in man (for short summary please see comment 3 of FR above). Some tumours, e.g., leukaemia, are in general more often observed in epidemiological studies with pesticides but more rarely found in rodents.
- Symptoms of sialodacryoadenitis virus (SDAV) infection was noted in a number of animals across all groups. Since this virus, as well as other coronaviruses, is highly contagious, it can be reasonably assumed that nearly all animals on study were infected. This infection apparently took place in an early phase of the study and will not have affected the terminal outcome. There is no evidence so far that a coronavirus infection would promote (or even initiate) cancer development in humans or animals. Even if this would be the case, a similar impact on all groups including the control must be expected.
- In fact, the study is old (1983) and flawed by some deficiencies. Accordingly, it was considered supplementary in the EU evaluation. However, the deviations from current protocols do not invalidate the results with regard to carcinogenicity, apart

(perhaps) from the histopathological examination of nasal turbinates that was first confined to animals with macroscopic lesions and might have resulted in underestimation of tumour rates. However, a subsequent analysis was performed and could clarify the issue. Anyway, there is no evidence to assume that the tumour frequency might have been overestimated in the treated groups (in particular at the high dose level) or underestimated in the controls.

- It is true that the presumed multisite carcinogenic effect of metolachlor in rats was confined to the highest dose level. But, on one hand, the MTD was not exceeded when mortality/survival and body weight effects were taken as the basis for such an assessment. On the other hand, classification of a substance is part of hazard assessment and, accordingly, different from risk assessment in which, e.g., the margin between the carcinogenic NOAEL and the proposed ADI would be of more relevance.

On balance, even though the original proposal of the DS had been Carc. 2, the French proposal (see comment 3) is supported for a detailed strength of evidence discussion by the RAC to establish whether Category 1B or Category 2 classification is warranted. In DS view the most convincing argument in favour of Carc. 1B is the epidemiological evidence that is complimentary to the animal data, which (as outlined in the response to Syngenta's comment above) might be not sufficient for the higher category as stand-alone information.

RAC's response

Thank you for your comment. RAC agrees with your comment that Category 2 is more appropriate based on the available data.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	Netherlands		MemberState	6

Comment received

The NL-CA agrees with the 'no classification' for germ cell mutagenicity.
It is noted that the in vivo testing for gene mutation was only performed with micronucleus assays that had clear deficiencies, and with UDS tests, which are indicator tests that are relatively insensitive. In vitro studies may be overall negative but some equivocal positive results are present as well.
Overall, more sensitive test systems (in vivo) and acceptable studies with a negative outcome would be needed to have conclusive data for no classification. It is noted that table 7 states there is conclusive data for no classification, please consider if the reason for no classification would be more appropriately described by 'data lacking' or 'inconclusive for classification'.

Dossier Submitter's Response

Thank you for the comment. The DS is aware that in some of the in vitro assays regarding clastogenicity/aneugenicity (i.e. micronucleus assays in human lymphocytes) equivocal results were seen. Two in vivo follow up micronucleus assays (Tif:MAGfmice and NMRI mice) revealed negative results. On the other hand, the power of both assays was reduced as only 2000 cells were analysed whereas the current OECD TG 471 (2014) recommends using 4000 cells. Bone marrow exposure in mice was demonstrated in a proof of exposure study. Some uncertainties may remain as S-metolachlor was only detectable one hour (in 2 out of 3 male mice) and four hours (in 1/3 male mice) after

exposure and not after 24 hours. This small window of exposure might be an issue to doubt on aneugenicity. However, based on the overall weight of evidence, the DS keeps still to its original opinion that there is sufficient data to conclude that S-metolachlor is unlikely to have a genotoxic potential. The database is also comparable to that one for other compounds for which the conclusion has been drawn in the past that they were not genotoxic. With active substances in plant protection products, equivocal or even positive results of in vitro tests for chromosome aberration (often in human cells) are common and, usually, it is accepted to contravene this evidence by negative in vivo micronucleus assays, provided that bone marrow exposure could be shown. From the NL comment itself, there is the impression that the overall assessment is not challenged.
RAC's response
Thank you for your comment. The micronucleus assay is an appropriate follow-up for the positive *in vitro* findings. Based on the negative results in the micronucleus assay, in presence of some indication of bone marrow exposure, RAC agrees with the DS's proposal for no classification based on conclusive data.

Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	France		MemberState	7
Comment received				
FR: No comment.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	France		MemberState	8
Comment received				
FR: FR agrees with the DS that a classification Repr 2 H361d is warranted for S-metolachlor.				
Dossier Submitter's Response				
Thank you for the support.				
RAC's response				
Thank you for your comment. Please see response to comment number 9.				

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2021	United Kingdom	Syngenta	Company-Manufacturer	9
Comment received				
Syngenta disagree with the dossier submitters proposal for H361d classification and believe that no classification for developmental toxicity is most appropriate for S-metolachlor. For developmental toxicity, there is no evidence that S-metolachlor demonstrates a teratogenic effect in rabbits as all findings are within the laboratory historical control range and do not demonstrate a clear dose response.				

Please see the detailed document attached - "S-metolachlor Syngenta Developmental Toxicity Classification Position" together with the supporting report "S-Metolachlor – Technical Position on the Classification of S-Metolachlor for Developmental Toxicity in Rabbits" ECHA note – An attachment was submitted with the comment above. Refer to public attachment Syngenta S-metolachlor PC.zip
Dossier Submitter's Response
Thank you for this comment but it was noted that the arguments put forward now against classification had been known before already. The arguments were already addressed in the CLH-report. It is not necessary to repeat this discussion in length but there are three points to be stressed: (1) The two independent studies in two rabbit strains were not combined in the CLH-Report. On the contrary, evidence coming from the first study was somewhat confirmed in the second study, thereby reducing the likelihood that the occurrence of hydrocephalus in the first study in another strain was a chance event. If the same finding is seen in two strains of a species, it becomes more reasonable to assume a general inherent property of a compound to cause a distinct adverse effect. (2) The available HCD indeed might raise doubts if hydrocephalus in rabbit foetuses was treatment-related since the incidences were numerically covered by its range. However, this HCD may be also interpreted in a different way to show that hydrocephalus is a very rare malformation and that its occurrence in two studies with a very similar compound (metolachlor, S-metolachlor) in two strains is alarming. It is worth noting that in 10 out of 12 studies in NZW rabbits, which constitute the HCD for this strain, no hydrocephalus was observed whereas one or two were detected in the remaining. (3) If there are that serious doubts on the technical procedures by which hydrocephalus or "possible hydrocephaly" had been detected, it has to be questioned why no new study has been commissioned in preparation of the upcoming re-evaluation in the EU. Either study quality is considered sufficient and, then, all results should be relied on, or a study according to current standards would have been needed but was apparently not performed.
RAC's response
RAC agrees with the DS that the presence of four hydrocephalus in three litters from two different strain of NZW rabbits in two independent studies is of concern. Nevertheless, one hydrocephalus occurred in a multimalformed litter in the first study and the two cases of hydrocephalus in the other study occurred in a dam that died, probably due to treatment. In the remaining litter, the presence of one case of hydrocephalus in one study, within HCD, is not considered sufficient for classification. Therefore, no classification is proposed.

Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	Netherlands		MemberState	10
Comment received				
The NL-CA favors a no-classification for developmental toxicity instead of the proposed Repr. 2. The proposal is based on four cases of hydrocephalus, observed in two independent				

studies with rabbits. However, in one of these studies, the two cases of hydrocephalus were observed in dead delivered pups, which were from the same litter. The pups also had exencephaly and incompletely ossified, highly domed parietals, and the doe had strongly reduced food intake (about 50%) and body weight loss. Rabbits are very sensitive to problems with their food intake or digestive system and secondary effects as a result are likely not relevant for humans. The related doe also died prematurely on day 29 with the incomplete delivery and dead delivered pups. Overall, it is reasonable to assume that the malformations are secondary to the maternal toxicity which in part might be a rabbit specific problem as well.
In the other study, one of the cases was observed in a litter where several other malformations were observed, including all cleft palates, all cases of abnormally flexed limbs/paws, reduced trachea size (sometimes considered rather a variation) and all skeletal findings seen in the high dose group. This heavily affected litter consisted of five fetuses whereas the median litter size in the same dose group was 8 and the mean 7.9. All five fetuses had multiple malformations. The doe producing this litter consumed only very little food (also about 50%) over the whole treatment period and had the lowest body weight in the high dose group between days 14 and 25. Again, the effects observed are likely secondary to maternal toxicity and might be rabbit specific since it seems related to food intake/digestion. It is unclear what the status of the mother was delivering the other pup with hydrocephalus. Perhaps it is possible to elaborate on this and make a case whether this effect had a mother with more limited maternal toxicity.
Overall, for the other 3 cases, although it is not unequivocally demonstrated that the developmental effects are secondary to maternal toxicity, it is reasonable to assume that the hydrocephalus is likely produced as a secondary consequence of maternal toxicity, which might also be species specific.

Dossier Submitter's Response

Thank you for this comment, this will certainly thoroughly be considered by the RAC. However, as the DS, the original proposal is maintained that S-metolachlor should be classified into category 2 for developmental toxicity, based on hydrocephalus in rabbits. The most important argument is the occurrence of this malformation in two independent studies. In addition, even, if these findings were indeed secondary to maternal toxicity, this would not preclude classification but rather support category 2 but not 1B as suggested.

RAC's response

Thank you for your comment. Please see response to comment number 9.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	France		MemberState	11

Comment received

FR: The CLH report proposes a STOT RE Category 2. Some observed skin effects of erythema, dry skin, fissuring, minimal hyperkeratosis and parakeratosis are not deemed severe enough to require a STOT RE proposal. Indeed, usual practices consider first absence or presence of severe effects, and if severity is encountered then related doses for classification are examined to rule out a Category 1 or 2. The other types of effects observed are focal subacute lymphocytic inflammation and focal congestion and we are of

the opinion than these effects are related to skin sensitisation, for which an H317 classification is already proposed. As such, in the absence of severity and in the presence of skin sensitisation effect, a specific target organ toxicity for repeated skin exposure is not necessary.
Dossier Submitter's Response
Thank you for this comment. It is agreed that the dermal effects in a subacute dermal study with metolachlor in rabbits might be considered borderline for classification but we have tried to take severity into account when proposing category 2 but not 1. Accordingly, the proposal for classification is maintained.
RAC's response
RAC considers that the skin effects observed in the subacute dermal study are not sufficient for classification as STOT RE. However, as in the rabbit repeated-dose toxicity study, skin dryness was noted in all exposed animals and fissuring in some animals, RAC concludes that additional warning for the local skin effects is necessary and that *S*-metolachlor meets the criteria for the additional hazard phrase EUH066 "Repeated exposure may cause skin dryness or cracking".

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	United Kingdom	Heath and Safety Executive	National Authority	12
Comment received				
S-metolachlor (ISO) (EC: -; CAS: 87392-12-9) We agree with the Aquatic Acute 1 classification and M-factor of 10 based on the Pseudokirchneriella subcapitata 72-h ErC50 of 0.056 mg/L. We note the short duration 7-day Elodea canadensis study with a 7-d ErC50 of 0.062 mg/L (based on shoot length) is in the same hazard classification range. The study is relevant for acute hazard classification given the MoA of S-metolachlor as a herbicide. The CLH report notes that when compared with OECD TG 239 for another higher aquatic macrophyte species, Myriophyllum spicatum, the validity criterion for the doubling of the mean total shoot length and mean total shoot fresh weight in control plants during the exposure phase was met. Please can you confirm if the second OECD TG 239 validity criterion was met: 'The mean coefficient of variation for yield based on measurements of shoot fresh weight (i.e. from test initiation to test termination) in the control cultures does not exceed 35% between replicates'. We agree that the mean measured 7-d NOErC of 0.0021 mg/L for Lemna gibba based on frond number (Eckenstein, 2014) leads to an Aquatic Chronic 1 classification with an M-factor of 10 for the not rapidly degradable substance. However, we note that the RAR states that EC10 and EC20 values were calculated for this study where possible, though these endpoints are not presented in the RAR or CLH report and no further explanation is provided. A clear concentration-response curve is apparent from the available data. Given that low ECx values are preferred over NOEC values for the purposes of hazard classification, please could the DS confirm whether these endpoints are available? In addition, there are uncertainties associated with dry weight endpoints from the study as fronds were removed from test vessels for use in the recovery phase before the final dry weight determination. It is unclear whether fronds were also removed from the control				

replicates for use in the recovery phase before dry weight determination. Therefore, it appears that dry weight endpoints should not be used for classification, as the endpoints based on frond number are more relevant.

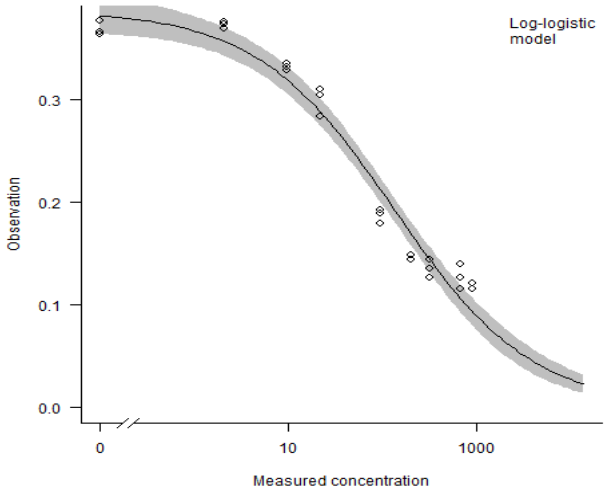
The Lemna gibba 7-d ErC10 of 0.00987 mg/L based on dry weight from a different valid study by Kümmrich (2019) is within the same concentration range as the 7-d NOErC above, which supports the proposed Aquatic Chronic 1 (M=10) classification.

The Elodea Canadensis 7-d ErC10 of 0.0049 mg/L (mm) based on shoot length is presented in Table 20 as a key endpoint and is also within the same concentration range. However, we note that the ErC10 of 0.0049 mg/L and the ErC20 of 0.013 mg/L are below the NOErC of 0.029 mg/L. In general, the mean CoV for control growth should not exceed the value of x used in the low ECx as expressed in OECD TG 239: 'It should be noted that estimates of EC10 and EC20 values are only reliable and appropriate in tests where coefficients of variation in control plants fall below the effect level being estimated, i.e. coefficients of variation should be <20% for robust estimation of an EC20.'. Please can you consider the CoV for this study with the ErC10 and ErC20 endpoints to determine if either endpoint are statistically robust in preference to the NOErC.

Dossier Submitter's Response

Thank you for the comment.
The coefficient of variation for yield based on shoot wet weight is 19.91% and the validity criteria given in OECD 239 (< 35%) is met.

Regarding the study by Eckenstein with *Lemna* it is stated in the RAR that there is a clear dose-response, however it is attributed to some uncertainties. The dose-response relationship is shown below:



All replicates of the second and third lowest treatment level are above the value predicted by the model. This adds high uncertainty in the model itself and the derivation of an ErC10. As the NOEC can unambiguously be set at 0.0021 mg/L, it is the more reliable endpoint relevant for classification purposes.

Endpoints related to dry weight are reliable and can be used for classification purposes. It is correct that 12 fronds were taken at the end of the 7-day exposure phase for a subsequent study of the recovery. In the treatments with expected low frond numbers

(100 – 1000 µg a.s./L) three additional treatments were available to conduct the recovery study. In the lower treatments (control, 2.1, 9.8 and 22 µg a.s./L) the amount of fronds observed in the replicates were between 87 and 167. The dry weights were corrected for the missing 12 fronds. Due to the high amount of fronds in the affected treatments, the missing 12 fronds randomly taken from each replicate are not expected to have an influence on the results. We agree that according to OECD 239 the 7-d ErC10 of 0.0049 mg/L (mm) is not reliable, as the CoV is 19.91% (> 10%). However, it should be noted that (i) OECD 239 for *Myriophyllum spicatum* is just used as surrogate guideline for the study with *Elodea canadensis*, (ii) the width of the confidence interval of the ErC10 (0.0013-0.011 mg/L) is acceptable and below the ErC20 (0.029 mg/L) and (iii) the 7-d ErC10 of 0.0049 mg/L is not a relevant endpoint for the classification of S-metolachlor. Therefore, a change to the NOErC as relevant long-term endpoint is not considered sufficiently justified and would not alter the classification.
RAC's response
Thank you for your comment. Noted.

Date	Country	Organisation	Type of Organisation	Comment number
03.09.2021	France		MemberState	13
Comment received				
FR: FR agrees with the classification for environmental hazards and with the acute and chronic M factor values proposed in the CLH report.				
Dossier Submitter's Response				
Thank you for the comment.				
RAC's response				
Thank you for your comment. Noted.				

PUBLIC ATTACHMENTS
1. Syngenta S-metolachlor PC.zip [Please refer to comment No. 4, 9]