Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

diuron (ISO); 3-(3,4-dichlorophenyl)-1,1-dimethylurea

EC Number: 206-354-4
CAS Number: 330-54-1

CLH-O-0000007019-74-01/F

Adopted

16 September 2021

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON DIURON (ISO); 3-(3,4-DICHLOROPHENYL)-1,1-DIMETHYLUREA

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: diuron (ISO); 3-(3,4-dichlorophenyl)-1,1-dimethylurea
EC number: 206-354-4
CAS number: 330-54-1
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
01.07.2020	Belgium	CEPE	Industry or trade association	1
Comment received				
Please find the attached document on behalf of our industry, the remaining one using diuron in Europe. Diuron is one of the 3 remaining effective algaecide for dry-film preservation. The proposed classification of diuron as Carc Cat 1B would make it a candidate for exclusion under the BPR. The number of effective algaecides available is max 3 and these all have uncertain future. We need to keep them to allow effective control of a wide spectrum of microorganisms and avoid development of tolerance. Therefore, with regards to this proposal for the re-classification from Cat 2 to Cat 1B, we would like to suggest that careful attention is given to the evidence available, in particular to historical control data on the laboratory animal studies and on the relevance to Human of the effects observed in animal. ECHA note – An attachment was submitted with the comment above. Refer to public attachment CEPE position on diuron public consultation.pdf				
Dossier Submitter's Response				
Most comments from industry are very similar and it will be sufficient to respond to them only once in length. Appropriate cross-references have been added. The main argument put forward against Carc. Cat. 1B is based on the use of diuron, its economic importance and the impact of such classification on decisions to be taken under BPR or other regulations. Accordingly, these considerations will be taken into account during socioeconomic analysis to be performed elsewhere and must not influence decision making on classification for intrinsic health hazards.				

The proposed classification for carcinogenicity is based on results from the two long-term studies in rats and mice. No reliable human (epidemiological) information is available. When the CLH report was prepared, historical control data and the available information on possible human relevance of the tumours observed in laboratory animals have been taken into account. With regard to bladder tumours in male and female rats, no further discussion is needed. The existing harmonised classification for carcinogenicity (Cat. 2) is based on these tumours. There were clear treatment-related increased tumour incidences in both sexes at the high dose level. There is convincing evidence for a plausible mechanism of human relevance. It must be emphasised that, in the light of published new mechanistic studies as reported in the RAR and the CLH report, the previous assumption that cytotoxicity was due to physical irritation can no longer be supported. Tumour promotion in the bladder has been demonstrated and this was clearly dose-related. We agree that the existing classification should be maintained if this was the only tumour type of concern.

However, re-evaluation of diuron as a pesticide (a process that was meanwhile discontinued since the company withdrew its application) revealed significant increases for another tumour type in rats and for two tumour types in mice. The proposal for classification into Carc. 1B is largely based on these additional findings. As these tumours can be attributed to treatment, the DS concluded that there is a multi-site response in two species and criteria for category 1B are thus met. HCD is limited and there is no information that would allow to exclude human relevance for these tumours.

For spontaneously occurring uterine adenocarcinoma in rats, a variable historical control incidence of 2 % - 20 % was based on studies in this strain from the same laboratory. Thus, the actual top dose incidence was at the upper edge of the historical control range but the mean of approximately 8 % was by far exceeded. With its detailed comments, LANXESS provided a new overview on HCD. Even though the overall picture with an upper limit of incidence around 20 % is not changed, this HCD is more detailed. It was not available when the CLH report was prepared and will be certainly taken into consideration by RAC. We still find it worth noting that the actual control incidence in the diuron study was well within the HCD range whereas the incidence in the high dose group was at its upper edge. In addition, the maximum historical control incidence of 20 % was reported only once within the set of selected control studies. Notably, there was only one of 21 other control groups for which the tumour incidence exceeded 10 % (16 %). Thus, the dose dependent/treatment-related increase in malignant uterine adenocarcinoma is considered biologically relevant.
It is noteworthy that the incidence of benign lesions in the uterus (polyps) was reduced at the top dose level suggesting a trend towards increasing malignancy. A mode of action for these tumours could not be proposed. We are not aware of any considerations on possible human relevance. In such a situation, it should be the default assumption that the increase in uterine adenocarcinoma in rats is relevant to women. It is also worth noting that the uterus was a target organ in mice as well, even though no increase in tumour frequency in this organ was observed in the long-term study.
Another argument put forward in the comments relates to general toxicity with severe reductions in body weight. It was speculated that this may result in the observed increase in uterine adenocarcinoma in rats. This has been shown for a few substances, e.g., according to the 2017 JMPR evaluation, for the new compound triflumezopyrim. On the other hand, hormonal disturbances (which may also cause uterine tumours) have not been investigated in case of diuron and, accordingly, cannot be excluded. We are sure

that RAC will thoroughly regard and weigh all these arguments. For the time being, we still consider the increase in adenocarcinoma treatment-related.

In the mouse long-term study, there was an increase in mammary adenocarcinoma and in benign ovarian tumours.
The incidence of adenocarcinoma in mammary glands was significantly increased (test for trend after Peto p = 0.0034) in the group receiving 2500 ppm, with the first case detected on day 574. No historical control data from the performing laboratory have been provided. According to published information, the prevalence in NMRI-150 mice may range from 6.7 % in studies over 24 months (Löhrke et al, 1984) to 14 % (observed at an age of 13-18 months as reported by Rehm et al, 1985). In the diuron study, however, an incidence of 17.2 % was observed in the 2500 ppm group, which was higher.
In the comments, the insufficient quality of the HCD was confirmed. The situation becomes more complicate since this was a study of longer duration than usual with that strain. This can make any comparison more difficult and less data can be used.
There is also no sufficient information to show non-relevance to humans. We agree with the industry comments that the (limited) mechanistic studies have not revealed a tumour-promoting potential in the mammary gland.

With regard to the luteoma, no HCD from the performing laboratory was provided. The following information was found in a publication by Rehm et al. (1984). In Han: NMRI mice, the luteoma are rare and found solely in a unilateral position varying in size between 2 and 10 mm, with low mitotic activity and an incidence of 3 % (age 19 - 24 months). Therefore, the high dose incidence in the study with diuron also exceeded the spontaneous incidences of these ovarian tumours in this mouse strain. No information is available that would be helpful to assess human relevance. Thus, again, the default assumption should be that these tumours are relevant to women.
The information provided as part of the industry comments confirmed the lack of suitable HCD. Indeed, the long study duration makes the assessment of most likely hormone-dependent tumours difficult. In the considerations on human relevance, there is quite a lot of uncertainty. That means it cannot be excluded.

RAC's response

RAC agrees with the DS's proposal to classify the substance as Carc. 1B, H350 based on the urinary tract tumour observed in male and female rats and the mammary gland tumours observed in mice. The tumours were not considered secondary to excessive general toxicity and human relevance cannot be excluded. The uterine tumours in rats and the ovarian tumours in mice did not provide sufficient evidence of carcinogenicity.

Date	Country	Organisation	Type of Organisation	Comment number
21.07.2020	France		MemberState	2

Comment received

Toxicological endpoints have not been peer-reviewed by FR experts.

Other endpoints not open for comments:
-Could you please report the purity of active substance for all physico-chemical properties?
-The temperature of decomposition (330 °C) could be added in the table 8 (boiling point).

Dossier Submitter's Response

The purities are:

Property	Purity
Physical state at 20°C and 101,3 kPa	98.8
Melting/freezing point	98.8 99.6
Boiling point	99.7
Relative density	-
Vapour pressure	99.9
Surface tension	99.7
Water solubility	98.0
Partition coefficient n-octanol/water	98.0 99.6 99.0 99.0 99.9
Flash point	-
Flammability	97.3
Explosive properties	97.3
Self-ignition temperature	97.3
Oxidising properties	98.0
Granulometry	-
Stability in organic solvents and identity of relevant degradation products	-
Dissociation constant	99.6
Viscosity	-

Following data for temperature of decomposition could be add:

Property	Value	Reference	Comment (e.g. measured or estimated)
Decomposition / Sublimation temperature	Exothermic decomposition occurs at 330°C	Klusacek and Krasemann (1986)	99.7 purity Method: OECD 113

RAC's response

Thank you for your comments and responses.

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2020	Germany	LANXESS Deutschland GmbH	Company-Manufacturer	3

Comment received

LANXESS would like to emphasize that Diuron is on the ECHA page Registry of CLH intentions until outcome „https://echa.europa.eu/de/registry-of-clh-intentions-until-outcome/-/dislist/details/0b0236e182d03d27" still described as an active substance in Plant Protection Products. This is no longer valid. The Diuron EFSA dossier was withdrawn on 2019-05-15. This means that Diuron will not be used in the EU in the future anymore for plant protection.

Diuron is still supported under REACH REGULATION (EC) No 1907/2006 and under Biocidal Products REGULATION (BPR) (EU) No 528/2012.

Under the BPR Diuron is used as algicide for the protection of house facades, in other words as material protection product. Diuron is very useful to extend the service life of facade materials. The extension of the service life of materials reduces the consumption of raw materials, waste and energy. In this regard Diuron is contributing like every material protection product to the reduction of CO2 emissions. In other words it contributes to prevent the climate change.

Despite the known hazards of Diuron which has to be carefully evaluated under consideration of the Historical Control Data (HCD) Diuron has a significant benefit in its application under the BPR which is generally underestimated.

Please see also our attachment "Cover Letter" in the provided zip folders.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2020-07-31 DIURON CLH consultation LANXESS comments Public Attachments.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 2020-07-31 DIURON CLH consultation LANXESS comments Confidential Attachments.zip

Dossier Submitter's Response

Please see our response to comment (1). Taking into account the benefits of diuron is beyond the toxicological evaluation. The HCD have been taken into account to the extent available from the studies. New and more detailed HCD was provided with the comments and will be considered by RAC. To our impression, these do not change the overall picture.

RAC's response

See response to comment (1)

Date	Country	Organisation	Type of Organisation	Comment number
29.07.2020	Germany	German Paint and Printing Ink Association (VdL)	Industry or trade association	4

Comment received

Diuron (CAS 330-54-1) is a substance, which is of high importance for the paint and coatings industry in Germany. We are aware that the public consultation on the proposed classification should only consider toxicological arguments on inherent properties and we refer to the work done by suppliers. Nevertheless, we would like to highlight the severe impact, which the supposed classification would have on our industry and especially the deco paint sector.

Diuron has been safely used for over 50 years as an herbicide in plant protection, and subsequently as an algaecide in outdoor coatings to protect materials against film destruction and discoloration. The latter is the only remaining use. Therefore, there is significant experience and data concerning the use of Diuron as film preservative, which allows the conclusion that it can safely be used for this application also in the future. Dry-film preservation (PT 7) is most important for organic resin-based coatings and prevents the growth of microorganisms like algae and fungi on coated surfaces, such as the facades of buildings. Dry-film preservatives allow long lasting outdoor coatings; thus, they contribute to circular economy objectives by reducing the use of materials, reducing the use of energy, and reducing waste generation, in line with the aims for the Green Deal.

Diuron is one of the key actives for dry-film preservation. The proposed classification as carcinogenic category 1B (Carc 1B) has the legal consequence that Diuron would fall under the exclusion criteria under the biocides legislation (regulation (EU) No. 528/2012, BPR) The number of effective algaecides for coatings available is very limited – basically three actives are remaining and all have an uncertain future due to the regulatory processes under the BPR. However, to allow effective control of a wide spectrum of microorganisms and avoid development of tolerance, a certain set of substances is needed. All biocides have their own technical characteristics and spectrum of activity. They are usually not replaceable one to one and several parameters must be considered: chemical and physical compatibility, stability in the wet stage and in the dry stage (such as pH on masonry), rate of degradation, leaching behaviour, intrinsic toxicity for Human Health and for the Environment etc. This explains why only a handful of fungicides is used on the market and less than a handful of algaecides. Due to the inherent costs and difficulties in supporting new biocide active substances under the BPR we do not expect any significant innovation in this area.

Therefore, with regards to this proposal for the re-classification from Carc 2 to Carc 1B, we would like to suggest that careful attention is given to the evidence available, in particular to historical control data on the laboratory animal studies and on the relevance to Human of the effects observed in animal.

We remain available to provide further information.

The German paint and printing ink association (VdL) represents over 200 – mostly mid-sized – manufacturers of paints, coatings and printing inks. The VdL stands for nearly 90

percent of this industry in Germany. In 2018 the German manufacturers of paints, coatings and printing inks realized sales of ca. 8 billion euros and employed ca. 25,000
Dossier Submitter's Response
Classification is based on inherent properties of a substance but not on its use (e.g. as biocid). The HCD have been taken into account to the extent avaialable from the studies. New and more detailed HCD was provided with the comments and will be considered by RAC. To our impression, they do not change the overall picture. Human relevance was also considered but there is a remarkable lack of information and still much uncertainty. See also our detailed response to comment (1), please.
RAC's response
See response to comment (1)

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
01.07.2020	Belgium	CEPE	Industry or trade association	5
Comment received				
We would like to suggest that careful attention is given to the evidence available, in particular to historical control data on the laboratory animal studies and on the relevance to Human of the effects observed in animal. ECHA note – An attachment was submitted with the comment above. Refer to public attachment CEPE position on diuron public consultation.pdf				
Dossier Submitter's Response				
The HCD have been taken into account to the extent available from the studies. New and more detailed HCD was provided with the comments and will be considered by RAC. It is our impression that they do not change the overall picture. Human relevance was also considered but there is a remarkable lack of information and still much uncertainty. See also our detailed response to comment (1), please.				
RAC's response				
See response to comment (1)				

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2020	Germany	LANXESS Deutschland GmbH	Company-Manufacturer	6
Comment received				
Carcinogenicity Summary Our comments are of particular relevance for the CLH report evaluation because the dossier submitter stated that "no valid detailed historical control data (HCD) were available". In these comments, we provide comprehensive HCD for the rat and mouse studies by the conducting laboratory in the relevant time frame. In addition, information on non-neoplastic endpoints in the carcinogenicity studies are discussed. The carcinogenic potential of diuron was assessed in a reliable 2-year chronic toxicity/carcinogenicity study in rats, conducted according to EPA 83-1 guideline (comparable to OECD 453) (XXXXXXX, 1985). Wistar rats were randomly assigned to 4 groups of 50 males and 50 females each. Ten additional males and females per group				

were included for interim sacrifice at 12 months. Three dose groups were administered 25, 250, or 2500 ppm of diuron in the diet for 12 or 24 months. This corresponded to an actual test substance intake of 1.0, 10, and 111 mg/kg bw/day in males, and 1.7, 17, and 203 mg/kg bw/day in females.
In mice, the carcinogenic potential of diuron was tested in a 2-year combined chronic toxicity/carcinogenicity study conducted according to OECD 453 (XXXXXXXXXXX., 1990). NMRI outbred mice (4 groups of 60 males and 60 females) were used in this study. Three dose groups received 25, 250 or 2500 ppm diuron in the diet. The concurrent control group received standard, un-treated diet. The overall study period was 24 months with an interim sacrifice after 12 months on 10 animals per sex and per group.
Based on the experimental data it is concluded that the available toxicological database shows a consistent picture, with urinary tract, and erythrocyte/spleen damage as consistent target organs of systemic toxicity.
In contrast, there is no consistent picture related to effects in the rat uterus, mouse ovary, and mouse mammary gland.
Where tumour observations were reported in other organs than the urinary bladder, these tumours were either within the range of the appropriate historical control data (rat uterine adenocarcinoma), or, where the historical control database is limited (mouse ovary luteoma, mouse mammary gland adenocarcinoma), there is for the ovary no obvious treatment related effect on the sex cord stromal tumour combined incidence. For the mammary gland there is one study in the limited historical control database that showed an incidence clearly higher than in the concurrent control group (5/39 (12.8%)), pointing to a variability that is of importance for the assessment of the diuron study.
In addition, there is a lack of consistency over species, a lack of pre- or non-neoplastic effects on the respective organs in rats and mice in all available repeated dose toxicity studies, and a lack of mechanistic evidence (no genotoxic potential, no respective response in mammary two-stage carcinogenesis studies in rats and mice, and no pre- or non-neoplastic findings in repeated dose toxicity studies in rats, mice, and dogs). These aspects put the biological relevance of the observations further in question.
Especially the human relevance of the findings is questionable. For the findings in the rat urinary bladder there is a clear dose-response relationship and the cytotoxic effect is clearly a high-dose effect. High-dose levels of diuron are required to produce the irritant metabolite(s) at urinary concentrations that will be cytotoxic to the urothelium, and these levels need to be sustained for lengthy time (Battalora, 2006). Given the expected pattern of human exposure the human relevance is highly debateable. Since humans are environmentally and occupationally exposed to low concentration levels of diuron that are not expected to produce urinary concentrations of metabolites that would be cytotoxic, it was concluded that humans will not have a carcinogenic response at usual occupational or environmental exposure levels (da Rocha et al., 2014). The incidence of neoplastic findings in the rat uterus (i.e. adenocarcinoma) was within the appropriate HCD range and follow-up statistics revealed only a borderline statistically significant trend. Thus, this finding is not considered as a biologically relevant, treatment-related effect. In accordance with a previous assessment (i.e. under the DSD), it should not be taken into account for the assessment of diuron. Moreover, body weight gain of Wistar rats was markedly decreased in high dose males (-18%) and high dose females (-21%), which clearly demonstrates that the MTD was exceeded for this species. Importantly, the observations made at this high dose level regarding urinary bladder carcinoma and uterus adenocarcinoma, should be carefully evaluated and considered together with the excessive systemic toxicity.
The available experimental data together with the limited historical control database for NMRI mice do not allow a definitive assessment. The historical control database is limited

because of the long study duration of the chronic toxicity/cancerogenicity study in NMRI mice with diuron. In connection with the long study duration, it needs to be taken into consideration that the number of surviving NMRI mice after 24 months of exposure to diuron was low and the current criteria regarding the number of survivors were undercut. Importantly, there is no epidemiological evidence of an increased tumour incidence in man, which could be attributed to diuron exposure (RAR, 2018). Based on all available data, it is concluded that the tumour observations of rat uterus adenocarcinoma, mouse ovary luteoma and mouse mammary gland adenocarcinoma are sporadic findings of spontaneously occurring tumours in very aged animals without biological relevance for the assessment of the carcinogenic potential of diuron. A substance has to be classified in Carc. Cat. 1 only if there is sufficient evidence that the substance is presumed to have carcinogenic potential for humans. For diuron, however, the limited evidence available together with the uncertain human relevance of the high-dose effect of diuron on the urothelium substantiates, classification for Carc. Cat. 2, Suspected human carcinogen is reasonable, but not Cat. 1B, Presumed human carcinogen, according to Regulation (EC) No. 1272/2008. Please see also our attachment "2020-07-30 DIURON CLH consultation LANXESS comments Cancerogenicity " in the respective confidential and public zip folders. Please see also the attachment "2018-07-04 Stropp Diuron Expert Statement HCD and Carcinogenicity confidential.pdf" in the confidential zip folder. Thanks. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2020-07-31 DIURON CLH consultation LANXESS comments Public Attachments.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 2020-07-31 DIURON CLH consultation LANXESS comments Confidential Attachments.zip
Dossier Submitter's Response
Please see our response to comment (1).
RAC's response
See response to comment (1)

Date	Country	Organisation	Type of Organisation	Comment number
29.07.2020	Germany	German Paint and Printing Ink Association (VdL)	Industry or trade association	7
Comment received				
With regards to this proposal for the re-classification from Carc 2 to Carc 1B, we would like to suggest that careful attention is given to the evidence available, in particular to historical control data on the laboratory animal studies and on the relevance to Human of the effects observed in animal.				
Dossier Submitter's Response				
The HCD have been taken into account to the extent avaialable from the studies. New and more detailed HCD was provided with the comments and will be considered by RAC. It is our impression that they do not change the overall picture. Human relevance was also considered but there is a remarkable lack of information and still much uncertainty. See also our detailed response to comment (1), please.				
RAC's response				
See response to comment (1)				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2020	Germany	LANXESS Deutschland GmbH	Company-Manufacturer	8

Comment received

LANXESS agrees with BAuA that based on reliable in vitro and in vivo data the criteria for classification as laid down in the ECHA Guidance document on the application of the CLP Criteria are not fulfilled. Thus, based on reliable data as currently available, no classification and labelling of Diuron for mutagenicity is warranted, according to the criteria in Annex I: 3.5.2.2 Table 3.5.1. This is further in line with the current status of Diuron as not classified for mutagenicity within Annex VI of CLP Regulation (EC) No 1272/2008.
Please see also our attachment "2020-07-30 DIURON CLH consultation LANXESS comments Mutagenicity" in the respective confidential and public zip folders. Please see also our attachment "1998-03-04 Herbold relevance of data from Agrawal 1996 Mutagenicity confidential" in the confidential zip folder. Thanks.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2020-07-31 DIURON CLH consultation LANXESS comments Public Attachments.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 2020-07-31 DIURON CLH consultation LANXESS comments Confidential Attachments.zip

Dossier Submitter's Response

There seems to be agreement and no detailed response is needed.

RAC's response

Thank you for the comment. RAC agrees that no classification is warranted for germ cell mutagenicity.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2020	Germany	LANXESS Deutschland GmbH	Company-Manufacturer	9

Comment received

LANXESS concludes that sufficient evidence is provided from reliable and more actual data to set the LD50 of Diuron for acute oral toxicity as > 2000 mg/kg bw. Consequently LANXESS agrees with the CLH report, that Diuron warrants no classification and labelling regarding acute oral toxicity. LANXESS thus supports the proposal of the BAuA to delete the harmonized classification and labelling for acute oral toxicity as Cat 4 (H302).

LANXESS agrees with the BAuA that no classification and labelling according to CLP is warranted for Diuron with respect to acute dermal and acute inhalation toxicity, which is further in accordance with the harmonized non-classification of the substance for acute dermal and inhalation toxicity.
Please see also our attachment "2020-07-30 DIURON CLH consultation LANXESS comments Acute Toxicity " in the respective confidential and public zip folders. Thanks.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2020-07-31 DIURON CLH consultation LANXESS comments Public Attachments.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 2020-07-31 DIURON CLH consultation LANXESS comments Confidential Attachments.zip
Dossier Submitter's Response
There seems to be agreement and no detailed response is needed.
RAC's response
Thank you for your comment. RAC agrees with the DS' proposal

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2020	Germany	LANXESS Deutschland GmbH	Company-Manufacturer	10
Comment received				
In agreement with the CLH report no sufficient evidence is provided from the sum of available reliable data that would support classification of Diuron as STOT RE 1 (H372). In addition, weight of evidence supports the current legal classification STOT RE 2 (H373) according to the CLP Regulation, which should therefore be kept. In agreement with the CLH report, sufficient evidence is provided from the sum of reliable data available, identifying blood as a main target organ for Diuron toxicity. In agreement with the CLH report and taking into account the information from long-term studies the bladder also should be mentioned as target organ of concern. Please see also our attachment "2020-07-30 DIURON CLH consultation LANXESS comments Repeated Dose Toxicity " in the respective confidential and public zip folders. Thanks. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2020-07-31 DIURON CLH consultation LANXESS comments Public Attachments.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 2020-07-31 DIURON CLH consultation LANXESS comments Confidential Attachments.zip				
Dossier Submitter's Response				
There seems to be agreement and no detailed response is needed.				
RAC's response				
Thank you for your comment. Regarding bladder, the available data do not support a classification of the substance as STOT RE. RAC agrees to classify the substance as STOT RE 2 for blood system by oral route only. In the studies performed by inhalation and dermal route, effects may have been rather adaptative than adverse.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2020	Belgium		MemberState	11
Comment received				
Based on the data in the CLH report, BE CA can support the proposed classification of Diuron for environmental hazards: - aquatic acute toxicity: on the basis of the 72hErC50 for the most sensitive species Synechoccus leopoliensis (algae) with 72hECr50 = 0.0078 mg/L (nom) Diuron is to be classified as Aquatic Acute 1, H400; M=100. - aquatic chronic toxicity: studies are available for the 3 trophic levels. Diuron is considered not rapidly degradable. The most sensitive species is the aquatic plant Ceratophyllum demersum. However we question the NOECgrowth rate of 0.000463 mg/L (lowest concentration tested). Although not statistically significant, 12.1% inhibition of the growth rate was seen at this concentration. Furthermore the 14dEC10 (= 0.000267 mg/l -geom. mean) was extrapolated and may contain remarkable uncertainties.				
Dossier Submitter's Response				
Thank you for your support. We agree with the comment of Member State Belgium concerning aquatic acute toxicity. For an answer concerning the comment on aquatic chronic toxicity, please refer to our answer to comment number 14.				
RAC's response				
Thank you for your support.				

Date	Country	Organisation	Type of Organisation	Comment number
21.07.2020	France		MemberState	12
Comment received				
Based on data from the CLH report, we agree with the classification proposal Aquatic Acute 1 (H400) M=100 and Aquatic Chronic 1 (H410) M=100 for the substance Diuron. The key study from Wenzel (2015) on Synechoccus leopoliensis, used to determine acute and long-term aquatic hazard, is considered valid and relevant for classification and labelling.				
Dossier Submitter's Response				
Thank you for your support. The Dossier Submitter agrees with the comment of Member State France.				
RAC's response				
Thank you for your support.				

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2020	Germany	LANXESS Deutschland GmbH	Company-Manufacturer	13
Comment received				
The Classification of Diuron as aquatic acute category 1 (H400) is justified. LANXESS agrees with the CLH report when supporting the current legal classification and labelling according to the CLP Regulation (EC) No 1272/2008.				

LANXESS agrees with the CLH report, that a M factor of 100 is justified for acute aquatic toxicity The Classification of Diuron as aquatic chronic category 1 (H410) is justified. LANXESS agrees with the CLH report when supporting the current legal classification and labelling according to the CLP Regulation (EC) No 1272/2008. LANXESS agrees with the CLH report, that a M factor of 100 is justified for chronic aquatic toxicity. No extra documents are provided in the zip folder. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2020-07-31 DIURON CLH consultation LANXESS comments Public Attachments.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 2020-07-31 DIURON CLH consultation LANXESS comments Confidential Attachments.zip
Dossier Submitter's Response
Thank you for your support. The dossier submitter agrees with the comment by LANXESS Deutschland GmbH.
RAC's response
Thank you for your support.

Date	Country	Organisation	Type of Organisation	Comment number
31.07.2020	United Kingdom	Health and Safety Executive	National Authority	14
Comment received				
diuron (EC 206-354-4; CAS 330-54-1) We agree that diuron should be classified as Aquatic Acute 1 with an Acute M-factor of 100 based on the ErC50 for Synechoccus leopoliensis. We also agree with the proposed Aquatic Chronic 1 classification and that the key studies driving this classification are those employed with Synechoccus leopoliensis and Ceratophyllum demersum. The study with Elodea canadiensis could additionally be considered a key study in a weight of evidence for the chronic classification. The proposed Chronic M-factor of 100 is based on the NOErC for Synechoccus leopoliensis and the ErC10 for Ceratophyllum demersum. However, we consider that more information is required to confirm the Chronic M-factor. Study using Synechoccus leopoliensis: We note that there is a preference for EC10 values compared to NOEC values under CLP given ErC10 endpoints are statistically more robust and not a function of test design. The Synechoccus leopoliensis study was well conducted meeting validity criteria and a clear dose-response relationship was determined. In addition, the ErC10 95% confidence intervals support a well-defined ErC10 endpoint of 0.0037 mg/L (95% CI 0.0036 to 0.004 mg/L). On this basis, we consider the ErC10 for Synechoccus leopoliensis is the most appropriate long-term endpoint from the study in preference to the NOErC. This would result in a Chronic M-factor of 10.				

Study using Ceratophyllum demersum:
The proposal considers the ErC10 is the preferential endpoint rather than the NOErC. However, we consider the reliability of the ErC10 is uncertain for the following reasons and more details on control growth / variability and measured concentrations are required to determine the most appropriate long-term endpoint from the study.

1. The ErC10 has been extrapolated beyond the dose-response range of the test concentrations, noting there was 12% inhibition at the lowest treatment which was statistically considered the NOErC.

2. The study followed OECD TG 239 which was validated using M. spicatum, although the TG can be adapted for alternative free floating species. In relation to appropriate endpoints, TG 239 states 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". We think this CoV for overall control growth rate should be derived to consider the level of control growth variation and whether an ErC10 endpoint is robust. Given the 95% confidence intervals for the reported ErC20, it may be that the EC20 of 0.00137 mg/l (95% CI 0.000343 to 0.00294 mg/L) is more appropriate for this species/study. The ErC20 would lead to an Aquatic Chronic 1 classification with a Chronic M-factor of 10.

3. We note the large range of initial measured concentrations from 86.6-121% of the nominal concentrations. At the end of the test, the test item recovery was 40.2-98% but it is unclear whether the low end reflected low treatments, and there is no information on the LOD. Therefore, more details of measured water concentrations and recoveries should be presented to assess whether the geometric mean measured endpoints are representative.

Study using Elodea canadiensis:
The study also followed OECD TG 239 with a sediment phase. The ErC10 was extrapolated outside the range of the tested concentrations leading to relatively high uncertainty of the estimate. As per the study with C. demersum, it would be useful to consider the CoV for the overall growth rate of the controls to determine whether an ErC10/ErC20 endpoint is appropriate for this study using a non-standard test species. We recognise the presence of the sediment phase and low test item recovery means endpoint interpretation is difficult, however it would be useful to decide whether the determination of reliable mean measured concentrations (and endpoints) from the water phase could still make such a test suitable for aquatic hazard classification purposes, at least in a weight of evidence approach.

Dossier Submitter's Response

The dossier submitter agrees with the comment concerning aquatic acute toxicity.

Study on *Ceratophyllum demersum*:
For the endpoint growth rate based on dry weight, the coefficient of variation was 16.7 % in the control and ranged between 14.9 % and 25.6 % in the treatments.
The LoQ was 0.3 µg/L in water and 1 µg/kg dw in sediment. For the nominal concentrations of 1, 3.16, 10, 31.6 and 100 µg/L, measured diuron concentrations in the overlying water were 86.6, 104, 121, 112 and 108 % of nominal at test start, and 28.7, 40.8, 47.7, 63.0 and 71.5 % of nominal at test termination. Total recovery for the water-

sediment system was 40.2, 49.9, 43.9, 69.4 and 97.9 % of initial. Therefore, it was seen as most appropriate to base the evaluation on geometric mean measured concentrations.

Study on *Elodea canadensis*:
For the endpoint growth rate based on fresh weight, the coefficient of variation was 24.5 % in the control and ranged between 12.7 % and 203.1 % in the treatments. The LoQ was 0.3 µg/L in water and 1 µg/kg dw in sediment. For the nominal concentrations of 1, 3.16, 10, 31.6 and 100 µg/L, measured diuron concentrations in the overlying water were 51.0, 72.0, 78.1, 83.9 and 92.0 % of nominal at test start, and 45.1. 57.0, 56.3, 64.0 and 50.8 % of nominal at test termination. Total recovery for the water-sediment system was 58.8, 60.0, 101, 69.5 and 75.6 % of initial.

The robustness of the calculated E_rC_{10} for *Ceratophyllum demersum* is also questioned in the comment number 11 by BE CA. We agree that the coefficient of variation, combined with the fact that the EC_{10} is extrapolated outside of the tested concentration range, casts some doubt on the robustness of the reported E_rC_{10} of 0.000267 mg a.s./L. However, the NOE_rC based on the same endpoint is 0.000463 mg a.s./L. This is also in the concentration range of 0.0001 to 0.001 mg/L, which would likewise lead to the classification of Aquatic Chronic 1 with a chronic M-factor of 100 if the evaluation is based on the NOE_rC. *Ceratophyllum demersum* showed to be the most sensitive of the tested species, hence the assessment should be based on this species. Although the E_rC_{20} can be estimated more robustly, we do not agree with the proposal to base the classification on the E_rC_{20}. This would lead to a lower chronic M-factor than the assessment based on NOE_rC. NOE_rC and E_rC_{10} are in a similar concentration range and the growth rate was already reduced by 12 % at the NOE_rC. Therefore, we do not see it justified to classify Diuron with a chronic M-factor lower than 100.

RAC's response

RAC takes note of the comment made of *Synechococcus leopoliensis* study.
RAC also notes that the E_rC_{10} of 0.0037 mg/L, although obtained with a high CI, is not the lowest valid effect concentration value obtained for this trophic level and should not be preferred when applying classification procedure.
RAC agrees with the DS *Ceratophyllum demersum* can be considered the most sensitive of the tested species. RAC also notes the EC10 is extrapolated outside of the tested concentration range and that the coefficient of variation is higher for the EC20 but does not support the use of EC20 values for classification purposes.

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2020	Netherlands		MemberState	15

Comment received

Biodegradation
According to the Dossier Submitter the substance diuron is considered as not 'readily biodegradable' by default because no study is available. We would like to point out that a ready biodegradability study (OECD 301 F) for diuron is available on the ECHA dissemination website (June 2020). The study was conducted under GLP conditions. No degradation (0%) for diuron was observed after 28 days of testing. Based on the available information on the ECHA website, the screening test appears to be reliable. If the reliability of the study can be confirmed, based on this study diuron can be regarded as not readily biodegradable.

We agree with the Dossier Submitter that the substance diuron should be regarded as not rapidly biodegradable, based on the data available and weight of the evidence. If the ready biodegradability study test is considered reliable, diuron can be regarded as not rapidly degradable based on this study.

ECHA database: https://echa.europa.eu/nl/registration-dossier/-/registered-dossier/13520/5/3/2/?documentUUID=ad6f02e3-acf6-43dd-8472-956b34e0c061

Aquatic Toxicity classification
The most sensitive concentration for acute toxicity is based on a study of Wenzel, A. (2015) (ASA-001/4-10/C/1). Freshwater cyanobacteria (Synechococcus Leopoliensis) were exposed to nominal test concentrations of 0,1, 0,2 , 0,632, 2,00, 6,32 and 20 µg/l for 72h. The experimentally determined ErC50 is 7.88 µg/l based on nominal concentrations. One small remark is that the lowest test concentration (0,1 µg/l) is outside ±20% of the nominal concentrations, therefore, concentrations should be reported as geometric mean concentrations according to OECD Test guideline 201. It is unclear whether the measurements of the tested concentrations (0,1 µg/l) were exceeding or below 20% of nominal or if the tested concentration was in the range of the LOD. However, as only the lowest test concentration is outside the ±20% range, and all higher concentrations are within the range of ±20%, we agree that the ErC50 is based on nominal concentrations, as the deviations in measured concentrations at a concentration of 0,1 µg/l do not affect the outcome of the ErC50. If, in addition, deviations were present at other test concentrations, we would have advised to use geometrical mean concentrations.

References
Wenzel, A. 2015 FRESHWATER CYANOBACTERIA, GROWTH INHIBITION TEST (OECD 201). DIURON (TECHNICAL): EFFECTS ON SYNECHOCOCCUS LEOPOLIENSIS, Report No.: ASA-001/4-10/C/1 Fraunhofer-Institute for Molecular Biology and Applied Ecology (IME), Schmallenberg, Germany, unpublished

Dossier Submitter's Response

Biodegradation:
We thank Member State Netherlands for mentioning the available study on ready biodegradability. Unfortunately, the original study is not available to the Dossier Submitter, so its validity and reliability cannot be confirmed. The data is considered as supplementary information, which confirms the classification as "not rapidly degradable". A short summary of the available data, taken form the ECHA database mentioned above, is provided separately.

Aquatic toxicity:
In the study on *Synechococcus leopoliensis* the recovery of diuron in the lowest tested concentration (0.1 µg/L) varied between 131 and 212 % of nominal, while the measured concentrations in all other treatments were very close to the nominal concentrations (89.5 – 107 %). In principle, we agree that assessments should be based on geometric mean measured concentrations if the measured concentrations are outside ± 20 % of nominal concentrations. However, relevant effects were only seen in concentrations higher than 0.632 µg a.s./L. Hence, the deviations in the 0.1 µg/L treatment will have negligible effect on the outcome of the ECx-calculations. Therefore, we see it as acceptable to base the calculations on nominal concentrations in this case.

Attachment: CLH_Diuron_Attachment_Ready biodegradability
RAC's response
RAC agrees with the DS that the use of the lowest E_rC_{10} from the *Synechococcus leopoliensis* study based on nominal concentrations is justified. The single variation at the lowest dose give little effect to the calculations of the effect concentrations. The NOEC was estimated to be 0.000632 mg/L. RAC takes note of the information provided on the ready biodegradability study (OECD 301 F).

PUBLIC ATTACHMENTS
1. 2020-07-31 DIURON CLH consultation LANXESS comments Public Attachments.zip [Please refer to comment No. 3, 6, 8, 9, 10, 13]
2. CEPE position on diuron public consultation.pdf [Please refer to comment No. 1, 5]

CONFIDENTIAL ATTACHMENTS
1. 2020-07-31 DIURON CLH consultation LANXESS comments Confidential Attachments.zip [Please refer to comment No. 3, 6, 8, 9, 10, 13]