COMPILED COMMENTS ON CLH CONSULTATION

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

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Last data extracted on 17.08.2022

Substance name: bixlozone (ISO); 2-(2,4-dichlorobenzyl)-4,4-dimethyl-1,2-oxazolidin-3-one
CAS number: 81777-95-9
EC number: -
Dossier submitter: The Netherlands

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2022	United States of America	FMC	Company-Manufacturer	1
Comment received				
FMC submits the following comments for consideration by the Risk Assessment Committee (RAC) regarding the proposed Harmonised Classification and Labelling for bixlozone: FMC agrees based on the physical and chemical properties of bixlozone that classification for physiochemical properties and physical hazards it not required. FMC agrees that bixlozone does not meet the classification criteria for the following toxicology endpoints: acute oral, dermal and inhalation toxicity, skin and eye irritation, and skin sensitization, specific target organ toxicity – single and repeat exposure, germ cell mutagenicity, carcinogenicity, and reproductive and developmental toxicity. FMC agrees with the acute and chronic classifications proposed for bixlozone for environmental hazards and the endpoints upon which these are based.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2022	United States of America	FMC	Company-Manufacturer	2
Comment received				
FMC agrees with the DS that bixlozone does not meet the classification criteria for carcinogenicity. FMC agrees that the low incidence of combined incidence of skin/subcutis fibroma and fibrosarcoma found in the male top dose (5000 ppm) group in the 2-year rat chronic study was not related to bixlozone treatment. The incidences of fibroma and fibrosarcoma across the dose groups did not show a dose response and were within the HCD range from the same laboratory. Therefore, the combined incidences represent background occurrences and are not related to treatment with bixlozone.				

Similarly, the low combined incidence of thyroid follicular cell adenoma and carcinoma observed in high dose (5000 ppm) female rats in the 2-year chronic study are considered to be of spontaneous origin and do not represent a treatment-related effect based on the lack of hypertrophy or hyperplasia in the thyroid and incidences within the laboratory historical control range.

FMC agrees with the DS that there was no treatment-related increase in neoplasia in mice in the 18-month carcinogenicity study. Increases in histiocytic sarcoma, bronchiolo-alveolar adenoma/carcinoma or leiomyoma/leiomyosarcoma in cervix/uterus in high dose mice either lacked a dose-response and/or were within the laboratory historical control data.

Date	Country	Organisation	Type of Organisation	Comment number
03.08.2022	France		MemberState	3

Comment received

Page 68 (rat): Historical Control Data (HCD) do not meet EFSA Administrative Guidance Requirements in terms of information provided (see excerpt below), only max. HCD are provided. In addition to the lack of information, the period of time largely exceeds 5 years (2009 to 2017 = 9 years). Given these two major issues, the HCD provided do not appear to be reliable or usable, it would be welcome if some clarification on that were provided. For skin/subcutis-combined Fibroma/Fibrosarcoma, there is unclear dose-response (due to response in the mid-dose group), however incidence at the top-dose is 2-fold greater than in the concurrent control, and the low-dose has also greater incidence than the concurrent control, it is therefore difficult to consider these increases incidental. Could a discussion covering and weighing these findings be included too for completeness?

Page 68: For thyroid gland, there is monotonic increase of incidence of combined follicular cell adenoma/carcinoma (i.e., the value never changes direction) and the incidence is null in concurrent negative control. ADME do confirm that thyroid is well exposed and hypertrophy were noted in the 90-day studies (rat, dog…). In this context and since HCD information is insufficient, one may deem that discarding the increase is not straightforward. Would it be possible to include a rationale discussing and weighing this increase in light of observations on thyroid in other studies?

Page 69 (mice): similar issues as page 68 (see above) are found with HCD. It is unclear too why combined adenoma and carcinoma, bronchio-alveolar HCD are "n.r." for "not reported" while HCD are available of these effects separated. Again, it would be welcome if clarification were provided on these issues with HCD.

Page 69 (mice): for low (250 ppm) and high (5000 ppm) doses, the corresponding incidences are greater than the HCD. Whilst no dose response is clearly found due to response in the mid-dose group, it is noted that at 5000 ppm the incidence is 2-fold greater than incidence observed in the concurrent control group (it is 1.5-fold at 250 ppm). This finding would probably be needed to be mentioned for completeness.

Excerpt from EFSA Administrative Guidance (EFSA Supporting publication 2019:EN-1612):
HCD are necessary to follow changes in the biology of the used test species and to differentiate the way to evaluate test results. HCD represent a summary of the observations made on the untreated or control groups from individual studies and a

complete assessment of their relevance should be provided by the applicant in the dossier based on the criteria as set out in Commission Regulation (EU) No 283/2013:
- the incidences of effects for control animals in studies with the same design conducted by the same laboratory; summarised by species, sex, route of administration and vehicle. If study via diet, the diet should be mentioned with reference to the diet characteristics.
- the data for control animals compiled from the concurrent five-year period.
Therefore the following information should be provided:
- the mean, the median, the SD and range of incidences among studies of the effect,
- the number and the dates of studies summarised,
- the use of percentiles could be further considered for HCD of growth or survival (presented as curves),
- Single values (mean, median, SD and range) from those studies that fulfil criteria as set out in Commission Regulation (EU) No 283/2013.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2022	United States of America	FMC	Company-Manufacturer	4
Comment received				
FMC agrees that bixlozone does not meet the classification criteria for genotoxicity/germ cell mutagenicity based on the results from a battery of in vitro and in vivo guideline genotoxicity studies. Bixlozone did not induce gene mutations in two in vitro assays and was negative for chromosome aberrations (numerical and structural) in an in vivo micronucleus assay.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2022	United States of America	FMC	Company-Manufacturer	5
Comment received				
FMC agrees that no classification is warranted for reproductive or developmental toxicity for bixlozone. There were no adverse effects observed in the rat two generation reproduction study and rabbit prenatal developmental toxicity study. In the rat developmental toxicity study, a slightly increased incidence of 14th rudimentary ribs and mal-aligned sternebrae was seen at high dose level. However, these are common variations observed only at high dose, occurred in the presence of significant maternal toxicity and showed no dose response or statistical significance when compared to the controls. The incidences were within historical control data range. Therefore, these variations are not considered to be of toxicological significance. No classification is warranted for reproductive or developmental toxicity for bixlozone.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2022	United States of America	FMC	Company-Manufacturer	6
Comment received				
FMC agrees bixlozone does not meet the criteria for classification for acute oral, dermal or inhalation toxicity based on the available data. • Acute oral LD50 >2000 mg/kg bw				

• Acute dermal LD50 >2000 mg/kg bw • Acute inhalation LC50 > 2.11 mg/L

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2022	United States of America	FMC	Company-Manufacturer	7
Comment received				
FMC agrees bixlozone does not meet the criteria for classification for skin corrosion/ irritation based on the available data.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2022	United States of America	FMC	Company-Manufacturer	8
Comment received				
FMC agrees bixlozone does not meet the criteria for classification for serious eye damage/irritation based on the available data.				

Date	Country	Organisation	Type of Organisation	Comment number
03.08.2022	France		MemberState	9
Comment received				
Ocular irritation/serious eye damage endpoint: two tests were conducted, EpiOcular based on RhCE (OECD 492) and Draize rabbit eye test (OECD 405). The two show conflicting results and no rationale has been provided on how to rule out this endpoint. EpiOcular test gave a clear positive result (cell viability 19% only) and should have been followed by another test like BCOP according to OECD Guidance Document 263. Rabbit eye test show scores in favour of a negative results. It would probably be beneficial to include a rationale, RMS seems to give precedence to the rabbit test but without justification. EpiOcular gave a cell viability far below the threshold of 60% i.e., is clearly positive and Draize test is well known to have too high variability (ref. OECD GD 263) and therefore sound justification would be welcome. Indeed, by following a bottom-up approach (OECD GD 263) one may consider that the EpiOcular is positive (i.e., NOT No Category, either Cat. 1 or Cat. 2) and based on scores form the Draize test the final overall outcome is Cat. 2.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2022	United States of America	FMC	Company-Manufacturer	10
Comment received				
FMC agrees bixlozone is not a dermal sensitizer and does not meet the criteria for classification for skin sensitization.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2022	United States of America	FMC	Company-Manufacturer	11
Comment received				
FMC agrees with the proposal of no classification of STOT-SE for bixlozone.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2022	United States of America	FMC	Company-Manufacturer	12
Comment received				
FMC agrees with the proposal of no classification of STOT-RE for bixlozone.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2022	United States of America	FMC	Company-Manufacturer	13
Comment received				
FMC agrees with the acute and chronic classifications proposed for bixlozone for environmental hazards and the endpoints upon which these are based.				

Date	Country	Organisation	Type of Organisation	Comment number
09.08.2022	Germany		MemberState	14
Comment received				
We thank the RMS for the detailed assessment. We support the conclusion to classify bixlozone as Aquatic Acute 1, with an M-factor of 1, and as Aquatic Chronic 1, with an M-factor of 10. However, we have some additional comments: 2.8.2.1.1: Ready biodegradability We agree that bixlozone is not readily biodegradable and that this study is a key study on the rapid degradability potential of bixlozone. But, could you please for reasons of clarity add the conclusion that bixlozone is not rapidly degradable. 2.8.2.2.1: Aerobic mineralisation We agree that the study is a supportive study to conclude on the rapid degradability potential of bixlozone. But, please, add the conclusion that bixlozone is not rapidly degradable. Aerobic metabolism in water/sediment systems We agree, that the study is a supportive study to conclude on the rapid degradability potential of bixlozone. But, please, add the conclusion that bixlozone is not rapidly degradable.				

Date	Country	Organisation	Type of Organisation	Comment number
03.08.2022	France		MemberState	15
Comment received				
Page 152: FR agrees with the classification proposal for environmental hazards and with the proposed acute and chronic M factor.				

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
11.08.2022	United States of America	FMC	Company-Manufacturer	16
Comment received				
FMC agrees based on the physical and chemical properties of bixlozone that classification for physiochemical properties and physical hazards it not required.				