Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

clomazone (ISO); 2-(2-chlorobenzyl)-4,4-dimethyl-1,2-oxazolidin-3-one

EC Number: -
CAS Number: 81777-89-1

CLH-O-0000006701-78-01/F

Adopted

20 September 2019

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON CLOMAZONE (ISO); 2-(2-CHLOROBENZYL)-4,4-DIMETHYL-1,2-OXAZOLIDIN-3-ONE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public 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 public 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 public 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.

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Substance name: clomazone (ISO); 2-(2-chlorobenzyl)-4,4-dimethyl-1,2-oxazolidin-3-one
EC number: -
CAS number: 81777-89-1
Dossier submitter: Denmark

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2019	United States	FMC Corporation	Company-Manufacturer	1
Comment received				
The DS has proposed harmonised classification and labelling for Clomazone in accordance with the CLP criteria. FMC submits the following comments in response to this proposal. Two documents are being submitted with this specific submission. A pdf version of our comments with a detailed review of the developmental toxicity data package and a recently conducted rat developmental toxicity study (Anon, 2019). Due to file size restrictions, a second submission by FMC is being made in order to provide two additional studies that accompany the new developmental toxicity study - a dose range finding study and a pharmacokinetic study. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Clomazone, ECHA Comment, 8Feb2019, FMC, No. 1.zip				
Dossier Submitter's Response				
DS has gone through the new material. A targeted consultation on this new study would be appropriate. The study shows no signs of treatment related developmental toxicity. This is not the same as previous studies should just be disregarded but it adds to the weight of evidence.				
RAC's response				
Noted, thank you. The new material was subjected to an ad hoc consultation and along with the comments received has been taken into account in the opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2019	United States	FMC Corporation	Company-Manufacturer	2
Comment received				
This submission accompanies Reference number 51fd5d3d-5e36-493d-b540-b94f6ade57d0. This submission contains two additional studies that accompany the new pre-natal developmental toxicity study and a detailed review paper referred to in the reference submission. These two reports are being supplied separately due to file size restrictions of the website. FMC asks that you kindly include these two accompanying studies with FMC's comments on the proposed classification of Clomazone. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Clomazone, ECHA Comment, 8Feb2019, FMC, No. 2.zip				
Dossier Submitter's Response				
See comment number 1				
RAC's response				
Noted, thank you, see reply to comment 1.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2019	United Kingdom	UPL Europe Ltd	Company-Manufacturer	3
Comment received				
Reference 2.6.5 ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH evaluation.pdf				
Dossier Submitter's Response				
No relevant comment was submitted for this hazard class. The comment referred to in the attachment only addresses developmental toxicity.				
RAC's response				
This comment refers to developmental toxicity and has been considered in developing the opinion for that hazard class accordingly.				

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2019	Germany		MemberState	4
Comment received				
Non-classification for this endpoint is supported. In section 2.6.5 Summary of long-term toxicity and carcinogenicity, p78 CLH report, more detail on the effects seen in the thymus of female mice is needed. In addition, the wording in "Females exposed for 1000 and 2000 ppm clomazone had a larger portion of persistent thymic glands" should include a specification of "larger".				
Dossier Submitter's Response				
Noted. 18 percent of the female mice in the 1000 ppm group and 13 percent in the 2000 ppm group had lymphoid hyperplasia in thymus compared with 4 percent in the control group.				

There were no other histopathology findings of the thymus different from the control group. As we understand the instructions from ECHA, the vol 1 will not be updated for CLH process therefore the thymus effects cannot be elaborated there.
RAC's response
Noted, thank you.

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2019	United States	FMC Corporation	Company-Manufacturer	5
Comment received				
FMC agrees that Clomazone is not carcinogenic and thus does not meet the classification criteria for carcinogenicity. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Clomazone, ECHA Comment, 8Feb2019, FMC, No. 1.zip				
Dossier Submitter's Response				
Noted				
RAC's response				
Noted, thank you.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2019	United Kingdom	UPL Europe Ltd	Company-Manufacturer	6
Comment received				
Reference 2.6.4 ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH evaluation.pdf				
Dossier Submitter's Response				
No relevant comment was submitted for this hazard class. The comment referred to in the attachment only addresses developmental toxicity.				
RAC's response				
This comment refers to developmental toxicity and has been considered in developing the opinion for that hazard class accordingly.				

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2019	United States	FMC Corporation	Company-Manufacturer	7
Comment received				
FMC agrees with the conclusion of the DS; the results from guideline genotoxicity studies performed with Clomazone were consistently negative. Thus, Clomazone does not meet the classification criteria for germ cell mutagenicity. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Clomazone, ECHA Comment, 8Feb2019, FMC, No. 1.zip				

Dossier Submitter's Response
Noted
RAC's response
Noted, thank you.

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2019	France		MemberState	8

Comment received

FR: In Table 18 the deviations quoted for the bone marrow MN test in mice do not correspond to the text in Vol.3.B6. Could you please check?
Furthermore, in Vol.3B.6, page 205-206, it is concluded that:
- "No increase in polychromatic erythrocytes was observed when compared to control – neither in number or PCE/NCE ratio." Do you mean no increase in micronucleated PCE/PCE ratio?
- "PCE/NCE ratio was reduced to more than 50%" which is not supported by the data reported in Table B.6.4.2/02-1. Could you please clarify?

Further evidence should be considered in order to support exposure of the bone marrow (e.g.: ADME data).

Dossier Submitter's Response

The deviations in Table 18 of vol 1 have been wrongly inserted. They are concerning the chromosome aberration test and should have been inserted in the row just above. The Chromosome aberration test is considered supportive, not acceptable. See Table below.

You are right the PCE/NCE was not reduced to more than 50%. However, clinical symptoms indicate bone marrow exposure. In addition, in the ADME studies of rat and in the newly submitted pharmacokinetic study after oral administration of female rats (study no. 036908-1; FMC tracking No: 2018MET-CLZ4349), Clomazone was measured in blood. Hence, bone marrow can be considered exposed.

Method, guideline, deviations[1] if any	**Test substance**	**Relevant information about the study (as applicable)**	**Observations/Results**	**Reference**
In vivo mammalian chromosome aberration test, (Sprague-Dawley rat bone marrow cells), OECD 475, ~~No deviations, Acceptable~~ Deviations: A minimum of 50 metaphase cells instead of 100 were analysed, the proportion of cells in mitosis was determined for a minimum of 500 cells	Clomazone technical Purity: 88.8 % Batch no.: E1756-146-20	200 to 2000 mg/kg bw/day	Negative	xx 1982 T1839.102

instead of 1000 cells, sampling performed 6 hours after final dosing (instead of 1.5 cycle length of usually 18-27 hours), Supportive				
Mammalian erythrocyte micronucleus test, OECD 474, Deviations: ~~A minimum of 50 metaphase cells instead of 100 were analysed, the proportion of cells in mitosis was determined for a minimum of 500 cells instead of 1000 cells, sampling performed 6 hours after final dosing (instead of 1.5 cycle length of usually 18-27 hours), Supportive~~ 2000 cells were scored per animal per sex. As no sex difference is expected it is now a requirement to score double the amount of cells (4000) in 5 animals of just one sex. In principle 2000 cells of each sex gives 4000 cells. Both methods totals to 20000 cells scored for PCE. 1000 cells were scored for proportion of PCE/NCE, this was more than required in either version of the guideline. No historical positive control data was included in the study, there is, however, a significant increase in polychromatic	Clomazone technical Purity: 96.6 % Batch no.: D-20071015-4	125-500 mg/kg bw	Negative	xx 2009 23881

erythrocytes for the positive control. It was not shown directly that bone marrow was exposed. However, clinical symptoms as well as measurement of clomazone in blood in rat ADME study and in new rat pharmacokinetic study indicate bonemarrow exposure. The study is acceptable.				
Unscheduled DNA synthesis test with mammalian liver cells in i*n vivo,* OECD 486 (1997), No deviations, Acceptable	Clomazone technical Purity: 96.6 % Batch no.: D-20071015-1	500 and 1000 mg/kg bw	Negative	xx 2009 23987

RAC's response

Noted, thank you.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
31.01.2019	United Kingdom		Individual	9

Comment received

Re: Section 2.6.6.2 of CLH report

The reviewers each have more than forty years of professional experience in the field of developmental and reproductive toxicity and are recognized internationally as experts in foetal pathology. We have reviewed the study reports and related documentation for clomazone as independent consultants for FMC. The evaluation below represents our own opinion on the data reviewed.

Summary
• Arthrogryposis, the terminology used to describe the apparent limb flexures recorded at skeletal evaluation in a rat embryofoetal developmental toxicity (EFD) study, conducted by Rallis Laboratories, India (2002), is considered to be a misdiagnosis.
• Arthrogryposis is defined as limb positional defects that develop in utero and are present at birth. None of the limb flexures recorded at skeletal evaluation were seen in the fresh state and it is considered that the apparent flexures recorded by Rallis at skeletal evaluation were artefacts introduced during the ex utero procedures.
• No limb flexures were recorded in a rat EFD study conducted at FMC Laboratories, USA, (1984) and none was seen in a recent third rat EFD study conducted at Charles River

Laboratories, USA, (report date: January 2019).
• One instance of isolated limb flexure was recorded in a rabbit EDF study conducted by Rallis Laboratories (2002), which was within the laboratory historical control range; none was seen in a rabbit EFD study conducted at WIL Laboratories, USA (1982).
• Because of misdiagnosis, the reported finding of "arthrogryposis" should not be used as the criterion to classify clomazone as a developmental toxin.

Background
In 1982, an embryofoetal developmental toxicity (EFD) study in New Zealand White rabbits was performed at WIL Laboratories, Ashland, Ohio, USA, on behalf of FMC Corporation, which investigated the effects of oral administration of clomazone at dose levels of 30, 240 and 1000 mg/kg bwt/day between gestation day (GD) 6 and GD 18. At 1000 mg/kg bwt/day, maternal body weight loss, abortions and deaths were recorded, and the dose was reduced to 700 mg/kg bwt/day from GD 13. At 240 mg/kg/bwt/day the only manifestation of toxicity was a slight reduction in maternal bodyweight gain and no adverse maternal effects were seen at 30 mg/kg bwt day. In 1984 an EFD study in Sprague-Dawley rats was performed by FMC Toxicology Laboratories, Somerville, New Jersey, USA, in which clomazone was administered by oral administration at dose levels of 100, 300 and 600 mg/kg bwt/day between GD 6 and GD 15. At 600 mg/kg bwt/day there were slight effects upon maternal body weight performance and food intake, but none was seen at the lower dose levels. Neither of these studies revealed any significant adverse effects upon foetal survival or morphological development at dose levels of up to 600 mg/kg bwt/day (rat) or 1000/700 mg/kg bwt/day (rabbit), dose levels which elicited maternal toxicity. EFSA reviewed these data in 2007 and concluded there were no grounds for classification for developmental toxicity.

In 2002, an EFD study in Wistar rats was performed by Rallis Laboratories, Bangalore, India, on behalf of AGAN Agrochemicals, which investigated the effects of oral administration of clomazone at dose levels of 250, 500 and 750 mg/kg bwt/day between GD 6 and GD 19. Maternal toxicity in the form of reduced body weight, body weight gain and food intake was recorded at 500 and 750 mg/kg/day and increased salivation, lethargy and one death occurred at 750 mg/kg bwt/day. Increased early post-implantation death and slightly reduced foetal weights were recorded at 750 mg/kg bwt/day. Following external foetal examinations 1/204 foetuses at 750 mg/kg bwt/day was described in the report text and summary table as having forelimbs flexed at wrist, whereas in the report appendix this was reported as arthrogryposis; none was seen at the lower dose levels. Following skeletal processing and evaluation, two foetuses at 500 mg/kg bwt/day and seven foetuses at 750 mg/kg/ bwt/day were described as having arthrogryposis, and for which the incidence at 750 mg/kg bwt/day was outside the laboratory historical control range for this observation. The foetus with flexed forelimbs seen at fresh examination was not one of these. The affected foetuses had no other morphological changes. Also in 2002, an EFD toxicity study was conducted in NZW rabbits by the same laboratory for the same sponsor at oral dose levels of 150, 350 and 700 mg/kg bwt/day between GD 6 and GD 28. Reduced body weight gain and food intake were recorded at 700 mg/kg bwt/day, two females aborted and one death occurred which was considered by the testing laboratory likely to be treatment related. No adverse maternal effects were recorded at the lower dose levels. Two foetuses at 700 mg/kg bwt/day were recorded as having flexed forelimbs/arthrogryposis, one case in isolation and the other in conjunction with multiple cranial and limb abnormalities. None was seen at the lower dose levels. These studies, together with the earlier studies, were submitted to ECHA in 2018 as part of a CLH dossier and the dossier submitter has proposed a classification of Repro 1B on the basis of the reported cases of arthrogryposis in the Rallis rat and rabbit studies.

Discussion
Arthrogryposis is defined in its simplest form as "joint contractures that develop before birth and are evident at birth. With arthrogryposis there is a lack of the normal range of motion in one or more joints." In humans the situation is often more complex and the syndrome of multiple joint defects has been termed arthrogryposis multiplex congenita (AMC). By definition "AMC is a disorder that develops before birth (prenatal), is present at birth (congenital), and is characterized by reduced mobility of multiple joints. In AMC the range of motion of the joints in the arms and legs is usually limited or fixed. Joints affected may include the shoulders, elbows, wrists and fingers and the hips, knees, ankles, and feet -- virtually any and all joints." AMC is not a problem with formation of the joint(s) but rather with the development of the connective tissues around the joint, which fixes the joint in place, severely restricting the joint movement which leads to the tendons around the affected joint being unable to stretch to their normal length. Underlying causes can include abnormalities of connective tissues per se, nerve connections to muscles, muscle structure or function, vascular compromise leading to loss of neurons, limited space or restricted movement within the uterus or certain maternal metabolic disorders. AMC is non-progressive, i.e. the lack of movement does not get worse after birth. (www.arthrogryposis.co.uk).

Initially there is no underlying skeletal disorder but secondary skeletal complications can develop during post-natal life.

Whichever of these definitions one considers, there are two critical points:
• the contractures develop in utero
• the contractures are present at birth or, in the case of pregnancies that are terminated before delivery, at Caesarian section.

It is a basic premise of foetal evaluations that all assessments of positional abnormalities, such as joint flexures, must be carried out on fresh foetuses. At this time the foetal tissues are elastic and by applying gentle pressure to the elbow or knee joints the potential for extension of the forelimbs or hindlimbs can be evaluated. If a joint that appears flexed genuinely has arthrogryposis, the flexure will remain. If the flexure is due to restriction within the uterus or is an artefact induced by handling or necropsy procedures, gentle pressure will permit the limb to straighten. Once the foetus has been placed in fixative, the elasticity of the tissues is lost, and there is no longer the possibility to distinguish between real and artefactual positional abnormalities.

In the Rallis rat EFD study, there was only one foetus (at 750 mg/kg bwt/day) for which a limb flexure was recorded at external examination in the fresh (unfixed) state at necropsy. All other instances of arthrogryposis were recorded at skeletal evaluation, following initial fixation in 70% alcohol, evisceration and skinning, further fixation/dehydration in 95% alcohol, skeletal processing via KOH clearing of soft tissues, alizarin staining of calcified tissues and storage in 100% glycerin. Unlike for rabbit foetuses, it is not common practise to skin rat foetuses prior to skeletal processing, unless a double-staining procedure for both bone and cartilage is required, as the foetal skin clears sufficiently to allow detailed examination of the alizarin stained skeleton. After the fresh external examination, the foetuses were partially fixed in 70% alcohol prior to skinning; no comments were reported regarding limb flexures when the foetuses were handled after this initial fixation period.

Manipulation of the limbs in order to remove the skin might well have resulted in artefactual positional changes or damage to the limbs, especially since the skinned

foetuses were immediately placed in 95% alcohol. This would have resulted in rapid and rigid fixation of the foetuses in whatever position they were in when dropped into the fixative or whatever position they assumed when in contact with the storage jar.

There is no information in the skeletal appendix of the Rallis report for the foetuses recorded as having arthrogryposis detailing how many joints were affected or the severity of the joint contractures. Based on the laboratory SOP, Rallis defined arthrogryposis as "Persistent flexure or contracture of a joint flexed paw (bent or twist)" and this definition included even flexures considered to be of "mild" severity [provided in clarification letter from Eurofins Advinus, the successor to Rallis and summarized in Bomann et al. (2017)]. It is not possible to determine, therefore, the extent of the "arthrogryposis" seen in the affected foetuses in this study, although they have all been classified as malformations.

The diagnosis of arthrogryposis appears to have been made purely on the observations at skeletal examination, without reference to the lack of necropsy findings for these foetuses. Interestingly, the one foetus that had been reported with a forelimb flexure at necropsy was not confirmed with arthrogryposis at skeletal evaluation, and this foetus has not been included as a malformation. There is no indication in the study report that any reference was made to the foetal findings at fresh examination in order to corroborate the diagnosis of arthrogryposis.

In our opinion, the lack of correlation between the rat foetal necropsy data and the skeletal evaluations in the Rallis study casts serious doubt upon the relationship of the reported arthrogryposis to maternal treatment with clomazone.

As additional information, in the clomazone dose-range finding embryofoetal developmental toxicity study in rats performed by Rallis Laboratories the highest dose level investigated was 1000 mg/kg bwt/day. None of the 5 litters evaluated externally at this level contained foetuses with "arthrogryposis".

Also, a two-generation study with clomazone in rats by dietary administration was conducted by Toxigenics Inc. on behalf of FMC Corporation. Up to the maximum dose level of 4000 ppm, equating to 314 mg/kg bwt/day when corrected for 88.8% purity of the test material, none of the F1 or F2 pups were found to have arthrogryposis. (A two-generation study was not performed by Rallis Laboratories.).

The occurrence of two foetuses with limb flexures in the Rallis rabbit embryofoetal developmental toxicity study has been used by the CLH dossier submitter as evidence that arthrogryposis is likely to be a consequence of maternal exposure to clomazone in two species, hence the proposed classification of Repro 1B. However, for one of the affected rabbit foetuses, arthrogryposis occurred in conjunction with other gross abnormalities, including acephalostomia, microtia and forelimb ectrodactyly. In foetuses with such a severe central nervous system abnormality it is not unusual or unexpected to see contractural abnormalities in the limbs, since central neural control has been disrupted. One cannot equate the arthrogryposis in this severely malformed foetus with that seen in isolation in the "affected" rat foetuses.
The second rabbit foetus was recorded at external examination as having both forelimbs flexed at wrist but no further comment was made regarding this abnormality at skeletal evaluation and, in the report text and summary table, it was not included in the total of foetuses with major external malformations. The single instance of this finding was within the laboratory historical control range and thus it should not be considered as a treatment-related finding.

Further investigations
There exist, therefore, for clomazone, two sets of EFD studies in the rat and the rabbit. The first rat and rabbit studies were performed in the 1980s in separate laboratories and in neither species was there any report of limb abnormalities. Both of the second rat and rabbit studies were performed in 2002 by a third laboratory (Rallis) and in both studies "arthrygryposis" was recorded, albeit of doubtful aetiology. The isolated incidence in the rabbit study was within the laboratory historical control range.

A peer review of the foetuses from the Rallis rat study would have helped clarify the situation but unfortunately the foetal specimens were no longer available. Therefore, in order to investigate further the situation in the rat, a third EFD study was performed during 2018, which was designed, as far as possible, to replicate the Rallis rat study but to include strict precautions to avoid the induction of foetal limb artefacts during the necropsy, processing and examination stages of the study (Anon. 2019). The study was performed at Charles River Laboratories, Ashland, Ohio, USA on behalf of Cheminova A/S, Denmark (a subsidiary company of FMC). Clomazone was administered to Wistar rats, the same strain used in the Rallis study, at dose levels of 100, 250, 500 and 750 mg/kg bwt/day by oral gavage between GD 6 and GD 20. At termination on GD 21, foetal examinations were conducted without knowledge of treatment group. Foetal specimens were handled and processed in compliance with the laboratory SOPs in such a way as to minimize foetal artefacts or mechanically induced alternations. Any malformation was verified by a second observer. Each foetus was examined in detail. Limbs were examined for size, shape and position; feet were examined for carpal/tarsal flexure, and digits were counted. After external examination all foetuses were examined by dissection for visceral changes and were then skinned, fixed in 95% alcohol, processed and stained with alizarin red-S and Alcian Blue prior to skeletal evaluation. Alcian Blue staining was included in this study in order to facilitate detection of any cartilage abnormalities.

Maternal toxicity was recorded at 750 mg/kg bwt/day in terms of reduced body weight gain, net body weight gain, and food consumption. Liver weights were increased in a dose-related manner at 250 mg/kg bwt/day and greater. Litter parameters were unaffected by treatment at any dose level, and foetal evaluations did not reveal any external, visceral or skeletal morphological changes that were considered to be related to treatment. In particular, there were no indications of limb flexures in any treated group. The only limb malformation occurred in a control foetus that was found to have bent radii and ulnae at skeletal examination (see text table 1 below):

Text table 1: Incidence of foetuses with malformations

Dose level mg/kg bwt/day	0	100	250	500	750
Number of foetuses (litters) examined	180 (19)	199 (20)	174 (20)	197 (21)	205 (21)
Foetal(litter) incidences:					
External – omphalocoele	0	0	0	0	1 (1)
Visceral – lung lobe dysgenesis	0	0	0	0	1(1)
Skeletal -					
Costal cartilage anomaly	1 (1)	0	1 (1)	1 (1)	0
Vertebral centra anomaly	0	0	1 (1)	1 (1)	0
8 cervical vertebrae	1 (1)	0	0	0	0
Bent forelimb bones	1 (1)	0	0	0	0
Lumbar vertebral anomaly	1 (1)	0	0	0	0
Total foetuses with malformations	3	0	2	2	2

In this carefully controlled study, therefore, administration of clomazone to the same rat

strain, at the same dose levels, and using the same dosing vehicle as in the Rallis study did not result in any treatment-related limb flexures at any dose level. This new study, therefore, reinforces the conclusion that the limb flexures recorded at skeletal examination in the Rallis study were artefacts introduced during the ex utero phases of the study. Since none of the apparent limb flexures recorded by Rallis at skeletal examination was present in the unfixed foetuses at necropsy, the diagnosis of arthrogryposis was incorrect.

Conclusion
The diagnosis of arthryogryposis, made by Rallis laboratories on the basis of apparent limb flexures in rat foetuses, recorded not in the fresh state but only after skeletal examination, is considered to be incorrect. The limb flexures were only seen when the foetuses had undergone initial fixation, skinning, further fixation and skeletal processing of the foetuses. They were, therefore, most likely to be artefacts introduced during the ex utero procedures and were thus unrelated to treatment with clomazone. The one instance of flexed forepaws recorded in a rabbit foetus was not an unusual finding in rabbits in this laboratory and, in isolation, should not be considered to be a treatment-related finding. No instances of flexed forelimbs were found in the FMC EFD studies in rats and rabbits. The new EFD study in Wistar rats reinforces the opinion that the limb flexures recorded in the Rallis rat EFD study were artefactual in origin.

There are, therefore, no foetal findings in the three rat EFD studies and the two rabbit EFD studies that would warrant classification of clomazone as a developmental toxin.

References

Anon. (2017): Clomazone technical: Overview of the reproduction and developmental toxic studies. Document No. R-90021084, FMC tracking No. 2017WHP-CLZ3783.

Anon. (2019): An oral (gavage) prenatal developmental toxicity study of clomazone in Wistar Han rats. Charles River Laboratories Project ID 00105205; FMC Tracking No. 2018TOX-CLZ4337

Dossier Submitter's Response

We have evaluated the new study from 2019. Overall, the study indicates no treatment related developmental toxicity.
All female dams survived to the scheduled necropsy. No test substance-related clinical observations were noted at the daily examinations at any dosage level.
The high dose excerted some adversed effects on the dams in the high group of 750 mg/kg bw/d (reduced mean body weight gain and reduced food consumption as well as increased liver weights)but not severe effects, unlike the same high dose of the 2002 rat study.
There were no incidences of limb flexure either at external or skeletal examination. The numbers of fetuses (litters) available for morphological evaluation were 180(19), 199(20),174(20), 197(21), and 205(21) in the control, 100, 250, 500, and 750 mg/kg/day groups, respectively. Malformations were observed in 3(3), 0(0), 2(2), 2(2), and 2(2) fetuses (litters) in these same respective dose groups and were considered spontaneous in origin. When the total malformations and develop-mental variations were evaluated on a proportional basis, no statistically signifi-cant differences from the control group were noted. Fetal malformations and de-velopmental variations, when observed in the test substance-treated groups, oc-curred infrequently or at a frequency similar to that in the control group, did not occur in a dose-related manner, and/or were within the Charles River Ashland historical control data ranges.

Based on the reduced body weight gain at 750 mg/kg/day and increased liver weights at 500 and 750 mg/kg/day, a dosage level of 250 mg/kg/day was considered to be the no-observed-adverse-effect level (NOAEL) for maternal toxicity. Based on the lack of adverse findings or test substance-related effects on embryo/fetal development, a dosage level of 750 mg/kg/day (the highest dosage level tested) was considered to be the no-observed-adverse-effect level (NOAEL) for embryo/fetal development when the test substance was administered orally by gavage to time-mated Wistar rats. As no incidences of limb flexure were observed in any of the Clomazone treated groups in this study, this study did not confirm a potential of Clomazone to induce 'arthrogryposis' or 'limb flexure'.

The results of the 2019 study add to the weight of evidence. However, one sound study cannot overrule the results from other sound studies. The question is whether the studies from the 1980s and from 2002 are sound. There are some limitations in the studies but these studies also add to the weight of evidence.
There are some indications in the 2002 studies from India that questions the quality of the study. However, it is difficult to verify the circumstances of the evaluations.

Against Repr 1B classification:

1) Limitations in the 2002 rat study which questions the quality and could lead the question of CLP classification towards no-classification or category 2.
   a) Evaluation bias: the evaluator of limb flexure/arthrogryposis new the exposure groups leading to potential evaluation bias.
   b) GLP or not: Formally the India laboratories were not GLP as India did not join the mutual recognition of data until later. However, the Netherlands GLP authority has inspected the laboratories for developmental studies.
   c) Broad definition of arthrogryposis: Even though the testing laboratory have utilized a broad definition of arthrogryposis, there are one pup in the rat study and one pup in the rabbit study both of which have forelimbs flexed, for these two pups were arthrogryposis not indicated in the study summary tables, thus, they didn't fall directly within the laboratory definition of arthrogryposis. Whereas the rabbit pup that was defined as having arthrogryposis had, in addition to other major malformations, forelimbs flexed at wrist and hind legs turned inward, which falls within the NHI definition. It is not possible to read within the rat study how many joints are affected in the two mid dose and seven high dose pups from two and four different litters, respectively, which are allocated as having arthrogryposis.
      The HCD does not use the term arthrogryposis or it was not a finding in the HCD. As the studies were performed at the same laboratory it must be expected that they use the same definition on the terms.
      The grouping of arthrogryposis as a major skeletal malformation in the study report is in contrast to the indication in the HCD of forelimbs flexed at wrist as a minor skeletal anomaly. It could indicate that the observed arthrogryposis was more severe than limited to forelims flexed at wrist.
   d) If arthrogryposis has been used also for mild cases of bent or flexed limbs the effects in these cases could perhaps be attributed to the maternal toxicity. However, if it in deed is the severe case of arthrogryposis then the maternal toxicity should not be used to explain the effects.

2) Arthrogryposis was not detected in the 1984 rat study or in the 2019 rat study nor in the 2-generation rat study from 1984. However, the two studies from 1984 were performed with lower dosing of the dams (600 mg/kg bw/d in rat developmental study and 350 mg/kg bw/d in 2-generation study as oppose to the 750 mg/kg

bw/d in the 2002 and 2019 rat developmental studies). And in the range-finding studies fewer animals were tested, which could explain the smaller likelihood to detect arthrogryposis.
In connection with the 2019 developmental study a pharmacokinetic study was performed indicating that the internal concentration will be saturated with higher doses. Hence, a higher dose of 1000 mg/kg bw/d in the range-finding study would then not be expected to reveal a higher incidence of arthrogryposis.
Biological variance can explain differences between two sound similar studies.
Although, doubts about the use of the wording arthrogryposis and flexed limbs.

3) The effects observed in the 1984 and 2002 studies with regard to resorptions, implantation loss and anomalies could in some instances be explained by severe maternal toxicity. However, in the 1984 study the mid-dose dams were not severely intoxicated and here the effects could not be explained by maternal toxicity. In addition, the exposure related abortions should also be considered developmental effects.

Overall,
One good sound and up to date study showing no developmental effects. On the other hand a handful of studies of older age with some limitations indicating more or less developmental effects. When taken into consideration the questioned quality of the 2002 study and no possibility to verify or disregard the arguments of the stakeholders the evidence is no longer so clear as to propose classification with Repro cat 1B. However, cat 2 should be considered based on the arthrogryposis effects, resorptions, implantations loss, abortion and malformations/variations as mentioned above.

RAC's response

Thank you for your comment. Your arguments have been taken into consideration by RAC in the evaluation of developmental toxicity of clomazone.

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2019	United States	FMC Corporation	Company-Manufacturer	10

Comment received

This submission contains two additional studies that accompany the new pre-natal developmental toxicity study and detailed review paper submitted under Reference number 51fd5d3d-5e36-493d-b540-b94f6ade57d0. These two reports are being submitted in a second submission due to file size restrictions of the website. FMC asks that you kindly include these two accompanying studies with FMC's comments on the proposed classification of Clomazone.

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Clomazone, ECHA Comment, 8Feb2019, FMC, No. 2.zip

Dossier Submitter's Response

See comment 1

RAC's response

Thank you for your comment. Your arguments have been taken into consideration during the evaluation of developmental toxicity of clomazone.

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2019	United States	FMC Corporation	Company-Manufacturer	11
Comment received				
FMC strongly disagrees with the proposal to classify Clomazone for developmental toxicity Repr. 1B, H360D and submits a new guideline compliant (OECD 414 & OPPTS 870.370) rat pre-natal developmental toxicity study (Anon., 2019) and an in-depth review of the Latha (2002), which purported an increase in limb flexures characterised as "arthrogryposis" in high dose foetuses. The observed skeletal findings of "arthrogryposis" in Latha (2002) are considered artefacts incurred during foetal processing, and therefore no conclusions can be drawn from this study for purposes of classification. The reproduction and developmental toxicity data package for Clomazone consists of five pre-natal developmental toxicity studies – three in rats and two in rabbits, as well as a multigeneration reproduction study. On the basis of these studies, the following conclusions regarding the potential of Clomazone to cause adverse effects on the developing foetus can be made: 1. There is no evidence of reproductive or developmental toxicity from a two generation reproduction study in Charles River CD rats (Salamon, 1984). 2. There is no evidence of pre-natal developmental toxicity from a study in SD rats (Freeman, 1984). 3. Highly doubtful evidence of "arthrogryposis" was reported in a deficient, unreliable study in Wistar rats by Rallis Research Centre, India (Latha, 2002). The disconnect between the recording of external and skeletal findings suggests that the noted skeletal finding of "arthrogryposis" was a result of artefacts induced during foetal handling. Evaluation of foetal morphology should have been conducted without knowledge of treatment group. The lab appears to have been relatively inexperienced when the study was conducted. 4. There is no evidence of pre-natal developmental toxicity in a recently conducted, statistically enhanced study in Wistar rats (Anon., 2019). This is the only study in the pre-natal development dataset conducted according to the current recommended guideline (OECD 414 & OPPTS 870.3700). 5. There is no evidence of pre-natal developmental toxicity from a study in New Zealand white rabbits (Rodwell, 1982). 6. There is no evidence of pre-natal developmental toxicity from a study in New Zealand white rabbits by Rallis Research Centre, India (Bhagavan, 2002). Incidences of limb flexure at the high dose are well within historical control data range. The occurrence of "arthrogryposis" in the control group in the dose range finding study was 8%, exceeding the incidence observed in high dose rabbit foetuses in the main study. 7. A comprehensive review of the updated dataset cannot establish that there is "…clear evidence of an adverse effect on…development" – such that classification as Category 1B would be appropriate. 8. Further, the pre-natal developmental toxicity dataset does not support a Category 2 classification: "substances are classified in Category 2…when there is some evidence from humans or experimental animals…of an adverse effect…on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification." No meaningful credibility can be ascribed to the Latha (2002) rat study considering incongruent findings and availability of other study data. 9. Therefore, based on the weight of evidence, classification of Clomazone for developmental toxicity is not warranted. A detailed review of the pre-natal developmental toxicity data package for Clomazone is provided in the accompanying document that has been uploaded with this submission				

along with the newly conducted pre-natal developmental toxicity study in Wistar rats (Anon., 2019). Due to file size restrictions, a second submission is being made to provide two accompanying studies - a dose range finding pre-natal developmental toxicity study and a pharmacokinetic study. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Clomazone, ECHA Comment, 8Feb2019, FMC, No. 1.zip
Dossier Submitter's Response
See response to comment 9
RAC's response
Thank you for your comment. Your arguments have been taken into consideration by RAC during the evaluation of developmental toxicity of clomazone.

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2019	Germany		MemberState	12
Comment received				
The proposal for Cclassification of clomazone for Repr. 1B, H360D May damage the unborn child, as proposed by the DS, seems appropriateis supported. The relevant effects include increases in complete resorptions, arthrogryposis, multiple skeletal malformations. DE agrees with the DS, that effects are not secondary to maternal toxicity. As the CLH-Report is often used as a stand-alone document, DE recommends to add specific details on the following points that are crucial for valid classification: Four comments concerning Concerning section 2.6.6.2 Adverse effects on development, the teratogenicity study in Wistar rats (2002), p83 CLH report information should be added on the following aspects: 1. The maternal body weight gain was significantly decreased at mid-dose level and above. It seems that also 4 dams with complete resorptions at the highest dose level were included into the calculation, which may lead to a possibly inaccurate picture regarding the severity of changes in body weight gain and maternal toxicity. This is particularly clear when comparing the absolute body weights in dams (minus uterine weights) on day 20: Body weights were only 5 % (mid dose) and 9 % (high dose) below control dams and the difference was without any statistical significance. Therefore, detailed information on body weight gain in dams (with foetuses) would be appreciated. 2. Four statistically significant incidences of complete resorptions at highest dose level compared to the control were reported with only one implantation site. However, according to the individual data in the original study report 4, 10, 11 and 15 implantation sites were observed in these 4 dams. Could you please clarify the different number of reported implantation sites? 3. Based on the statistically significant increase in sceletal arthrogryposis (outside HCD) observed in the more recent developmental toxicity study in rats, the proposal for classification as Repr. 1B, H360D (may damage the unborn child) is may be supported. However in external examinations significantly less findings were diagnosed, which is unlikely to occur in true cases of arthrogryposis. Remark: In the previous submitted developmental toxicity study arthrogryposis was not observed, may be based on several differences to the more recent study: shorter treatment period,				

different rat strain, lower purity of the test substance and lower dose levels.

4. Both findings – complete resorptions and significant increase in arthrogryposis are not considered secondary to maternal toxicity.
Therefore, both the absolute body weight and clinical signs in pregnant rats should be presented more detailed to underline the missing link of maternal toxicity.

5. Historical control data: Please add in the results box on p83 of the CLH-report the information that in the HCD study by Chethana, 2.1 % incidences of arthrogryposis were observed only in one study out of eleven (external observations) and at 0,7-0.9 % in four out of 10 studies reported (skeletal observations). For assessment of developmental effects and comparing to HCD, both the mean value and the range should be considered. The mean is in fact 0.19 % and 0.3 % for external and skeletal observation, respectively. Considering the mean instead of the % high range, the incidences observed in the clomazone study by Latha were found clearly outside the HCD for both, external and skeletal findings in Wistar rats. This is also true for the study in New Zealand rabbits by Bhagavan. The information gap (Reg. 283/2013) regarding supplier, laboratory, conduct, mortality, clinical data and scientists should be mentioned in the CLH-report as proposed in the Vol. 3 on p289 in B6.6.2/06.

Dossier Submitter's Response

The vol 1 will be updated for the EFSA process, but as we understand not for the CLH process. The DE considerations should be taken into account for the CLH decision.
See also response to comment 9

RAC's response

Thank you for your comment. Your arguments have been taken into consideration by RAC during the evaluation of developmental toxicity of clomazone.

In the teratogenicity study in Wistar rats (2002), mean maternal body weights of dams were the following:

Mean maternal body weight (in g) (Anon., 2002 (2840/2000))

	0	250	500	750
Number of animals examined	25	23	25	24
GD 0	213	215	214	213
GD 6	230	234	230	229
GD 7	233	232	226	227
GD 8	236	232	226*	226**
GD 9	239	237	227*	224**
GD 10	242	241	233	227**
GD 11	246	244	237	231**
GD 12	249	248	241	232**
GD 13	253	251	242*	232**
GD 14	255	254	248	235**
GD 15	264	263	252*	239**
GD 16	270	268	257*	244**
GD 17	281	278	268*	253**
GD 18	294	291	278*	260**
GD 19	304	302	290*	267**
GD 20	316	312	289	278**

** Significantly different from control by Dunnett's test criteria, at 0,01
* Significantly different from control by Dunnett's test criteria, at 0,05

Absolute body weight of dams (day 20 bwt – uterine wt) was 252 ± 16.3, 249 ± 15.1, 239 ± 15.6 and 229 ± 13.8 for the control, 250, 500 and 750 ppm dose groups. The statistical calculation concluded that there was a significant dose correlation at $p \leq 0.05$ level for the 750 ppm dose group.

Individual data showed that most of the dams affected by early resorption in the high dose group only had clinical signs of slight salivation. In addition, very transient lethargy was reported in four of them between study days 7 and 11 (a single observation for each animal).

The maternal parameters were as follows:

Table : Summary of maternal data in a Wistar rat developmental toxicity study (Anon. 2002, 2840/2000).

Dose (mg/kg)	0	250	500	750
Number of corpora lutea (mean ± SD)	13 ± 2.0	13 ± 1.6	12 ± 1.6	13 ± 2.6
Number of implantations (mean ± SD)	11 ± 2.2	11 ± 2.1	11 ± 1.7	11 ± 2.9
Mean early resorptions ± SD (%)	0.2 ± 0.4 (2.1%)	0.3 ± 0.6 (2.7%)	0.6 ± 0.9 (5.1%)	2.2 ± 4.1 (20.3%)
Mean late resorptions ± SD (%)	0.5 ± 0.9 (4.6%)	0.1 ± 0.3 (0.8%)	0.1 ± 0.3 (1.1 %)	0.2 ± 0.4 (1.5%)
Mean pre-implantation loss ± SD (%)	1.4 ± 2.2 (11.3%)	1.3 ± 1.3 (10.5%)	1.3 ± 1.7 (10.4%)	1.7 ± 1.9 (13.6%)
Mean post-implantation loss ± SD (%)	0.7 ± 0.9 (6.0%)	0.4 ± 0.7 (3.4%)	0.7 ± 1.0 (6.1%)	2.4 ± 4.1 (21.8%)
Dams with any resorption (%)	11 (44%)	7 (30%)	11 (44%)	10 (42%)
Dams with all resorptions (%)	0	0	0	4* (17%)
** Significantly higher than control group*				

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2019	United States	<confidential>	Industry or trade association	13
Comment received				
B.6.6 Reproduction Toxicity ECHA note – An attachment was submitted with the comment above. Refer to public attachment ClomazoneOutreachDocAdama_DC (5 Feb 2019)WBMSFeb11PUBLIC.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment ClomazoneOutreachDocAdama_DC (5 Feb 2019)WBMSFeb11CONFIDENTIAL.pdf				
Dossier Submitter's Response				
See response to comment 9				
RAC's response				
Thank you for your comment. Your arguments have been taken into consideration by RAC during the evaluation of developmental toxicity of clomazone.				

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2019	Netherlands	ADAMA Agriculture BV on behalf of ADAMA Agan Ltd.	Company-Manufacturer	14

Comment received

In the CLH dossier for Clomazone (September 2018) a classification regarding adverse effects on development "Repr. 1B, H360D May damage the unborn child" is proposed (page 87-88) based on skeletal findings in the rat with supporting evidence of skeletal findings in the rabbit. The main concern related to the Wistar rat study (2002) in which skeletal malformations of arthrogryposis or malformed fore- and hindlimbs were observed.

In the table below the incidence of major external and skeletal malformations are reported.

Parameters Doses [mg/kg bw/d]
Control 250 500 750
Major external malformations (%)
Number of foetuses examined 265 254 260 204
Forelimbs flexed at wrist 0.0 0.0 0.0 0.5a
RE2792 n=1
Anasarca 0.0 0.0 0.4@
RE2750 n=1 0.5
RE2771 n=1
Major skeletal malformations (%)
Number of foetuses examined 132 127 130 102
Multiple malformationsb 0.0 0.0 0.8@
RE2750 n=1 0.0
Arthrogryposis 0.0 0.0 1.5
RE2751 n=1
RE2752 n=1 6.9**
RE2789 n=1
RE2790 n=1
RE2794 n=3
RE2795 n=2
Forelimbs malformed 0.0 0.0 0.0 1.0
RE2797 n=1

a recorded as forelimb flexed in report summary data, however recorded as arthrogryposis in individual litter data; b Delayed skeletal ossification of skull bones, malformed forelimb with radius ulna bent, hind limb malformed with femur absent, tibia hypoplastic and malformed and fibula absent.

@ same fetus

** statistically significantly different

RExxxx = dam/litter no.; n = number of foetuses with the finding in the litter

For the litter for which forelimbs flexed at wrist/arthrogryposis was recorded during the external examinations, no skeletal malformations were recorded. In addition, for litters for which arthrogryposis or forelimbs malformed were recorded, no external malformations were recorded. This discrepancy in recording of these findings (external vs skeletal) questions whether the skeletal observations are real or artefacts of skeletal processing of the foetuses. Since arthrogryposis develops in utero, the contractures are present at birth and thus should have been observed at the external examination. Since the arthrogryposis was recorded in a higher incidence at the skeletal examinations it is more likely that these observations are artefacts resultant from inadequate foetal

processing procedures. It has been reported in literature that artefacts resulting from less than optimal foetal processing procedures can occur and can lead to misidentification as malformations by inexperienced investigators (Principles and methods of toxicology 5th edition, Edited by Wallace Hayes, p1681).

In addition, there was some concern expressed in the CLH dossier regarding the developmental toxicity study in the rabbit (2002) for the incidence of malformations related to arthrogryposis. The incidence of major malformations related to arthrogryposis are reported in the table below for the dose range finding element of the study.
Parameters Doses [mg/kg bw/d]
Control 100 500 750 1000
Major external malformations (%)
Number of foetuses examined 49 60 48 34 12
Arthrogryposis 8.2 0 0 0 0

In the main developmental toxicity study in the rabbit the following malformations related to arthrogryposis were recorded.
Parameters Doses [mg/kg bw/d]
Control 150 350 700
Major external malformations (%)
Number of foetuses examined 157 158 138 137
Forelimbs flexed at wrist 0.0 0.0 0.0 0.7
Rb4173 n=1
Multiple malformations 0.0 0.0 0.0 0.7
Rb4174 n=1
Major skeletal malformations (%)
Number of foetuses examined 157 157 137 135
Hind limb (Rt/Lt/B) (+++) flexed at wrist 0.0 0.0 0.0 0.74@
Rb4174 n=1
Fore limb (Rt/Lt/B) (+++) flexed at wrist 0.0 0.0 0.0 0.74@
Rb4174 n=1
@= same fetus;
Rbxxxx = dam/litter no.; n = number of foetuses with the finding recorded in the litter; +++=severe; Rt= right; Lt=left; B= both

The malformations related to arthrogryposis in the rabbit study fell within the historical control data of the period the study was conducted in the laboratory (max. incidence 3.2%). In addition, in the dose range finder with pregnant rabbits the incidence of arthrogryposis in the control group was 8.2% whereas no incidence of arthrogryposis was recorded in the treated groups. This clearly demonstrates that the incidence of fore- and hindlimbs flexed at wrist noted in the main study falls within the normal background incidence in this laboratory and is thus not treatment related.
Finally, a new previously not submitted developmental toxicity study in the Wistar rat was conducted (2019), in this study all foetuses were examined for morphological changes (external, visceral and skeletal) with no skeletal malformation related to arthrogryposis recorded. There were no treatment related effects on the incidences of supernumerary ribs, which are a sensitive indicator of an effect on the skeleton. In addition, there was no dose-related effect on ossification. These observations support the lack of an overall effect of clomazone on the developing skeleton following in-utero exposure.

In conclusion
It is ADAMA's position that a developmental toxicity classification is not warranted for clomazone for the following reasons:

- Arthrogryposis was only recorded in one of the three developmental toxicity studies in the rat.
o One of these studies is a modern (2019) study in the same rat strain:
☐ no external, visceral or skeletal foetal malformations or variations related to treatment were recorded
☐ no indication of any increase in limb flexures (or arthrogryposis) were recorded.
o If the skeletal findings in the one rat study were true findings, a similar pattern of effects should have been observed in all rat studies during both external and skeletal examination. Since this is not the case it is more probable that these findings are artefacts of foetal processing and not a true indication of a developmental effect of clomazone.
- The incidence of skeletal malformation related to arthrogryposis in the rabbit study fell within the normal background incidence of the laboratory.
Based on the weight of evidence presented, it is ADAMA's position that a developmental toxicity classification for Clomazone is not warranted.

This comment is also included in the attachment, in case the tables are not displayed correctly.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Clomazone summary position statement_final.pdf

Dossier Submitter's Response

See response to comment 9

RAC's response

Thank you for your comment. Your arguments have been taken into consideration by RAC during the evaluation of developmental toxicity of clomazone.

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2019	Italy	Oxon-Albaugh-Sapec EU Task Force (OAS)	Company-Manufacturer	15

Comment received

The group of companies Oxon-Albaugh-Sapec (OAS) are a second applicant task force for active substance clomazone in the AIR 3 EU revision process, due to timing issues it was not possible to make a joint submission with the other applicant, i.e. FMC ADAMA Task Force (CATF). As such, the OAS dossier does not contain any developmental toxicity studies referenced in the CATF dossier and we have access only to the publicly available study summaries prepared by Rapporteur Member State.
In spite of this we hereby make comment as far as possible on the interpretation of the Rallis studies (study reports No 2840/2000 and 2841/2000).
The questionable methodology used in the studies relied on to allocate the proposed classification of reproductive toxicity category 1B has been clearly highlighted in the RAR issued by the Rapporteur Member State in the document Bomann, W. et al, 2017 submitted by CATF. The terminology of "arthrogryposis" used in the Rallis studies is not aligned with standard foetal pathology classification and it is misleading as it likely overstates the nature of findings in the foetuses. The many deficiencies in the Rallis rat pre-natal developmental toxicity study and the lack of statistical significance for developmental findings in the submitted rabbit data do not support a classification proposal for reproductive toxicity. Therefore significant doubts exist as to the quality and suitability of the findings in these studies for use in the classification of clomazone.
Additionally the two existing pre-natal development studies in rats and rabbits evaluated

during the first EU review of clomazone clearly demonstrate a lack of any developmental effects of clomazone and are still considered relevant to support the renewal of approval of the active substance. Therefore considering a weight-of-evidence approach and the existing data package a classification of reproductive toxicity category 1B for clomazone is not supported by the available data. Finally the OAS task force is aware of the existence of a recent rat pre-natal development toxicity carried to current guidelines that demonstrates a lack of any concern around observations of limb flexures. In conclusions The OAS task force considers that the proposed classification of reproductive toxicity category 1B, H360D is not warranted and requests review
Dossier Submitter's Response
See response to comment 9
RAC's response
Thank you for your comment. Your arguments have been taken into consideration by RAC during the evaluation of developmental toxicity of clomazone.

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2019	France		MemberState	16
Comment received				
FR: Table 21 page 82 and 2.6.6.2.1 - Rat study 1984 and Vol.3 B.6.6.2/01 In this study, maternal toxicity is limited to clinical signs. Could you please report more details on clinical findings (type, intensity, number of dams affected) especially at the mid dose? Indeed based on the reported text, the LOAEL of 300 mg/kg bw/d is challengeable since the adversity of the clinical findings at this dose level is questionable. Developmental toxicity: The wording dedicated to fetal findings is confusing. Malformations are not an indicator of delayed ossification (page 245). According to the internationally harmonized terminology, the absence of bones (malformation) is different from a delay of ossification. Was double staining methodology performed, (which could have allowed to distinguish real skeletal malformations from delayed ossification)? In the absence of double staining, in a conservative approach, the skeletal findings should be considered as malformations. Besides structural anomalies, death of developing organisms (non-significant upward trend in numbers of resorptions at the two high doses) and altered growth (reduced fetal weight at the high dose level) were also observed and should be discussed against CLP criteria for reproductive classification. - Rabbit study, 1982 Vol.3 B.6.6.2/02 Since abortions at the top dose are considered treatment related the developmental NOAEL should also be set at the mid dose level based on death of developing organisms. Furthermore, are there any HCD available for sternebrae fused and rib anomaly? Indeed while not observed in the top dose it is noteworthy that at this dose level, only 11 litters and 60 fetuses were examined which could compromise the dose-response analysis. - Rat study 2002 Vol.3 B.6.6.2/03 As regard developmental toxicity, besides structural anomalies, death of developing organisms (4 dams with all resorption) and altered growth (reduced fetal weight) observed at the high dose level, should also be discussed against CLP criteria for reproductive classification.				

- Rabbit study, 2002 Vol.3 B.6.6.2/04
It is acknowledged that forelimbs flexed at wrist and arthrogryposis were observed in comparable incidences in the HCD. However, this pattern of malformations was also observed in rat, it is therefore difficult to totally disregard them as not treatment related. Furthermore, death of developing organisms (due to abortions) should also be discussed against CLP criteria.

Structural anomalies were observed in rats in the presence of very slight if any in the first study, or in the presence of moderate maternal toxicity in the second study. Neither the severity of the maternal toxicity nor any specific modes of action can support that those structural abnormalities should be considered as secondary to non- specific consequence of other toxic effects.
Death of developing organisms and altered growth were also observed in rats at higher dose levels.
In the rabbit studies, structural anomalies and death of developing organism were observed in the presence of maternal toxicity.
Based on the above-mentioned considerations, the proposal for classification Repr 1B H360D seems to be warranted.

Dossier Submitter's Response

Rat 1984 study:
The only maternal tox signs in the middle group of 300 mg/kg bw/d were 3 out of 25 dams with abdomino genital staining. Two of these dams also had chromorhinorrhea. The mean food consumption (176.9 g) on day 13-20 was statistically significant increased compared to control (166.8 g). Agree that the maternal tox at this level is not so severe that potential developmental findings should be excluded.

Development: all foetuses were mascerated, stained with Alizarin
Red-S, cleared and observed for skeletal variations.
Agree that developmental variations observed at 300 mg/kg bw/d should be considered for comparison with the CLP criteria.

Rabbit 1982 study:
Agree that treatment related abortions at top dose should also be considered a developmental effect (death of developing organism).
HCD for sternebrae fused and rib anomaly were attached to the original study report page 111 in the tif-file. However, it is not clear which period it is covering.
We do see the point made by France that the high group could not be included for the comparison as too few (2/3) foetuses and/or litters available for the examination.

WIL HISTORICAL CONTROL DATA - NEW ZEALAND WHITE RABBITS 23 FEB-82 PAGE 1

SUMMARY INCIDENCE OF MALFORMATIONS

TOTAL NUMBER OF LITTERS EXAMINED	93	
TOTAL NUMBER OF FETUSES EXAMINED EXTERNALLY	762	
TOTAL NUMBER OF FETUSES EXAMINED VISCERALLY	310	
TOTAL NUMBER OF FETUSES EXAMINED SKELETALLY	520	

	NUMBER FETUSES	NUMBER LITTERS	PERCENT (RANGE) FETUSES	PERCENT (RANGE) LITTERS
OMPHALOCELE	2	2	(0.0 0.7)	(0.0 5.6)
MALROTATED HINDLEGS	1	1	(0.0 0.7)	(0.0 6.7)
HERMAPHRODITE	1	1	(0.0 0.7)	(0.0- 6.7)
SPINA BIFIDA	1	1	(0.0 0.6)	(0.0- 5.0)
TOTAL NUMBER OF FETUSES WITH EXTERNAL MALFORMATIONS	5	5		
RETINA(S) FOLDED	6	5	(0.0 9.3)	(0.0 16.7)
OMPHALOCELE	1	1	(0.0- 2.3)	(0.0- 5.6)
TOTAL NUMBER OF FETUSES WITH SOFT TISSUES MALFORMATIONS	7	6		
SKULL ANOMALY	2	2	(0.0- 2.0)	(0.0- 11.8)
STERNEBRAE FUSED	6	6	(0.0 2.6)	(0.0 15.0)
6 CERVICAL VERTEBRAE	1	1	(0.0 1.1)	(0.0- 6.7)
VERTEBRAL ANOMALY	2	2	(0.0- 1.5)	(0.0 9.1)
RENT HYOID	1	1	(0.0- 0.9)	(0.0- 5.0)
RIB ANOMALY	1	1	(0.0 1.2)	(0.0- 5.9)

See also response to comment 9

RAC's response
Thank you for your comment. Your arguments have been taken into consideration by RAC during the evaluation of developmental toxicity of clomazone.

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2019	United Kingdom	UPL Europe Ltd	Company-Manufacturer	17

Comment received
Reference 2.6.6 ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH evaluation.pdf
Dossier Submitter's Response
See response to comment 9
RAC's response
Thank you for your comment. Your arguments have been taken into consideration by RAC during the evaluation of developmental toxicity of clomazone.

Date	Country	Organisation	Type of Organisation	Comment number
04.02.2019	Netherlands		MemberState	18

Comment received
The dossier submitter proposes to classify clomazone as a reproductive toxicant category 1b H360D based on the increased incidence of arthrogryposis in rats and rabbits. The incidence of arthrogryposis was treatment related with a dose-dependent increase, which was only significant in the highest dose group in rats. Maternal toxicity was also observed at this dose level, but the DS considers this unrelated to the skeletal malformations because in literature, arthrogryposis only occurs after longer periods of maternal illness.

Arthrogryposis (multiple joint contractures) is a very unusual finding in animal studies. It is caused by reduced fetal movements, for example due to neurological problems, severe maternal illness or neuroactive drugs. However, arthrogryposis is not separate disease entity, but is rather a descriptive diagnosis and thus sensitive to interpretation. Considering the rareness of this finding, we would like to ask whether more information is available from the study report on the exact malformations, and in particular, why in these studies they were indicated as arthrogryposis rather than (limb)malformations?
Dossier Submitter's Response
See response to comment 9
RAC's response
Noted, thank you.

Date	Country	Organisation	Type of Organisation	Comment number
04.02.2019	United Kingdom		Individual	19

Comment received

I have worked in the areas of chemical risk assessment and developmental and reproductive toxicity for 45 years. As a consultant for the manufacturer, FMC Corporation, I have assessed the original study reports and related documentation on clomazone developmental toxicity.

My comments relate to the three rat and two rabbit developmental toxicity studies and focus on the issue of arthrogryposis (persistent flexure or contracture of a joint). All of the developmental toxicity studies were conducted in accordance with OECD Test Guideline 414 (1981 or 2001, depending on when conducted), used the oral gavage route, and were in compliance with Good Laboratory Practice.

Findings in the rat

In the first study (A83-1142, 1984), Sprague-Dawley rats were used and nominal doses of 0, 100, 300 and 600 mg/kg body weight (bw) per day of clomazone (88.8% purity) were given on gestation days (GDs) 6-15. No cases of arthrogryposis, flexure or contracture of a joint were reported in the fetal examinations. Dose-related delays in ossification of some bones were observed in fetuses in the mid- and high-dose groups. At the high dose only, reduced weight of female fetuses and an increase in hydroureter were observed. Dams in both mid- and high-dose groups showed dose-related clinical signs of toxicity and the high-dose group had significantly reduced food consumption.

In the second study (2840/2000, 2002), Wistar rats were used and nominal doses of 0, 250, 500 and 750 mg/kg bw per day of clomazone (95% purity) were given on GDs 6-19. Two fetuses, each from different litters, in the mid-dose group, and 8 fetuses from 5 litters in the high-dose group were reported to have arthrogryposis. The increase, on a per fetus basis, was statistically significant in the high-dose group. Both cases of arthrogryposis in the mid-dose group were recorded only at skeletal examination and not at the external examination of fresh specimens. In the high-dose group, 1 of the cases of arthrogryposis was recorded only at external examination; the remaining 7 cases of arthrogryposis were recorded only at skeletal examination. Dams in the high-dose group showed clinical signs of salivation and lethargy, one died (considered a treatment-related death), and four had no live fetuses, only complete resorptions. There were also dose-related reductions in absolute maternal body weight, maternal body weight gain, and food intake in the mid- and high-dose groups. When corrected for purity, the high dose in this second study was greater than that in the first study (697 versus 533 mg/kg bw per day, respectively). It should also be noted that in the dose range-finding study that preceded

the main study, using doses of 250, 500 and 1000 mg/kg bw per day, no instances of arthrogryposis were recorded in the fetuses at external examination.
In the third study (2018TOX-CLZ4337, 2019), Wistar strain rats were used and doses of 0, 100, 250, 500 and 750 mg/kg bw per day of clomazone (96.3% purity) were given on GDs 6-20. No cases of arthrogryposis, flexure or contracture of a joint were reported in the fetal examinations (external and skeletal). Maternal toxicity was evident at 750 mg/kg bw per day from reduced maternal body weight gain and reduced food consumption during most of the dosing period. The net maternal body weight gain (terminal maternal body weight minus gravid uterine weight) was reduced by 25% in the 750 mg/kg bw per day group compared with controls. At 250 and 500 mg/kg bw per day, there was an effect on maternal weight gain at the start of the dosing period but not thereafter. Maternal liver weight was also increased at 250, 500 and 750 mg/kg/bw per day. It is also worth noting that no cases of arthrogryposis, flexure or contracture of a joint were observed in the preceding dose range-finding study (2018TOX-CLZ4336, 2018), in which doses up to 750 mg/kg bw per day were given on GDs 6-20.
Findings in the rabbit
No cases of arthrogryposis were reported in the first rabbit study, which used doses of 30, 240 and 1000 mg/kg bw per day (latter reduced to 700 mg/kg bw on GDs 13-18 due to severe maternal toxicity) (A81-655, 1982).
In the second rabbit study (2841/2000, 2002), which used doses of 0, 150, 350 and 700 mg/kg bw per day, 2 fetuses in the high-dose group had limb abnormalities; 1 fetus had flexed wrists and inward-turning hind limbs together with other major abnormalities, while the other fetus had both forelimbs flexed at the wrist. These 2 instances of flexure (0.7% on a per fetus basis) were not statistically significant and were within the historical control data range for the laboratory (0 – 3.2%). In both cases, the limb abnormalities were noted at the external examination, which would be usual for such abnormalities. Only 1 of these 2 limb abnormalities were observed on skeletal examination. In the dose range-finding study preceding the second rabbit study (also described in 2841/2000, 2002), it should be noted that 4 out of a total of 49 fetuses (8.2% on a per fetus basis) were recorded as showing arthrogryposis in the control group during the external examination of fresh specimens. No instances of arthrogryposis were found in any of the groups dosed with clomazone up to 1000 mg/kg bw per day in this dose range-finding study. Arthrogryposis is known to be a common background variant in the New Zealand White (NZW) rabbit (Palmer, 1968), as can also be seen from its occurrence in controls in the clomazone pilot/dose range-finding study.
Discussion of the findings
The only one of the three rat studies to report an increase in arthrogryposis was the second study (2840/2000, 2002). Arthrogryposis is not a common abnormality in the rat, as can be seen, for example, from the historical control data for Wistar rats from the Charles River Laboratories, USA, dated 2016, (provided in reference 2018TOX-CLZ4337, 2019), in which only 1 fetus from a total of 2082 fetuses from 9 datasets had carpal and/or tarsal flexure recorded at the external examination. It is also unusual to see it recorded only at skeletal examination when it has not been observed as a contracture or flexure of the joint in the same fetuses during the earlier external examination of fresh specimens. In this regard, it is notable that in the second rat study, neither of the 2 fetuses stated to have arthrogryposis in the mid-dose group were reported at the external examination, only at the skeletal examination, while in the high-dose group, 7 out of the 8 fetuses affected were only reported at skeletal examination and not when examined as fresh specimens. The laboratory that conducted the second study defined arthrogryposis as "Persistent flexure or contracture of a joint, flexed paw (bent or twist)" but did not provide any grading of the abnormality and included flexures of "mild" severity as arthrogryposis. The laboratory also conducted the fetal examinations unblinded, i.e. having knowledge of the treatment group to which a fetus belonged. These limitations,

together with the very important lack of corroborative findings between the external and skeletal examinations, strongly suggest that the observations in the second rat study were not indicative of true arthrogryposis; the one case observed at the external examination (an incidence of 0.5%) was well within the historical control range (0 – 2.1%, see dRAR, 2018). It is well known that fetuses become fragile following the processing stage of maceration in 1% potassium hydroxide before the skeletal examination. Thus, the limb abnormalities reported in 9 fetuses during skeletal examination may well have been artefacts, possibly as a result of damage during fetal processing and/or observation procedures

The observations in the second rat study (2840/2000, 2002) also are in contrast with the lack of any instances of arthrogryposis, or flexure, or contracture of a joint in the first (A83-1142, 1984) or third (2018TOX-CLZ4337, 2019) rat studies. The third study was carried out recently, to a more modern protocol than the second study, using the same strain (Wistar), route, vehicle and similar dose range, but a larger number of doses than those used in the second study. In this third study, knowing what had previously been reported in the second study, particular care was taken to ensure thorough examination of the limbs and careful handling of fetuses during in processing and skeletal examination. It should also be noted that in the third rat study, all fetuses underwent skeletal examination, whereas in the second rat study only half of the fetuses were examined for skeletal effects. In addition, the degree of maternal toxicity at the high dose in the third study was greater than that at the mid-dose in the second study, at which 2 cases of arthrogryposis were reported. The absence of any cases of flexure or contracture of joints in this very robust third study casts considerable doubt on the reliability of the observations reported in the second rat study.

In rabbits, there were no cases of arthrogryposis in the first study (A81-655, 1982) and two cases at the high dose in the second study (2841/2000, 2002b), which was within the historical control data range.

Conclusions

The reported cases of arthrogryposis in the second rat study (2840/2000) cannot be relied on as 9 out of the 10 fetuses said to be affected were not recorded during the examination of fresh specimens, as would normally be expected, but only during the skeletal examination. The reported cases are most likely attributable to damage to fragile tissues that can occur during processing and skeletal observations. This conclusion is supported by the absence of any such abnormalities in two other rat studies.

The occurrence of 2 cases of arthrogryposis in the second rabbit study (2841/2000) is likely to be a chance finding, unrelated to treatment, given that it is a common background variant in NZW rabbits and that 4 cases were seen in the control group in the dose range-finding study. Thus, this study in rabbit does not support a conclusion that clomazone induces arthrogryposis.

There were no other significant developmental findings in the developmental toxicity studies and, in my opinion, classification for reproductive toxicity for clomazone is not appropriate.

References

A81-655 (1982). A Teratology Study in Rabbits with FMC 5720. Wil Research Laboratories, Inc., Ashland, Ohio, USA. September 14, 1982. Sponsored by FMC Corporation.

A83-1142 (1984). Rat Teratology Study with FMC 57020 Technical. FMC Toxicology Laboratory, New Jersey, USA.

2840/2000 (2002). Teratogenicity Study in Wistar Rats with Clomazone Technical. Rallis Research Centre, Bangalore, India. November 11, 2002. Sponsored by Agan Chemical Manufacturers Ltd, Ashdod, Israel.

2841/2000 (2002). Teratogenicity Study in Rabbits with Clomazone Technical. Study No.

2841/2000. Rallis Research Centre, Bangalore, India. November 06, 2002. Sponsored by Agan Chemical Manufacturers Ltd, Ashdod, Israel.
2018TOX-CLZ4336 (2018). An Oral (Gavage) Dose Range-Finding Prenatal Developmental Toxicity Study of Clomazone in Wistar Han Rats. Charles River Laboratories, Ashland Ohio, USA. 10 January 2019. Sponsored by Cheminova A/S, Haarboøre, Denmark.
2018TOX-CLZ4337 (2019). An Oral (Gavage) Prenatal Developmental Toxicity Study of Clomazone in Wistar Han Rats. Charles River Laboratories, Ashland Ohio, USA. 10 January 2019. Sponsored by Cheminova A/S, Haarboøre, Denmark.
dRAR (2018). Draft Renewal Assessment Report prepared according to the Commission Regulation (EU) N° 1107/2009. Clomazone Volume 3-B.6 (AS), Table 6.6.2/06-1, page 286.
Anon (1968). Spontaneous malformations of the New Zealand White rabbit: the background to safety evaluation tests. Laboratory Animals 2: 195-206.

Dossier Submitter's Response
See response to comment 9
RAC's response
Thank you for your comment. Your arguments have been taken into consideration by RAC during the evaluation of developmental toxicity of clomazone.

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2019	United States	FMC Corporation	Company-Manufacturer	20
Comment received				
See comment below for acute toxicity. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Clomazone, ECHA Comment, 8Feb2019, FMC, No. 1.zip				
Dossier Submitter's Response				
noted				
RAC's response				
Noted, thank you.				

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2019	United Kingdom	UPL Europe Ltd	Company-Manufacturer	21
Comment received				
Reference 2.6.2.6 ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH evaluation.pdf				
Dossier Submitter's Response				
No relevant comment was submitted for this hazard class. The comment referred to in the attachment only addresses developmental toxicity.				
RAC's response				
This comment refers to developmental toxicity and has been considered in developing the opinion for that hazard class accordingly.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2019	France		MemberState	22
Comment received				
FR: - Conclusion on classification and labelling for acute oral toxicity page 53 : The proposed classification, Acute tox 4, H302 is supported. - Conclusion on classification and labelling for acute inhalation toxicity page 55 : The proposed classification, Acute tox 4, H332 is supported.				
Dossier Submitter's Response				
noted				
RAC's response				
Noted, thank you.				

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2019	Germany		MemberState	23
Comment received				
Acute inhalation toxicity: Acute tox 4, H332 harmful if inhaled, is supported. Acute oral toxicity: Acute tox 4, H302 harmful if swallowed, is supported.				
Dossier Submitter's Response				
noted				
RAC's response				
Noted, thank you.				

Date	Country	Organisation	Type of Organisation	Comment number
04.02.2019	Netherlands		MemberState	24
Comment received				
We agree with the proposed classifications for acute toxicity and with the proposed ATEs				
Dossier Submitter's Response				
noted				
RAC's response				
Noted, thank you.				

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2019	United Kingdom	UPL Europe Ltd	Company-Manufacturer	25
Comment received				
Reference 2.6.2.1 ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH evaluation.pdf				

Dossier Submitter's Response
No relevant comment was submitted for this hazard class. The comment referred to in the attachment only addresses developmental toxicity.
RAC's response
This comment refers to developmental toxicity and has been considered in developing the opinion for that hazard class accordingly.

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2019	United States	FMC Corporation	Company-Manufacturer	26
Comment received				
FMC agrees Clomazone does not meet the criteria for classification for acute dermal toxicity, skin or eye irritation or respiratory and skin sensitization. Based on the available data, FMC agrees with the proposal that Clomazone be classified for acute oral and inhalation toxicity (Acute Tox Category 4, H302 and H332, respectively). ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Clomazone, ECHA Comment, 8Feb2019, FMC, No. 1.zip				
Dossier Submitter's Response				
noted				
RAC's response				
Noted, thank you.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2019	United States	FMC Corporation	Company-Manufacturer	27
Comment received				
See comment above. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Clomazone, ECHA Comment, 8Feb2019, FMC, No. 1.zip				
Dossier Submitter's Response				
noted				
RAC's response				
Noted, thank you.				

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2019	United Kingdom	UPL Europe Ltd	Company-Manufacturer	28
Comment received				
Reference 2.6.2.4 ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH evaluation.pdf				
Dossier Submitter's Response				
No relevant comment was submitted for this hazard class. The comment referred to in the attachment only addresses developmental toxicity.				

RAC's response
This comment refers to developmental toxicity and has been considered in developing the opinion for that hazard class accordingly.

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2019	United States	FMC Corporation	Company-Manufacturer	29
Comment received				
See comment above. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Clomazone, ECHA Comment, 8Feb2019, FMC, No. 1.zip				
Dossier Submitter's Response				
noted				
RAC's response				
Noted, thank you.				

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2019	United Kingdom	UPL Europe Ltd	Company-Manufacturer	30
Comment received				
Reference 2.6.2.5 ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH evaluation.pdf				
Dossier Submitter's Response				
No relevant comment was submitted for this hazard class. The comment referred to in the attachment only addresses developmental toxicity.				
RAC's response				
This comment refers to developmental toxicity and has been considered in developing the opinion for that hazard class accordingly.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2019	United States	FMC Corporation	Company-Manufacturer	31
Comment received				
See comment above. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Clomazone, ECHA Comment, 8Feb2019, FMC, No. 1.zip				
Dossier Submitter's Response				
noted				
RAC's response				
Noted, thank you.				

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2019	United Kingdom	UPL Europe Ltd	Company-Manufacturer	32
Comment received				
Reference 2.6.2.7 ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH evaluation.pdf				
Dossier Submitter's Response				
No relevant comment was submitted for this hazard class. The comment referred to in the attachment only addresses developmental toxicity.				
RAC's response				
This comment refers to developmental toxicity and has been considered in developing the opinion for that hazard class accordingly.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2019	United States	FMC Corporation	Company-Manufacturer	33
Comment received				
FMC agrees that Clomazone does not meet the criteria for classification for STOT-SE. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Clomazone, ECHA Comment, 8Feb2019, FMC, No. 1.zip				
Dossier Submitter's Response				
noted				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2019	United Kingdom	UPL Europe Ltd	Company-Manufacturer	34
Comment received				
Reference 2.6.2.10 ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH evaluation.pdf				
Dossier Submitter's Response				
No relevant comment was submitted for this hazard class. The comment referred to in the attachment only addresses developmental toxicity.				
RAC's response				
This comment refers to developmental toxicity and has been considered in developing the opinion for that hazard class accordingly.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2019	United States	FMC Corporation	Company-Manufacturer	35
Comment received				
FMC agrees that Clomazone does not meet the criteria for classification for STOT-RE. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Clomazone, ECHA Comment, 8Feb2019, FMC, No. 1.zip				
Dossier Submitter's Response				
noted				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2019	United Kingdom	UPL Europe Ltd	Company-Manufacturer	36
Comment received				
Reference 2.6.3.1 ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH evaluation.pdf				
Dossier Submitter's Response				
No relevant comment was submitted for this hazard class. The comment referred to in the attachment only addresses developmental toxicity.				
RAC's response				
This comment refers to developmental toxicity and has been considered in developing the opinion for that hazard class accordingly.				

OTHER HAZARDS AND ENDPOINTS – Aspiration Hazard

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2019	United States	FMC Corporation	Company-Manufacturer	37
Comment received				
Clomazone is not an organic solvent and hence, FMC agrees with that no classification is warranted. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Clomazone, ECHA Comment, 8Feb2019, FMC, No. 1.zip				
Dossier Submitter's Response				
noted				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2019	United Kingdom	UPL Europe Ltd	Company-Manufacturer	38
Comment received				
Reference 2.6.2.9 ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH evaluation.pdf				
Dossier Submitter's Response				
No relevant comment was submitted for this hazard class. The comment referred to in the attachment only addresses developmental toxicity.				
RAC's response				
This comment refers to developmental toxicity and has been considered in developing the opinion for that hazard class accordingly.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2019	France		MemberState	39
Comment received				
FR: We agree with the proposed classification.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted				

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2019	Germany		MemberState	40
Comment received				
Page 121, point 2.9.2.3 Long-term aquatic hazard (Table 27): The cited studies for aquatic macrophytes Lemna gibba and Myriophyllum spicatum are rel-evant for acute and chronic classification. Therefore, the relevant ErC10 or NOEC values should be given for these studies. Unfortu-nately, all EC50 values have no dimension. Page 124, point 2.9.2.4 Comparison with the CLP criteria (Table 28): We would prefer to use for acute aquatic toxicity for algae/ aquatic macrophytes the ErC50 (7 days) of 34 mg/L with Lemna gibba (Reference CA B.9.2.7/02). Page 124, point 2.9.2.4 Comparison with the CLP criteria (Table 29): We would prefer to use for long-term aquatic toxicity for algae/ aquatic macrophytes the NOErC (dry weight,14 days) of 0.1 mg/L with Myriophyllum spicatum (Reference CA B.9.2.7/05). Because of these minor changes, there is no influence on classification and labelling as Aquatic acute 1, Aquatic chronic 1, M-factor of 1.				
Dossier Submitter's Response				
Available ErC10/NOEC values will be provided together with units of EP. EP for CLP will be amended accordingly.				

RAC's response
RAC agrees with these comments. The relevant endpoints for aquatic chronic classification are NOEC and E_rC_{10} for the duckweeds and macrophytes. These data are reported in the DAR but the DS did not report them in the CLH dossier. Nevertheless, these EC_{50} values should be quoted in the list of the tests relevant for aquatic acute classification. As noted by MS, those changes do not modify the classification and labelling as Aquatic acute 1, M-factor of 1; Aquatic chronic 1, M-factor of 1

Date	Country	Organisation	Type of Organisation	Comment number
04.02.2019	Netherlands		MemberState	41

Comment received
Rapid degradability (section 2.8.2.1 and section 2.9.2.4.2): We agree that clomazole can be considered as not rapidly degradable for classification purposes. However, we note that a summary of the degradation data and assessment using the data in comparison with CLP criteria is not included in the CLH report. The dossier submitter should provide a comparison with the criteria for degradability. Bioaccumulation (section 2.9.2.1): Based on the information provided, the reported BCF value is not derived using the OECD test guideline 305 or equivalent test method. Therefore, the measured LogKow data (logKow=2.49) should be used as the primary data for the assessment of bioaccumulation with the reported BCF value of 40 as supporting information. That said, this does not change the bioaccumulation conclusion for clomazone, low potential for bioaccumulation. Aquatic toxicity: We do agree with the proposed aquatic acute classification. However with the data as currently presented we cannot conclude whether the current aquatic chronic classification is correct. We wish to point out that for the aquatic acute classification, EC50 values for growth rate for algae and aquatic macrophytes should be considered. For aquatic chronic classification the NOEC or (preferably) EC10 values for growth rate should be considered. Currently, in the CLH report, only the EC50 values for algae are given in the overview tables for acute aquatic hazard and the EC50 values for aquatic macrophytes are presented with the data for the long-term aquatic hazard. The dossier submitter is requested to provide an overview of all EC50 values for algae and aquatic macrophytes for the aquatic acute classification and a separate overview of all EC10 values for algae and aquatic macrophytes for the aquatic chronic classification to ensure that the NOECs and EC10s for aquatic macrophytes and algae are not lower than the current key endpoint for Americamysis bahia. Study summaries For the relevant studies only brief summaries are available in the CLH report. Robust study summaries should be available in the CLH report to enable to assess the study for quality and reliability of tests. Therefore the dossier submitter is requested to provide robust study summaries for at least all key-studies.

Dossier Submitter's Response
The comparison of clomazone data with the criteria for degradability will be provided. The bioaccumulation assessment will be corrected accordingly. Regarding aquatic toxicity, please see response to comment number 40. More elaborate study summaries will be provided for all key studies.

RAC's response
Agree. The relevant endpoints for aquatic chronic classification are NOEC and ErC10 for the duckweeds and macrophytes. These data are reported in the DAR but the DS did not report them in the CLH dossier. Nevertheless, these EC50 values should be quoted in the list of the tests relevant for aquatic acute classification. As noticed by MS, those changes do not modify the classification and labelling as Aquatic acute 1, M-factor of 1; Aquatic chronic 1, M-factor of 1

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2019	United Kingdom	UPL Europe Ltd	Company-Manufacturer	42
Comment received				
Reference 2.9.2 ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH evaluation.pdf				
Dossier Submitter's Response				
No relevant comment was submitted for this hazard class. The comment referred to in the attachment only addresses developmental toxicity.				
RAC's response				
Noted				

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2019	United States	FMC Corporation	Company-Manufacturer	43
Comment received				
FMC agrees with the key studies relevant for assessing environmental hazards, the endpoints identified for assessing acute and chronic aquatic toxicity, and the conclusions reached on the classification and labelling of Clomazone for environmental hazards. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Clomazone, ECHA Comment, 8Feb2019, FMC, No. 1.zip				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Ozone Layer

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2019	United Kingdom	UPL Europe Ltd	Company-Manufacturer	44
Comment received				
Reference 2.8.3.1 ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH evaluation.pdf				

Dossier Submitter's Response
No relevant comment was submitted for this hazard class. The comment referred to in the attachment only addresses developmental toxicity.
RAC's response
Noted

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2019	United Kingdom	UPL Europe Ltd	Company-Manufacturer	45
Comment received				
Reference 2.2.1.1 ECHA note – An attachment was submitted with the comment above. Refer to public attachment CLH evaluation.pdf				
Dossier Submitter's Response				
No relevant comment was submitted for this hazard class. The comment referred to in the attachment only addresses developmental toxicity.				
RAC's response				
This comment refers to developmental toxicity and have been considered in developing the opinion for that hazard class accordingly.				

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2019	United States	FMC Corporation	Company-Manufacturer	46
Comment received				
FMC agrees based on the physical and chemical properties of Clomazone that classification for physiochemical properties and physical hazards it not required. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Clomazone, ECHA Comment, 8Feb2019, FMC, No. 1.zip				
Dossier Submitter's Response				
Noted. The document just states the same as stated above.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
07.02.2019	France		MemberState	47
Comment received				
2.2.1 (p35) FR: characteristics of IR, NMR and MS fragments should be reported. 2.2.1.1.13 (p42) FR: a data gap has been identified for oxidizing solid. A new test should be provided to be in accordance with CLP regulation. 2.2.1.1.15 (p43) FR: no test has been provided to demonstrate that the active substance is not corrosive				

to metals. A demonstration using method C.1 described in manual UN RTDG or a scientific case should be provided by the applicant.
Dossier Submitter's Response
2.2.1: According to pesticide data requirements these spectra and information should be reported. However, it is not a CLP requirement. 2.2.1.1.13: Agree that it has not been clarified if solid Clomazone is oxidising. A test or justification based on structure can resolve this issue. A test on liquid Clomazone did not show oxidising properties. 2.2.1.1.15: Corrosive to metals is not a Pesticide data requirement.
RAC's response
Noted, thank you.

PUBLIC ATTACHMENTS
1. ClomazoneOutreachDocAdama_DC (5 Feb 2019)WBMSFeb11PUBLIC.pdf [Please refer to comment No. 13]
2. Clomazone summary position statement_final.pdf [Please refer to comment No. 14]
3. CLH evaluation.pdf [Please refer to comment No. 3, 6, 17, 21, 25, 28, 30, 32, 34, 36, 38, 42, 44, 45]

CONFIDENTIAL ATTACHMENTS
1. Clomazone, ECHA Comment, 8Feb2019, FMC, No. 2.zip [Please refer to comment No. 2, 10]
2. Clomazone, ECHA Comment, 8Feb2019, FMC, No. 1.zip [Please refer to comment No. 1, 5, 7, 11, 20, 26, 27, 29, 31, 33, 35, 37, 43, 46]
3. ClomazoneOutreachDocAdama_DC (5 Feb 2019)WBMSFeb11CONFIDENTIAL.pdf [Please refer to comment No. 13]