STATEMENT ON CLOMAZONE FOR ECHA PUBLIC CONSULTATION

Werner Bomann, PhD
Toxconsult LLC
February 7, 2019

1. Summary

During the process of EU renewal of clomazone, the RMS Denmark proposed a Repro Tox Cat 1B classification for clomazone based on concerns about potential developmental toxicity findings, i.e. a finding of 'arthrogryposis' or 'limb flexure' in a rat developmental toxicity study (XXXXXX) and a slightly higher incidence (within historical control ranges and not considered treatment related) of forelimb flexure in a rabbit developmental toxicity study (XXXXXX). A re-evaluation of these two studies which were conducted by Rallis Laboratories with regard to study conduct, scientific experience in the developmental toxicity area, the handling techniques and the nomenclature used at that time in the conducting laboratory led to the conclusion that the recordings of 'arthrogryposis' and 'joint flexure' as they were called by the laboratory were not treatment-related but the consequence of insufficient experience, inappropriate handling methods and inappropriate and unclear nomenclature at use at this laboratory at that time. This was especially the case for the developmental toxicity study in the rat. These deficiencies in the rat and rabbit developmental toxicity studies and the lack of statistical significance for this finding in the rabbit study question that these findings were real or treatment-related such that they do not warrant a classification proposal for reproductive toxicity. This is supported by the fact that two earlier developmental toxicity studies, one in the rat (XXXXXX) and one in the rabbit (XXXXXX), and furthermore a 2-generation reproduction toxicity rat study (Salamon, 1984) did not reveal any evidence of such effects nor did they reveal evidence of a direct developmental toxic potential of clomazone in general.

Importantly, a recent pre-natal developmental toxicity rat study with a study design which was as close as possible to the one of XXXXXX, did not confirm a potential for clomazone to induce the finding 'arthrogryposis' or 'joint flexure'. The study was conducted by a highly proficient and experience laboratory, using standard procedures that prevent artefactual limb flexure in conjunction with conventional best-practice terminology for recording such findings. This newer study further supports the absence of such a potential and that the findings which were only ever reported in one rat study were in fact artefacts due to deficient methodology as compared with a newer study conducted according to the state-of -the-art.

Therefore, based on the whole reproduction and developmental toxicity data package which did not show evidence of a direct reproduction or developmental toxic potential of clomazone, considering a weight of evidence assessment against the classification framework detailed in Regulation 1272/2008, the data are sufficiently convincing to warrant no reproductive toxicity classification for clomazone.

2. Introduction

Clomazone is a broad-spectrum herbicide which is currently undergoing routine evaluation for EU renewal of approval. The RMS Denmark proposed a Repro Tox Cat 1B classification for clomazone based on potential developmental toxicity findings, consisting of a finding called by the conducting laboratory 'arthrogryposis' or 'forelimb flexure' in rats and on a slight increase of forelimb flexures within historical control data in rabbits. However, based on a re-evaluation of these findings it is

questioned that these findings were real, since evidence of deficiencies in study conduct, methodology and nomenclature became apparent for the developmental toxicity studies of XXXXXX and XXXXXX, particularly of the rat study. Therefore, the finding of 'arthrogryposis' or 'forelimb flexure' is not regarded as a treatment-related finding but a spurious finding or artefact due to these deficiencies such that this does not support a classification proposal for reproductive toxicity.

A weight-of-evidence approach has considered the whole existing data package for reproductive and developmental toxicity on clomazone and based on the deficiencies apparent in the rat developmental toxicity study, the RMS's proposed classification of reproductive toxicity category 1B for clomazone is not supported by the available data. To demonstrate why a classification is not regarded as warranted, an overview of the existing data and the methodologies and techniques which may have led to the results of debate are presented.

Four developmental toxicity studies are available and are discussed in this paper:

1. Rat teratogenicity study with clomazone in Sprague-Dawley rats (XXXXXX)

2. Development toxicity study in rabbit (XXXXXX)

3. Developmental toxicity study in Wistar rats with Clomazone (XXXXXX)

4. Developmental toxicity study in rabbit (XXXXXX)

A more detailed summary is given in Appendix 1.

3. Discussion of findings under debate

From the aforementioned studies 3 and 4 it is concluded that the high dose levels caused marked maternal toxicity and even exceeded the maximum tolerated dose level. In the rabbit study, there was no apparent suggestion of preferential developmental toxicity to the foetuses based on the nature and incidence of the findings observed. However, in the rat study a slight increase in the number of foetuses with 'arthrogryposis' (at skeletal, but not external examination) as classified by the laboratory was evident at the high dose level, a slightly higher incidence at the mid-dose level was found not to be statistically significant and was also within historical control data ranges and thus not regarded as a compound effect. Since the re-evaluation showed that the laboratory SOP recorded even mild limb flexures as 'arthrogryposis', the true incidence and severity of this finding was most likely overestimated as compared to conventionally used nomenclatures. The conducting laboratory provided the feedback that "*As defined in our SOP Arthrogryposis is Persistent flexure or contracture of a joint flexed paw (bent or twisted). During the study period, the severities of flexion or extensions like mild, moderate and severe were not recorded. Even a mild flexion was reported as arthrogryposis*." Therefore, this finding was based on an unclear and inappropriate nomenclature in this laboratory which left too much room for inconsistent use and interpretation of an observation, so that the incidences are questionable and most likely exaggerated. Arthrogryposis Multiplex Congenita (AMC) is commonly defined as multiple congenital contractures in new-borns and to fit the general definition of AMC, contractures of the joints should be present in more than one area of the body. Generally, testing laboratories that undertake pre-natal developmental toxicity studies do not use the term "arthrogryposis" or AMC while classifying foetal pathologies, but rather describe the findings in a more explicit manner - such as "forelimb flexure". The use of this term in pre-natal developmental toxicity studies is considered unusual and not aligned with foetal pathology classification best

practices in use at major contract research laboratories. Therefore, the increased incidences in the discussed study are not regarded as real effects on the foetuses.

With regard to historical control data, the external findings of limb flexure which would be expected to correlate strongly with effects at skeletal examination fit within the expected background range in this rat strain. Unlike the external findings, the number of foetuses with ‘arthrogryposis’ and of dams with major malformed foetuses as a result, are above the historical control data range. However, since they were not seen at external examination, they are unlikely to be true findings of “arthrogryposis” and most likely due to a combination of artefactually induced limb flexure and subjective interpreter recording based on the mentioned unclear SOP in this laboratory.

The results of the rat range finding test (in the XXXXXX study) are clearly an additional argument against a treatment effect for the discussed finding, since in the rat dose range finding study with doses of 0, 250, 500, and 1000 mg/kg bw/day from day 6 to 15 of gestation (7 animals per group), clinical signs were observed at the highest dose but no case of arthrogryposis was reported. Further support comes from the reproduction toxicity rat study (XXXXXX) in which no evidence of an ‘arthrogryposis/limb flexure’ finding was observed.

The re-evaluation of the finding of concern for the authorities, i.e. ‘arthrogryposis’ or ‘forelimb flexure’ suggested that they mainly were concluded based on insufficient study conduct, methodologies including handling techniques and unusual nomenclature used by this laboratory at that time. In more detail, the re-evaluation resulted in the following arguments:

The testing laboratory diagnosed significantly more findings of arthrogryposis in skeletal examinations than in external examinations in the XXXXXX rat study, which is unlikely to occur in true cases of arthrogryposis. The skeletal findings not supported by external findings could be artefacts caused by inappropriate handling during processing of specimens (i.e., during foetal skinning procedures, placement in containers for preservation etc.). It is known that mishandling of specimens can cause arthrogryposis among others if fetuses were not removed from the uterus in a timely manner (Hood, R., in Developmental and Reproductive Toxicology, second edition, 2006). Especially milder effects which fall within the laboratory’s definition of ‘arthrogryposis’ are more likely the consequence of inappropriate handling or timing at necropsy and post-mortem handling than a true clinical arthrogryposis.

The cases of joint flexures detected at external examination which may be argued to be more likely to be true findings (1 foetus (0.5% of all foetuses examined)) are clearly within the historical control data range (2.1%).

In the rat dose range finding study, no cases of arthrogryposis were observed during external examinations even at the highest dose of 1000 mg/kg bw/day.

The rabbit findings of ‘joint flexures/arthrogryposis’ are within historical control ranges which indicate a lack of toxicological relevance.

To clarify if clomazone truly has a potential to cause ‘limb flexure’ or ‘arthrogryposis’, a new study was conducted (XXXXXX) which had a study design and methodology which was as similar as possible to the one of the Rallis Laboratory study (XXXXXX) . This new study did not confirm a potential of clomazone to induce the discussed findings ‘arthrogryposis’ or ‘limb flexure’. No indication of developmental effects of clomazone across all parameters assessed was demonstrated in this study. A summary of this study is provided in the appendix 2.

4. Comparison with the CLP criteria

According to the CLP guideline "*Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility, or on development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans.*"

For clomazone, adverse effects on sexual function and fertility or on development in humans are not known therefore such classification can be excluded.

According to the CLP guideline "*Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or 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. Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects.*"

In the XXXXXX rat study, the number of foetuses with 'arthrogryposis' and of dams with major malformed foetuses as a result, are unlikely to be true findings of arthrogryposis. The most likely reason for the observations of "arthrogryposis" during skeletal examinations is artefactual induction due to mishandling of specimens. It is known that mishandling of specimens, can lead to apparent instances of arthrogryposis caused by less than optimal foetal processing techniques (Hood, R., in Developmental and Reproductive Toxicology, second edition, 2006).
An additional argument against a treatment effect with regard to the discussed finding are the results of the rat range finding test; in the rat dose range finding study with doses of 0, 250, 500, and 1000 mg/kg bw/day from day 6 to 15 of gestation, i.e. even a higher dose than the highest dose of 750 mg/kg bw/day in the XXXXXX study, clinical signs were observed at the highest dose but no case of 'arthrogryposis' was reported. Also, in a 2-generation rat reproductive toxicity study (XXXXXX), among the results no developmental findings in the progeny of 'limb flexure' were seen. In addition and most importantly, a new rat developmental toxicity study with similar study design as that in the XXXXXX study did not confirm a potential of clomazone to induce the discussed findings 'arthrogryposis' or 'limb flexure'.

Overall therefore, no findings which would warrant a classification are evident from the whole reproduction and developmental toxicity data package.

5. Conclusion on classification and labelling for reproductive toxicity

It was demonstrated in this paper that a more thorough investigation of conduct and results of the rat pre-natal developmental toxicity study undertaken at Rallis (XXXXXX) revealed doubts as to the diagnosis of the 'arthrogryposis' finding in this study and calls into question the validity of this finding as a treatment-related effect in this study. Additionally, as the rabbit findings are clearly within Rallis historical control data ranges, the rabbit study (XXXXXX) does not provide corroborating evidence for a test article-related induction of 'arthrogryposis' or 'limb flexure' in developmental toxicity studies, especially since in the dose range finding study there was a high incidence of arthrogryposis in the control group, but not in the high dose group of 1000 mg/kg bw.

Overall, based on the whole reproduction and developmental toxicity data package which did not show evidence of a direct reproduction or developmental toxic potential of clomazone, and due to the technical deficiencies and inconsistencies in the XXXXXX and XXXXXX studies, considering a weight of evidence assessment against the classification framework detailed in Regulation 1272/2008, the data are sufficiently convincing to warrant no reproductive toxicity classification for clomazone.

6. References

XXXXXX: Teratogenicity study in Rabbits with Clomazone technical. Study no. 2841/2000, Rallis Research Centre, Rallis India Ltd., Post box no. 5813, Plot nos. 21 & 22 Peenya Phase, Bangalore 560 058, India. Nos. 11, 2002

XXXXXX: Rat Teratology Study with FMC 57020 Technical. FMC Toxicology Laboratory, 76 Fourth Street, Somerville, New Jersey 08876, Study Number A83-1142, June 29, 1984

XXXXXX: An Oral (Gavage) Prenatal Developmental Toxicity Study of Clomazone in Wistar Han Rats. Laboratory Project ID 00105205; FMC Tracking No. 2018TOX-CLZ4337; Charles River Laboratories, Ashland, LLC, 1407 George Road, Ashland, OH 44805, United States, 10 January 2019

Hood, R.D. (2006): Developmental and Reproductive Toxicology, a practical approach, Published in 2006 by CRC Press, Taylor & Francis Group, 6000 Broken Sound Parkway NW, Suite 300, Boca Raton, FL 33487-2742, second edition, 2006

XXXXXX: Teratogenicity study in Wistar rats with Clomazone technical. Study no. 2840/2000, Rallis Research Centre, Rallis India Ltd., Post box no. 5813, Plot nos. 21 & 22 Peenya Phase, Bangalore 560 058, India. Nos. 11, 2002

XXXXXX: A Teratology Study in Rabbits. WIL Research Laboratories, Inc. FMC Corporation, FMC study A 81-655, September 14, 1982

XXXXXX: Two-generation reproduction study in albino rats with FMC 57020 technical Toxigenics, Inc., Decatur, IL, USA, Study Number A82-757

Appendix 1

Short summary and overall relevance of the provided information on adverse effects on development

1. Rat teratogenicity study with clomazone in Sprague-Dawley rats (XXXXXX)

In this developmental toxicity study in rats, animals were administered with clomazone technical in corn oil at dose levels of 0, 100, 300 or 600 mg/kg bw/day on gestation days 6 through 15. Reduced maternal food consumption and clinical signs were seen. Abdominogenital staining and decreased locomotion were observed in most dams receiving 600 mg/kg bw/day. These signs were observed after the onset of dosing on Day 6 and were considered treatment-related. In addition, some incidences of oral discharge, pupil opacity, chromorhinorrhea and prostration were observed. Also, three dams in the 300 mg/kg bw/day group had abdominogenital staining, and two had chromorhinorrhea after the start of dosing. Thus, the two highest doses clearly caused maternal toxicity.
There was a small, non-statistically-significant upward trend in the number of resorptions at 300 and 600 mg/kg bw/day, but otherwise no effects on fertility were noted. There was no effect on sex ratio or viability in any of the treated groups. At the maternal-toxic dose of 600 mg/kg bw/day, mean female foetal body weights were reduced. Mean male foetal body weights showed a non-significant downward trend. Mean foetal body weights were similar in the other groups; therefore the aforementioned slight effects occurred only at a dose with a high degree of maternal toxicity.
No significant external findings were reported in any dose group in this study. The only minor visceral finding was a slightly increased incidence of hydroureter at 600 mg/kg bw/day. The fetal incidence of this finding was minimal with only 3.8%.
There were no major skeletal malformations noted in the foetuses in any group. Several incidences of delayed skeletal ossification were observed in the 600 mg/kg bw/day foetuses, attributable to an increased absence or partial ossification of the sternebrae, absence of the caudal vertebrae, and absence of the metacarpal bones, which occurred also at 300 mg/kg bw/day, but mostly at a lower degree.
Since these developmental toxic effects occurred only at doses with strong maternal toxicity, these effects were evaluated to be a secondary response to the maternal toxicity and not evidence of primary developmental toxic potential of clomazone. This evaluation was not changed upon re-evaluation by the RMS. The lowest dose of 100 mg/kg bw/day was established as a NOAEL.

2. Development toxicity study in rabbit (XXXXXX)
In a developmental toxicity study in rabbits, oral doses of 0, 30, 240 or 1000 mg/kg bw/day (reduced to 700 mg/kg bw from day 13 onwards) were administered from day 6 through 18 of gestation. Maternal toxicity was seen in the highest dose group with effects on maternal body weight, death of three females, abortion in four females and red vaginal discharge which was most often seen in females which aborted. Additionally, decreased or no defecation was observed in the highest dose group. No dose- or treatment-related differences with respect to the number or percentage of foetuses with malformations or developmental variations between control and treatment groups were noted. No evidence of a primary developmental toxic potential was seen. The maternal NOAEL was 240 mg/kg bw/day and the NOAEL for developmental effects was 700 mg/kg bw/day, which was the highest dose tested. No significant external malformations were seen in any foetus in any dose group.

Based on the results of the two studies it is clear that they did not indicate a primary developmental toxic potential but only secondary effects at maternal-toxic doses. Even at maternally toxic dose levels there was no indication of a treatment-related effect on any form of ‘limb flexure’ or ‘arthrogryposis’ in either species.

3. Developmental toxicity study in Wistar rats with Clomazone (XXXXXX)

In this newer study, clomazone in 0.5% aqueous carboxymethyl cellulose was administered to pregnant Wistar rats at doses of 0, 250, 500 and 750 mg/kg bw/day orally *via* gavage from gestation day 6 to 19.

A reduced food intake was observed at doses of ≥ 250 mg/kg bw/day and significant reduction of body weight and body weight gains at and above dose levels of 500 mg/kg bw/day. In addition to these maternal-toxic effects at 750 mg/kg bw/day, clinical signs, including salivation, lethargy and wet perineum were observed. In addition, one dam was found dead during the treatment period. Reductions of body weight and weight gain and food intake were significant at the highest dose level.

Thus, it can be concluded that marked maternal toxicity occurred at 500 and especially at 750 mg/kg bw/day, with slight maternal toxicity already present at 250 mg/kg bw/day. The highest dose of 750 mg/kg bw/day of clomazone, was severely toxic to the dams, with mortality, clinical signs, reduced body weight gains and reduced food intakes by 52 and 76% of control, respectively. This high toxicity is supported by results of a 28-day dietary rat study (DAR, 2005) in which at doses of ≥ 8000 ppm strong effects on body weights, adrenal weights and liver effects (GPT increase and liver weight increase) were observed. While 8000 ppm is approximately equivalent to 800 mg/kg bw/day, it must be assumed to cause lower peak plasma and tissue levels than after gavage treatment due to exposure *via* multiple feeding events over the day rather than a single bolus administration. Therefore, toxic effects have to be expected to be more pronounced after gavage administration. Thus, the highest dose of 750 mg/kg bw/day in this developmental toxicity study has to be in principle regarded as inappropriate for evaluation of developmental toxic effects.
At the two highest doses with significant maternal toxicity, increased incidences of developmental toxicity findings were recorded. At the highest dose, visceral examination showed a tendency towards an increased incidence of renal pelvis dilatation and skeletal examination indicated an increase in findings classified as ‘arthrogryposis’ as well as some skeletal ossification effects; however, minimal external findings were noted to correlate with the skeletal effects, and the laboratory definition of ‘arthrogryposis’ was overly broad, encompassing even mild joint flexures in single joints, as previously discussed.

4. Developmental toxicity study in rabbit (XXXXXX)

In this rabbit developmental toxicity study, clomazone was administered to 25 pregnant New Zealand rabbits per group at doses of 0, 150, 350 and 700 mg/kg bw/day orally *via* gavage from gestation day 6 through 29. The doses were based on dose range finding studies. A 0.5% aqueous carboxymethyl cellulose in Tween 80 vehicle was used. A caesarean section was performed on study day 29. Clinical signs were observed which consisted of diarrhoea in all treatment groups and weakness, dullness, wet perineum and abortion in the highest dose group. Deaths occurred in the control, mid and high dose. The deaths were regarded as consequence of gavage errors in the control and mid dose group, whereas the death at the highest dose was regarded as treatment-related, based on the necropsy finding of haemorrhagic gross lesions in the stomach. In the two rabbits that aborted, one had gross lesions of lung petechiae and the other hard and haemorrhagic stomach and haemorrhagic intestines. At the highest dose level severe maternal toxicity was apparent, based on clinical signs, mortality, abortion and significant effects on body weights and feed intake, with lesser, but still significant maternal toxicity at 350 mg/kg bw/day. Maternal parameters, such as number of corpora lutea, implantations, resorptions and implantation loss were not affected at all dose levels tested.

Regarding developmental toxic effects, incidences of dead foetuses were seen in all groups, including the control group. Also, the number of foetuses with external malformations was not affected by treatment. The visceral observations did not indicate dose- or treatment-related findings. Skeletal

observations did not indicate dose- or treatment-related effects; the observed signs of delayed or incomplete/poor ossification did not show a dose-response and thus no treatment-relationship was concluded. There was one foetus at the highest dose with multiple abnormalities detected, which included absent skull bones, both forelimbs flexed at wrist and hind limbs turned inwards in the high dose group, which was the same foetus exhibiting multiple malformations at external and visceral examination. The abnormalities in this single foetus (in only one litter) were regarded as incidental to an effect of clomazone administration.

Appendix 2

New developmental toxicity study in rats (XXXXXX**)**

The 2019 pre-natal developmental toxicity study has been carried out by Charles River Laboratories (Ashland-Ohio) who have strong scientific and procedural expertise in carrying out pre-natal developmental studies. Great emphasis was placed on conducting the study in such a manner to eliminate the possibility of artefactual induction of limb flexure by insufficient methodologies. The study was undertaken according to modern test guidelines to include test substance administered daily from implantation (e.g. day 6 post-mating) to the day prior to delivery.
The use of diagnostic terminology, including 'arthrogryposis', is not being used by the testing laboratory due to modern conventional best practice regarding nomenclature (and consistency with the laboratory's historical control data) avoiding the misuse of such medical diagnostic language when recording foetal pathology observations. The standard lexicon (e.g., "flexed") for findings has been used in the 2019 study, which then allows for a more transparent interpretation of findings relating to limb flexure without the additional level of interpretation and potential confusion that may surround the use of a diagnostic term such as 'arthrogryposis'.
This new study was therefore undertaken to provide additional robust data upon which to make an informed decision whether clomazone has a potential to influence the incidence of limb flexures (as well as any other potential *in-utero* developmental findings) in the rat. It is therefore considered that results obtained in this study can be viewed as being of high quality and reliability in the context of performing a weight-of-evidence assessment of the data.

Wistar Han rats were treated with clomazone formulated in 0.5% CMC of medium viscosity and 0.1% Tween® 80 and dosed via oral gavage once daily during Gestation Days 6–20. Three higher dose levels (250, 500 and 750 mg/kg bw/day) were selected to match those used in the XXXXXX rat study in which the same doses and the same strain of Wistar rats were employed.
The following parameters and endpoints were evaluated in this study: clinical signs, body weights, body weight gains, gravid uterine weights, food consumption, gross necropsy, liver weights, intrauterine growth and survival, and foetal morphology. All foetuses were examined for external, visceral and skeletal alterations.
All female dams survived to the scheduled necropsy. No test substance-related clinical observations were noted at the daily examinations at any dosage level. At 500 and 750 mg/kg bw/day incidences of dilated pupils were noted (4/21 and 12/21, respectively) between 2 and 4 hours post-dosing, primarily during the first 3 days of dose administration. Red material around the mouth was also noted sporadically in the 750 mg/kg/day group at 2-hours post-dosing throughout the dosing period. These findings were considered test substance related but not adverse due to their transient nature.

Lower maternal mean body weight gains and food consumption were noted in the 250 and 500 mg/kg bw/day groups following the first 1 or 2 days of dosing (Gestation Days 6-7 and/or 7-8). Thereafter, mean body weight gains and food consumption in the 250 and 500 mg/kg bw/day groups were comparable to the control group. Lower mean body weight gains and food consumption were noted in the 750 mg/kg bw/day group during Gestation Days 6-8 and 6-10, respectively. Mean body weight gain in the 750 mg/kg bw/day group was also lower during Gestation Days 12–15, and mean food consumption in this group was lower during Gestation Days 15–21 compared to the control group. Mean net body weight and net body weight gain in the 750 mg/kg bw/day group were also lower than the control group. The magnitude of the body weight and food consumption decrements at 250, 500, and 750 mg/kg bw/day were not sufficient to result in lower mean absolute body weights, and therefore were considered test substance-related but not adverse. Mean body weights, body weight gains, and food consumption in the 100 mg/kg bw/day group, mean net body weights and net body

weight gains in the 100, 250, and 500 mg/kg bw/day groups, and mean gravid uterine weights at all dosage levels were comparable to the control group.
No test substance-related maternal macroscopic findings were noted. Mean absolute liver weights were 10.61%, 25.4%, and 23.3% statistically significantly higher in the 250, 500, and 750 mg/kg bw/day groups, respectively, compared to the control group.
Fetal intrauterine growth and survival and fetal morphology were not affected by maternal test substance administration at all dosage levels. No test item related increases in developmental effects were observed. Based on the increased liver weights at 250, 500 and 750 mg/kg bw/day, a dosage level of 100 mg/kg bw/day was considered to be the no-observed-adverse-effect level (NOAEL) for maternal toxicity. No incidences of limb flexure were observed in any of the clomazone treated groups in this study. Based on the lack of adverse findings or test substance-related effects on embryo/fetal development, a dosage level of 750 mg/kg bw/day (the highest dosage level tested) was considered to be the no observed adverse effect level (NOAEL) for embryo/fetal development when clomazone was administered orally by gavage to time-mated Wistar Han rats. No incidences of limb flexure were observed in any of the clomazone treated groups in this study.

Thus, this new study did not confirm a potential of clomazone to induce the discussed findings ‘arthrogryposis’ or ‘limb flexure’.