Committee for Risk Assessment

RAC

Annex 3

Records of the targeted public consultation following the submission of additional studies on the skin sensitising properties of

pendimethalin (ISO); *N*-(1-ethylpropyl)-2,6-dinitro-3,4-xylidene

EC Number: 254-938-2
CAS Number: 40487-42-1

CLH-O-0000006863-66-01/F

Adopted

8 October 2020

ANNEX 3 - RECORDS OF THE TARGETED PUBLIC CONSULTATION FOLLOWING THE SUBMISSION OF ADDITIONAL STUDIES ON THE SKIN SENSITISING PROPERTIES OF PENDIMETHALIN (ISO); N-(1-ETHYLPROPYL)-2,6-DINITRO-3,4-XYLIDENE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

The proposal for the harmonised classification and labelling (CLH) of (pendimethalin (ISO); N-(1-ethylpropyl)-2,6-dinitro-3,4-xylidene, EC 254-938-2; CAS 40487-42-1) was submitted by The Netherlands and was subject to a consultation, from 15/04/2019 to 14/06/2019. The comments received by that date are compiled in Annex 2 to the opinion.

During its opinion drafting, the Committee for Risk Assessment (RAC) asked for further information to clarify the skin sensitising properties of pendimethalin (ISO). Two studies were submitted therefore an ad hoc consultation was held from 13/07/2020 to 10/08/2020 and the received comments are listed below.

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

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

ECHA accepts no responsibility or liability for the content of this table.

Substance name: pendimethalin (ISO); N-(1-ethylpropyl)-2,6-dinitro-3,4-xylidene
EC number: 254-938-2
CAS number: 40487-42-1
Dossier submitter: The Netherlands

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
24.07.2020	United Kingdom	ADAMA Agricultural Solutions Ltd	Company-Manufacturer	1
Comment received				
CLH Report Reference: Section 10.7 Skin Sensitization. Based on a Weight of Evidence approach, taking into consideration all the available data (5 studies) for assessing skin sensitization potential, ADAMA supports the conclusion presented in the ODD. Pendimethalin does not warrant classification as a skin sensitizer. The two most recent mouse LLNA studies are well conducted meeting the requirements of current test guidelines (OECD 429) and GLP. Both studies achieved high concentrations (50%) with skin application using a vehicle (acetone:olive oil) which would allow maximal penetration and showed clearly negative responses. The studies represent two different sources of pendimethalin (both of high purity, 96.8 and 97.7% w/w, respectively) and were conducted at two independent laboratories. In contrast, the initial guinea pig maximization tests were conducted with test material of unknown purity and did not seem to achieve high concentrations. Without knowing the levels or relevance (e.g. highly reactive entities) of any impurities in these batches, these may have contributed towards the positive response observed in one of these studies.				

RAC's response
Agreed, the proposal is for no classification based on a weight of evidence approach along with significant concerns over the reliability of the positive result (at the 24 hour time period only) in the 1995 M&K study.

Date	Country	Organisation	Type of Organisation	Comment number
07.08.2020	Germany		MemberState	2

Comment received

Five studies are available to assess the endpoint skin sensitisation.

Three skin sensitization studies in guinea pigs were previously submitted. Two of these studies (see CLH-report Study 1, IIA 5.2.6/01 Doc ID 84-4639A; Study 2, IIA 5.2.6/01 Doc ID 8230) were negative for skin sensitisation and one (Study 3, IIA 5.2.6/01 Doc ID PRO 705) was positive. The purities of the pendimethalin technical used in Study 2 and in Study 3 are unknown. Given that the sources of pendimethalin technical were different for each study, it is unclear whether the positive result seen in Study 3 was due to pendimethalin technical, an impurity or something else.

Two newly submitted LLNAs yielded negative results, but both have deviations and potential deficiencies.

No concurrent positive controls were included in either of the two studies. It is not clear whether the studies referred to (BSL Project ID 1146I2B from 2011 and study no. 881400 from 2005), in which positive controls had been included, were in fact the latest periodic positive control and laboratory proficiency tests for the LLNA in the respective laboratories. However, OECD TG429 requires such tests (2010). This critical point has to be clarified for both studies before a conclusion can be made concerning the validity of the LLNA results.

No signs of systemic toxicity or skin irritation were observed in either LLNA. Concentrations of 12.5, 25 and 50 % (w/v) in acetone:olive oil 4:1 (v/v) were used in both studies.

The first LLNA (Report No.: 114632) by K.L. from 2011 yielded SI-values of 2.1 (12.5 %), 1.9 (25 %) and 2.2 (50 %) showing no increasing dose response relationship. It is mentioned that p-phenylenediamine is used as positive control instead of 25 % hexyl cinnamic aldehyde or 5 % mercaptobenzothiazole, a corresponding reasoning as requested in OECD 429 is not given in the submitted documents. However, this deviation need not considered critical because p-phenylenediamine is also mentioned in OECD 429 (table 1 of annex 1) as reference substance.

The second LLNA (Report No.: RCC-CCR 893601) by N.H. from 2005 reported SI-values of 2.42 (12.5 %), 1.43 (25 %) and 1.7 (50 %). An increase in SI with increasing concentration was not observed. Individual housing instead of group-housing is mentioned as deviation from the guideline and a reason for this, as required by OECD 429, was not given.

The maximum tested concentration in both LLNAs was 50 %. The OECD 429 recommends solid substances be dissolved or at least suspended. A pure solid substance should not be tested. The topical induction concentration of the positive maximization test was higher (75 %), so a higher concentration could have been tested in the LLNAs.

It is also noted, that arachis oil was used as vehicle in the positive maximization test while acetone:olive oil (4:1) was used in both LLNAs. The vehicle can have a significant influence on the result of an LLNA. The maximum concentrations were quite high (LLNA: 50 %, maximization test: 75 %), thus a different solubility might have an influence on the results.

Overall, the above mentioned uncertainties concerning substance purity in the maximum tested concentration, the appropriateness of the vehicle and the missing positive controls in the LLNAs all need to be carefully weighed in a final weight of evidence approach. If the negative results of both LLNA studies are regarded as valid, then it may be possible to drop the classification as Skin Sens. 1B, H317.

RAC's response

There were no missing positive controls in the LLNAs. BSL Project ID 1146I2B from Oct 2011 and study no. 881400 from Mar 2005 were the latest periodic positive control and laboratory proficiency tests for the LLNA in the respective laboratories. Both LLNA studies were valid and their validity with respect to positive controls was noted previously in the opinion document.

Some of the uncertainties mentioned are minor and do not invalidate the LLNA studies.

According to the 2011 LLNA study, a solubility test determined the maximum technically applicable concentration of pendamethalin was 50% in AOO (w/v). The 2005 study did not explicitly state that the highest concentration that could be achieved was 50% (w/v) it just indicated this was so.

The uncertainty regarding substance purity for the 1995 M&K positive study raises questions over the validity of this study and it's positive result. The strong response at 24 hours does not hold up over 48 hours.

The negative results of both LLNA studies are regarded as valid, RAC proposes to delete the classification of Skin Sens. 1, H317.

Date	Country	Organisation	Type of Organisation	Comment number
05.08.2020	Netherlands		MemberState	3

Comment received

Two additional skin sensitization studies were submitted. Both studies were LLNA studies conducted with batches from different production sites. The studies have been previously evaluated in the EU in the context of technical equivalence evaluations.

The studies where conducted under GLP, in accordance with OECD 429 and appear to be acceptable.

In the first study (Study # 114632) pendimethalin (batch 20101207, purity 97.7% according to the equivalence report) was tested at concentrations of 10, 25 and 50%. The highest dose was indicated to be the maximum technically possible concentration. Stimulation Indices were below 3 in all three dose groups and pendimethalin was concluded to be a non-sensitizer.

In the second study (Study # 893601) pendimethalin (batch D-TR00389, purity 96.5%) was tested at concentrations of 10, 25 and 50%. Stimulation Indices were below 3 in all three dose groups and pendimethalin was concluded to be a non-sensitizer.

Taken together the available information on skin sensitization is:
1. A negative Buehler assay which was concluded to be unacceptable due to a low number of animals.
2. A Maximisation study which was conducted up to a concentration of 5% and gave a negative response.
3. A Maximisation study which was conducted 10% and 25% and which gave a positive response. A higher number of animals had a positive challenge response in the 25% compared to the 10% group.
4. Two negative LLNA studies conducted with batches from other production sites.

Unfortunately for the Maximisation study the purity or composition of the tested batch is not known. It is however noted that the purity in the two new studies are quite a lot higher than the minimum purity of 90% set for pendimethalin during the renewal evaluation (source: EFSA conclusion). The difference in outcome of the Maximisation test and LLNA studies might be due to a difference in impurity profile.

Little information is available on the skin sensitization potential of the individual impurities in the reference specification of pendimethalin approved at EU level. However, it is noted that one impurity (Reg. No. 4157268) gave alerts for skin sensitization in the available QSAR analysis according to Volume 4 of the RAR. We were not able to retrieve the full impurity profile of batch D-TR00389, but the impurity profile for batch 20101207 as provided in the equivalence check did not include this specific impurity.

Since the two new studies were conducted with batches of much higher purity than the reference specification from the RAR we consider that these studies are not sufficient to conclude that pendimethalin as approved at EU level is not a skin sensitizer.

Paragraph 1.1.1.4 of Annex VI of CLP allows inclusion of impurities in the chemical name when they contribute significantly to the classification of the substance or specifying the purity of the substance. As the name of the impurity is currently confidential and it is not certain that this impurity caused the skin sensitizing test result for pendimethalin, including the impurity is not an option. However, specifying a purity range for the form as approved for the European market (90%) up to the purity that was tested negative (96%) may be an option.

RAC's response

It is not possible to explain the difference in outcome of the Maximisation test and LLNA studies, a difference in impurity profile remains speculative. An impurity in the original batch would need to be an extreme sensitiser to have any expression in the final technical material. This would seem unlikely considering that the positive result from the 1995 M&K study was only confined to the first 24 hours after removal of dressing period and found not to persist to 48 hours after removal of the dressing.

The two new studies were conducted with batches of much higher purity than the reference specification from the RAR, this lends weight to the results of tests using such material because we concentrate on the innate hazardous properties of the pure active substance. RAC considers a weight of evidence approach is warranted for pendimethalin and proposes removal of the skin sensitisation classification.

ANNEX 3 - RECORDS OF THE TARGETED PUBLIC CONSULTATION FOLLOWING THE SUBMISSION OF ADDITIONAL STUDIES ON THE SKIN SENSITISING PROPERTIES OF PENDIMETHALIN (ISO); N-(1-ETHYLPROPYL)-2,6-DINITRO-3,4-XYLIDENE

Date	Country	Organisation	Type of Organisation	Comment number
24.07.2020	Germany	BASF SE	Company-Manufacturer	4
Comment received				
Based on the two new studies BASF also is of the opinion that a weight of evidence approach should be taken. As indicated in the ODD, the two LLNA studies were performed according to the new guidelines in different labs with different personnel and to higher concentrations. Both studies used an acetone mixture to solubilize Pendimethalin, which ensures maximal penetration. In addition, the studies were performed with material of two independent Pendimethalin sources from India and China. On the contrary, the initial GPMT test was performed with a batch of unknown purity and impurity spectrum. The production process of dinitroanilines is prone to form nitrosamines, which are highly reactive and can lead to sensitization reactions. Therefore, one possible reason for the positive test might have been the presence of an unspecified e.g. nitrosamine impurity. Based on the totality of the available data a classification for skin sensitization is therefore not warranted.				
RAC's response				
Agreed.				