Possibility for

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SUBSTANCE EVALUATION

CONCLUSION DOCUMENT

as required by REACH Article 48

for

1,1´- iminodipropan-2-ol

EC No 203-820-9

CAS No 110-97-4

Evaluating Member State(s): Czech Republic

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Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2013

Member State concluded the evaluation without the need to ask further information from the registrants under Article 46(1) decision.

Please find (search for) further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

The Conclusion document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work.

In order to ensure a harmonised approach, ECHA in cooperation with the Member States developed risk-based criteria for prioritising substances for substance evaluation. The list of substances subject to evaluation, the Community rolling action plan (CoRAP), is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by the Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. In this conclusion document, the evaluating Member State shall consider how the information on the substance can be used for the purposes of identification of substances of very high concern (SVHC), restriction and/or classification and labelling. With this Conclusion document the substance evaluation process is finished and the Commission, the registrants of the substance and the competent authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

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1. CONCERN(S) SUBJECT TO EVALUATION

1,1´- iminodipropan-2-ol (Diisopropylamine (DIPA) or bis(2-hydroxypropyl)-amine (DHPA)) was originally selected for substance evaluation in order to clarify suspected risks about:

- Classification for Eye irritation/Eye damage – the substance is classified as Eye Irrit. 2 but some notifications give self-classification as Eye Dam.1.
- Classification for Skin irritation
- (Suspected) Skin Sensitiser - the substance is not classified for skin irritation or sensitization. However individual cases of contact sensitisation in response to DIPA exposure have been reported in human studies. In a human study, in which 24 volunteers received undiluted DIPA on the skin, dermal irritation was observed in six individuals.
- High worker exposure and high RCR
- (Suspected) CMR with respect to the formation of N-nitroso-bis(2-hydroxy-propyl)amine (NDHPA) - Bis(2-hydroxypropyl)-amine (DHPA) alone induced no foci, but putative pre-neoplastic GST-P-positive foci were observed in the liver and increased dose-dependently in rats which had received DHPA and $NaNO_2$. The results indicate that endogenously synthesized NDHPA from DHPA and $NaNO_2$ is capable of initiating neoplastic development in the rat liver.
- Data gap for the fertility toxicity (read-across approach) – two-generation study was waived and One-generation study and Combined Repeated Dose Toxicity study with Reproduction/Developmental Screening using read-across were given to cover the endpoint requirement. Therefore no experimental data on the substance are available for fertility endpoint.

2. CONCLUSION OF SUBSTANCE EVALUATION

The available information on the substance and the evaluation conducted has led the evaluating Member State to the following conclusions, as summarised in the table below.

Conclusions	**Tick box**
Need for follow up regulatory action at EU level *[if a specific regulatory action is already identified then, please, select one or more of the specific follow up actions mentioned below]*	
Need for Harmonised classification and labelling	
Need for Identification as SVHC (authorisation)	
Need for Restrictions	
Need for other Community-wide measures	
No need for regulatory follow-up action	x

3. JUSTIFICATION FOR THE CONCLUSION ON THE NEED OF REGULATORY RISK MANAGEMENT

3.1. NEED FOR FOLLOW UP REGULATORY ACTION AT EU LEVEL

3.1.1. Need for harmonised classification and labelling

Not applicable.

3.1.2. Need for Identification as a substance of very high concern, SVHC (first step towards authorisation)

Not applicable.

3.1.3. Need for restrictions

Not applicable.

3.1.4. Proposal for other Community-wide regulatory risk management measures

Not applicable.

3.2. NO FOLLOW-UP ACTION NEEDED

The concern could be removed because	**Tick box**
Hazard and /or exposure was verified to be not relevant and/or	
Hazard and /or exposure was verified to be under appropriate control and/or	***X***
The registrant modified the applied risk management measures.	
other: <Please specify>	

All available information (registration dossiers, Chemical Safety Report(s) and literature data and review) was used to clarify the concerns. The available information is sufficient and reliable to conclude the substance evaluation. There is no need for new studies and information under SEv process.

The following conclusions were prepared to conclude the SEv process:

Eye irritation/Eye damage

The substance 1,1´- iminodipropan-2-ol (DIPA) has a harmonized classification as Irritating to eyes (Category 2).

All available information on Eye irritation for DIPA was evaluated. The criteria for classification as Irreversible effects on the eye (Category 1) have not been met in any available study. Further information used for C&L notification is not known and therefore it could not be verified for the accuracy.

One study was conducted according to guideline OECD 405 which is comparable with EU method B.5. The study design and results are described sufficiently to compare the results of this study with the classification criteria stated in CLP regulation.

Conclusions on classification and labelling

The results of this study are consistent with the harmonized classification of the substance. The classification of DIPA as Irreversible effects on the eye (Category 1) is not warranted.

Skin irritation

In a well performed skin irritation study with rabbits, very slight erythema (score 1) was observed 1 hour after application of DIPA in 4/6 rabbits and 24 hours after application of DIPA in 1/6 rabbit. No signs of irritation were observed at later time points.

Classification is required when a score at or above 2.3 is observed in 2 or more out of 3 animals. According to the guidance such score is required in at least 4 animals if the test is performed with 6 animals. Classification is also required if persistent effects are observed or very definite positive effects. No such effects were observed. The substance does not meet the criteria for classification.

Evidence of skin irritation in other dermal studies depended on study design. In those studies the exposure duration was longer than 4 hours and the occlusive coverage was used. The concentration, exposure duration, and patch occlusivity can affect skin irritancy significantly.

Some studies are not described sufficiently. Information on skin reaction and used scoring system are missing.

Conclusions on classification and labelling

Available information on skin irritation does not result in the classification of the substance DIPA as skin irritant. Based on this information classification is not warranted.

(Suspected) Skin Sensitiser

In a Buehler test guinea pigs were induced topically with 50% of the DIPA (purity 99.61%). The induction caused no dermal responses. Following challenge with 50% of DIPA, no dermal responses were observed in any of the test animals.

The human studies are poorly documented. In some studies the diluted substance was tested only. For these reasons, the results of human studies cannot be used for the classification purposes.

Conclusions on classification and labelling

Based on available data the criteria for classification as Skin sensitiser (Category 1) are not met. Therefore classification is not warranted.

High worker exposure and high RCR

It is stated by registrants that updated assessment was performed after the thorough discussion with technical workers and substance is now assessed as aqueous solution or as slightly warmed-up substance more like to waxy texture than high dustiness solid as the substance was assessed earlier. In addition, the concentration ranges for some ESs were discussed in consortium.

Concurrently the registrant took into account that previously used model ECETOC TRA v2.0 is conservative tool and higher tier assessment by EasyTra tool and ART tool was performed.

The exposure assessment was overviewed by MSCA and the concern has been clarified. The Exposure Scenarios are prepared with variations over individual PROCs where it is necessary within industry sectors. This enables to downstream users to choose the most corresponding safe use and eventually adjust their current conditions in appropriate way.

Updated risk assessment results in lower RCRs. Only two cases represent RCRs combined routes > 0.8 in relation with type of PROC or if uses vary by using different personal protection equipment within specific PROC.

(Suspected) CMR with respect to the formation of N-nitroso-bis(2-hydroxy-propyl)amine (NDHPA)

The review of publications and studies indicates the conclusion, that carcinogenic potential cannot be linked to DIPA alone, but rather to general processes in body, which could occasionally lead to formation of NDHPA when any inflammatory processes take place in the body.

Information on this issue stated in grounds for concern was proved. However DIPA as a secondary amine could be the safe part of the potentially hazardous process, which principally cannot be fully avoided, due to fact, that nitrosating agents are formed endogenously.

The conditions of endogenous formation of N-nitrosamine based on bacterial and cell-mediated nitrosation were evaluated. It was found, that this formation is increased when endogenous NO synthesis is increased.

It was revealed that the addition of nitrite and amines to non-stimulated cells produces negligible yields of N-nitrosamines. Thus, if cells are not activated due to inflammatory processes in the body the formation NDHPA from DIPA is likely to be negligible.

Therefore, there is no evidence that effects of NDHPA will occur in healthy individuals. However, workers with chronic inflammation could be considered as vulnerable group of workers in the context of contact with amines.

For the maximal reduction of likelihood of such process the circumstances of exposure to the substance were considered including its bioavailability potential, as the substance is precursor of such reaction but based on available information there is no significant concern.

Fertility toxicity

No two-generation reproduction toxicity study is available for DIPA. A category approach based upon the functional group (isopropanol substituent(s) bonded to amine group) was provided for the endpoint on reproduction toxicity.

The structural similarity is supported by the physicochemical properties that are similar or reflect the incremental changes expected in the series of alcoholic amines. Available data reflect the trend of decreasing mammalian toxicity with increasing molecular weight.

One-generation study with 1,1', 1''-nitrilotripropan-2-ol (TIPA) does not conform to the OECD test guideline referred to in the REACH Annexes but nevertheless provides a suitable level of information for the evaluating Member State to clarify the concern. The derived NOAEL from this study is based on the highest tested dose.

The available combined repeated dose toxicity study according to OECD 422 can provide for tested substance only limited information on possible effects on fertility and developmental toxicity and although read-across MIPA-DIPA is possible, the study is not sufficient itself to clarify the concern for fertility.

No effects on reproductive organs in adult animals were observed in sub-acute dermal toxicity study and in sub-chronic oral toxicity study.

Results of available studies for repeated dose toxicity and reproduction toxicity for members of the category are sufficient for the evaluating Member State to clarify the concern with respect to fertility toxicity of DIPA.

An exposure consideration was carried out in order to omit the two generation reproduction toxicity study for DIPA. This provided a suitable level of information for the evaluating Member State to clarify the concern.

4. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Not applicable.