SUBSTANCE EVALUATION REPORT

Background document for the purpose of substance evaluation under REACH

for

1,1´- iminodipropan-2-ol

EC No 203-820-9

CAS No 110-97-4

Evaluating Member State(s): Czech Republic

Dated: 28.2.2014

Evaluating Member State Competent Authority

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Conclusions of the most recent evaluation step*	Tick relevant box(es)
Concern not clarified; Need to request further information from the Registrant(s) with the draft decision	
Concern clarified; No need of further risk management measures	x
Concern clarified; Need for risk management measures; RMO analysis to be performed	
Other:	

**Include details in the executive summary.*

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Executive summary

Grounds for concern

The substance has a harmonised classification according to Regulation (EC) No 1272/2008 (CLP Regulation) as Eye Irrit. 2 but some notifications give self-classification as Eye Dam.1. It is not classified for skin irritation or sensitization. However individual cases of contact sensitisation in response to 1,1'-iminodipropan-2-ol (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.

There is high worker exposure and high RCR were identified for Dermal and Long-term exposure, systemic, combined RCR.

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 NaNO2 is capable of initiating neoplastic development in the rat liver.

Finally, the 2-generation study was waived and 2 studies (an OECD Test Guideline 422 and one-generation study according to U.S. FDA Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food - 21 CFR 314.50(d)(2)) using read-across were given to cover the endpoint requirement. Therefore no data on the substance are available for fertility endpoint.

Procedure

The substance evaluation is based on information in the registration dossiers, including Chemical Safety Reports (CSR)s as well as on the other available information (Databases, OECD SIDS and publications).

The reliability of available information relevant to the concern was evaluated.

The Czech CA was in contact with Lead registrant by e-mail. The comments to "Grounds of concern" were received in the middle of September. The spontaneous dossier update with respect to the concern stated in Justification document for the selection of substance to the CoRAP was submitted at the end of September 2013.

The following issues were evaluated with respect to concerns:

- classification (Eye irritation, Skin irritation, Skin sensitisation)

- read-across used (Fertility toxicity)

- clarification of the possible neoplastic development initiation (Formation of NDHPA)

It was concluded that no new information is necessary for the substance evaluation. Therefore the draft decision was not submitted and the evaluation process was concluded in February 2014.

Conclusions

Eye irritation/Eye damage

The substance DIPA has a harmonized classification according to CLP Regulation 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.

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

Numerous studies of the dermal irritancy of DIPA were conducted with mixed results. Only one study was conducted according to guideline OECD 404 which is comparable with EU method B.4. The study design and results are described sufficiently to compare the results of this study with the classification criteria stated in CLP regulation.

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. [8]

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

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.

Skin sensitisation

The substance DIPA was tested for the assessment of skin allergic effects using albino guinea pigs (strain Hartley). The test was performed according to the OECD Test Guideline No. 406, Skin sensitisation, which is analogous to the EU Method B.6, Skin sensitisation.

The Buehler test was followed. The test was performed on albino guinea pigs (10 males). The exposed animals showed no allergic skin reactions.

The study design and results are described sufficiently to compare the results of this study with the classification criteria stated in CLP regulation.

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

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.

High worker exposure and high RCR (for dermal RCR and Long-term exposure, systemic, combined RCR)

It is stated by registrants that updated assessment is 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 ECETOC TRA v2.0 model 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 the downstream users to choose the most corresponding safe use and eventually adjust their current conditions in appropriate way.

Updated risk assessment results in safer RCRs. Only two cases in LR dossier 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.

Endogenously synthesized 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 an inflammatory process takes 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.

Read across approach for Two-generation reproductive toxicity study

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 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 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 by itself to fulfil the fertility endpoint.

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 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.

CONTENTS

TABLES

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Table 1: Substance identity

Public Name:	1,1'-iminodipropan-2-ol
EC number:	203-820-9
EC name:	1,1'-iminodipropan-2-ol
CAS number:	110-97-4
CAS name:	2-Propanol, 1,1'-iminobis-
IUPAC name:	1,1'-iminodipropan-2-ol
Index number in Annex VI of the CLP Regulation	603-083-00-7
Molecular formula:	C6H15NO2
Molecular weight range:	133.19
Synonyms:	2-Propanol, 1,1'-iminobis- 1,1'-iminodipropan-2-ol 1,1'-Iminobis[2-propanol] 2-Propanol, 1,1'-iminobis- (9CI) 2-Propanol, 1,1'-iminodi- (6CI, 7CI, 8CI) Bis(2-hydroxypropyl)amine Bis(2-propanol)amine Diisopropanolamine DIPA DIPA (alcohol) N,N-Bis(2-hydroxypropyl)amine 1-(2-hydroxypropylamino)propan-2-ol

Structural formula:

1.2 Composition of the substance

Stated in Confidential Annex

1.3 Physico-chemical properties

Physical state: organic, waxy or crystalline, colourless solid

Melting point: 44.5 - 45.5 °C at 101.3 kPa

Boiling point: 248 °C at 101.3 kPa

Relative density: 0.99 g/cm^3 at 20°C

Partition coefficient n-octanol/water (log value): - 0.79 at 20 °C

Water solubility: 1 000 g/L at 20 °C

Vapour pressure: 0.02 hPa at 20 °C

2 MANUFACTURE AND USES

2.1 Quantities

Aggregated tonnage (per year)

Stated in Confidential Annex

2.1.1 Manufacturing processes

Not relevant for this evaluation

2.2 Identified uses

2.2.1 Uses by workers in industrial settings

Due to a number of uses refer to the list on the ECHA website.

2.2.2 Use by professional workers

Due to a number of uses refer to the list on the ECHA website.

2.2.3 Uses by consumers

Due to a number of uses refer to the list on the ECHA website.

2.3 Uses advised against

2.3.1 Uses by workers in industrial settings advised against

No information available.

2.3.2 Use by professional workers advised against

No information available.

2.3.3 Uses by consumers advised against

No information available.

3 CLASSIFICATION AND LABELLING

3.1 Harmonised Classification in Annex VI of the CLP Regulation

Index No: 603-083-00-7

Chemical name: 1,1'-iminodipropan-2-ol

EC No: 203-820-9

CAS No: 110-97-4

Classification: Eye Irrit. 2; Hazard statement: H319: Causes serious eye irritation.

3.2 Self-classification

Not applied.

4 ENVIRONMENTAL FATE PROPERTIES

Not relevant for this evaluation.

5 HUMAN HEALTH HAZARD ASSESSMENT

Conclusions related to the concern

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

5.1.1 Non-human information

Oral absorption: 90%

No data available for oral absorption on DIPA, but based on read-across data on TIPA the default value was changed to 90%, which is accepted by evaluating MSCA.

Dermal absorption: 20%

Consideration for dermal absorption and excretion was addressed under SEv evaluation as part of evaluation endogenous formation of NDHPA concern in relation with NDHPA carcinogenicity potential (section 5.8).

Inhalation absorption: 100% (no data available)

Consideration for inhalation absorption was addressed under SEv evaluation as part of evaluation endogenous formation of NDHPA concern in relation with NDHPA carcinogenicity potential (section 5.8).

5.1.2 Human information

No data available.

5.1.3 Summary and discussion on toxicokinetics

Available study on toxicokinetics established the absorption of DIPA by dermal route.

The DIPA substance is slowly absorbed after dermal exposure. One fifth of the dose has the potential to be absorbed and is readily eliminated primarily in urine almost solely as unchanged DIPA after delay of several hours. No metabolites were identified.

In a sub-acute dermal toxicity study in rats no systemic toxicity was observed. In sub-chronic study the NOAEL is based on increased absolute kidney weight but relative kidney weight was similar to controls.

The information about oral absorption based on read-across data on TIPA enabled slight modification of the default value to 90%. There are no data for inhalation route, although available data on inhalation toxicity from publications indicate some signs of upper airways irritation, thus potential absorption.

5.2 Acute toxicity

5.2.1 Non-human information

5.2.1.1 Acute toxicity: oral

The studies on acute toxicity after oral administration result in LD50 ≥ 2000 mg/kg bw based on test substance.

5.2.1.2 Acute toxicity: inhalation

The available information on acute inhalation toxicity was used for exposure consideration. See section 5.8

5.2.1.3 Acute toxicity: dermal

The information from acute dermal toxicity study was used for the evaluation of the skin irritation potential. See section 5.3.1.

5.2.1.4 Acute toxicity: other routes

No data available.

5.2.2 Human information

No data available.

5.2.3 Summary and discussion of acute toxicity

The information on acute toxicity was used as supporting information for the evaluation skin irritation potential and for the exposure assessment (routes of exposure).

5.3 Irritation

5.3.1 Skin

All available results from dermal studies were used for evaluation of skin irritation potential:

Test guideline: according to OECD 404 (reliability 1)

Species: rabbit

Reference: [9]

MSCA Conclusion: non irritating

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Test guideline: equivalent or similar to OECD 404 (reliability 2)

Species: rabbit

Reference: [1]

MSCA Conclusion: Mean score for erythema in 2 tested animals from gradings at 24 and 48 hours after patch removal was 2,5. Data from this study are not sufficient for classification purpose.

***

Species: rabbit

Effect: mild, Class of compounds – Primary Irritant (S)

Reference: [19]

MSCA Conclusion: The following RTECS descriptor codes tumorigen, mutagen, reproductive effector, primary irritant, and human data do not represent an evaluation of the overall toxicity of a substance by NIOSH. They rather indicate the type(s) of toxicity data found in the substance record.

***

1. experiment

Dose level: no data (undiluted substance)

Species: rabbit

2. experiment

Dose level: no data (undiluted substance)

Species: rabbit

3. experiment

Dose level: no data (10% aqueous solution)

Species: rabbit

4. experiment

Dose level: no data (10% aqueous solution)

Species: rabbit

5. experiment

Dose level: no data (10% aqueous solution)

Species: rabbit

Reference: [5]

MSCA Conclusion: Undiluted DIPA and 10% aqueous solution of DIPA were applied to intact and abraded sites on the abdomens and to sites on the ears of rabbits. Hyperemia and necrosis or denaturation were observed in rabbits. No information on exposure time and scoring system is available. This information is not sufficient for classification purpose.

***

Species: human

Test type: patch test

Reference: [3]

MSCA Conclusion: No other information on test design is available. This information is not sufficient for classification purpose.

Weight of Evidence

QSAR

TOPKAT 6.2 Acyclics (acids, amines, esters) – negative or mild

Acute toxicity dermal

Test guideline: no guideline followed. Basic data on study design are given.

Species: rabbit

Reference: [20]

MSCA Conclusion: Skin irritation consisting of erythema and necrosis where pressure of stocks was present, was observed at all dose levels. The dose proportional to body weight is applied to the skin in dermal toxicity studies whereas a small fixed dose is applied in skin irritation studies.

Skin sensitization

Information on irritating properties from skin sensitisation tests cannot be used to conclude a specific classification regarding acute skin irritation but may be used in a WoE analysis.

Test guideline: Equivalent or similar to OECD 406, GLP study

Species: Guinea pig. The skin of guinea pigs is less sensitive than the skin of rabbits.

Reference: [6]

MSCA Conclusion: The dose 50% aqueous solution was the highest non-irritating concentration as this dose was used in the induction phase and in the challenge phase. But the skin of guinea pigs is less sensitive than the skin of rabbits.

Repeated dose toxicity, dermal

Test guideline: OECD 410, GLP study

Species: rat

Reference: [18]

Conclusion: NOAEL 100 mg/kg bw/day (local toxicity – dermal irritancy) was established for long-term exposure. This value corresponds to 0,8 mg/cm^2 assuming a body weight of 0,2 kg and as 25 cm^2 skin was exposed.

It should be recognised that prolonged contact with some substance may cause irritation. It is not clear whether inflammation resulting from repeated contact in experimental studies should require a substance to be classified as irritant, since the criteria provided only relate to inflammation occurring as a consequence of a 4 hours exposure.

5.3.2 Eye

Available information for eye irritation

Harmonised classification - Annex VI of Regulation (EC) No 1272/2008

International Chemical Identification: diisopropanolamine, 1,1'-iminodipropan-2-ol

Index number: 603-083-00-7

CLP classification: Eye Irrit. 2, H319

C&L notification

This database contains classification and labelling information on notified and registered substances received from manufacturers and importers. It also includes the list of harmonised classifications. But data in C&L database are not reviewed and the accuracy of the information is not verified.

***

Test guideline: according to OECD 404 (reliability 1)

Species: rabbit

Reference: [10]

MSCA Conclusion: irritating

***

Test guideline: equivalent or similar to OECD 405 (reliability 2)

Species: rabbit

Reference [1]

MSCA Conclusion: irritating

***

Species: rabbit

Effect: severe, Class of compounds – Primary Irritant (S)

Reference [19]

Conclusion: The following RTECS descriptor codes tumorigen, mutagen, reproductive effector, primary irritant, and human data do not represent an evaluation of the overall toxicity of a substance by NIOSH. They rather indicate the type(s) of toxicity data found in the substance record.

***

Test guideline: no data on the amount administered, duration of exposure or number of animals used in the test

Species: rabbit

Reference: [15]

MSCA Conclusion: Diisopropanolamine is moderately irritating and injurious to the eyes.

5.3.3 Respiratory tract

Not relevant for evaluation

5.3.4 Summary and discussion of irritation

The substance DIPA has a harmonized classification as Irritating to eyes (Category 2).

All available information for skin and eye irritation was evaluated. The results of reliable studies were compared with classification criteria.

The results of the Eye irritation 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.

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.

5.4 Corrosivity

Not relevant for this evaluation.

5.5 Sensitisation

5.5.1 Skin

Available information for skin sensitisation was evaluated.

Test guideline: according to OECD 406 (reliability 1), Buehler test

Species: guinea pig, male

Reference: [6]

Study conclusion: non sensitising

***

The indication of the skin sensitisation in response to DIPA exposure was reported in human studies:

Subject: Diisopropanolamine in Eyeshadow

Reference: [3]

Study Conclusion: No other information on test design is available. This information is not sufficient for classification purpose.

***

Contact dermatitis due to 1,1'-iminodi-2-propanol was observed in occupationally exposed workers. Weak sensitization was observed. [17]

***

In a repeated patch-test, Diisopropanolamine did not cause allergic or photoallergic dermatitis. [11]

5.5.2 Respiratory system

No data available.

5.5.3 Summary and discussion on sensitisation

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.

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

5.6 Repeated dose toxicity

5.6.1 Non-human information

5.6.1.1 Repeated dose toxicity: oral

The sub-chronic toxicity study was performed according to OECD Guideline 408 (GLP study).

The results of sub-chronic oral toxicity study were used as supporting information to evaluate the fertility toxicity potential.

See section 5.9.2.

5.6.1.2 Repeated dose toxicity: inhalation

No data available.

5.6.1.3 Repeated dose toxicity: dermal

The sub-acute toxicity study was performed according to OECD Guideline 410 (GLP study).

The results of sub-acute dermal toxicity study were used as supporting information to evaluate the skin irritation potential and fertility toxicity potential.

See section 5.3.1 and 5.9.2.

5.6.1.4 Repeated dose toxicity: other routes

No data available.

5.6.2 Human information

No data available.

5.6.3 Summary and discussion of repeated dose toxicity

No data are available on inhalation route. The results of sub-acute dermal toxicity study and sub-chronic oral toxicity study were used as supporting information to evaluate the skin irritation potential and fertility toxicity potential.

The NOAEL value 100 mg/kg bw/day from the sub-chronic oral toxicity and NOAEL value 750 mg/kg bw/day from the sub-acute dermal toxicity study were used as the dose descriptors for the exposure assessment.

5.7 Mutagenicity

5.7.1 Non-human information

No adverse effect was observed with respect to genetic toxicity in all performed *in vitro* and *in vivo* tests. Based on the available data no classification criteria have been met.

5.7.2 Human information

No data available.

5.7.3 Summary and discussion of mutagenicity

No adverse effect was observed with respect to genetic toxicity in all *in vitro* and *in vivo* performed tests. Based on the available data no classification criteria have been met.

5.8 Carcinogenicity

Endogenously synthesized 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.

As dermal toxicokinetics study revealed, the DIPA substance is slowly absorbed, one fifth of dose has potential to be absorbed and the absorption is followed by ready elimination primarily in urine almost solely as unchanged DIPA after delay of several hours. No metabolites were identified.

There are no data for absorption by inhalation route. The properties as low volatility, boiling point higher than 150°C and using substance as melt decrease probability of inhalation absorption, although DIPA is very soluble and can be detained in mucus, swallowed or pass through water pores due to Mw<200 and Kow favourable for passive diffusion.

Available data on inhalation toxicity from publications indicate some signs of upper airways irritation, but potential to dermal and inhalation exposure and absorption is decreased based on the nature of the evaluated substance.

In addition, the exposure is actively prevented by measures according to Part E due to classification of the substance as eye irritant and by using of the substance as melt. The substance concentration is less than 5% for most of uses.

These uses are not considered as critical given the circumstances of endogenous formation of NDHPA following the 4% conversion of the initial DIPA.

The major route of synthesis N-nitroso compounds could be in the stomach, but oral exposure to DIPA is not relevant for industrial uses and probably very unlikely for professional uses as well.
The measures for worker exposure in ESs from aggregated dossier addressed in chapter 9 are applied.
Cosmetics products are involved in registrant´s ESs but for personal cosmetic care, which usually contain 0.1-1% [7] the effects in relation with exposure were not proved as critical.

Detailed information is stated in Confidential Annex.

5.9 Toxicity for reproduction

5.9.1 Effects on fertility

5.9.1.1 Non-human information

No two-generation reproduction toxicity study is available for DIPA. The category based upon the functional group (isopropanol substituent(s) bonded to amine group) was created to fulfil the information requirement on reproduction toxicity.

The members of the category:

1-aminopropan-2-ol (MIPA), CAS 78-96-6

1,1´-iminodipropan-2-ol (DIPA), CAS 110-97-4

1.1´, 1´´-nitrilotripropan-2-ol (TIPA), CAS 122-20-3

The structural similarity is supported by the physico-chemical 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.

The justification for category including data matrix provided in the registration dossiers supports using of the results of one-generation study for TIPA and Combined Repeated Dose Toxicity study with Reproduction/Developmental Screening for MIPA.HCl to clarify the concern for fertility endpoint of DIPA.

Table 2: Data matrix for long-term toxicity studies*

	MIPA	DIPA	TIPA
	78-96-6	110-97-4	122-20-3
Repeated dose toxicity, oral (NOAEL in mg/kg bw/day)	*read-across*	100[a]	272[b]
Repeated dose toxicity, dermal (NOAEL in mg/kg bw/day)	-	750[c]	3000[c]
Reproduction toxicity (NOAEL in mg/kg bw/day)	1000[f]	*read-across*	609[d]
Developmental toxicity (NOAEL in mg/kg bw/day)	1000[f]	1000[e]	1000[e]

[a] 90-days study (rat)

[b] 102-104 days study (dog)

[c] 28-days study (rat)

[d] One-generation study (rat) - FDA guideline

[e] Prenatal developmental toxicity study (rat)

[f] Combined Repeated Dose Toxicity study with Reproduction/Developmental Screening for MIPA.HCl

*The complete registrant´s data matrix table is part of Confidential Annex.

Table 3: Available studies for long-term toxicity studies for DIPA, including read-across

Repeated dose toxicity study (28 days), dermal	NOAEL 750 mg/kg bw/day
Repeated dose toxicity study (90 days), oral	NOAEL 100 mg/kg bw/day
Reproduction screening	*read across* – MIPA.HCl (NOAEL 1000 mg/kg bw/day)
One-generation reproduction study, oral	*read across* - TIPA (NOAEL 609 mg/kg bw/day)
Prenatal developmental toxicity study	NOAEL 1000 mg/kg bw/day

One-generation study with TIPA does not conform to the OECD test guideline referred to the REACH Annex but nevertheless provides suitable level of information for the evaluating Member

State to clarify the concern. The derived NOAEL from this study is based on the highest dose tested.

The 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 for fulfilment fertility endpoint.

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 category are sufficient for the evaluating Member State to clarify the concern with respect to fertility toxicity of DIPA.

Hypothesis for the derivation of NOAEL for DIPA with respect to fertility toxicity

The trend in the established category is the decreasing mammalian toxicity with increasing molecular weight. The NOAEL values for DIPA are approximately one third of the values determined in TIPA studies. Based on this assumption NOAEL for DIPA for fertility toxicity could be estimated 200 mg/kg bw/day.

Of course, this is hypothesis, but is based on no truly serious effects related to TIPA studies. Such information is not expected from the two-generation study that significantly alters an exposure assessment. Exposure assessment is based on value from 90-day repeated dose toxicity study on DIPA, which is only 100 mg/kg bw/day. This value is determined based on increased kidney weight, which is the only observed effect and for this dose a NOAEL is laid down because of the absolute weight even though relative kidney weight was similar to controls.

In this study, no effects were observed on reproductive organs as there were not observed any signs in gross pathology or histopathology (non-neoplastic or neoplastic).

Exposure considerations in relation to the reproductive toxicity

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.

No evidence of toxicity

The toxicity symptoms were in sub-chronic oral study based only on increased absolute not relative weight of kidney. NOAEL on male is the lowest testing value but still based on not truly serious effects.

The DIPA substance was not classified as acutely toxic as well as for chronic toxicity based on repeated toxicity studies.

In a sub-acute dermal toxicity study in rats no systemic toxicity was observed (NOAEL 750 mg/kg bw/day (the highest dose tested) were established).

In a sub-chronic oral toxicity study the increased absolute and relative kidney weights were observed in the 500 mg/kg bw/day group for males and females as the only effect without subsequent histopathological findings. The mean relative kidney weights were increased (by 12%) more for males. In the 100 mg/kg bw/day male group absolute kidney weights were increased but the relative kidney weights were not statistically different than controls (NOAELs of 100 and 500 mg/kg bw/day were established for males and females, respectively).

Finally, no adverse effect was observed in genotoxicity tests as well as no differences in tumour incidence were observed between controls and rats (male) in dietary carcinogenicity study.

No systemic absorption

In a sub-acute dermal toxicity study in rats no systemic toxicity was observed and in sub-chronic study the NOAEL is based on increased absolute kidney weight but relative kidney weight was similar to controls.

Study on toxicokinetics stated the slow absorption of one-fifth from exposure dose by dermal route but is followed by ready elimination of DIPA after delay of several hours primarily in urine. No metabolites were identified. An analysis of the urine by LSC indicated that over 99% of the radioactivity in the urine was unchanged ^{14}C DIPA.

As the substance has irritating potential, there are the measures implemented, which prevent dermal absorption and consequently potential risk for systemic absorption and even toxicity on fertility arising from the eventual dermal absorption of the substance.

This applies especially for rather open processes, where it is assumed in addition to eye protection and gloves also overall protection.

Available data on inhalation toxicity from publications indicate some signs of upper airways irritation, but potential to dermal and inhalation exposure and absorption is decreased based on the nature of the evaluated substance.

Inhalation exposure was addressed above in section 5.8 and taken into account physico-chemical data. Data on toxicokinetics after intravenous administration and dermal absorption proved the fast start of elimination with slower rate at the end of study (concentration in plasma was under LOD after 12h with maximal peak after 0.5 h after i.v. administration).

But even if it is fully absorbed, exposure assessment is calculated with the default value for absorption 100% by inhalation and based on NOAEL of 100 mg/kg bw/day. Further, DIPA does not accumulate and it is not expected that new data would reveal lower NOAEL on the basis of which the exposure assessment would need to be modified.

No or no significant human exposure in accordance with the PROCs

See sections Endogenously synthesized NDHPA and High worker exposure and high RCR which both addressed exposure circumstances. Futher details about the applied measures for worker exposure are addressed in chapter 9.

5.9.1.2 Human information

No data available.

5.9.2 Developmental toxicity

5.9.2.1 Non-human information

Test guideline: OECD 414 (GLP study)

Species: rat

MSCA Conclusion: The Prenatal Developmental Toxicity study for DIPA is available. The GLP study was performed according to the method OECD 414. No deviations from the guideline are reported.

Available information on prenatal developmental toxicity is sufficient for the conclusion on the classification. The classification of DIPA with respect to developmental toxicity is not warranted.

5.9.2.2 Human information

No data available.

5.9.3 Summary and discussion of reproductive 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 at the endpoint on reproduction toxicity.

One-generation study with TIPA does not conform to the OECD test guideline referred to the REACH Annex 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.

Available information on prenatal developmental toxicity is sufficient for the conclusion on the classification. Based on this information classification of DIPA is not warranted with respect to developmental toxicity.

5.10 Endocrine disrupting properties

No data available.

5.11 Other effects

No data available.

5.12 Combined effects

No data available.

5.13 Derivation of DNEL(s) / DMEL(s)

MSCA concluded that DNEL(s) in exposure assessment provided in lead registrant dossier are accepted.

5.13.1 Quantitative descriptor for critical health effects

The NOAEL value 100 mg/kg bw/day from the sub-chronic oral toxicity and NOAEL value 750 mg/kg bw/day from the sub-acute dermal toxicity study were used as the dose descriptors for the exposure assessment. Assessment factors were revised and accepted.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO CHEMICAL PROPERTIES

Not relevant for this evaluation.

7 ENVIRONMENTAL HAZARD ASSESSMENT

Not relevant for this evaluation.

8 PBT AND VPVB ASSESSMENT

Not relevant for this evaluation.

9 EXPOSURE ASSESSMENT

Risk assessment

It is stated by registrants that updated assessment was performed after the thorough discussion with technical workers. The substance is assessed now as aqueous solution or as slightly warmed-up substance more like to waxy texture than high dustiness solid as the substance was assessed earlier before update. 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 performed a higher tier assessment by EasyTRA Tool and ART tool (inhalation exposure) with consideration following parameters:

- the change from high to low dustiness
- influence the vapour pressure
- revision of concentration ranges

The EasyTRA Tool uses the highest number of predefined SpERCs which better represent operational conditions and potential exposure.

ART tool (Advanced REACH Tool) enables more refined estimates of inhalation exposure and reduced uncertainty.

The exposure assessment was overviewed over Contribution Scenarios 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 the downstream users to choose the most corresponding safe use and eventually adjust their current conditions in appropriate way by variations of OCs and RMMs (gloves plus indoor RPE/no RPE or outdoor RPE/no RPE, LEV/no LEV, limited working time, etc.)

In most of the cases the SpERCs were utilized and a tool for refinement of inhalation exposure (ART) was used for contribution scenarios (CSs) described by PROC 7 and PROC11 (Industrial spraying and Non-industrial spraying resp.) and PROC 17 or PROC18 (Lubrication or Greasing at high energy conditions resp.)

Therefore higher RCR in previous registrant´s CSR for specific process PROC 11 non-industrial spraying is assumed as refined now. In the previous version it was stated in the introduction to exposure assessment that for the dustiness it is assumed default value “high” and it was meant as “worst case”.

Updated risk assessment results in safe RCRs. Only two cases represent RCRs combined routes > 0.8 in relation with type of PROC or if uses vary in using PPE within specific PROC.

No classification is applied if the DIPA concentration in the mixtures is < 10%. For worker exposure to the pure substance risk management measures according to Part E guidance on Qualitative Risk Characterisation related with low hazard band are applied as the substance is classified as Eye Irritant. Qualitative Risk Characterisation is generally based on minimization opportunity to exposure by organizational conditions and general risk management measures and PPE (good practices, goggles, shield, gloves, overall).

When applying measures stated above, the risk of irritation is considered as controlled for PROC 1, 2, 3, 8b, 9 and 15. Those processes are regarded in general as closed and during process PROC 15 the samples are in a waxy state.

Exposure is unlikely and eventually non-significant for these PROCs. However for rather open processes PROC 4, 5, 8a, 19 the probability of exposure together with frequency and intensity increases, but the probability is still low with measures according to Part E.

The substance is not classified, when its concentration is less than 10%, therefore no qualitative assessment for irritating effects on the eyes is needed to be performed for relevant ESs with concentration up to 5%. However, for PROCs with increased possibility of exposure the preventive measures are applied anyway and variations for specific PROCs (general measures as ventilation, gloves, RPE, indoor/outdoor) are available as well.

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11 ABBREVIATIONS

BHP	Nitrosobis(2-hydroxypropyl)amine, *equivalent NDHPA*
BSA	Body Surface Area
CLP	Classification, labelling and packaging
CoRAP	Community Rolling Action Plan
CS	Contribution Scenario
DHPA	Bis(2-hydroxypropyl)-amine, *equivalent DIPA*
DIPA	1,1'-iminodipropan-2-ol, *equivalent DHPA*
DNEL	Derived No Effect Level
EA	Exposure Assessment
EBA	Exposure based adaptations
ECHA	European Chemical Agency
ES	Exposure Scenario
HSDB	Hazardous Substances Data Bank
IUCLID	International Uniform Chemical Information Database
LOQ	Limit of quantification
LR	Lead registrant
LSC	Liquid-Solid Chromatography
MIPA	1-aminopropan-2-ol
NDHPA	N-nitroso-bis(2-hydroxy-propyl)amine, *equivalent BHP*
NOAEL	No Observable Adverse Effect Level
OECD	Organisation for Economic Co-operation and Development
PROC	Process Category
RCR	Risk Characterisation
RDT	Repeated Dose Toxicity
RMM	Risk Management Measure
RMO	Risk Management Option
RPE	Respiratory Protective Equipment
SEV	Substance Evaluation
SIDS	Screening Information Data Set
TIPA	1.1´, 1´´-nitrilotripropan-2-ol