EUROPEAN CHEMICALS AGENCY

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DECISION ON SUBSTANCE EVALUATION PURSUANT TO ARTICLE 46(1) OF REGULATION (EC) NO 1907/2006

For 2,2'-Iminodiethanol - CAS No 111-42-2 (EC No 203-868-0)

Addressees: Registrants of 2,2'-Iminodiethanol (concerned registrants)

This decision is addressed to all Registrants of the above substance with active registrations on the date on which the draft for the decision was first sent, with the exception of the cases listed in the following paragraph. A list of all the relevant registration numbers subject to this decision is provided as an annex to this decision.

Registrants meeting the following criteria are not addressees of this decision: i) Registrants who exclusively use the above substance as an on-site isolated intermediate and under strictly controlled conditions and ii) Registrants who have ceased manufacture/import of the above substance in accordance with Article 50(3)of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation) before the decision is adopted by ECHA.

Based on an evaluation by the Federal Institute for Occupational Safety and Health (BAuA) as the Competent Authority of Germany (evaluating MSCA), the European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 52 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

This decision does not take into account any updates of the registrations of the concerned registrants after 5 September 2013, the date upon which the draft decision was circulated to the other Competent Authorities of the Member States and ECHA pursuant to Article 52(1) of the REACH Regulation.

This decision does not imply that the information provided by the concerned registrant in the registrations is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on the dossiers of the concerned registrants at a later stage, nor does it prevent a new substance evaluation process once the present substance evaluation has been completed.

I. Procedure

Pursuant to Article 45(4) of the REACH Regulation the Competent Authority of Germany has initiated substance evaluation for 2,2'-Iminodiethanol (DEA), CAS No 111-42-2 (EC No 203-868-0) based on registration dossiers submitted by the addressees (concerned registrants) and prepared the present decision in accordance with Article 46(1) of the REACH Regulation.

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to: Human health/Potential formation of CMR transformation products; Exposure/Wide dispersive use, high aggregated tonnage was included in the Community rolling action plan (CoRAP) for substance evaluation pursuant to Article 44(2) of the REACH Regulation to be evaluated in 2012. The updated CoRAP was published on the ECHA website on 29 February 2012. The Competent Authority of Germany "evaluating MSCA" was

appointed to carry out the evaluation. In the course of the evaluation, the evaluating MSCA noted additional concerns regarding the human health effects of the substance.

The evaluating MSCA considered that further information was required to clarify the above mentioned concerns. Therefore, it prepared a draft decision pursuant to Article 46(1) of the REACH Regulation to request further information. It submitted the draft decision to ECHA on 28 February 2013.

On 4 April 2013 ECHA sent the draft decision to the concerned registrants and invited them pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

By 6 May 2013 ECHA received comments from concerned registrants of which it informed the evaluating MSCA without delay.

The MSCA considered the registrants' comments received and amended the draft decision.

In accordance with Article 52(1) of the REACH Regulation, on 5 September 2013 the evaluating MSCA notified the Competent Authorities of the other Member States and ECHA of its draft decision and invited them pursuant to Articles 52(2) and 51(2) of the REACH Regulation to submit proposals to amend the draft decision within 30 days.

Subsequently, one Member State Competent Authority and ECHA submitted proposals for amendment to the draft decision.

On 11 October 2013 ECHA notified the concerned registrants of the proposals for amendment to the draft decision and invited them pursuant to Articles 52(2) and 51(5) of the REACH Regulation to provide comments on those proposals for amendment within 30 days of the receipt of the notification.

The evaluating MSCA has reviewed the proposals for amendment and amended the draft decision accordingly.

On 21 October 2013 ECHA referred the draft decision to the Member State Committee.

On 11 November 2013 the Registrants provided comments on the proposed amendments. The Member State Committee took into account the comments the Registrants made on the proposals for amendment. However, the Member State Committee did not consider the Registrant's comments that were not related to the proposals for amendment.

After discussion in the Member State Committee meeting on 10-13 December 2013, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 12 December 2013. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Information required

A. Test on the registered substance

Pursuant to Article 46(1) of the REACH Regulation registrants shall submit the following information using the indicated test method and the registered substance:

1. Extended One Generation Reproductive Toxicity Study in rats, oral route, according to test method OECD TG 443 with the developmental neurotoxicity and immunotoxicity (DNT/DIT) cohorts but without the extension of Cohort 1B to mate the F1 animals to produce an F2 generation.

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B. Information on a transformation product of the registered substance to be reflected in the CSR

Pursuant to Article 46(1) of the REACH Regulation the registrants shall also submit the following information on a transformation product of the registered substance in a revised version of the chemical safety report:

2. Perform an exposure assessment and risk characterisation for the carcinogenic transformation product 2,2'-(nitrosoimino)bisethanol (NDELA), CAS No 1116-54-7 (EC No 214-237-4) resulting from the manufacturing and use of the registered substance in particular downstream use(s).

3. Exposure assessment and risk characterisation to the carcinogenic transformation product 2,2'-(nitrosoimino)bisethanol (NDELA), CAS No 1116-54-7 (EC No 214-237-4) for consumer use.

C. Information on the registered substance to be reflected in the CSR

Pursuant to Article 46(1) of the REACH Regulation the concerned registrants shall submit the following information on the registered substance in a revised version of the chemical safety report:

4. Conduct a higher tier exposure assessment for dermal and inhalation exposure in accordance with the procedure laid down in the 'REACH Guidance on Information Requirements and Chemical Safety Assessment', Chapter R.14 and a risk assessment in accordance with the procedure laid down in Part E for particular exposure scenarios with Risk characterisation ratio (RCR) > 1.

5. Provide a higher tier exposure assessment for dermal exposure in accordance with the procedure laid down in the 'REACH Guidance on information requirements and chemical safety assessment', Chapter R.14 and a risk assessment in accordance with the procedure laid down in Part E for the use of 2,2' Iminodiethanol in metal working fluids involving moving objects (e.g. rotating machinery parts) during which wearing gloves comprises a risk of entanglement.

6. Provide information on personal protective equipment regarding the type of material, thickness and breakthrough times of the gloves and the duration of use for all exposure scenarios where the use of gloves is advised.

7. Information on operational conditions, exposure estimations and risk characterisation for exposure scenarios related to consumer products and articles.

Pursuant to Article 46(2) of the REACH Regulation, the concerned registrants shall submit to ECHA by 25 May 2015 an update of the registration dossiers containing the information required by point 2-7 of Section II. The remaining information, listed under point 1 of this Section II, shall be submitted in an update of the registration dossiers by 25 May 2016 from the date of the decision.

At any time, the concerned registrants shall take into account that there may be an obligation to make every effort to agree on sharing of information and costs with other registrants.

III. Statement of reasons

Based on the evaluation of all relevant information submitted on DEA and other relevant and available information ECHA concludes that further information is required in order to enable the evaluating MSCA to complete the evaluation of whether the substance constitutes a risk to human health.

During the consultation phase the lead registrant submitted separately an updated list of identified uses collected within the Ethanol-amines Consortium and other members of the SIEF. However, this information was not included in a dossier update. Thus, the decision still addresses the identified uses given in the available registration dossiers as to 05 September 2013. The expected update of the registration dossiers on the basis of this decision does not need to fulfill requirements for uses which are no longer supported by the registrants.

The evaluating MSCA has noticed that the new list does not reflect service life in articles, e.g. rubber articles. Therefore, the registrants shall review whether the new list contains all relevant service life stages of the substance.

A. Test on the registered substance

Therefore, pursuant to Article 46(1) of the REACH Regulation, the concerned registrants are required to carry out the following study using the registered substance subject to this decision:

1. Extended One Generation Reproductive Toxicity Study in rats, oral route, according to test method OECD TG 443 with the developmental neurotoxicity and immunotoxicity (DNT/DIT) cohorts but without the extension of Cohort 1B to mate the F1 animals to produce an F2 generation.

There is concern for reproductive toxicity. This has been noted as an additional concern by the evaluating MSCA in the course of this substance evaluation.

The registrants did not present any study results needed for the evaluation of effects of DEA on the complete reproductive cycle. Thus the evaluation of pre- and postnatal effects of the registered substance on development is not possible and a thorough evaluation of systemic toxicity in pregnant and lactating females and young adult offspring cannot be performed. This information shall be present in the technical dossier to clarify the risk on reproductive toxicity. Furthermore the information is necessary for meeting standard information requirements.

The registrants have provided a read-across from a structurally related substance, monoethanolamine (MEA), for which a two-generation study is available. Also a robust study summary for this test was provided in the technical dossier. In addition, short reference (without a detailed study summary) was made to a reproductive toxicity screening assay with triethanolamine (TEA).

In the view of the evaluating MSCA, these data are not sufficient to assess the concern for reproductive toxicity from the registered substance.

The information on read-across provided by the registrants does not meet the requirements of the general rules for adaptation of the standard testing regime. In particular, the registrants failed to demonstrate that apart from the structural similarity, the physicochemical and toxicological properties of source and target compound are sufficiently similar to allow the proposed read-across approach. Consequently, there is an information gap and it is necessary to generate the data for this endpoint. The need for such data is

further underlined by the fact that the available repeated dose toxicity studies in rats have shown adverse effects of the registered substance on the male reproductive system. These adverse effects on fertility to the male reproductive system were found at 202 mg/kg bw/d after oral application (sub-chronic drinking water study, rat, NOAEL 48 mg/kg bw/d, and LOEL 97 mg/kg bw/d) and 0.4 mg/L, 6h/d following inhalation (sub-chronic inhalation toxicity study, rat). Following repeated oral exposure for 13 weeks, there were decreases in testis and epididymis weights associated with degeneration of seminiferous epithelium and with reduced sperm motility and hypospermia in the cauda epididymis, and degeneration of the seminiferous tubules. Diffuse testicular atrophy and minimal atrophy of the prostate were observed after repeated exposure by inhalation for three months.
These findings alone are not sufficiently robust for risk assessment as only adult animals have been studied.

The registrants also indicate that "Accumulation of DEA at high levels in liver and kidney is assumed by a mechanism that normally conserves ethanolamine, a normal constituent of phospholipids. DEA is incorporated as the head group to form aberrant phospholipids, presumably via the same enzymatic pathways that normally utilize ethanolamine". From there it cannot be ruled out that the substance can be released during lactation.

An Extended One Generation Reproductive Toxicity Study shall be the method of choice to address the information gaps for the following reasons:

The OECD test guideline for an Extended One Generation Reproductive Toxicity Study (EOGRTS, OECD TG 443) has been adopted by the OECD Council on 28 July 2011. Consequently, the OECD TG 443 is now an internationally accepted test method. According to Article 13(3) of the REACH Regulation it can be applied to generate information on intrinsic properties of a substance.

The observed testis toxicity giving concern on fertility effects, the presumed mode of action via incorporation of DEA to essential components of the cells and the clarification of lactation effects will be covered by the proposed EOGRTS.

Moreover, several tests with DEA have shown its potential to cause neurotoxic effects in mammals. The OECD TG 443 offers the possibility to address these effects by including a DNT (Developmental Neurotoxicity) cohort. The assessment of the developing nervous system in addition to the development of the reproductive system is a major improvement in assessing the hazardous properties of the registered substance in particular in relation to sensitive life stages, e.g. the developmental life stage.
The available data have shown that DEA may affect the immune system of adult rats and mice. But the evaluation of the potential impact of DEA exposure on the developing immune system was not assessed. The OECD TG 443 provides the opportunity to address the possible effects by including a DIT (Developmental immunotoxicity) cohort.

Therefore, testing according to OECD TG 443 is requested here with an explicit reference to the assessment of the DNT/DIT cohorts.

The registrants have agreed to perform the EOGRTS (OECD TG 443, oral, rat) with the developmental neurotoxicity and immunotoxicity (DNT / DIT) cohorts without the extension of Cohort 1B to mate the F1 animals to produce an F2 generation.

B. <u>Information on a transformation product of the registered substance to be reflected in the CSR</u>

Pursuant to Article 46(1) of the REACH Regulation the registrants shall also submit the following information on the degradation product of the registered substance subject to the present decision in a revised version of the chemical safety report:

2. Perform an exposure assessment and risk characterisation for the carcinogentic transformation product NDELA, CAS No 1116-54-7 (EC No 214-237-4) resulting from the manufacturing and use of the registered substance in particular downstream use(s).

Secondary amines react with nitrosating agents to N-nitrosamines. Nitrosating agents are ubiquitously found in the air at the workplace.
Areas in which state of the art technology will inevitably lead to the formation and potential release of carcinogenic N-Nitrosamines of category 1A or 1B:

- metal industry and metal processing industry
- rubber industry
- chemical industry manufacturing/using secondary amines
- leather industry
- foundries and others [1]

Article 44 of the REACH Regulation states that a criterion for the prioritisation for further evaluation is that the transformation product of a substance has properties of concern. It is well known that DEA forms NDELA when reacting with nitrosating agents. NDELA is classified as Carc. 1B, H350 according to Annex VI of the CLP Regulation (EC) No. 1272/2008. Nitrosating agents are ubiquitous in the environment and their occurrence at the workplace in particular is frequently unavoidable.[1] NDELAis a non-threshold carcinogen meaning that any exposure comprises a risk.
A number of publications show that NDELA I is formed under real work conditions and is even detected in biological samples of workers handling metal working fluids.[2] In Germany a number of recognised and indemnified cases of occupational diseases related to N-nitrosamine exposure exist (internal communication with German Social Accident Insurance (DGUV), 2010). This information leads to the initial concern.

The manufacture and use of DEA leads inevitably to the formation of the non-threshold carcinogen NDELA meaning that the use comprises a risk which may not be adequately controlled. The possibility of NDELA formation is not addressed in the CSR. A recommendation to avoid contact to nitrosating agents in the guidance on safe use is not sufficient, as nitrosating agents are a ubiquitous part of the air. In all registration dossiers an evaluation of the cancer risk arising from exposure to NDELA, the derivation of tolerable risk levels (DMEL values) for workers, a risk characterisation and the recommendation of appropriate risk management measures are missing. For each use that registrants identify and address in their exposure scenarios they are oblidged to identify and apply and/or recommend the appropriate measure to adequately control the risk. This was not addressed in the given registration dossiers.

During substance evaluation a preliminary exposure assessment and risk characterisation based on available measurement data from the literature were performed (see below). The estimated values are above the indicative tolerable risk levels announced in the REACH Guidance Document of 1 : 100 000. These estimations can only be judged as preliminary

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[1] Committee on Hazardous Substances (AGS), The German Technical Rule for Hazardous Substances 552: N-nitrosamines, 2007.
[2] Spiegelhalder, B., Preussmann, R. and Hartung, M.: Biological monitoring in the metal working industry. IARC Sci. Publ., 57:943-946, 1984
Wolf, D.: N-Nitrosamine am Arbeitsplatz. Staub - Reinhaltung der Luft, 49(Nr. 6):183-186, 1989
Jarvholm, B., Zingmark, P.A. and Osterdahl, B.G.: N-nitrosodiethanolamine in commercial cutting fluids without nitrites. Ann. Occup Hyg., 35(6):659-663, 1991
Monarca, S., Scassellati, S.G., Spiegelhalder, B., Pasquini, R. and Fatigoni, C.: Monitoring nitrite, N-nitrosodiethanolamine, and mutagenicity in cutting fluids used in the metal industry. Environ. Health Perspect., 101(2):126-128, 1993
Fadlallah, S., Cooper, S.F., Perrault, G., Truchon, G. and Lesage, J.: N-Nitroso Compounds in the Ambient Air of Metal Factories Using Metal-Working Fluids. Bulletin of Environmental Contamination and Toxicology, 57(6):867-874, 1996
Breuer, D., van Gelder, R.: Nitrosamine in Arbeitsbereichen - ein gelöstes Problem? Gefahrstoffe - Reinhaltung der Luft, 61(Nr. 1/2):49-55, 2001
BGIA: B.I.f.A. N-Nitrosamine 9103. 4. Lfg(VIII), 2003;
Breuer, D.: N-Nitrosamine in Korrosionsschutzfolien oder Korrosionsschutzpapieren. IFA-Arbeitsmappe, Kennziffer 8175(IV Lfg.30), 2003
Ducos, P. and Gaudin, R.: N-nitrosodiethanolamine urinary excretion in workers exposed to aqueous metalworking fluids. Int. Arch. Occup Environ. Health, 76(8):591-597, 2003

since the underlying data may not reflect the current situation in the EU. As a result, it can not be concluded, whether an unacceptable community wide risk exists, which needs further risk management measures. Therefore the level of the NDELA shall be determined on the basis of realistic workplace measurements which are representative for the whole European Union for all identified uses.

The registrants are required to perform an exposure assessment and risk characterisation for the carcinogentic transformation product NDELA, CAS No 1116-54-7 (EC No 214-237-4) resulting from the manufacturing and use of the registered substance in particular downstream use. As basis for the exposure assessment the registrants shall generate and provide realistic and representative workplace measurement data for all exposure scenarios and corresponding PROCs in accordance with 'REACH Guidance on Information Requirements and Chemical Safety Assessment', Chapter R.14. Measurements have to be conducted for the full work-shift. In cases where adequate measurements are already available from company monitoring programmes or from the literature the exposure assessment can be based on these. If the registrants can provide a worst case assessment for a use which covers the operational conditions and risk management measures of other uses the corresponding results can be used.

In order to characterise the formation of NDELA during manufacture and use of the registered substance, the following parameters shall be collected and provided in the documentation where applicable:

- country
- company size: in accordance with Commission Recommendation 2003/361/EG
- number of exposed workers
- number of measurements per exposure scenario (ES): according to R.14
- process temperature
- pH-value
- age of the used mixture
- concentration of DEA in mixture
- nitrite concentration in mixture
- concentration of inhibitors for nitrosamine formation in mixture (e.g. primary amines)
- concentration of nitrogen oxides in the air

N-nitrosamine formation depends on good work practice and all applied risk management measures. The better a mixture containing a secondary amine is maintained, the less N-nitrosamine formation takes place.
The listed parameters are known to influence the amount of N-nitrosamine formation. It is well known that these parameters significantly differ between different workplaces. Therefore they have to be assessed to judge, if real work place conditions which are representative for the European Union were chosen. They have to be regarded when applying or recommending appropriate operational conditions and measures for the identified uses.

The exposure assessment regarding NDELA shall be based on measurement data and not only modelled data for all given scenarios. The reaction of secondary amines and nitrosating agents depends on a variety of different factors (e.g. the concentration and properties of the precursors, process parameters and external influences). Therefore it is not possible to predict the amount of the corresponding N-nitrosamine formed with the existing modelling tools.[3]

The requested information will allow a full evaluation whether the occupational risk associated with the carcinogenic transformation product NDELA can be controlled during

[3] Wolf, D.: N-Nitrosamine am Arbeitsplatz. Staub - Reinhaltung der Luft, 49(Nr. 6):183-186, 1989

manufacture and use of 2,2'-Iminodiethanol.

The registrants agree to perform an exposure assessment and risk characterisation for NDELA resulting from the manufacture. Furthermore, they propose to use literature data to communicate occupational exposure limits and risk management measures to the downstream users. The eMSCA is of the opinion that the registrants have the duty to perform an exposure assessment and risk characterisation to choose adequate measures for downstream uses identified by the registrants. For transformation products exposure assessment based only on the existing modelling tools is not possible.[4]

Thus, the real exposure situation has to be addressed by measurements of NDELA. However, the registrants may not be able to enter downstream user premises to perform such measurements. Moreover, the registrants have claimed that there is not a method available on measuring dermal exposure to NDELA and proposed to conduct biomonitoring data instead.

Basically, if the registrants are unable to provide such information for reasons outside their own competence then the registrants, due to inability of establishing that the measures recommended to downstream users indeed enable the safe use of the substance, would need to withdraw the identified use. Consequently, a downstream user who wishes to continue the use of the substance would have to prepare his own chemical risk assessment and provide his downstream user report to ECHA if he wishes to have a use which is outside the scope of the registration (Article 37 of the REACH Regulation).

The eMSCA indicates that different ways exist to fulfil the requirement to perform an exposure assessment and risk characterisation for the carcinogenic transformation product NDELA:

A) Inhalation and dermal exposure assessment is addressed separately

Inhalation exposure assessment is based on inhalation exposure levels
a) from existing unpublished measurements by using personal sampling or
b) from measurement results taken from literature by using personal sampling or
c) obtained by new measurements by using personal sampling
or a combination of the above.

Dermal exposure assessment is based on dermal exposure levels
a) estimated as shown below on the basis of the measured concentration of NDELA in DEA or in mixtures containing DEA:
    i) from existing unpublished measurements or
    ii) from measurement results taken from literature or
    iii) obtained by new measurements or
b) on the basis of new exposure measurements which need to be developed in a way described below.
or a combination of the above.

The data used for inhalation and dermal exposure assessment shall be realistic and representative workplace measurement data for all exposure scenarios and corresponding process categories (PROCs) in accordance with 'REACH Guidance on Information Requirements and Chemical Safety Assessment', Chapter R.14.

B. Biomonitoring can be conducted

The Registrant(s) proposed biomonitoring as one option. The eMSCA agrees that in principle

[4] Wolf, D., N-Nitrosamine am Arbeitsplatz. Staub - Reinhaltung der Luft, 49 (Nr. 6):183-186, 1989

biomonitoring of NDELA is possible and a method to detect NDELA in urine is available.[5] This approach would be accepted instead of separate inhalation and dermal exposure assessment. In case this option is chosen the registrant shall describe the used biomonitoring approach in detail and prove that the used analysis method is valid by estimation of performance characteristics of analytical method. As reference an internal value based on the T25 value of 0.15 mg/kg bw/d need to be derived.

Notes for consideration by the registrants

In the following considerations to fulfil the given options are described more extensively and examples for the approach are given. During substance evaluation a preliminary exposure assessment and risk characterisation based on available measurement data from the literature were performed for the manufacturing process and the use of DEA in metal working fluids:

Exposure assessment

Considered area:
Manufacturing, filling and drumming of amines in the chemical industry

Inhalation exposure
According to the German Technical Rule "N-Nitrosamines" TRGS 552 a N-nitrosamine air concentration of 0.5 µg/m^3 can be achieved if the safety measures conform to the state of the art in 2007.[6] For this calculation, we assume that this exposure level is achieved in the whole EU.

Dermal exposure
An assessment of dermal exposure to NDELA during manufacturing of DEA was not possible due to missing information about the concentration of NDELA in DEA.

Considered area:
Use of Metal Working Fluids (MWF)

Inhalation exposure
Exposure to NDELA prior to the implementation of TRGS 611 in Germany was about 1 µg/m³ (95th percentile). After implementation of TRGS 611 exposure to N-nitrosamines from MWF was reduced to levels below 0,2 µg/m^3.[7]

Dermal exposure
No quantitative figures exists on dermal exposure to N-nitrosamines linked to occupational handling of MWF. However, the quantitative relevance may roughly be approximated by providing a very uncertain order of magnitude figures:

As a first approximation based on unpublished information of Kalberlah 2011, risk is calculated for estimated median exposure to MWF.[8] The RISKOFDERM calculator (version 2.1, January 2008) contains a model for the "mechanical treatment of solid objects", which refers to MWF and some other scenarios (e.g. sawing and carpentry and electroplating),

[5] Ducos, P. and Gaudin, R.: N-nitrosodiethanolamine urinary excretion in workers exposed to aqueous metalworking fluids. Int. Arch. Occup Environ. Health, 76(8):591-597, 2003

[6] Committee on Hazardous Substances (AGS), The German Technical Rule for Hazardous Substances 552: N-nitrosamines, 2007.
[7] Committee on Hazardous Substances (AGS), The German Technical Rule for Hazardous Substances 611. Restrictions on the use of watermiscible or water-mixed cooling lubricants whose use can result in the formation of N-nitrosamines, 2007
Breuer, D., van Gelder, R.: Nitrosamine in Arbeitsbereichen - ein gelöstes Problem? Gefahrstoffe - Reinhaltung der Luft, 61(Nr. 1/2):49-55, 2001
[8] Kalberlah, unpublished data, preliminary title: Investigation of the Exposure to Carcinogenic N-Nitrosamines from Metal-working Fluids and Corrosion Inhibitors in Various Processes and Sectors of Industry, to be Identified and Described Regarding their Economic Importance, and Identification of N-Nitrosamine Precursors, 2011

with the MWF data being based on the paper by Roff et al. (2004).[9] This model does not allow calculating dermal exposure to the hands due to lacking/unreliable data. Empirical data, while indicating higher loading rates for the hands than the rest of the body, are available only for one individual as actual dermal exposure (inside protective gloves, seven data points) of questionable validity, e.g. due to possible saturation of the protective gloves and removal of the protective gloves so that the sampling gloves may have become wet (Roff et al., 2004).[6] Using the most conservative assumptions (i.e. no local exhaust ventilation, short distance to source (up to one arm's length), frequent or constant contact etc.) and assuming the maximum cumulative spray duration of a shift inside the applicability domain of the model (214 min.), the median potential body load (excluding hands) is calculated to be 9,920 mg/d (or 530 µg/cm^2 x d with the assumed surface area of 18,720 cm^2). This potential dermal exposure can also be converted to a dose of 141.7 mg/kg x d using a body weight of 70 kg. This value is almost identical to the maximum dermal exposure assumed for PROC 19 in ECETOC TRA (141.43 mg/kg x d), although the latter refers to hand exposure (assumed surface area of 1980 cm^2). As a conservative assumption, the RISKOFDERM value for body exposure (excluding hands) and the ECETOC TRA value for hand exposure are added, resulting in a total dermal exposure of 283 mg/kg x d (19810 mg/d).

These exposures relate to MWF and not to N-nitrosamines. In order to estimate dermal exposure to N-nitrosamines, the concentration of N-nitrosamines in MWF must be taken into account. An NDELA concentration in MWF of 1 ppm approximately represents the 90th percentile in the post-TRGS 611 period in Germany and also appears to represent a higher end estimate for nitrite-free MWF in other European countries.[10] On this basis of 1 ppm NDELA in MWF, potential dermal NDELA exposure is 0.283 µg/kg x d. If protective clothing is assumed to provide a protection by a factor of 10, actual dermal (body) exposure is reduced to 0.0283 µg/kg x d. Note that wearing protective gloves is not allowed during the operation of some machines. In these cases, a reduction of the hand exposure by a factor of 10 is not justified. Taking this into account the actual dermal exposure increases to 0.156 µg/kg x d.

DMEL derivation of NDELA – workers

In the consultation phase the registrants described their intended approach for DMEL derivation. The eMSCA proposes the following proceeding based on the risk characterisation of the Scientific Committee on Consumer Safety (SCCS) report:
It is suggested that the derivation of DMEL values follows the procedure laid out in the REACH Guidance on Information Requirements and Chemical Safety Assessment. For derivation of a DMEL for the non-threshold carcinogen NDELA the 'linearised' approach is applied. **Either the BMD(L)10 approach or the T25 approach can be used as a dose-descriptor.**
For the derivation of DMEL values for NDELA data from studies with animals shall be used. A justification for the selection of the study for the DMEL derivation should be given.
Below you will find the DMEL **derivation of NDELA for worker with the T25 approach**, performed by the eMSCA according to the REACH guidance on information requirements and chemical safety assessment (Chapter R8).

No long term inhalation cancer studies are available. The carcinogenic risk calculation has been performed by route-to-route extrapolation from oral studies.
For the calculation of the DMEL for NDELA the T25 of 0.60 mg/kg bw/d was used as point of departure obtained in the SCCS report Opinion on NDELA in Cosmetic Products and

[9] Roff M., Bagon DA., Chambers H. et al. (2004) Dermal exposure to electroplating fluids and metal working fluids in the UK. Ann Occup Hyg; 48:20917
[10] BGIA: B.I.f.A. N-Nitrosamine 9103. 4. Lfg(VIII), 2003
Järvholm, B.; Zingmark, P.A.; Österdahl, B.G. N-Nitrosodiethanolamine in commercial cutting fluids without nitrites, 1991
Ducos, P. and Gaudin, R.: N-nitrosodiethanolamine urinary excretion in workers exposed to aqueous Occup Environ. Health, 76(8):591-597, 2003

Nitrosamines in Balloons 2012.[11]
Dose response information are used from the following studies; Berger et al. (1990)[12], Hecht et al. (1989)[13], Lijinski et al. (1984)[14], Lijijnski and Kovatch (1985)[15], Preussmann et al. (1982)[16], Zerban et al. (1988)[17]. All studies are drinking water studies in rat with an exposure time from 50 to 130 weeks. The T25 is calculated for hepatocellular tumors from the experimental data as described by Dybing et al. 1997.[18] The T25 were calculated for each of the six rat studies and a range of T25 values between 1.05 and 3.21 was obtained. The mean T25 from this studies was 2.09 mg/kg bw/d corresponds to a human HT25 of 0.60 mg/kg bw/d estimated from the rat studies by using the scaling factor based on body weight to the power of ¾ as the following defaults are used (human 70 kg, male rats 0.5 kg, female rats 0.35 kg (ECHA 2008)[19].

The REACH Guidance on information requirements and chemical safety assessment (Chapter R8)[20] provides several examples and states that 'based on experiences, cancer risk levels 10^{-5} could be seen as indicative tolerable risk levels when setting DMELs for workers' respectively. Thus, the DMELs for inhalation and dermal exposure are:

Risk: inhalation exposure 1: 100 000	**DMEL 0.12 µg/m³**

Risk dermal exposure 1: 100 000	**DMEL 0.026 µg/kg bw/d**

Risk characterisation:

Considered Area:	Estimated exposure level	risk
1. Manufacturing, filling and drumming of amines in the chemical industry	Inhalation exposure post the implementation of TRGS 552: **0.5 µg/m³**	Risk: 4.3 : 100 000
1. Manufacturing, filling and drumming of amines in the chemical industry	Dermal exposure data missing	-
2. Use of Metal Working Fluids (MWF)	Inhalation exposure prior to the implementation of TRGS 611: **1 µg/m³**	Risk: 8.5 : 100 000
2. Use of Metal Working Fluids (MWF)	Inhalation exposure post to the implementation of TRGS 611: **0.2 µg/m³**	Risk: 1.7 : 100 000
2. Use of Metal Working Fluids (MWF)	Actual dermal exposure added RISKOFDERM and ECETOC TRA value	Risk: 1.1 : 100 000

[11] SCCS (Scientific Committee on Consumer Safety)/1486/12, Opinion on NDELA in Cosmetic Products and Nitrosamines in Balloons. Adopted by the SCCS during the 15th plenary meeting of 26 - 27 June 2012, EU 2012
[12] Berger MR, Schmähl D, Edler L (1990). Implications of the carcinogenic hazard of low doses of three hepatocarcinogenic N-nitrosamines. Jpn J Cancer Res; 81:598-606
[13] Hecht, et al., Comparative tumorigenicity of N-nitroso-2-hydroxymorpholine, N-nitrosodiethanolamine and N-nitrosomorpholine in A/J mice and F344 rats, Carcinogenesis 10(8):1475-7, 1989
[14] Lijinski, et al., Carcinogenesis in rats by some hydroxylated acyclic nitrosamines, Carcinogenesis 5: 167-170, 1984
[15] Lijinski and Kovatch, Induction of liver tumors in rats by nitrosodiethanolamine at low doses, Carcinogenesis 6:1679-168, 1985
[16] Preussmann, et al., Carcinogenicity of *N*-Nitrosodiethanolamine in Rats at Five Different Dose Levels, Cancer Research 42(12): 5167-5171, 1982
[17] Zerban, et al., Dose-time relationship of the development of preneoplastic liver lesions induced in rats with low doses of N-nitrosodiethanolamine, Carcinogenesis 9: 607 – 610, 1988
[18] Dybing, et al., T25: A simplified carcinogenic potency index. Description of the system and study of correlations between carcinogenic potency and species/site specificity and mutagenicity, Pharmacol Toxicol 80: 272-279, 1997
[19] ECHA, Guidance on information requirements and chemical safety assessment. Part E: Risk characterisation, 2008
[20] ECHA, Guidance on information requirements and chemical safety assessment. Chapter R.8: Characterisation of dose [concentration]-response for human health, 2010

	0.0283 µg/kg bw/d	
2. Use of Metal Working Fluids (MWF) without protective gloves	Actual dermal exposure added RISKOFDERM and ECETOC TRA value without protective gloves **0.156 µg/kg bw/d**	Risk: 6.2 : 100 000

The estimated values are above the indicative tolerable risk levels announced in the REACH Guidance Document of 1 : 100 000. These estimations can only be judged as preliminary since the underlying data may not reflect the current situation in the EU. As a result, it can not be concluded, whether an unacceptable community wide risk exists, which needs further risk management measures. Therefore the level of the NDELA shall be determined on the basis of realistic workplace measurements which are representative for the whole European Union for all identified uses.

The measurements especially concerning downstream user facilities may be conducted by a certified laboratory as an independent expert to avoid inconsistencies between measurement approaches and confidentiality issues.

Notes concerning dermal exposure measurements
The registrants claimed that there is no method available on measuring dermal exposure of NDELA. eMSCA would like to stress that although no ready to use substance specific method for the measurement of dermal exposure to NDELA in the workplace seems to be available, many methods do exist to evaluate skin exposures to chemicals. In this regards, the eMSCA would like to make reference to CEN/TS 15279-2006 workplace exposure - measurement of dermal exposure - principles and methods. This Technical Specification establishes principles and describes methods for the measurement of dermal exposure in workplaces. It gives guidance on the commonly used approaches to the measurement of dermal exposure, their advantages and limitations and how these might be assessed in specific circumstances for specific compounds. The CEN/TS 15279 should enable users of dermal sampling methods to adopt a consistent approach to method validation and provide a framework for the assessment of method performance. It describes the requirements against which sampling methods need to be assessed and indicates methods for agreement with these requirements. Requirements include specification of the following: sampling efficiency; recovery efficiency; sample stability; maximum capacity; bias, precision, overall uncertainty; core information; contextual information.

A practical example for the development of a substance specific method (PAH) for the measurement of potential dermal exposure is described in a study report of the Bundesanstalt für Arbeitsschutz und Arbeitsmedizin.[21] In this context a method, using whole body polyethylene overalls and gloves as dosimeters, was developed and validated. The registrants may use this example as orientation for their own development of a method for the measurement of dermal exposure to NDELA.

3. Exposure assessment and risk characterisation of the carcinogenic transformation product NDELA, CAS No 1116-54-7 (EC No 214-237-4) for consumer uses.

Pursuant to Article 46(1) of the REACH Regulation, the concerned registrants are requested to carry out a risk assessment of NDELA, CAS No. 1116-54-7 generated during the handling of consumer products and articles containing DEA. Such a risk assessment shall comprise an analysis of exposure levels in the context of the identified uses and a risk characterisation for consumers handling the respective products and articles.

[21] Schäferhenrich, A., Hebisch, R., Holthenrich, D., Krutz, K., Göen, Th., Messung von Hautbelastungen durch chemische Stoffe bei der Imprägnierung mit Holzschutzmitteln, Projekt F2053, BAuA, Dortmund, Berlin, Dresden 2012

According to Article 44(1) of the REACH Regulation, hazardous transformation products are within the scope of the substance evaluation.

As a secondary amine, DEA can be converted to a carcinogenic nitrosamine under favourable conditions (e.g., low pH and heat, microbial contamination, nitrogen oxides from air, nitrosating agents in the water added), in this case NDELA. There is convincing analytical evidence on the formation of NDELA from DEA in cosmetic products.[22] Moreover, the generation of this transformation product may also occur in other consumer products, e.g. finger paints and rubber balloons. There is evidence from monitoring data that the carcinogenic transformation product NDELA, is released in considerable amounts from rubber balloons[23] [24].

Therefore, it is expected that the carcinogenic transformation product NDELA will occur in other consumer products or articles containing DEA, and it inadvertently could lead to consumer health risks. Exposure assessments and risk characterisations shall be performed for consumer exposure to NDELA, resulting from use of DEA in consumer products including plastic and rubber articles.

No evaluation of the cancer risk from exposure to NDELA has been performed and no tolerable risk levels (DMEL values) for the general population have been deduced in the registration dossiers. Clarification is needed on the risks arising from NDELA as a hazardous transformation product of DEA. In detail, the registrants need to provide estimates of consumer exposure to NDELA resulting from the uses which they have identified in their CSRs in order to assess the additional carcinogenicity risk of exposed consumers.

<u>DMEL derivation of NDELA – general population</u>
The evaluating MSCA remarks that the derivation of DMEL values should follow the procedure laid out in the REACH Guidance on Information Requirements and Chemical Safety Assessment. For derivation of a DMEL for the non-threshold carcinogen NDELA the 'linearised' approach is applied. Either the BMD(L)10 approach or the T25 approach can be used as a dose-descriptor.

The evaluating MSCA recommends to use the study of Preussman et al. (1982) as it is the most suitable study for the calculation of the dose descriptors. In this study a significant number of animals with benign and malignant liver tumours (predominantly hepatocellular carcinomas and adenomas but also mesenchymal hemangioendotheliomas, cholangiofibromas and cholangiocarcinomas) was observed. Neoplasms in the nasal cavity (comprising squamous cell carcinomas and neuroepitheliomas) were also seen. The liver tumour data appears to be the most sensitive effect for the calculation.

Dermal contact, inhalation and also ingestion are relevant exposure routes for the general population. Therefore, the DMEL calculation for NDELA shall be performed for all three possible exposure routes. It is advised to use the following values for DMEL calculation:
for oral and dermal: total assessment factors (AF) of 4;
and for inhalation: route specific bioavailability of 50/100, standard respiratory volume of 0.8 L/min/kg, 24h, total AF of 1

The registrants have informed that an exposure assessment and risk characterisation for the carcinogenic transformation product NDELA will be performed for the remaining consumer scenario "use in concrete and cement".

However, the evaluating MSCA has noticed that as to 05 September 2013 the identified consumer uses given in the available registration dossiers have not been revised. Therefore,

[22] SCCS/1458/11. Opinion on Nitrosamines and Secondary Amines in Cosmetic Products. Adopted by the SCCS during the 13th plenary meeting of 13-14 December 2011
[23] http://www.kantonslabor-bs.ch/files/berichte/JBer_Luftballone_2010_EN.pdf
[24] U.Hauri, personal communication, 2012

the decision has not been amended.

Moreover, the revised use list does not reflect service life in articles, e.g. rubber articles. Industrial use of DEA as an additive in plastic, e.g. rubber, is still supported by the revised list of uses announced in the registrants´comments. This use may include the production of consumer articles made of plastic, e.g. rubber. If such uses are identified exposure assessments and risk characterisations shall be performed for consumer exposure to NDELA resulting from use of DEA in plastic, e.g. rubber.

Without the requested information it will not be possible to verify whether there remains an uncontrolled risk from this transformation product of the registered substance that should be subject to further risk management measures.

C. Information on the registered substance to be reflected in the CSR

Pursuant to Article 46(1) of the REACH Regulation the concerned registrants shall submit the following information on the registered substance in a revised version of the chemical safety report:

4. Conduct a higher tier exposure assessment for dermal and inhalation exposure in accordance with the procedure laid down in the 'REACH Guidance on Information Requirements and Chemical Safety Assessment', Chapter R.14 and a risk assessment in accordance with the procedure laid down in Part E for the exposure scenarios with RCR >1.

The registrants have estimated workplace exposure to DEA using the Tier 1 model ECETOC TRA V2.0 and RISKOFDERM V2.2 with non standard factors for glove efficiency without justification. In the registration dossiers for exposure estimation an efficiency of up to [redacted] % for the protective gloves is assumed for industrial and professional uses. This very high efficiency is not discussed any further. Such values are usually not considered realistic and are not justified within the documentation of the used model (e.g. ECETOC TRA V3 features for professional setting 80 % glove efficiency without employee training, 90 % with basic training, for industrial settings 90 % glove efficiency with basic training and 95 % with special training). The assumption of [redacted] % protection may lead to an underestimation of the exposure. The registrants state to provide additional data and recommendations on the recommended material for gloves (together with available break-through-times) in the CSR to corroborate a 95% efficiency together with practical and special training. Anyhow, if the registrants want to use glove efficiencies >90% in the risk assessment for professional users, this has to be justified on the basis of valid experimental studies.
The registrants agree to perform a higher TIER exposure assessment for dermal and inhalation exposure in case of critical exposure scenarios resulting in high risk where RCRs are greater than 1. They further state that the latest ECETOC Version No. 3 represents a state of the art exposure model and is appropriate to assess the majority of DEA uses (especially where no aerosol is being formed). The eMSCA states that since the logic behind the ECETOC TRA V3 only addresses exposure to the vapour phase a more clear distinction between aerosol and vapour exposure in the revised CSA may be useful as well. However, the eMSCA wants to point out that for all uses with RCRs >1 a higher Tier model is necessary not only for uses where exposure to aerosols is given.

In addition the registrants used the MAK value as threshold limit instead of deriving DNELs for worker. Firstly, this is not in agreement with 'REACH Guidance on Information Requirements and Chemical Safety Assessment', Chapter R.8, because the MAK value is not a national threshold limit. Secondly, the MAK value has been derived in view of local effects only and a systemic DNEL is lacking in the dossier. Thirdly, the dermal DNELs have been derived incorrectly. During consultation phase the registrant derived DNELs based on the NOAEC from the study also used by the eMSCA. The registrant followed the guidance

proposed by ECETOC. This is not accepted by the eMSCA, because this proceeding is not in accordance with the REACH guidance document, Chapter R.8. However, the eMSCA accepted the registrants specific justification to omit the assessment factor regarding remaining uncertainties. The corresponding DNEL inhalation long-term, local effects derived by the eMSCA, was adapted accordingly.

In consequence a recalculation of the registrants' exposure estimates using the standard factors of ECETOC TRA version 3 for glove efficiency was performed. For comparison of the exposure recalculated DNELs derived in accordance with the procedure laid down in REACH Guidance were used. Inhalation exposure estimates were not recalculated, but the values derived by the registrants were directly compared to the recalculated DNELs.

Calculated DNELs derived in accordance with 'REACH Guidance on Information Requirements and Chemical Safety Assessment', Chapter R.8

DNEL – inhalation long-term, systemic effects:	0.3 mg/m^3
DNEL - inhalation long-term, local effects:	0.15 mg/m^3
DNEL – dermal long-term, local and systemic effects:	0.053 mg/kg bw/d
DNEL-dermal long-term, local effects:	3 µg/cm^2

The combined (inhalation and dermal) risk characterisation ratios (RCRs) exceed the value of 1 in the scenarios stated below. It is to be expected that within the Tier I model the change of input parameters that reasonably reflect workplace conditions will still result in RCRs > 1 for the addressed scenarios.

The used Tier I model might lead to higher exposure estimates than the actual workplace exposure. The use of protection factors higher than the standard parameters is only valid, if an acceptable justification is given. This justification is missing for the protection factors used in the registration dossiers. Hence, it can not be concluded if the used protection factors are valid. These factors can only be determined by justification based on experiments regarding permeation through the glove fabric, penetration of the gloves and human factors. On the basis of the current information from the registration dossier a final conclusion on the risk can not be drawn.

Therefore the registrants are requested to conduct a higher tier exposure assessment for dermal and inhalation exposure in accordance with the procedure laid down in the 'REACH Guidance on Information Requirements and Chemical Safety Assessment', Chapter R.14 and a risk assessment in accordance with the procedure laid down in Part E for the following exposure scenarios with RCRs >1:

1. Manufacturing of DEA: PROC 2, 3, 4, 8a, 8b, 15
2. Formulation of products containing DEA: PROC 3, 5, 8a, 8b, 9
3. Use of DEA as an intermediate: PROC 2, 3, 8a, 8b, 9
4. Use as additive in concrete and cement (Professional) PROC 5, 8a, [redacted] 10, 13, 19, 21, 24
6. Processing aid for paper, textile, leather: PROC 7, 10, 13
7. Gas treatment: PROC 2, 3, 8a, 8b, 22
8. Use of DEA in metal working fluids: PROC 2, 3, 7, 8a, 8b, 10, 13, 17, 18
9. Use of DEA in detergents and cleaners (Industrial, Professional): [redacted] 7, [redacted] 10, 11, 13, 19
10. Use of DEA as additive in plastic (Industrial, Professional), e.g. rubber: PROC 14
11. Use of DEA as a laboratory chemical (Industrial, Professional): [redacted] 15
12. Use of DEA as additive in fuel: PROC 2, 3, 4, 8a, 8b, 19
13. Use of fuel (Industrial, Professional): PROC 8a

16. Use of DEA in wood protection formulations (Industrial): PROC 3
18. Use of DEA as processing aid for paper, textile and leather: PROC 7, 10, 13

In a higher tier approach for dermal exposure assessement, higher protection factors for gloves could be used to display more realistic exposure estimates. Nonetheless, these factors can only be used, if a justification based on experiments is given taking into account potential variables encountered in the workplace (industrial/professional) that can influence glove efficiency (in particular: permeation through the glove fabric; penetration of the glove (drips, flaws, worn gloves); and human factors (taking gloves off, contaminating the hands, then putting the gloves back on). Feasible methods are described by Klingner et al. and Henriks-Eckerman et al.[25]

To enable evaluation of the assessment all used models and parameters shall be clearly stated. When using non-standard parameters a justification must be given, otherwise the use of the parameter cannot be assumed to be justified.

The requested information will allow a full evaluation whether the occupational risks associated with dermal and inhalation exposure are controlled at all workplaces.

5. Provide a higher tier exposure assessment for dermal exposure in accordance with the procedure laid down in the 'REACH Guidance on information requirements and chemical safety assessment', Chapter R.14 and a risk assessment in accordance with the procedure laid down in Part E for the use of DEA in metal working fluids involving moving objects (e.g. rotating machinery parts) during which wearing gloves comprises a risk of entanglement.

'Use of DEA in metal working fluids' is an identified use for the registered substance. Metal working fluids are used at plants with rotating machinery parts. In these workplaces there exists a particular risk for gloves being caught up by a moving object thereby creating a danger for the user (see also Directve 89/686/EEC). When moving objects are involved in the working process wearing gloves comprise a risk due to entanglement which leads to serious injuries.[26] It is well known that these working conditions are common, even though the registration dossiers do not cover this operational condition.

To assess the risks for this scenario 'use of DEA in metal working fluids involving rotating machinery parts' the glove efficiency would have to be set to zero because wearing of gloves is not possible. The recalculation of ES 8 'use of DEA in metal working fluids' professional setting PROC 17 and 18 was conducted using standard factors and assumptions where possible. In addition, recalculated DNELs were used, as the DNELs used by the registrants were assumed not to be justified (see statements of reasons 4.). RCRs for these scenarios are already well above 1 when wearing gloves is assumed. Therefore the scenario in which moving objects are involved leads to even higher risks.

The used Tier I model might lead to a higher exposure estimate than the actual workplace exposure. On the basis of the current information from the registration dossiers, a final conclusion on the risk cannot be drawn.

Therefore the registrants are requested to conduct a higher tier exposure assessment for dermal exposure in accordance with the procedure laid down in the 'REACH Guidance on information requirements and chemical safety assessment', Chapter R.14 and a risk assessment with the procedure laid down in Part E for the use of DEA in metal working fluids involving moving objects (e.g. rotating machinery parts) during which wearing gloves

[25] Klingner T.D. and Boeninger, M.F. A Critique of Assumptions about selecting Chemical-Resistant Gloves: A Case for Workplace Evaluation of Glove Efficacy. Applied Occupational and Environmental Hygiene 360-367, 2002
Henriks-Eckerman M.L., Suuronen K., Jolanki R., Riala R., Tuomi, T., Determination of Occupational Exposure to Alkanolamines in Metal-Working Fluids, Ann. Occup. Hyg., Vol. 51, No. 2, pp. 153–160, 2007
[26] Hauptverband der gewerblichen Berufsgenossenschaften (HVBG). Tätigkeiten mit Kühlschmierstoffen vom Januar 2006. Berufsgenossenschaftliche Regeln für Sicherheit und Gesundheit bei der Arbeit, BG-Regel 143, 2006

comprises a risk of entanglement.

To enable evaluation of the assessment all used parameters shall be clearly stated. When using non-standard parameters a justification must be given, otherwise the use of the parameter cannot be assumed to be justified.

The registrants agreed to perform a higher tier exposure assessement for dermal exposure for this scenario without gloves.

The requested information will allow a full evaluation whether the occupational risks associated with dermal exposure from use of DEA in metal working fluids involving moving objects are controlled.

6. Provide information on personal protective equipment regarding the type of material, thickness and breakthrough times of the gloves and the duration of use for all exposure scenarios where the use of gloves is advised.

Appropriate risk management measures have to be derived, recommended and applied during use in order to cope with risks from hazardous substances. The order of risk management measures is laid down in the Directive 98/24/EC. Personal protective equipment is the last resort, in cases where the other measures are not applicable or could not sufficiently reduce the risks.

The Directive 89/656/EEC (on the minimum health and safety requirements for the use by workers of personal protective equipment at the workplace) states that the personal protective equipment used must be appropriate for the risk involved, without itself leading to any increased risk. This Directive has to be considered for the derivation of exposure scenarios as the REACH Regulation shall apply without prejudice to the community workplace legislation.

The specification of the recommended personal protective equipment is necessary to assure that the equipment does have a protective effect. Without further specification the protection by gloves and respiratory protection cannot be judged. Therefore the efficiency of gloves has to be set to zero. The recalculation of exposure scenarios including standard protection factors for gloves resulted in RCRs well above one (see statements of reasons 4.). The exposure would be even higher if no protection factor for gloves would be assumed. The registrants agreed to provide this information.

In some contributing scenarios a duration of the task of up to 8 h is specified by the registrants. This may imply an 8 h use of personal protective equipment such as gloves whenever such PPE is recommended[27]. As indicated in Directive 89/656/EEC, wearing of PPE should not comprise a burden to the worker. It is well recognised that exceeding a certain duration of use comprises such a burden and can express a risk for workers by itself. For example the German Technical Rule for Hazardous Substances 401 "Risks resulting from skin contact - identification, assessment, measures" limits the duration of use to a maximum of 4 hours.

Therefore, the specified maximum duration of use of gloves shall be taken into account in the exposure scenarios. The maximum duration either has to be calculated from the breakthrough time mentioned above or to be specified in accordance with Directive 89/656/EEC. The registrants agreed to adapt the exposure scenarios, accordingly.

[27] ES No. 1: Manufacturing of DEA, ES No. 2: ES No. 3: Use of DEA as an intermediate, ES No. 4: Use as additive in concrete and cement (Professional), ES No. 6: Processing aid for paper, textile, leather, ES No. 7: Gas treatment with DEA, ES No. 8: Use of DEA in metal working fluids, ES No. 9: Use of DEA in detergents and cleaners (Industrial, Professional), ES No. 10: Use of DEA as additive in plastic (Industrial, Professional), e.g. rubber, ES No. 11: Use of DEA as a laboratory chemical (Industrial, Professional), ES No. 12: Use of DEA as additive in fuel, ES No. 13 Use of fuel (Industrial, Professional), ES No. 18 Use of DEA as processing aid in paper, textile and leather.
[28] Information on detailed uses has been removed for reasons of confidentiality.

On the basis of the current information no final conclusion can be drawn on the level of estimated exposure and consequently not on the risk, as it is not clear if the use of a protection factor for gloves is justified. To conclude that protection factors for gloves can be used for the exposure assessment the specification of gloves is necessary.

Therefore the registrants are required to provide information on personal protective equipment regarding the type of material, thickness and breakthrough times of the gloves and the duration of use for all exposure scenarios where the use of gloves is advised.

7. Information on operational conditions, exposure estimations and risk characterisation for exposure scenarios related to consumer products and articles

In order to protect potentially confidential use information the reasons are reported on a general level. More details can be found in the confidential Annex[28].

The evaluating MSCA has evaluated the consumer exposure scenarios and estimates provided by the registrants with the result that there are inadequacies in the data base and there is concern that the identified uses of DEA pose risks for the general population and that the risks are not adequately controlled.

- In some cases the demonstration of safe use could not be verified by the evaluating MSCA because operational conditions and model inputs were not clearly communicated or lacked conservatism or because the results could not be numerically verified. Therefore, the registrants shall provide revised operational conditions and exposure calculations for the corresponding contributing scenarios allowing a full verification. This refers to ES No. 5 Use of concrete and cement (Consumer), ES No. 15 Use of DEA in detergents and cleaners (Consumer), ES No. 17 Use of DEA in wood protection formulations (Consumer).
- In nearly all consumer exposure calculations, the registrants have used a function of the ConsExpo 4.1 tool which averages out exposures from infrequent uses over a year in order to compare the resulting average "long-term systemic exposure" to a corresponding DNEL. However the REACH Guidance on information requirements and chemical safety assessment Chapter R.8 states (ECHA (2010): Guidance on information requirements and chemical safety assessment. Chapter R.8: Characterisation of dose [concentration]-response for human health, p.8): *'The actual daily dose is independent of the exposure frequency. This means that if for a certain scenario, worker or consumer exposure is for instance only for a number of days per year, the exposure value is the actual dose on the exposure days, and not the daily dose averaged out (and thus divided!) over the whole year.'* Therefore the registrants shall provide revised exposure estimations and risk characterisations for exposures with a frequency of only a few days per year in ES No. 5 Use of concrete and cement (Consumer) and ES No. 17 Use of DEA in wood protection formulations (Consumer).
- Some title sections and use descriptors refer to product or article categories which are not covered by the corresponding operational conditions and exposure estimates. This may lead to misunderstandings in supply chain communication and to support of uses which have not been demonstrated to be safe. Therefore the registrants are requested to supply revised title sections and use descriptors for the scenarios ES No. 5 Use of concrete and cement (Consumer), ES No. 15 Use of DEA in detergents and cleaners (Consumer), ES No. 17 Use of DEA in wood protection formulations (Consumer)

In addition, the evaluating MSCA found that consumer exposure to DEA in certain articles is not covered by the exposure estimations provided by the registrants:

- DEA is used as a processing agent in the production of plastic and rubber and as an additive in textile, leather and paper products. The consumer use scenario ES 19, Service life of DEA when used as processing aid for paper, textile and leather, does not include any information on human exposure and no concentrations have been given for DEA residues in the above mentioned products. Exploratory Tier 1 calculations performed by the evaluating MSCA under the assumption of a DEA residue level of 1 % result in consumer exposure estimates which raise concern, potentially exceeding the relevant DNELs. Therefore the registrants shall provide exposure estimations and risk characterisations for human health for consumer use of plastic, rubber, textile, leather and paper products in order to demonstrate safe use.
- Secondary exposure of consumers due to releases from articles which have been treated with DEA in detergents, cleaners or wood protection formulations has to be expected. The ConsExpo exposure estimations provided by the registrants do not cover these sources. Therefore, the registrants are requested to provide additional exposure scenarios and estimations for residues on textiles and food contact materials for ES No. 15 Use of DEA in detergents and cleaners (Consumer). In addition, they shall provide scenarios for secondary exposure for ES No. 17 Use of DEA in wood protection formulations (Consumer). These shall comprise sanding of treated wood by adults, chewing of treated wood by children, inhalation of volatilised residues indoors by adults and children playing and mouthing on treated structure. Without these scenarios, exposure of the general population to DEA due to these uses is underestimated and there is concern that there are uncontrolled risks for the general population.

The evaluating MSCA also found inadequacies in the risk characterisations provided by the registrants:

Single and rare uses of DEA, where a peak exposure with relatively short duration is expected, are not adequately covered by the risk assessment of the registrants.
The registrants did not provide estimates for short-term exposure of consumers to the registered substance in the context of the identified uses and they did not derive acute DNELs for the inhalation, dermal and oral route of exposure. However, based on the consumer exposure scenarios of the registration dossiers, there is concern on acute toxicity hazards.

DEA has a moderate acute oral toxicity and it is classified for this endpoint (Acute Tox 4 (H302)). Based on the available data on acute inhalation toxicity, there is a reasonable suspicion that DEA should also be classified for this endpoint. In addition, DEA is classified for skin irritation and serious eye damage/eye irritation. Peak exposures can be significantly higher than the average daily exposure and the long-term DNEL is insufficient to adress short term effects. Thus, DNEL values for acute toxicity have to be derived in order to address possible health effects after single exposures to DEA with durations of a few minutes up to 24 hours. Single and rare uses of DEA with a relatively short duration have been reported in the consumer exposure scenarios of the registration dossiers and a potential of acute hazard is given for the inhalation, dermal and oral route of exposure. Therefore, DNEL values for acute effects for the general population have been derived by the evaluating MSCA.

The preliminary RCR reassessment by the evaluating MSCA for the available contributing scenarios for such short-term consumer exposures resulted in RCR values significantly exceeding 1 in many cases indicating that the respective risks are not adequately controlled. This is of particular importance for ES No. 5 Use of concrete and cement (Consumer), ES No. 15 Use of DEA in detergents and cleaners (Consumer) and ES No. 17

Use of DEA in wood protection formulations (Consumer) for the inhalation and dermal route of exposure.

In order to demonstrate the control of human health risks for consumers from the identified short-term exposures from consumer uses, the registrants shall provide revised exposure estimations and risk characterisations. These estimations shall not average the dose over a year for such single, short-term exposures. Instead short-term exposure estimates and risk characterisations for single, acute exposures have to be provided.

Without the requested information it will not be possible to verify whether there remains an uncontrolled risk with the substance that should be subject to further risk management measures.

The registrants have agreed to derive acute DNELs for the general population.

The evaluating MSCA gives the following recommendations for the derivation of acute DNEL values for DEA: The exposure of the general population to DEA may result from dermal contact, inhalation and also ingestion. Thus, DNEL values for acute toxicity shall be derived for these routes of exposure to 2,2'-Iminodiethanol. There is no established accepted methodology for the setting of acute toxicity DNEL values. According to the Guidance on information requirements and chemical safety assessment Chapter R.8 (2012), an acute toxicity DNEL can by default be set by multiplying the long term DNEL with a factor of 1-5 (default 3). Further options for the derivation of acute toxicity DNEL values are given by using of LD50/LC50 values, findings from repeated-dose-toxicity studies, human data or other relevant data. In the following, one example for the derivation of the acute oral toxicity DNEL value for the general population is given:

Acute/short-term exposure – systemic effects – oral

1) $DNEL_{long\text{-}term\text{-}systemic\ effects}$ of 0.023 mg/kg bw/d (derived by the eMSCA) multiplied by 3 (default) results in $DNEL_{acute\text{-}systemic\ effects}$ for the oral route of 0.069 mg/kg bw/d.

2) Using the LD50 value for DEA observed in rats (1600 mg/kg bw; BASF AG 1966). According to the REACH Guidance R.8 (2012) the following assessment factors (AF) shall be applied: AF for severe of effects (LD50) of 100 (default); AF for interspecies extrapolation of 4 (default; for allometric scaling, rat); AF for remaining uncertainties of 2.5 (default); AF for intra species differences of 10 (default for general population); AF for quality of whole database of 1 – in total AF of 10000. Following this approach, the resulting $DNEL_{acute\text{-}systemic\ effects}$ for the oral route is 0.16 mg/kg bw.

For the general population, long-term DNEL values for the dermal, inhalation, and oral route of exposure have been derived by the registrants. However, for the derivation of the DNEL for local/systemic effects following long-term inhalation, they have used the so-called MAK value ('maximale Arbeitsplatz-Konzentration', maximum workplace concentration) as derived by the German 'MAK Commission' as starting point (Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, http://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/index.html).

This approach is not appropriate for the general population, since MAK values promote the protection of health at the workplace in Germany. The MAK value is defined as the maximum concentration of a chemical in the workplace air which generally does not produce known adverse effects on the health of employees nor causes unreasonable annoyance even when the person is repeatedly exposed during long periods, usually 8 hours daily, but assuming on average a 40-hour working week. In addition, a DNEL combined for local and systemic effects is not acceptable.

The evaluating MSCA has calculated long-term DNELs for local and systemic effects for the dermal and the inhalation route and a long-term DNEL for systemic effects for the oral route according to the REACH IR/CSA Guidance R.8 (ECHA (2012): Guidance on information requirements and chemical safety assessment. Chapter R.8: Guidance on information requirements and chemical safety assessment). A comparison of the derived long-term dermal DNELs with the exposure values obtained by the registrants and the recalculated consumer exposure estimates by the evaluating MSCA resulted in RCRs significantly exceeding 1 in several cases indicating that the respective risks are not adequately controlled. This is of particular importance for ES No. 15 Use of DEA in detergents and cleaners (Consumer).

The process of risk characterisation under REACH is described in section 5.1.1 of the REACH Regulation: *"If the initial assumptions lead to a risk characterisation indicating that risks to human health and the environment are not adequately controlled, then it is necessary to carry out an iterative process with amendment of one or a number of factors in hazard or exposure assessment with the aim to demonstrate adequate control."*

It is thus evident that the registrants need to revise their risk characterisations in order to demonstrate that the identified uses of the registered substance are safe.

Furthermore, the evaluating MSCA found that the proposed measures to control consumer risks of severe eye damage are not adequate. Therefore, the concern for this consumer risk remains. Exposure to the eyes can occur in two ways: directly from the air (splashes, aerosols, dust) or indirectly via hand-eye contact. Because of the severe nature of the effect, all risks should be avoided. Consumer exposure to the eyes has been addressed in the CSR by introducing a consumer instruction. In all cases where contact to liquid or dusty consumer preparations could occur, the registrants have included the following advice into the contributing exposure scenarios: 'Do not touch eyes while handling this product'.

However, the REACH Guidance on information requirements and chemical safety assessment Chapter R.15 states (ECHA (2012): Guidance on information requirements and chemical safety assessment. Chapter R.15: Consumer exposure estimation, p.10): *"The use of consumer instructions as RMMs cannot be expected to be highly effective, unless consumer behavioural data provide evidence that a sufficient degree of compliance can be assumed. ..."* This is also in line with the REACH Guidance on information requirements and chemical safety assessment Chapter R.13 (ECHA (2012): Guidance on information requirements and chemical safety assessment. Chapter R.13: Risk management measures and operational conditions, p.10). The registrants did not provide such data.

Therefore the registrants shall provide revised consumer exposure scenarios and risk characterisations for health risks from eye contact. This is of particular importance for ES No. 5 Use of concrete and cement (Consumer) and ES No. 17 Use of DEA in wood protection formulations (Consumer).

The registrants submitted a comment announcing a revised use list and that the only remaining consumer use for DEA is as an additive in concrete and cement.

However, as the registration dossiers still have not been updated reflecting the revised uses as provided in the consultation phase as to 05 September 2013, the decision has not been amended by the evaluating MSCA.

The registrants also have announced "to communicate the use of eye protection to the consumer in the CSR" in order to prevent eye irritation/corrosion resulting from consumer use of DEA as additive in concrete and cement. They stated that the use of eye protection for consumers has been recommended by the German Federal Institute for Risk Assessment (BFR) to consumers as concrete and cement exert a high pH in contact with water (BFR

Press release 04/2003, 18.02. 2003), and that according to this press release a possible risk for eye damage results from concrete / cement itself. They also stated that the percentage of DEA within concrete and cement can be assumed to be rather low, and they announced to revise this information in the CSR.
However, as to the 05 September 2013 the dossiers have not been updated accordingly. Moreover, there are serious doubts whether the simple recommendation of eye protection for consumer use of concrete and cement would result in a sufficient reduction of the risk of eye damage to demonstrate control of risks under the REACH regulation. The use of eye protection for consumers using cement and concrete has been recommended by the German Federal Institute for Risk Assessment (BfR) because this measure may reduce the risk of eye damage in case that it is applied. However, as cement dust will be released during mixing and loading, close fitting goggles may be needed to prevent eye contact, and it is not clear whether consumers would be willing and able to purchase the right goggle type in building centers. Moreover, the advice of using eye protection still is a consumer instruction and without further evidence it cannot be assumed that consumer compliance is sufficient to demonstrate control of risks. The REACH Guidance on information requirements and chemical safety assessment Chapter R.15 states: *"Effective risk management measures for consumers are usually product-integrated measures (see Chapter R.13). For quantitative exposure estimation, only those RMMs which can be controlled by the manufacturer of the product should be applied. This means that RMMs may be implemented by changing operational conditions or product composition, e.g.: maximum concentration used in the product, change of the product form (pellets or granules instead of powder) or maximum amount of product used (package size). The use of consumer instructions as RMMs cannot be expected to be highly effective, unless consumer behavioural data provide evidence that a sufficient degree of compliance can be assumed. ..."*[29] This is also in line with the REACH Guidance on information requirements and chemical safety assessment Chapter R.13 [30]. As the registrants did not provide such data, the risk management measures for consumer use of DEA in concrete and cement shall be revised and product-integrated measures shall also be considered.

IV. Adequate identification of the composition of the tested material

In relation to the required test, the sample of substance used for the new study shall have a composition that is within the specifications of the substance composition that are given by all concerned registrants. It is the responsibility of all the concerned registrants to agree on the tested materials to be subjected to the test subject to this decision and to document the necessary information on composition of the test material. The substance identity information of the registered substance and of the sample tested must enable the evaluating MSCA and ECHA to confirm the relevance of the testing for the substance subject to substance evaluation. The substance identity information submitted in the registration dossiers has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation. Finally, the study must be shared by the concerned registrants.

V. Avoidance of unnecessary testing by data- and cost- sharing

Avoidance of unnecessary testing and the duplication of tests is a general aim of the REACH Regulation (Article 25). The legal text foresees the sharing of information between registrants. Since several registrants of the same substance are required to provide the same information, they are obliged to make every effort to reach an agreement for every endpoint as to who is to carry out the test on behalf of the other concerned registrants and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation.

[29] ECHA (2012): Guidance on information requirements and chemical safety assessment. Chapter R.15: Consumer exposure estimation, p.10
[30] ECHA (2012): Guidance on information requirements and chemical safety assessment. Chapter R.13: Risk management measures and operational conditions, p.12

If ECHA is not informed of such agreement within 90 days, it shall designate one of the concerned registrants to perform the tests on behalf of all of them. If a registrant performs a test on behalf of other registrants, they shall share the cost of that study equally and the registrant performing the test shall provide each of the others concerned with copies of the full study reports.

This information should be submitted to ECHA using the following form stating the decision number above at:
https://comments.echa.europa.eu/comments_cms/SEDraftDecisionComments.aspx

Further advice can be found at http://echa.europa.eu/datasharing_en.asp.

VI. General requirements regarding Good Laboratory Practice

ECHA always reminds registrants of the requirements of Article 13(4) of the REACH Regulation that ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP). National authorities monitoring GLP maintain lists of test facilities indicating the relevant areas of expertise of each facility.

VII. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Articles 52(2) and 51(8) of the REACH Regulation. Such an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://echa.europa.eu/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

[redacted]

Jukka Malm
Deputy Executive Director

Annexes:
1. List of registration numbers for the addressees of this decision. This annex is confidential and not included in the public version of this decision.
2. Table 1: Dose-descriptor(s) used for derivation of DNELs
3. Confidential uses. [Information on detailed uses has been removed for reasons of confidentiality].

Annex

Table 1: Dose-descriptor(s) used for derivation of DNELs

Repeated dose toxicity: sub-acute / sub-chronic / chronic dermal	$LOAEL_{local, systemic}$: 8 mg/kg bw/day Target organs: cardiovascular / hematological urogenital: kidneys digestive: liver other: skin	Repeated, unoccluded dermal application of ethanolic 2,2'-Iminodiethanol solutions in sub-chronic animal study (13 weeks, protocol similar to OECD TG 411) a NOAEL for systemic effects or local skin irritation could not be achieved (LOAEL 32 mg/kg bw in rats; 80 mg/kg bw in mice). The 2 year dermal studies (NTP, 1999, protocol similar to OECD TG 451) with rats and mice also showed non-carcinogenic effects. Critical effects appear to be kidney (nephropathy) and liver toxicity, anaemia and dermal hyperkeratosis/acanthosis. The overall dermal LOAEL based on the 13 week and 2 years study is concluded to be 8 mg/kg bw/day.
Repeated dose toxicity: sub-acute / sub-chronic / chronic inhalation	$NOAEC_{local}$: 3 mg/m³ NOAECsystemic: 15 mg/m^3 Target organs: respiratory: larynx urogenital: kidneys digestive: liver	Nose-only exposure of rats to 2,2'-Iminodiethanol aerosols for 3 months (OECD TG 413) resulted in a systemic NOAEC of 15 mg/m³ and the NOAEC for local respiratory tract effects was 3 mg/m³.