Helsinki, 23 February 2017

Substance name: Reaction mass of 4,4'-methylenediphenyl diisocyanate and o-(p-isocyanatobenzyl)phenyl isocyanate / methylene diphenyl diisocyanate
EC number: 905-806-4
CAS number: N/A
Date of Latest submission(s) considered[1]: 29 October 2015
Decision/annotation number: Please refer to the REACH-IT message which delivered this communication (in format SEV-D-XXXXXXXXXX-XX-XX/F)
Addressees: Registrant(s)[2] of Reaction mass of 4,4'-methylenediphenyl diisocyanate and o-(p-isocyanatobenzyl)phenyl isocyanate / methylene diphenyl diisocyanate (Registrant(s))

DECISION ON SUBSTANCE EVALUATION

1. Requested information

Based on Article 46(1) of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), you are requested to submit the following information on:

1. *In vivo* mammalian alkaline comet assay using the substance 4,4'-methylenediphenyl diisocyanate (4,4'-MDI, EC: 202-966-0); test method: OECD TG 489 in Wistar rats, inhalation route with examination of lungs and liver; glandular stomach tissue shall be harvested and stored, and analysed if negative results are obtained in liver and lungs.

Based on Article 46(1) of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), you are requested to submit the following exposure related-information, regarding the transformation products, 2,4'-methylenedianiline (2,4'-MDA, EC: 214-900-8) and 4,4'-methylenedianiline (4,4'-MDA, EC: 202-974-4) of the registered substance:

2. Information concerning worst case scenarios for consumer uses in relation to generation of and consequent possible exposure to 2,4'- and 4,4'-MDA;

3. Specification of the process categories for the intended uses where the use of the registered substance simultaneously with aprotic polar solvents occurs and specification of the recommended measures to ensure that 2,4'- and 4,4'-MDA is either not formed or exposure to 2,4'- and 4,4'-MDA is controlled.

ECHA notes that the study requested under point 1. above has already been requested in the substance evaluation decision for 4,4'-MDI of 13 April 2016. The deadline for submitting the information is 20 July 2017. ECHA notes that there should be no duplication of vertebrate animal studies.

As further explained in Appendix 1 (Reasons), Section 1, it appears to be plausible to

[1] This decision is based on the registration dossier(s) at the end of the 12 month evaluation period

[2] The terms Registrant(s), dossier(s) or registration(s) are used throughout the decision, irrespective of the number of registrants addressed by the decision.

use the results obtained with 4,4'-MDI (source substance) in an *in vivo* mammalian alkaline comet assay to predict the test result of this experimental study for the registered substance (target substance). However, whether this read-across approach is applicable for this property (test result in the comet assay) can only be determined once the requested information is submitted. Then it will be considered whether further information needs to be requested to clarify the concerns.

You shall provide an update of the registration dossier(s) containing the requested information, including robust study summaries and, where relevant, an update of the Chemical Safety Report by **30 November 2017**.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Further information, observations and technical guidance as appropriate are provided in Appendix 3 and references are listed in Appendix 4. Appendix 5 contains a list of registration numbers for the addressees of this decision. The Appendix is confidential and not included in the public version of this decision.

2. Appeal

You can appeal this decision to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals

Authorised[3] by Leena Ylä-Mononen, Director of Evaluation

[3] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons

Based on the evaluation of all relevant information submitted on reaction mass of 4,4'-methylenediphenyl diisocyanate and o-(pisocyanatobenzyl)phenyl isocyanate and other relevant available information, ECHA concludes that further information is required in order to enable the evaluating Member State Competent Authority (MSCA) to complete the evaluation of whether the substance constitutes a risk to human health.

The evaluating MSCA will subsequently review the information submitted by you and evaluate if further information should be requested in order to clarify the concern for genotoxicity of the registered substance and possible exposure to its transformation products 2,4'-methylenedianiline (2,4'-MDA, EC: 214-900-8) and 4,4'-methylenedianiline (4,4'-MDA, EC: 202-974-4).

1. *In vivo* mammalian alkaline comet assay, using the substance 4,4'-methylenediphenyl diisocyanate (4,4'-MDI, EC: 202-966-0); test method: OECD TG 489 in Wistar rats, inhalation route, with examination of lungs and liver; glandular stomach tissue shall be harvested and stored, and analysed if negative results are obtained in liver and lungs

The concern(s) identified

One of the main constituents of the registered substance, accounting potentially up to 80% of the composition is 4,4'-methylenediphenyl diisocyanate (4,4'-MDI, EC: 202-966-0), for which there is concern related to carcinogenicity and possible genotoxic mode of action for tumour induction.

Consequently, as further explained below, it is assumed that also the registered substance may exhibit genotoxic effects at the site of contact, as a parent compound or due to the formation of toxicologically relevant metabolites (e.g. 2,4'- and 4,4'-MDA). 4,4'-MDA is classified *inter alia* as Muta. 2, Carc. 1B and is included in Annex XIV of REACH Regulation as substance of very high concern subject to authorisation (Entry 2 of Annex XIV) and 2,4'-MDA has the same notified classification. The study conducted with 4,4'-MDI can inform on the properties of the registered substance and should be considered.

Why new information is needed

- Analysis of the read-across approach between 4,4'-MDI and the registered substance to predict the results of the comet assay

The constituents of the registered substance and 4,4'-MDI have common functional group (– NCO group) and belong to the common chemical class - diisocyanates. Regarding the composition, based on the available data, the main difference between the registered substance and 4,4'-MDI appears to be the relative amount of the two main diisocyanate isomeric constituents 4,4'-MDI and 2,4'-MDI (see Table 1). Table 1 also shows that for the registered substance the 4,4'-MDI concentration in the composition may vary between 25 and 80% and the 2,4'-MDI concentration may vary between 10 and 70%. 4,4'-MDI in contrast contains between 0 and 20 % of 2,4'-MDI. It is noted that the three MDI isomers (4,4'-, 2,4'- and 2,2'-MDI) that make the composition of the registered substance and of 4,4'-MDI, have the same harmonised classification and are covered by a group entry in Annex VI of CLP Regulation, Index No. 615-005-00-9.

Table 1. Composition of the registered substance, 4,4'- and 2,4'-MDI.

Name	CAS	EC	MDI components (w/w%)				
			4,4'-MDI	2,4'-MDI	2,2'-MDI	Total 2-ring MDI	Higher oligomers
Registered substance	N/A	905-806-4	25-80	10-70	0-5	95-100	0-5
4,4'-MDI	101-68-8	202-966-0	80-100	0-20	0-5	95-100	0-5
2,4'-MDI	5873-54-1	227-534-9	0-20	80-100	0-5	95-100	0-5

In order to assess the impact of the isomeric constituents on the toxicity and the plausibility of the read-across approach between 4,4'-MDI and the registered substance, the following information was taken into account. [redacted] (2002) investigated reactions of 2,4'-toluene diisocyanate (2,4'-TDI) in aqueous solution with N-acetyl-L-cysteine. A peculiarity of this diisocyanate is the difference in reactivity of the two isocyanate groups. Depending on the reaction conditions the isocyanate group in the 4-position is more reactive than the isocyanate in the 2-position by a factor of 5 to 10. This is partly due to the steric hindrance of the *o*-NCO group; another factor is the electronic effect of the isocyanate in the 4-position which changes from electron withdrawing to electron releasing after transformation to the thiocarbamoyl moiety. You applied the same theory to the MDI isomers. You provided a justification document in the registration dossier(s) where it is stated that the local toxicity of the isomers depends on the relative reactivities of different NCO-groups that have been measured during the experiments that were conducted under real use conditions, i.e. during polyurethane manufacturing and the application of products. The differences in the reactivity are caused by sterical hindrance and no mesomerism according to "Hückel-Law" can occur (i.e. none or only very minor electronic effects originating from the other aromatic moieties and their substituents). This experimental evidence is indicating that the most reactive NCO-group is the NCO-group in 4-position since 4,4'-MDI reacts 1.8 times faster than 2,4'-MDI and 5.4 faster than 2,2'-MDI. The molecular formula of the three MDI isomers is the same, they have the same molecular weights and NCO-values.

The registered substance and 4,4'-MDI have common precursors in the manufacturing process. You stated in the dossier(s) that toxicologically relevant breakdown products can be predicted based on the reactivity of the functional group. Polyurea is claimed to be the major and the common metabolite of both 4,4'-MDI and the registered substance. However, there is no specific data on the metabolism of the registered substance. The assumption about similarities regarding toxicological endpoints of 4,4'-MDI and the registered substance is mainly based on the chemical reactivity of the common functional group. It is noted that toxicological information is mainly available only for 4,4'-MDI and there is no information available on mutagenicity studies with the registered substance *in vivo*. ECHA considers that the chemical reactivity differences do not necessarily translate into the same differences in reactivity towards a biological molecular target, such as DNA, in a cell nucleus under *in vivo* conditions. In fact, less reactive molecules may be even favoured to reach such target whereas more reactive molecules react already prior to reaching this target. Currently, there is no information available to exclude such possibility.

In your comments on the proposals for amendment regarding the applicability of the read-across approach between 4,4'-MDI and the registered substance, you have re-iterated your claims regarding the difference in reactivity of the NCO-group in 4-position compared to NCO-group in 2-position and the influence on the local toxicity. However, you did not provide any new experimental evidence on reactivity in *in vivo* systems that would allow excluding a higher genotoxic potential of the 2,4'-MDI. As an experimental proof of concept, you indicated data on a series of *in vitro* bacterial reverse mutation assays conducted with 4,4'-MDI, 2,4'-MDI, a mixture of 2,2'-, 2,4'-MDI and 4,4'-MDI, and pMDI, where consistent negative response has been shown in all of the strains tested with and without metabolic activation (Herbold et al., 1998; see also below). However, ECHA considers that based on these negative results no conclusion can be drawn on the difference in reactivity of the different isomers or on the genotoxic potential at the site of contact *in vivo*. In your comments, you did not address the variation in the concentration of different constituents.

You also provided comments regarding the potential genotoxicity at the site of contact of the registered substance due to MDA formation. However, since this was not addressed in the proposal for amendment, these comments have not been considered.

ECHA therefore concludes that based on the possible variations in the composition of the registered substance and lacking knowledge on the reactivity of the involved isomers towards macromolecules under *in vivo* conditions, the applicability of the proposed read-across approach may be limited. Some compositions may have only 25% of 4,4'-MDI and 70% of 2,4'-MDI. A result of the comet assay conducted with 4,4'-MDI which demonstrates a genotoxic response informs on this property also for the registered substance, since at least 25% of 4,4'-MDI is present in the composition of the registered substance. However, if a result is obtained with the 4,4'-MDI which does not demonstrate a genotoxic response in this specific test, the absence of genotoxic effects for the registered substance cannot be concluded, since 70% of the composition of the registered substance may be 2,4'-MDI which is not tested.

- Review of the available information related to carcinogenicity and possible mode of action

The majority of the information provided in the registration dossier(s) on toxicity of the registered substance is obtained from 4,4'-MDI. There is no information available on mutagenicity or carcinogenicity studies conducted with the registered substance.

Regarding 4,4'-MDI, there is a concern related to carcinogenicity and possible genotoxic mode of action for tumour induction. A reliable 2-year chronic toxicity/carcinogenicity inhalation study ([redacted], 1990) is available where the formation of a pulmonary adenocarcinoma in one male as well as pulmonary adenomas, described as rare in this strain, in males (6/60) and females (2/59) exposed to 6.03 mg/m^3 of pMDI were found.You claimed a non-genotoxic mode of action for tumours formation due to the observation of chronic inflammation/irritation in the lungs following lifetime inhalation exposure. This claim is based on the negative bone marrow micronucleus test via inhalation and the fact that the available inhalation studies did not detect free MDA. However, as further elaborated below, it is considered that the mechanism of carcinogenicity is not sufficiently clear and it is not possible to conclude based on the available data whether tumour formation is attributed to a genotoxic or a non-genotoxic mode of action.

The available tests assessing the genotoxic potential of 4,4'-MDI *in vivo* provide no information on genotoxic activity at the site of contact. Most of the test results of *in vitro*

genotoxicity assays rather reflect the properties of the reaction products formed under specific assay conditions than the ones of the parent compound. Only in the available *in vitro* bacterial reverse mutation assay where solutions of 4,4'-MDI, 2,4'-MDI, a mixture of 2,2'-, 2,4'- and 4,4'-MDI, and pMDI were tested in ethyleneglycoldimethylether (EGDME) as a solvent, consistent negative response has been shown in all of the strains tested with and without metabolic activation (Herbold *et al.*, 1998). The results of a positive *in vitro* gene mutation study in mammalian cells conducted with 4,4'-MDI ([redacted] *et al.*, 1981) were considered by you as not reliable due to the use of inappropriate solvent. The results of an *in vivo* micronucleus test indicated that 4,4'-MDI administered by inhalation did not induce cytogenetic damage ([redacted] *et al.*, 2001). However, there is a concern that bone marrow was not adequately exposed because this is not proven in this study.

In another *in vivo* micronucleus study in mice by inhalation (Lindberg *et al.*, 2011) the ratio of polychromatic erythrocytes to normochromatic erythrocites was reduced at the highest concentration which is an indication that bone marrow was exposed in this study. The results of this study demonstrated that 4,4'-MDI aerosols at concentration of 10.7-23.3 mg/m^3 did not significantly increase the frequency of micronucleated polychromatic erythrocytes in mouse bone-marrow or in peripheral blood. However, the authors mentioned that the daily exposure duration was limited to 1h because of the irritating properties of 4,4'-MDI, and the negative result may thus be related to the short exposure time. Authors acknowledged the concern for potential local genotoxic activity by stating that "*because diisocyanates are very reactive and react also at the site of first contact, it may have been possible to detect genotoxic effects locally in the respiratory tract*".

A recently conducted comet assay that was performed as an exploratory work and not according to GLP ([redacted]) showed positive results. Inhalation exposure to 4,4'-MDI led to a dose dependent mild positive response observed at day 0 and 1 at 20 mg/m^3 3h. Increase in tail length (ca. 2.3 fold increase compared to ca. 11 – 22 fold increase in the positive control) correlated with markers of cytotoxicity, apoptosis and inflammation. You interpreted the results of the study as "irrelevant positive" explaining the results by the assumption that genotoxic effects may occur secondary to interaction with the local environment. Overall, the study is marked as not reliable in the dossier. Indeed, the reliability of this study is questionable for the following reasons:

- Different routes of administration were used for the positive control (oral) and test substance (inhalation), while the test guideline recommends using the same route of administration when measuring site of contact effects;
- According to the test guideline, in the absence of kinetic data a suitable compromise for the measurement of genotoxicity is to sample at 2-6h after the last treatment for two or more treatments, or at both 2-6 and 16-26h after a single administration. It appears that in the present study this recommendation has not been followed.

A large number of studies are available evaluating the fate of inhaled MDI (e.g. [redacted] 2003a, 2003b, Gledhill *et al.*, 2005). These studies illustrate consistent metabolic pathway in which toxicologically relevant metabolite MDA is not detected. Biomonitoring studies demonstrate that the intermediary steps of MDI metabolism under plasma physiological conditions proceed entirely without formation of any free amines, including MDA.

Although MDA was not detected systemically following inhalation exposure in any of the reported studies there is still a concern because local formation of MDA cannot be

excluded. In *in vitro* studies ([redacted] *et al.*, 2002; 2003) formation and stability of conjugates of N-acetyl-L-cysteine with 4,4'-MDI in the buffer solution in pH range 5-7 has been shown without formation of 4,4'-MDA. However the provided studies cannot exactly mimic the processes that occur *in vivo*. Therefore, to further evaluate the mode of action of tumour formation, investigation of the genotoxic effects of the registered substance and its metabolites at the site of contact is deemed necessary.

A positive comet assay would contribute to improved risk management by you and may require a reconsideration of the current classification for mutagenicity and carcinogenicity as regulatory measures.

Considerations on the test method and testing strategy

It is noted that comet assay can detect genotoxic effects which may manifest themselves as gene and/or chromosome mutations. The method is suitable in this particular case because of the remaining uncertainties whether 4,4'-MDI (including metabolites) and consequently also the registered substance may cause genotoxicity *in vivo* locally at the site of contact or in liver despite that evidence of causing chromosome aberrations in more distant tissues such as bone marrow seems absent or very weak.

After obtaining the information requested in the present decision, the evaluating MSCA will assess whether there is still a concern for genotoxicity and consider whether further studies need to be requested to clarify the concern.

Alternative approaches and proportionality of the request

Comet assay is proved to be of comparable performance in detecting the micronucleus-negative or equivocal carcinogens compared to a transgenic rodent somatic and germ cell gene mutations assay (TGR) as an alternative test guidline to investigate genotoxicity *in vivo* at local site of contact (Kirkland *et al.*, 2008). Comet assay is less expensive than the potential alternative TGR assay. There are no animal free alternative to investigate *in vivo* genotoxicity as a concern for the substance subject to the present decision.

ECHA notes that the requested study has already been requested in the substance evaluation decision for 4,4'-MDI, dated 13 April 2016. There should be no replication of vertebrate animals studies. The study conducted with 4,4'-MDI can inform on the properties of the registered substance and should therefore be taken into account before any additional testing is considered.

Consideration of Registrant(s)' comments

As indicated in your comments on the draft decision, you accepted the request.

Conclusion

Therefore, based on the substance evaluation and pursuant to Article 46(1) of the REACH Regulation, ECHA concludes that you are required to submit the following information on *in vivo* mammalian alkaline comet assay using the substance 4,4'-methylenediphenyl diisocyanate (4,4'-MDI, EC: 202-966-0)*;* test method OECD TG 489 in Wistar rats, inhalation route, on the following tissues: lungs and liver; glandular

stomach tissue shall be harvested and stored, and analysed if negative results are obtained in liver and lungs.

2. Information concerning worst case scenarios for consumer uses in relation to generation of and consequent possible exposure to 2,4'- and 4,4'-MDA

The concern(s) identified

During the end use of the substance by consumers, a polymerisation process takes place where residual -NCO groups may react with water vapour in air and theoretical exposure via inhalation and other routes to the corresponding hydrolysis products methylenedianilines (2,4'- and 4,4'-MDA) which are classified *inter alia* as Muta. 2, Carc. 1B, although expected to be relatively low can not be fully excluded.

Why new information is needed

No information is provided within the dossier(s) in relation to 2,4'- and 4,4'-MDA during and after the application phase of consumer products, where most critical level of exposure can be expected.

Therefore, it is necessary to show that inhalation and other exposure risks arising from the use of the worst case consumer products in relation to 2,4'- and 4,4'-MDA are controlled, and as such additional information shall be presented in the dossier(s) to better demonstrate that the generation of 2,4'- and 4,4'-MDA is not of significance.

The worst case shall be determined upon the maximum concentration of the registered substance in the consumer products, the maximum duration of the application phase, high use frequency, use at elevated temperatures and/or other factors that could increase the potential to be exposed to 2,4'- and 4,4'-MDA.

In the event significant generation of 2,4'- and 4,4'-MDA cannot be excluded it would be necessary to consider the need for developing exposure scenarios to further characterise exposure and risk. This will allow to assess whether any possible risks arising from the substance are adequately controlled during manufacture and use(s) included in the supply chain or whether further regulatory measures are necessary in this regard.

Consideration of Registrant(s)' comments

As indicated in your comments on the draft decision, you accepted the request and are willing to map the product portfolio available for consumers and provide data on the possible generation of and exposure to 2,4'- and 4,4'-MDA.

Conclusion

Therefore, based on the substance evaluation and pursuant to Article 46(1) of the REACH Regulation, ECHA concludes that you are required to provide additional information concerning worst case scenarios for consumer uses in relation to generation of and possible exposure to 2,4'- and 4,4'-MDA.

3. Specification of the process categories for the intended uses where the use of the registered substance simultaneously with aprotic polar solvents occurs and specification of the recommended measures to ensure that 2,4'- and 4,4'-MDA is either not formed or exposure to 2,4'- and 4,4'-MDA is controlled

The concern(s) identified

It is indicated in the available information in the dossier(s) that all MDI isomers and forms are highly unstable in dimethylsulhpoxide (DMSO) solvent and the water content of the DMSO increases the breakdown into corresponding diamines. MDI is more stable in ethyleneglycoldimethylether (EGDME) as solvent. In general the available information in the dossier(s) indicates that polar aprotic solvents (including DMSO, acetone, NMP, DMF etc.) considerably accelerate the reaction with water and facilitate the formation of amines. (Herbold *et al.*, 1998; Seel *et al.*, 1999)

Because 2,4'- and 4,4'-MDA are classified *inter alia* as Carc. 1B, Muta. 2, it must be ensured that the registered substance is not used together with any such solvents without proper measures.

Why new information is needed

The available information in the dossier(s) indicates that the use of polar aprotic solvents in combination with polymeric MDI is taken into account in selecting appropriate protective equipment (API, 2002). However, it is not clear from the available data where the use of the registered substance (and mixtures containing the registered substance) together with aprotic polar solvents (and mixtures containing such solvents) can be expected and whether the applicable measures are protective towards risks arising from the possible exposure to 2,4'- and 4,4'-MDA. Furthermore, there are no clear recommendations for simultaneous use of the registered substance and aprotic polar solvents down the supply chain.

Additional information on the process categories for the intended uses is needed to assess whether any possible risks arising from the substance are adequately controlled during manufacture and use(s) included in the supply chain or whether further regulatory measures are necessary in this regard.

Consideration of Registrant(s)' comments

As indicated in your comments on the draft decision, you accepted the request and are willing to add, where relevant, exposure scenarios and process categories for intended uses together with risk management measures required to ensure that 2,4'-MDA and 4,4'-MDA is either not formed or exposure to these substances is controlled.

Conclusion

Therefore, based on the substance evaluation and pursuant to Article 46(1) of the REACH Regulation, ECHA concludes that you are required to provide specification of the process categories for the intended uses where the use of the registered substance, simultaneously with aprotic polar solvents occurs and specification of the recommended measures to ensure that 2,4'- and 4,4'-MDA is either not formed or exposure to 2,4'- and 4,4'-MDA is controlled.

Deadline to submit the requested Information

In the draft decision communicated to you the time indicated to provide the requested information was 6 months from the date of adoption of the decision. Taking into account the deadline for submitting the information for 4,4'-MDI which is 20 July, 2017, ECHA decided to extend the deadline of the present decision to 9 months from the date of adoption of this decision to allow you to consider the applicability of the read-across approach between 4,4'-MDI and the registered substance subject to this decision.

Appendix 2: Procedural history

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to Human health/CMR; Sensitiser; Environment/Suspected PBT; Exposure/Wide dispersive use; Consumer use; Aggregated tonnage, Reaction mass of 4,4'-methylenediphenyl diisocyanate and o-(p-isocyanatobenzyl)phenyl isocyanate / methylene diphenyl diisocyanate CAS No. N/A (EC No 905-806-4) was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2015. The updated CoRAP was published on the ECHA website on 17 March 2015. The Competent Authority of Estonia (hereafter called the evaluating MSCA) was appointed to carry out the evaluation.

Pursuant to Article 45(4) of the REACH Regulation the evaluating MSCA carried out the evaluation of the above substance based on the information in your registration(s) and other relevant and available information.

The evaluating MSCA considered that further information was required to clarify the concerns related to the potential genotoxic properties of the substance, the life cycle of the substance with regards to the consumer uses and the simultaneous use of the registered substance with solvents. 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 14 March 2016.

The decision making followed the procedure of Articles 50 and 52 of the REACH Regulation.

ECHA notified you of the draft decision and invited you to provide comments.

Registrant(s)' commenting phase

ECHA received comments from you and forwarded them to the evaluating MSCA without delay.

The evaluating MSCA took into account the comments from you, which were sent within the commenting period, and they are reflected in the Reasons (Appendix 1).

Proposals for amendment by other MSCAs and ECHA and referral to Member State Committee

The evaluating MSCA notified the draft decision to the Competent Authorities of the other Member States and ECHA for proposal(s) for amendment.

Subsequently, the evaluating MSCA received proposals for amendment to the draft decision regarding the applicability of the read-across approach. They are reflected in the Reasons (Appendix 1).

ECHA referred the draft decision, together with your comments, to the Member State Committee.

ECHA invited you to comment on the proposed amendment(s). Any comments on the proposal(s) for amendment were taken into account by the Member State Committee and are reflected in the Reasons (Appendix 1). The Member State Committee did not take into account any comments on the draft decision as they were not related to the

proposal(s) for amendment made and are therefore considered outside the scope of Article 52(2) and Article 51(5).

A unanimous agreement of the Member State Committee on the draft decision was reached on 28 November 2016 in a written procedure launched on 17 november 2016 and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided by you in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on your dossier(s) at a later stage, nor does it prevent a subsequent decision under the current substance evaluation or a new substance evaluation process once the present substance evaluation has been completed.

2. Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

Appendix 4: References

API, Alliance for the Polyurethanes Industry "PMDI User Guidelines for Protective Clothing Selection" Technical Bulletin AX178, (2002, January).

[redacted]

Gledhill A, Wake A, Hext P, Leibold E, Shiotsuka R (2005) Absorption, distribution, metabolism and excretion of an inhalation dose of (14C) 4,4'-methylenediphenyl diisocyanate in the male rat; Xenobiotica 35(3), 273-92.

Herbold B, Haas P, Seel K, Walber U (1998) Studies on the effect of the solvents DMSO and EGDE on the mutagenicity of four types of diisocyanates in the Salmonella/microsome test; Mutation Research 412, 167-175.

Kirkland D, Speit G (2008) Evaluation of the ability of a battery of three in vitro genotoxicity tests to discriminate rodent carcinogens and non-carcinogens III. Appropriate follow-up testing in vivo; Mutation Research 654(2), 114-32.

Lindberg H K, Korpi A, Santonen T, Säkkinen K, Järvelä M, Tornaeus J, Ahonen N, Järventaus H, Pasanen A-L, Rosenberg C, Norppa H (2011) Micronuclei, hemoglobin adducts and respiratory tract irritation in mice after inhalation of toluene diisocyanate (TDI) and 4,4'-methylenediphenyl diisocyanate (MDI); Mutation Research 723, 1-10.

[redacted]

OECD 489 guideline for the testing of chemicals: In Vivo Mammalian Alkaline Comet Assay. 29 July 2016

[redacted]

Seel K, Walber U, Herbold B and Kopp R (1999) Stability of 4,4'-MDI and its isomers in DMSO and EGDE under conditions of the Bacterial Reverse Mutation Assay; Mutation Research 438, 109-1