Helsinki, 13 April 2016

Decision/annotation number: Please refer to the REACH-IT message which delivered this communication (in format SEV-D-XXXXXXXXX-XX-XX/F)" and delete the section above

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

For 4,4'-methylenediphenyl diisocyanate, CAS No 101-68-8 (EC No 202-966-0)

Addressees: Registrant(s)[1] of 4,4'-methylenediphenyl diisocyanate (Registrant(s))

This decision is addressed to the Registrant(s) of the above substance with an active registration pursuant to Article 6 of the REACH Regulation on the date on which the draft for the decision was first sent for comments. A list of all the relevant registration numbers of the Registrant(s) that are addressees of the present decision is provided as an Annex to this decision.

Based on an evaluation by Health Board as the Competent Authority of Estonia (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 is based on the registration dossier(s) on 4 July 2014, i.e. the day until which the evaluating MSCA granted an extension for submitting dossier updates which it would take into consideration.

This decision does not imply that the information provided by the Registrant(s) in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on the dossier(s) of the Registrant(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.

I. Procedure

Pursuant to Article 45(4) of the REACH Regulation the Competent Authority of Estonia has initiated substance evaluation for 4,4'-methylenediphenyl diisocyanate (4,4'-MDI), CAS No 101-68-8 (EC No 202-966-0) based on registration(s) submitted by the Registrant(s) and other relevant and available information 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/CMR; Sensitiser; Environment/Suspected PBT; Exposure/Wide dispersive use; Consumer use; Aggregated tonnage, 4,4'-MDI was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2013. The updated CoRAP was published on the ECHA website on 20 March 2013. The Competent Authority of Estonia was appointed to carry out the evaluation.
The evaluating MSCA considered that further information was required to clarify concerns related to the potential genotoxic properties of the substance, the life cycle of the substance

[1] The term Registrant(s) is used throughout the decision, irrespective of the number of registrants addressed by the decision.

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 20 March 2014.

On 29 April 2014 ECHA sent the draft decision to the Registrant(s) 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.

Registrant(s) commenting phase

By 5 June 2014 ECHA received comments from the Registrant(s) of which it informed the evaluating MSCA without delay.

By 4 July 2014 Registrant(s) submitted update(s) of the registration dossier(s). The evaluating MSCA considered the comments received from the Registrant(s) and the dossier updates. On basis of this information, the Statement of Reasons (Section III) was changed accordingly.

Commenting by other Member State Competent Authorities (MSCAs) and ECHA

In accordance with Article 52(1) of the REACH Regulation, on 3 September 2015 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 of the receipt of the notification.

Subsequently, three Competent Authorities of the Member States and ECHA submitted proposals for amendment to the draft decision.

On 9 October 2015 ECHA notified the Registrant(s) 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 reviewed the proposals for amendment received and amended Section II: Information required and Section III: Statement of Reasons of the draft decision.

Referral to Member State Committee

On 19 October 2015 ECHA referred the draft decision to the Member State Committee.

By 9 November 2015, the Registrant(s) provided comments on the proposals for amendment, in accordance to Article 51(5) and on the draft decision. The Member State Committee took the comments on the proposal(s) for amendment of the Registrant(s) into account.

Taking into account the proposal for amendment and the Registrant(s)' comments an initial request regarding the qualitative risk characterisation for respiratory sensitisation for workers, professionals and consumers was no longer deemed necessary.

Taking into account the proposals for amendment and the Registrant(s) comments, the initial request regarding reproductive toxicity endpoint was considered not necessary at this stage of the process and was removed from the decision. However, the possible need to

request studies on reproductive toxicity will be reconsidered during the follow-up evaluation process pursuant the Article 46(3) of the REACH Regulation, after the data requested in this decision will become available.

The proposals for amendment for an *in vivo* test for genotoxicity were provided by two Member States Competent Authorities: comet assay, oral gavage (OECD 489) and comet assay, inhalation or Transgenic Rodent Gene Mutation Assay (TGR). Taking into account the proposals for amendment, the concern regarding genotoxicity of the registered substance is addressed in the present decision as elaborated below. The Member State Committee discussion resulted as well in the conclusion that a toxicokinetics study *in vivo* is not merited at this stage.

After discussion in the Member State Committee meeting on 7 to 11 December 2015, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 11 December 2015. ECHA took the decision pursuant to Article 52(2) and Article 51(6) of the REACH Regulation.

II. Information required

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit the following information using the indicated test methods/instructions (in accordance with Article 13(3) and (4) of the REACH Regulation) and the registered substance subject to the present decision:

1. *In vivo* mammalian alkaline comet assay (OECD 489), Wistar rat, via inhalation route as specified in section III of the decision, 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.

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall also submit the following information regarding the registered substance subject to the present decision:

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

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

Deadline for submitting the required information

Pursuant to Article 46(2) of the REACH Regulation, the Registrant(s) shall submit to ECHA by **20 July 2017** an update of the registration(s) containing the information required by this decision[2], including robust study summaries and, where relevant, an update of the Chemical Safety Report.

III. Statement of reasons

1. *In vivo* mammalian alkaline comet assay (OECD TG 489) in Wistar rat, via inhalation route with examination of lungs and liver; glandular stomach

[2] The deadline set by the decision already takes into account the time that registrants may require to agree on who is to perform any required tests and the time that ECHA would require to designate a registrant to carry out the test(s) in the absence of the aforementioned agreement by the registrants (Article 53(1) of the REACH Regulation).

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

Based on the evaluation of all relevant information submitted on 4,4'-MDI it was concluded that further information is required in order to clarify the concern related to genotoxic properties of the registered substance and to clarify whether the substance constitutes risk to human health due to a non-threshold genotoxic mode of action. One of the potential metabolites is 4,4'-methylenedianiline (4,4'-MDA) which is classified pursuant to Regulation (EC) No 1272/2008 concerning classification and labelling of substances *inter alia* as mutagenic (Muta. 2), carcinogenic (Carc. 1B) and is included in Annex XIV of the REACH Regulation as a substance of very high concern subject to authorisation (Entry 2 of Annex XIV).

There is a concern related to carcinogenicity of 4,4'-MDI and possible genotoxic mode of action for tumour induction. A reliable 2-year chronic toxicity/carcinogenicity inhalation study ([redacted] *et al.*, 1990) is available where 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. The Registrant(s) claimed a non-genotoxic mode of action for tumours formation due to 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 genotoxic or non-genotoxic mode of action.

During the consultation phase with MSCAs and ECHA, a proposal for amendment was submitted to perform a comet assay via inhalation to investigate whether genotoxic effects in the somatic cells are observed. Following this proposal for amendment, the available data was reconsidered and it was concluded that 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 reaction products formed under specific assay conditions than the ones of the parent compound. Only in one available *in vitro* bacterial reverse mutation assay (Ames test) (solutions of 4,4'-MDI in ethyleneglycoldimethylether (EGDME) as 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 ([redacted] *et al.*, 1981) were considered by the Registrant(s) 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 as 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 erythrocytes 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 this 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*".

The concern is that the registered substance may exhibit genotoxic effects at the site of contact, as parent compound or due to the formation of toxicologically relevant metabolites (e.g. 4,4'-MDA). The Registrant(s) has claimed that no free MDA is formed after inhalation exposure to 4,4'-MDI. 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 MDA is not detected. In addition, the Registrant(s) has noted that biomonitoring studies demonstrate that the intermediary steps of MDI metabolism under plasma physiological conditions proceed entirely without formation of any free amines, including MDA. In *in vitro* studies ([redacted] *et al.*, 2003) formation 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, provided studies cannot exactly mimic the processes that occur *in vivo*.

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. 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.

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) 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. Additionally, comet assay has 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 guideline to investigate genotoxicity *in vivo* at local site of contact (Kirkland *et al.*, 2008). A comet assay is less expensive than the potentially alternative TGR assay. There are no animal free alternatives to investigate genotoxicity as a concern for the substance subject to the present decision.

Test design:

- The study shall be conducted in Wistar rats, because the inhalation carcinogenicity study in which lung tumours were observed was conducted in this species and strain. This would enable establishing the link between the cause and the observed effects.
- The animals shall be exposed via inhalation nose-only to 4,4'-MDI aerosol; whole body exposure should be avoided to prevent exposure to the substance via grooming. Aerosol particle size shall be in line with Guidance Document on Acute Inhalation Toxicity Testing (OECD GD 39, 2009).
- The tissues sampled and analysed in the comet assay shall be lungs as the first site of contact tissue after inhalation dosing, liver as this is a primary site of xenobiotic metabolism and is often highly exposed to both parent substance(s) and metabolite(s); because the toxicologically relevant metabolite 4,4'-MDA may be potentially formed in gastrointestinal tract tissues following indirect exposure via mucociliary escalator, glandular stomach tissue shall be harvested and stored and analysed if negative results from liver and lungs would be obtained. Considerations and references provided in the TG 489 in relation to freezing of tissues should be taken into account.
- The optimum sampling time(s) should be established according the considerations in the test guideline OECD TG 489.
- The considerations in relation to the choice of vehicle shall be applied. The formation of 4,4'-MDA or 4,4'-MDA adducts was detected after exposure to 4,4'-MDI (human

data: Schütze *et al.*, 1995; animal studies: Sepai *et al.*, 1995; Sabbioni *et al.*, 2000; [redacted] *et al.*, 1996) and was considered by the Registrant(s) to be due to the procedure of sample treatment. Therefore the Registrant(s) has to ensure that 4,4'-MDA is not formed due to use of inappropriate solvent or due to treatment procedure.

The registered substance is widely used including professional and consumer uses. The possibility of exposure that goes beyond the normal controlled exposure levels may be relevant when investigating inherent properties such as non-threshold genotoxic events. In particular professional spray applications may have the possibility of generating high levels of aerosol. Furthermore, other exposure may occur via the dermal route and inadvertent transfer to the peri-oral region.

A positive comet assay will contribute to improved risk management by the Registrant(s) and require a reconsideration of the current classification for mutagenicity and carcinogenicity as regulatory measures.

Therefore, pursuant to article 46(1) of the REACH Regulation, the Registrant(s) is required to carry out the following study: ***In vivo* mammalian alkaline comet assay (OECD TG 489) in Wistar rat, via 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.**

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

One proposal for amendment to the draft decision by a Competent Authority of a Member State suggested to consider the life cycle of the substance from the chemical use to the service life of manufactured articles in relation to 4,4'-MDI, the most relevant metabolite/hydrolysis product 4,4'-MDA and/or other relevant reaction/degradation substances.

The Registrant(s) provided extensive comments on the proposal for amendment concerning the life cycle of 4,4'-MDI. However, no information is provided within the dossier(s) in relation to 4,4'-MDA during and after the application phase of consumer products, where most critical levels of exposure can be expected. It may be foreseen during the application and post application phase that residual -NCO groups may theoretically react with water vapour in the air and exposure to 4,4'-MDA via inhalation and other routes, although expected to be relatively low can not be fully excluded. The Registrant(s) stated in the comments that "*the amine immediately reacts with any –NCO group present under the formation of urea. The reaction of the intermediate amine is significantly faster than its formation from MDI and water, since an amino group is a much stronger nucleophile. Therefore, if both an –NH2 group and an -OH group are present at the same time, the primary amino group will always react first and much faster with the isocyanate group than the water can react with it*". However, it is necessary to show that inhalation and other exposure risks arising from the use of the worst case consumer products in relation to 4,4'-MDA are controlled, and as such additional information shall be presented in the dossier(s) to better demonstrate that the generation of 4,4'-MDA is not of significance.

The worst case shall be determined upon the maximum concentration of 4,4'-MDI 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 4,4'-MDA.

In the event significant generation of 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 assessing whether any possible risks arising from the substance are adequately controlled during consumer use(s) included in the supply chain or whether further regulatory measures are necessary in this regard.

Therefore, pursuant to article 46(1) of the REACH Regulation, the Registrant(s) is required to provide additional **information concerning worst case scenarios for consumer uses in relation to generation of and possible exposure to 4,4'-MDA**.

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

There is evidence from the available information in the dossier(s) from the mutagenicity studies that 4,4'-MDI is highly unstable in dimethylsulhpoxide (DMSO) solvent and the water content of the DMSO increases the breakdown into 4,4'-MDA. MDI is more stable in EGDME as solvent. HPLC analysis showed that after 4 hours 87,6% of MDI was found in EGDME but any was detected in DMSO and, contrary, 3% of MDA was found in DMSO but not in EGDME. Traces of water that are always found in dried commercial DMSO degraded the diisocyanates and led to a number of reaction products, including small amount of MDA. 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 4,4'-MDA has harmonised classification, *inter alia* as Carc. 1B and Muta. 2 according to Regluation (EC) No 1272/2008, it must be ensured that 4,4'-MDI is not used together with any such solvents without proper safety measures.

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). Furthermore, it is indicated by the Registrant(s) in the comments to the proposal for amendment that dipolar solvents are only used in laboratories and polar aprotic solvents behave as solvents for MDI applications. The Registrant(s) has also stated in the comments that dipolar and polar aprotic solvents can be used without the risk of 4, 4'-MDA formation, if their water content is appropriately controlled. However, it is not clear from the available data where the use of 4,4'-MDI (and mixtures containing 4,4'-MDI) 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 4,4'-MDA. Furthermore, there are no clear recommendations for simultaneous use of 4,4'-MDI and aprotic polar solvents down the supply chain.

This specification of the process categories for the intended uses 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.

Therefore, pursuant to article 46(1) of the REACH Regulation, the Registrant(s) is required to provide **specification of the process categories for the intended uses where the use of 4,4'-MDI simultaneously with aprotic polar solvents occurs and specification of the recommended measures to ensure that 4,4'-MDA is either not formed or exposure to 4,4'-MDA is controlled.**

IV. Deadline to provide the requested information

Whereas initially a longer timeline of 44 months was considered appropriate to provide the information as set out in the draft decision, the amendments incorporated during the decision making process resulted in information requests that can be met within a shorter period of time. ECHA considers that a period of 15 months is appropriate to provide all information requested in this decision including the time that Registrant(s) need to agree who is to carry out the experimental study on behalf of the other Registrant(s).

V. Adequate identification of the composition of the tested material

In relation to the required experimental stud(y/ies), the sample of the substance to be used shall have a composition that is within the specifications of the substance composition that are given by all Registrant(s). It is the responsibility of all the Registrant(s) to agree on the tested material to be subjected to the test(s) 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. Finally, the test(s) must be shared by the Registrant(s).

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

In relation to the experimental stud(y/ies) the legal text foresees the sharing of information and costs between Registrant(s) (Article 53 of the REACH Regulation). Registrant(s) are therefore required to make every effort to reach an agreement regarding each experimental study for every endpoint as to who is to carry out the study on behalf of the other Registrant(s) and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation. 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/regulations/reach/registration/data-sharing

If ECHA is not informed of such agreement within 90 days, it will designate one of the Registrant(s) to perform the stud(y/ies) on behalf of all of them.

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://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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.

Annex: List of registration numbers for the addressees of this decision. This annex is confidential and not included in the public version of this decision.

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]

Sabbioni G, Hartley R, Henschler D, Höllrigl-Rosta A, Koeber R, Schneider S (2000) Isocyanate-specific hemoglobin adduct in rats exposed to 4,4'-methylenediphenyl diisocyanate; Chemical Research in Toxicology 13, 82-89.

Schütze D, Sepai O, Lewalter J, Miksche L, Henschler D, Sabbioni G (1995) Biomonitoring of workers exposed to 4,4'-methylenedianiline or 4,4'-methylenediphenyl diisocyanate; Carcinogenesis 16(3), 573-82.

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, 109-123.

Sepai O, Schütze D, Heinrich U, Hoymann HG, Henschler D and Sabbioni G (1995) Hemoglobin adducts and urine metabolites of 4,4'-methylenedianiline after 4,4'-methylenediphenyl diisocyanate exposure of rats; Chemico-Biological Interactions 97, 185-198.