HBM4EU science and policy for a healthy future

HORIZON2020 Programme
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HBM4EU comments on the ECHA Scientific report for evaluation of limit values for diisocyanates at the workplace

HBM4EU is a joint effort of 28 countries, the European Environment Agency and the European Commission, co-funded under Horizon 2020. The initiative is coordinating and advancing human biomonitoring (HBM) in Europe. HBM4EU is generating evidence of the actual exposure of citizens to chemicals and the possible health effects in order to support policy making.

The HBM4EU initiative represents a novel collaboration between scientists and chemical risk assessors and risk managers, including several Commission services, EU agencies and representatives for the national level. The project has built bridges between the research and policy worlds in order to deliver benefits to society in terms of enhanced chemical safety.

In developing priorities for HBM4EU under the first annual work plan, the consortium conducted a prioritisation exercise in 2016 to identify those substances to be the focus of activities. A second round of prioritisation was conducted from 2017 to 2018. One of the priority compound groups prioritized under HBM4EU is diisocyanates. Therefore, there are plenty of activities under way related to the diisocyanates under HBM4EU. These include the planning of the targeted biomonitoring study on occupational exposure to diisocyanates in five European countries, gathering of HBM data on diisocyanates, development of a physiologically-based pharmacokinetic (PBPK) model for occupational diisocyanate exposure and, for example, characterization of adverse outcome pathways (AOPs) for diisocyanate toxicity.

This response has been prepared by the experts from research institutes involved in the occupational task group of HBM4EU, who are involved in the diisocyanate related activities.

First of all, we would like to express our support to the plans to set an EU-wide occupational exposure limit value for diisocyanate exposure to prevent occupational asthma. However, since respiratory protection is often a control measure, and skin exposure may be a significant route of entry which may contribute to the induction of respiratory sensitization by diisocyanates, we would like to emphasize the role of biomonitoring in the control of occupational exposure to diisocyanates. Therefore, we consider it necessary to give clear recommendations concerning biomonitoring and the setting of at least BGV for the recommended biomarkers. We would like to point out that even though the levels of urinary diamines remain below the detection limits in occupationally non-exposed population, BGV may be set as equivalent to the detection limit of the biomonitoring

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method, which then should be specified in the document (ECHA, 2019)[1]. Such an approach already has a precedent[2].

Under HBM4EU, we have prepared a systematic review on the biomonitoring data on the occupational exposure to diisocyanates (Scholten et al., Biomonitoring for occupational exposure to diisocyanates: a systematic review). This has been recently submitted for publication in Annals of Work Exposures and Health. Since this has not been published yet, we attach the manuscript here as a confidential annex (annex 1). It includes some studies which have not been included in the current version of the ECHA scientific report but which may be useful to add. These include e.g. the studies by Cocker (2009), Keen (2012), Sakkinen 2011 and Rosenberg (2002) in section 5.3.3. (uses in polyurethane industry – data from biomonitoring). Further in table 12 (page 35) a number of studies are missing for the motor vehicle repair industry: Flack (2010), Gaines (2010), Robbins (2018), Hu (2017) and Jones (2013). Please note that this list is probably not complete hence we attach our review paper to enable a full comparison of the studies we retrieved and the studies you have included. A paper by Stocks et al, 2015 looked at diisocyanate exposure (as measured by urinary diamines) and asthma and may be worth considering. Under HBM4EU also a report on the prioritized biomarkers and analytical methods for priority substances has been prepared (Deliverable Report D9.5, Prioritised list of biomarkers, matrices and analytical methods for the 2nd prioritisation round of substances). This includes also recommendations concerning diisocyanate biomarkers. The report can be found from the HBM4EU website, https://www.hbm4eu.eu/deliverables/.

In the document, it is stated at Table 12 that non-EU/US data is not included. No reason appears to be given for this exclusion and later in the document there is discussion around the Mirmohammadi et al, 2010 (Iran) studies (Table 17). To exclude non-EU/US data also excludes a large motor vehicle repair survey carried out in Australia (Hu et al, 2017).

On p47 it is stated that “different excretion kinetics of different diisocyanates together with the inter-individual differences and the contribution of dermal uptake, make it difficult to find a correlation between air monitoring data and biomarker concentration”. However, it should be noted that most workers are not exposed to multiple diisocyanates at the same time. Correlations have been reported where conditions are appropriate i.e. no RPE or significant skin exposure. As the ECHA study does not seem time-bound (some references go back to the 1950s) then there are quite a few correlations between air and urine biomonitoring published. (In addition to Brorson et al, 1990 and Maitre et al, 1996 reported in Table 17, Tinnerberg et al, 1995 have also reported chamber studies for HDI and IPDI, the reference is listed but not included in the table; for TDI, in addition to

[1] ECHA (2019) Appendix to Chapter R.8: Guidance for preparing a scientific report for health-based exposure limits at the workplace, https://echa.europa.eu/documents/10162/23036412/ircsa_r8_appendix_oels_en.pdf/f1d45aca-193b-a7f5-55ce-032b3a13f9d8

[2] ECHA (2017) Opinionon4,4’-methylene-bis-[2-chloroaniline](MOCA), https://echa.europa.eu/documents/10162/13641/opinion_moca_en.pdf/35756093-0eb9-e468-2ba2-786ca73c5aaa

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Brorson et al 1991 and Skarping et al 1991 (where correlations can be derived but have not been), Rosenberg and Savolainen 1986 report that "excretion was linearly related to the product of sampling time and concentration"). Although these are looking at the specific isocyanate in air and comparing to urine there is very limited discussion of such correlations in the document, given the number of studies available. Such correlations could also be converted from specific diisocyanates to total NCO, especially where controlled studies of monomer have been conducted.

Section 8.2.3 (BLV) is incredibly short and does not discuss the approaches of other standard setting bodies, unlike the air limit section which does discuss alternative approaches used by, for example, ACGIH and DFG, both of which also set BLVs.

Section 8.2.4, see earlier comments on setting a BGV at the current detection limit. Also, Sennbro et al (2005) have reported background range for TDI, MDI and NDI. The reference is listed but is not discussed in section 8.2.4. Also if saying "the background levels of the general population are in most cases non detectable", the detection limit needs to be defined.

Additionally, we have following detailed comments:

Page, line	Comment
p27	4,4'-Diphenylmethane Diisocyanate (DDI) should be labelled MDI for consistency
6.2 (p46) and 7.1.4 (p53)	"the exposure of the data collection (Cocker, 2011)" – should say "day of collection"?
Throughout e.g. Table 9, p48, p50, p51	A number of autocorrections from HDA to HAD
Throughout in Tables 1, 2, 4	ordering of TDI and MDI isomers
p12, Table 2	"1 ppm in mg/m^{34}" – should be corrected to "1 ppm in mg/m$^{3\ 3,4}$
P14, line 3	"are all are" – second "are" to suppress
p15, Table 3	"*, STOT SE 3, STOT RE 2, **" – specify what it refers to
p19, 3.4(a)	(*) – specify what it refers to
p21, 4.	(OEls) – (l) in upper case
p21, Table 5	"ppm mg/m^{3}" for Diisocyanates TWA-8 hrs – ppm in front of the first column and mg/m^3 in front of the second column
Throughout in Tables 6, 7, 8	"Ppm" column 2 – should be corrected to "ppm" (1) referring to 15 minutes reference period added in the columns related to TWA-8hrs
p23, Table 8	(2) (3) – what it refers to
p24, Biological limit values (BLVs)	To move somewhere else as chapter 4 is dedicated to OELs
p24, Table 9	"10 µg/l 4,4' " – should be corrected to "10 µg/l"
Throughout e.g. p30, p48	"µg/m3" – should be corrected to "µg/m^{3}"
p31, Data from biomonitoring (line18)	"from below the detection limit to 0.08" – should be corrected to "from below the detection limit to 0.8"

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p37, Table 12	(**) – specify what it refers to
p40, first paragraph	"Table13Table13. (FIOH, 2019) – second "Table13" to suppress
P40, Table13	"The bolded industry sector has have exposures" – should be corrected by "The bolded industry sector has had exposures"
p46, line 3	"DPA" – should be corrected by "DBA" What "DMSO" refers to should be added as for the others acronyms
Throughout e.g. Tables 9, 17, 18, 19	Lettering styles to be harmonized
p48, 6.2.2.2 MDI (Table 18 and line 5)	"2.58 (0.3-3.7) µg MDA/g creatinine" – MDA to delete since already indicated at the top of the column "2.1 µ/L" – should be corrected to "2.1 µg/l" "in terms of MDA per/l" – to correct "in terms of MDA / l"
p48, 6.2.2.3 TDI (line 4)	"Table 19:" – should be corrected by "Table 19."
p49, Table 19 (line 3)	"84/91" – 91: what it refers to (not found in the article)
p49, Table 20	Throughout "in urine/urine" – to delete and put it at the top of each column
p49, Notes (after Table 20)	TDA, IPDA, MDA should be presented first (as for HDA)
p50, Excretion	"In the sudy of Brorson et al. (1991) (see above)" – the study is not mentioned above
p77-78, Genotoxicity	Review by Bolognesi et al., 2001 could be mentioned here as well (included in Carcinogenicity section). It could be noted that there are no *in vivo* studies on the local genotoxicity of diisocyanates. Since diisocyanates are very reactive substances and some of them has caused local respiratory cancers in animal studies, local genotoxicity cannot to be ruled out.

We hope that these comments are of value and will be considered.

Yours sincerely

The occupational working group on diisocyanates within HBM4EU

Additional references

Hu, J., P. Cantrell, and A. Nand, Comprehensive biological monitoring to assess isocyanates and solvents exposure in the NSW Australia motor vehicle repair industry. Annals of work exposures and health, 2017. 61(8): p. 1015-1023.

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Rosenberg C, Savolainen H. Determination of occupational exposure to toluene diisocyanate by biological monitoring. J Chromatogr. 1986 Oct 3;367(2):385-92.

Stocks SJ, Jones K, Piney M, Agius RM. Isocyanate exposure and asthma in the UK vehicle repair industry. Occup Med (Lond). 2015 Dec;65(9):713-8.

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