Supplementary Table 2: Use of HBM in risk assessments under REACH: illustrating examples

Risk Assessment	Description
Phthalates restriction	Entry 51 of REACH Annex XVII to Regulation (EC) No 1907/2006 restricts three phthalates in plasticised materials of toys and childcare articles: bis(2-ethylhexyl phthalate (DEHP), dibutyl phthalate (DBP) and benzyl butyl phthalate (BBP). In 2016, ECHA in cooperation with Denmark prepared a restriction report to propose a restriction on these three phthalates, including additionally also diisobutyl phthalate (DIBP) and expanding in the scope of the restriction to plasticized materials of all articles(ECHA, 2017a). The Dossier Submitter's exposure assessment relied mostly on the urinary HBM data generated by the EU-wide DEMOCOPHES project. Daily intakes were estimated from the spot urinary samples extrapolating spot sample excretion data to full day excretion. Risk Characterisation Ratios (RCRs) were then calculated for each individual phthalate by comparing the DNEL with the intake estimate based on the DEMOCOPHES HBM data. Total risk was calculated summing the RCRs of the individual phthalates into a combined RCR. Based on the 95th percentile of the combined exposure to the four phthalates measured, a risk (combined RCR $\geq$ 1) was identified for children in 13 out of 15 Member States; for women in six out of fifteen Member States. Reasonably good agreement was found between the HBM-based RCRs and RCRs calculated from the modelled exposure estimates for exposure via indoor environment, food and contact data with articles. Based on RAC's and SEAC's opinions on the restriction proposal, the EC concluded in 2017 that the 4 phthalates pose an unacceptable risk to human health when present in any plasticized material in articles, and that the risk had to be addressed on a EU-wide basis. Hence, in March 2018, a draft amendment was submitted to amend the REACH Annex XVII entry 51 – phthalates restriction.
Restriction of Bisphenol A in thermal paper	A proposal to restrict BPA because of health risks for pregnant workers and consumers exposed via thermal papers was submitted by the French authorities in May 2014. The health risk assessment for consumers and workers (cashier) was based on the calculation of the disease burden for the effects of concern from modelled exposure data only, because HBM data evaluating the exposure specifically through thermal paper were not available at the time of the proposal's elaboration. Later, RAC refined the assessment and complemented it with newly published HBM data on cashiers' exposure to BPA. ANSES and EFSA's assessments of the published HBM studies were included into an updated version of the restriction dossier. Even if the HBM data assessments by the two agencies differed (related to some assumptions and methods used in the HBM studies) (ECHA, 2015c), contribution of the cutaneous route of exposure via thermal paper handling was retained by the RAC, based on a significant increase of BPA urinary concentrations measured after testing cashiers during exposure scenarios. RAC thus concluded that the risk for consumers was adequately controlled but confirmed the risk for workers (more specifically for the unborn child exposed in utero to BPA contained in thermal-paper handled by his/her mother). As HBM data were confirming that the consumer exposure did not exceed the DNEL, good confidence was given to the risk characterization. Regarding workers, the integrated assessment of worker exposure was based on both modelling data and available biomonitoring data, which were considered to give a reasonable consistency

Authorization of MOCA	MOCA (4,4'-methylene-bis-[2-chloroaniline]) is an aniline derivative used as a curing agent in polyurethane production. Because of its carcinogenic properties, the uses of MOCA need to be authorized under REACH. In occupational studies in polyurethane industry, urinary MOCA levels has correlated best with the MOCA surface contamination, whereas correlations with air levels have been often low (Cocker et al., 2009; Keen et al., 2012). ECHA has performed a dose-response analysis for the carcinogenicity of MOCA (ECHA, 2015a). In its dose-response documentation, ECHA also presents estimated cancer risks for different urinary MOCA levels measured as total urinary MOCA in the end of the work-shift in the end of the work week. Since there are no established correlations between urinary and air levels nor PBTK/PBPK models for MOCA ECHA uses simple open one-compartment model based approach to roughly estimate the daily doses corresponding to urinary MOCA level of 5 µmol/mol creatinine in the end-shift Friday afternoon samples (ECHA, 2015b). This was provided to the applicants of authorization to facilitate the use of HBM in the exposure assessment of MOCA in its industrial uses. In the single upstream application for the use of MOCA (application by (REACHLaw Ltd, 2016) HBM data gathered from the industry was used to assess the workers' exposure to MOCA (ECHA, 2017b) together with literature data (Cocker et al., 2009; Keen et al., 2012; Robert et al., 1999). These all show urinary MOCA levels in the manufacturing of polyurethane which are about 10 µmol/mol creatinine or below. When compared to the exposure estimates based on dermal exposure modelling, the use of HBM resulted in up to 10-fold lower exposure estimates (ECHA, 2014, 2017b). This example demonstrates how HBM can be used for more accurate exposure and RA. Benefits of HBM include also that it considers hand-to-mouth exposure.

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