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Human biomonitoring as a pragmatic tool to support health risk management of chemicals – Examples under the EU REACH programme

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ABSTRACT

REACH requires health risk management for workers and the general population and introduced the concept of Derived No-Effect Level (DNEL). DNELs must be derived for all substances that are classified as health hazards. As with analogues to other health-risk based guidance values, such as reference doses (RfDs) and tolerable daily intakes (TDIs), risk to health is considered negligible if the actual exposure is less than the DNEL. Exposure assessment is relatively simple for occupational situations but more complex for the general public, in which exposure may occur via multiple pathways, routes, and media. For such complex or partially defined exposure scenarios, human biomonitoring gives a snapshot of internal or absorbed dose of a chemical and is often the most reliable exposure assessment methodology as it integrates exposures from all routes. For human risk management human biomonitoring data can be interpreted using the recently developed concept of Biomonitoring Equivalents (BE). Basically, a BE translates an established reference value into a biomarker concentration using toxicokinetic data. If the results of an exposure assessment using human biomonitoring indicate that the levels measured are below the DNEL-based BE (BE_{DNEL}), it would indicate that the combined exposure via all potential exposure routes is unlikely to pose a risk to human health and that health risk management measures might not be needed. Hence, BEs do not challenge existing risk assessments but rather build upon them to help risk management, the ultimate goal of any risk assessment. A challenge in implementing this approach forms the limited availability of toxicokinetic information for many substances. However, methodologies such as generic physiologically-based toxicokinetic models, which allow estimation of biomarker concentrations based on physicochemical properties, are being developed for less data-rich chemicals. Use of BE by regulatory authorities will allow initial screening of population exposure to chemicals to identify those chemicals requiring more detailed risk and exposure assessment, assisting in priority setting and ultimately leading to improved product stewardship and risk management.

1. Introduction and aims

In December 2006, new chemicals legislation was adopted in the European Union that aims to evaluate and control environmental and human health risks for all substances on the European market (EC, 2006). This legislation is known under its acronym REACH (Registration, Evaluation, and Authorisation of Chemicals) and requires producers and importers to register all substances placed on the European Union market. For every substance that is classified for toxicological and ecotoxicological hazards, an evaluation of the risk for environment and human health is required. Both the environmental and health risk assessments are based on the fundamental assumption that risk is a function of hazard and exposure. As a logical consequence, the risk assessment of chemicals involves at first the determination whether or not the chemical poses a toxicological or ecotoxicological hazard. If a hazard is identified, the next step is to establish the relationship between exposure (dose) and the effect. Once the actual exposure has been assessed, it can be used in combination with the exposure-effect relationship to estimate the actual risk to determine whether risk management measures are required. In this process, uncertainties associated with extrapolations, availability and quality of the hazard data, the exposure-effect relation, and the actual exposure are compensated with assessment factors to obtain a conservative estimate of the risk.

With the introduction of the Existing Substances Regulation in the European Union in 1993, the concept of PNEC (predicted no-effect concentration) was introduced for ecotoxicological risk assessment (EC, 1993). The PNEC is the environmental concentration of a substance below which exposure to a substance is not

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expected to cause adverse effects in the ecosystem. The PNEC is compared to the PEC (predicted exposure concentration) in the ecosystem and if the PEC is below the PNEC, the actual risk for the environment is deemed to be negligible. There are a number of fundamental differences between ecotoxicological and toxicological risk assessment. The most important being that in ecotoxicology the main focus is protection of a species population or ecosystem whilst in toxicology the main focus is to protect the individual. Despite this difference, in the REACH legislation a new concept, coined after PNEC, was introduced: DNEL. DNEL stands for derived no-effect level and is defined as the level of a substance above which a human should not be exposed (EC, 2006). In the risk characterisation process, the exposure of all human populations known to be or likely to be exposed should be compared to this DNEL. In practice, DNELs must be derived for all hazardous substances placed on the market in quantities exceeding 10 tonnes per year and should reflect route, duration and frequency of exposure. DNELs should be derived for occupational settings, for consumer use, and for the general population for indirect exposure via the environment.

The approach to derive a DNEL for a given substance and toxicological endpoint is provided in the technical guidance made available by the European Chemicals Agency (ECHA, 2008). The standard methodology involves the setting of a point-of-departure, which is a modified dose descriptor, usually based on a no-observed adverse effect level from an animal study. To the point of departure a series of default assessment factors is applied to compensate for variation as well as uncertainties with regard to the hazard of the substance for which the DNEL is derived. When specific information on the substance is available, informed assessment factors should be used to derive a DNEL (ECETOC, 2010; Gade et al., 2008; Gebel et al., 2009). In addition, when there is an indicative or binding occupational exposure limit (IOEL or BOEL) as established by the Scientific Committee of Occupational Exposure Limits (SCOEL) or when there is an adopted occupational exposure limit set by national authority in one of the Member States, these can be used as DNEL values for occupational settings, provided they are health-based (EC, 2009). There is still substantial debate on the way DNELs should be derived and how OELs can be used (ECETOC, 2010; Schäfer et al., 2009) but this is beyond the scope of this paper.

Once a DNEL has been derived, it needs to be compared to an actual exposure level. For the occupational situation, exposure assessment is relatively straightforward, as both the exposure source and situation are usually well defined and may be described with specific exposure scenarios. For a wide variety of industrial settings exposure scenarios are being developed by registrants. Verification of these exposure scenarios, however, may be more difficult, especially if there are other exposure routes than inhalation. The development of exposure scenarios for consumers is in most cases far more complex since there is wide variation in quantities and frequencies of use. Estimating exposure is particularly difficult if exposure occurs through multiple different exposure routes, e.g. dermal and inhalation. The assessment of the exposure of the general public via the environment is most complex as exposures are usually even less well defined and may involve inhalation, dermal and oral exposures.

Human biomonitoring is most helpful in both the actual exposure assessment for complex scenarios and the validation of exposure scenarios. By definition, human biomonitoring is the determination of a chemical or its metabolites in bodily fluids (e.g. urine, blood or saliva), tissues (e.g. hair), or exhaled air. For poorly defined exposure scenarios, biomonitoring is often the most reliable exposure assessment methodology as it determines integrated exposure regardless the route of exposure. In risk characterisation, biomonitoring is also frequently superior to other methods of exposure assessment, such as personal air measurements or dermal deposition assessments, because it determines the actual exposure (body burden) by capturing individual differences in behaviour (e.g. personal hygiene), physiology (e.g. respiration rate). In addition, biomonitoring may reflect differences in metabolism and hence susceptibility. When the parameter measured is the toxic compound or a compound proportionally related to the ultimate toxicant, its biomonitoring directly reflects the inter- and intra-individual variation and potentially reduces the uncertainty compared to external exposure measurements considerably. However, when the parameter measured is not related to the toxicity, variability in metabolism will not reduce overall variability and may on some occasions contribute to the overall variability (Boogaard, 2009).

Human biomonitoring has a long history in Europe and is fully integrated in EU legislation, including REACH (EC, 1995, 2006; SCOEL, 1999a). However, guidance on how to use human biomonitoring in risk characterisation and management is very limited (ECHA, 2008). This paper aims at providing pragmatic guidance how human biomonitoring can be applied in risk characterisation using DNELs and the concept of Biomonitoring Equivalents (BEs).

Historically, human biomonitoring was, by and large, restricted to occupational settings. With the developments in analytical techniques over the past decades, population-based biomonitoring has become feasible and large human biomonitoring projects, such as the NHANES (National Health and Nutrition Examination Survey) project in the USA (CDC, 2008; Paustenbach and Galbraith, 2006) and the GerES (German Environmental Survey) project in Germany (GerES, 2008; Kolossa-Gehring et al., 2007), have generated extensive (internal) exposure databases on a variety of chemicals. These surveys address general societal concerns about contamination of food, water and the environment with chemicals. The same concerns are also addressed by setting safe exposure levels for chemicals in food and in the environment. Various regulatory bodies, such as the European Food Safety Authority (EFSA), the Joint FAO/WHO Expert Committee on Food Additives (JECFA), and the USA Environmental Protection Agency (EPA), establish reference values, which represent safe, acceptable or tolerable intake levels, such as acceptable or tolerable daily intakes (ADIs and TDIs), reference doses (RfD), or minimal risk levels (MRLs). These values may be based on epidemiology and/or animal studies and have essentially the same goal as the DNEL values for consumers as defined under REACH.

Although human biomonitoring has many advantages, the understanding of biomonitoring data in terms of health risks is often not straightforward. Especially the interpretation of data obtained from consumers and the general public may be complicated (Boogaard et al., 2005; Boogaard and Money, 2008). To aid in the interpretation of human biomonitoring data, the concept of Biomonitoring Equivalent (BE) was recently developed (Hays et al., 2007). BE values represent quantitative benchmarks of safe or acceptable concentrations of a chemical or its metabolite in biological specimens that are consistent with selected reference values, such as the above mentioned ADI, TDI, MRL and RfD, using the knowledge about the toxicokinetic properties of the chemical. Basically, the BE translates a reference value into a biomarker concentration by integrating the risk assessment underlying the reference value with available toxicokinetic data for a compound in order to predict steady-state biomarker concentrations consistent with those reference values. Dependent on the available scientific information, this conversion can be done with greater or lesser reliability and a communication system was proposed to communicate the results to the general public (LaKind et al., 2008). For a variety of substances BEs have recently been derived (Aylward et al., 2008a,b,c, 2009a,b; Aylward and Hays, 2008; Hays and Aylward, 2008; Hays et al., 2008).