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Insights

Biomonitoring — more than analysis of biomarkers: advancing the use of biological guidance values

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For exposure to xenobiotics a biomonitoring outcome aggregates all routes and sources of exposure and integrates this exposure over time. Furthermore, a well-chosen biomarker provides important toxicological information such as the bioavailability of the bioactive species (parent, intermediate or metabolite) that may attenuate risk. Biomonitoring data are also relevant to understanding any forthcoming adverse effects on internal organs and tissues. Therefore, biomonitoring provides clear added value over environmental monitoring, primarily for chemicals that are systemically available and that reach tissues where an adverse effect is expected (Hauser and Mínguez-Alarcón, 2023). This justifies an increased effort to derive health-based biological guidance values (BGV) such as those already developed by the Human Biomonitoring for Europe (HBM4EU) initiative. This work is continued by the i-HBM Working Group of the International Society of Exposure Sciences (ISES) (Nakayami et al, 2023); Human Biomonitoring Health-Based Guidance Values (HB2GVs) are available online (https://www.intlexposurescience.org/i-hbm/). Three data streams can be used to support derivation of BGVs: human, animal and mechanistic. Fig. 1 shows approaches for the derivation of BGVs; blue lines indicate current approaches, and future approaches are shown with red dotted lines.

Most existing BGVs are derived using dose–response data generated in controlled exposure of animals sensitive to the endpoint of interest (1.1 in Fig. 1). To determine a point of departure to derive a BGV it is important to identify a biological significant adverse effect that presents first when increasing the dose from zero/low to high exposure, the so-called critical effect. The upper 95% confidence interval of the fitted dose-response curve is used to derive the point of departure, taking into account uncertainties in the data, an approach referred to as "benchmark dose modelling" for which an online application is available (https://www.epa.gov/bmds). For extrapolation from animals to humans, factors are needed to cover uncertainties such as inter- and intraspecies differences. Physiologically-based biokinetic (PBK) models can be used to determine the BGV for a relevant biomarker in a preferred biological sample matrix that can be collected and analysed (1.2 in Fig. 1). Macey et al. (2025) describe how this is done for BGVs using PBK models established using data from human subjects who were exposed to a very low dose in a controlled laboratory setting. For phthalates, dedicated BGVs were derived for women of childbearing age and for adolescents of 6–13 years, providing BGVs based on the most relevant urinary biomarkers for each of these vulnerable groups. Currently, many BGVs are derived from existing environmental guidance values (EGVs) such as occupational exposure limits for workers and air quality guidance values for the general population.

A second option is to derive EGVs and BGVs directly from epidemiological studies that have characterised exposure by use of biomonitoring to provide quantitative exposure–response relationship for a relevant health outcome. A good practice is to derive an exposure–response function as part of the data synthesis step in a systematic review and meta-analysis using a biomarker as exposure metric, such as was done for hair mercury (Hu et al., 2018) and blood lead (Sezavar et al., 2022). If such exposure–response data are available only in workers, it should be possible to extrapolate a BGV derived for the worker population to the general population as long as the available studies provide sufficient confidence for a causal link between the chemical of interest and a relevant health outcome (ECHA, 2019). BGVs can be derived indirectly, e.g., from existing EGVs using these PBK models (1.2 in Fig. 1). These EGVs can be based on human or animal data. In the near future BGVs will more likely be derived directly from population-based studies in line with the molecular epidemiology concept developed by Wild et al. (2011) (2.2 in Fig. 1).

An increasing number of epidemiological studies reports biomonitoring data as part of the exposure assessment, providing the opportunity of using exposure–response data from a relevant population, taking into account the variability of the real-world exposure and human health risk. *Post hoc* analysis of samples from biobanks (Li et al., 2024) may be an alternative but sometimes do not sufficiently support inferences on causation due to inherent limitations of the original study design e.g. related to co-exposures associated with health endpoint of interest where adjustment is not always possible because of the lack of suitable contextual data.

The third and currently least developed option uses PBK modelling-facilitated quantitative *in vitro* to *in vivo* extrapolation (QIVIVE) to

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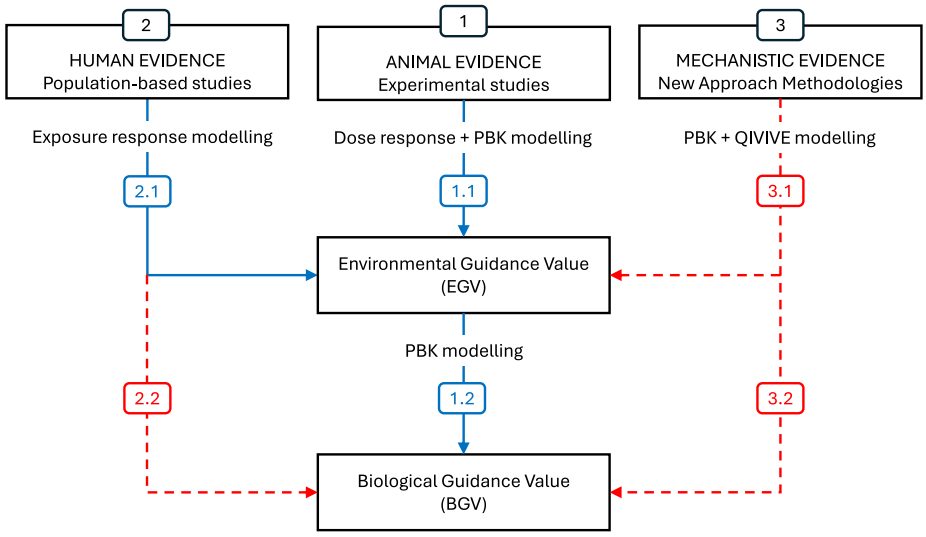

Fig. 1. Perspective for derivation of health-based BGVs based on three streams of evidence: animal (1.1 and 1.2), human (2.1 and 2.2), and mechanistic (3.1 and 3.2). PBK, physiologically-based biokinetic; QIVIVE, quantitative *in vitro* to *in vivo* extrapolation. Existing approaches in blue and future approaches in red.

predict dose–response relationships in humans based on *in vitro* concentration–response data. These are called New Approach Methodologies (NAMs) and were developed in response to the Replacement, Reduction, Refinement (3R) testing strategies as alternatives to *in vivo* animal testing (Punt et al., 2020; Najjar et al., 2022). This is a work-in-progress with the goal of deriving both EGVs and BGVs (3.1 and 3.2, respectively, Fig. 1). An example is the NAM-based toolbox approach (Cable et al., 2025). However, these approaches are currently not yet accepted by regulators and for better policy uptake there is still work to do. For instance, harmonisation of the choice of biomarkers together with stakeholders would probably help (Zare Jeddi et al., in preparation). Also, the scientific community needs to establish more rigor regarding procedures for sample collection and analysis (Schwedler et al., 2017). Last but not least, more guidance is needed regarding ethics requirements respecting the integrity of the human body and privacy protection (Knudsen et al., 2023).

If the requirement of causality and a quantified relation between exposure and health outcome is not sufficiently supported from a single stream of evidence, a weight of evidence approach may be needed to support the derivation of health-based BGVs but without a predefined strict hierarchy of the use of aforementioned streams of evidence. In this way establishing more BGVs will undoubtedly further increase the role for biomonitoring to support health-based exposure guidance to inform decisions in the interest of occupational and environmental health. As an example of a way forward for regulatory uptake of BGVs, recently the Health Council of the Netherlands recommended that BGVs be introduced and given the same weight as EGVs in an existing legal framework the Netherlands (Health Council of the Netherlands, 2025). With a robust set of BGVs, other countries may be willing to take similar steps. All of the approaches described in this paper would help to meet the goal of using BGVs for the protection of human health.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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