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OECD Activities Using Relevant Effect Biomarkers and AOPs For Assessing Known and Unknown Mixture Risks.

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19-21 March, 2024
Advancing Exposure Science in Europe – today's results for a safer future
International Society of Exposure Science – Europe Chapter Workshop

Some reasons for Occupational Biomonitoring

➢ **Biomonitoring can address multiple exposures and health risks** of dangerous substances at workplaces.

➢ **Many substances cannot be assessed only by air measurements** and limit values, e.g. having a skin notation and/or dermal uptake.

➢ **Health and productivity of workers should be protected** in an efficient and sustainable way.

➢ **The existing biomonitoring guidance until December 2022 was fragmented** in different national guidances and no harmonised biomonitoring guidance was available.

∑ **Motivation for bringing OECD key experts together to develop a common biomonitoring guidance and recommendation.**

Working together with >40 institutes/ organisations for a 3 year work programme

- ACC (American Chemistry Council), US
- ANSES (French Agency for Food, Environmental and Occupational Health & Safety), FR
- ARC (Arnot Research & Consulting, CA)
- BAuA, The Federal Institute for Occupational Safety and Health, DE
- BASF, DE
- Belgium DG Environment, BE
- BfR (German Federal Institute for risk assessment), DE
- BIAC (Business at OECD)
- CEFIC (The European Chemical Industry Council), EU
- Covestro, DE
- Currenta, DE
- DFG Germany (German Research Foundation), DE
- ECHA (European Chemicals Agency), EU
- ESTeSL (Escola Nacional de Saúde Pública, Universidade Nova de Lisboa), PT
- EU-OSHA (European Agency for Safety and Health at Work), EU
- ExxonMobil Biomedical Sciences, US
- FIOH (Finnish Institute of Occupational Health), FI
- Health Canada, CA
- HSE (Health and Safety Executive), UK
- IfADo, Leibniz Research Centre for Working Environment, DE
- INRS (Reference body for occupational risk prevention in France), FR
- ISES EU (Europe Regional Chapter of the international Society of Exposure Science), EU
- Japan MHLW (Ministry of Health Labour and Welfare), JP
- Japan National Institute of Occupational Safety and Health, JP
- JRC (Joint Research Centre), EU
- Katholieke Universiteit Leuven, BE
- KI (Karolinska Institutet), SE
- National Health Laboratory (LNS), Dudelange , LU
- Orthoanalytik GmbH, CH
- RIVM (National Institute for Public Health and Environment), NL
- SCAHT (Swiss Centre for Applied Human Toxicology), CH
  SECO (State Secretariat for Economic Affairs), CH
- (Swedish Chemicals Agency, SE)
- Swiss FOPH (Federal Office of Public Health), CH
- SUVA (Swiss National Accident Insurance Fund), CH
- UBA (German Environment Agency), DE
- Unisanté (Center for Primary Care and Public Health), CH
- University of Erlangen, DE
- University Zürich, CH
- US-EPA (United States Environmental Protection Agency), US & US NIOSH
- VITO NV, BE

Ethical use of Biomonitoring (BM) is necessary and possible

BM is an effective tool for assessing exposure to and effects of hazardous substances in occupational health context. It can be used to complement other strategies and tools for exposure or risk assessment.

In contrast to other tools however, **BM requires the use of human samples and thus additional fundamental ethical principles and data protection legislation have to be respected**.

Options and recommendations are provided in guidance

Occupational Biomonitoring Guidance

Available at:
www.oecd.org/chemicalsafety/risk-assessment/occupational-biomonitoring-guidance-document.pdf

Moreover, 2 follow up publications for derivation & application of biomonitoring assessment values are submitted by Nancy B. Hopf & colleagues.

The challenge

The methods described in the Occupational Biomonitoring Guidance Document pave the way for **high quality and globally harmonised occupational risk assessment**, but are also limited to:

- Availability of data sets
- Analytical capacities
- Speed of regulatory processes

This is relevant for:

Occupational Biomonitoring Levels (**OBL**)

and also for:

Occupational Exposure Limits (**OEL**)

Risks are underestimated and regulation is too slow

By far, for less than 1% of work place relevant substances internationally harmonised OEL or OBL are available. No international mid-term solution to cope with this challenge is in sight.

Moreover, the **risk assessment** is limited to inhalation risks and **is mostly ignoring dermal and oral exposure pathways.**

This can be partially done with:

more and better OBL & OEL derivations → we recommend to make them transparently available.

But: Mixture effects are often ignored → options via OECD are in preparation using relevant effect-biomarkers and using the AOP concept.

Effect-biomarkers are highly underused

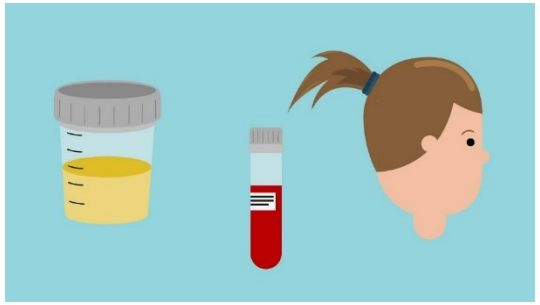
- **Effect-biomarkers are the only option to assess known & unknown exposures and mixtures in an integrative way.**

- **Validated effect biomarkers can be used to address** relevant health effect endpoints and **Mode of Actions (MoAs) in humans,** we found **a strong link to the growing Adverse Outcome Pathway (AOP) knowledge.**

- **A systematic understanding of both the relevance and interpretation of effect- biomarker data will lead to increased protection for workers.**

- **An integrative effect-biomarker AOP project was started in Oct. 2022** to develop specific mixture threshold levels for regulatory use

Regulatory Application of Effect-Biomonitoring is given



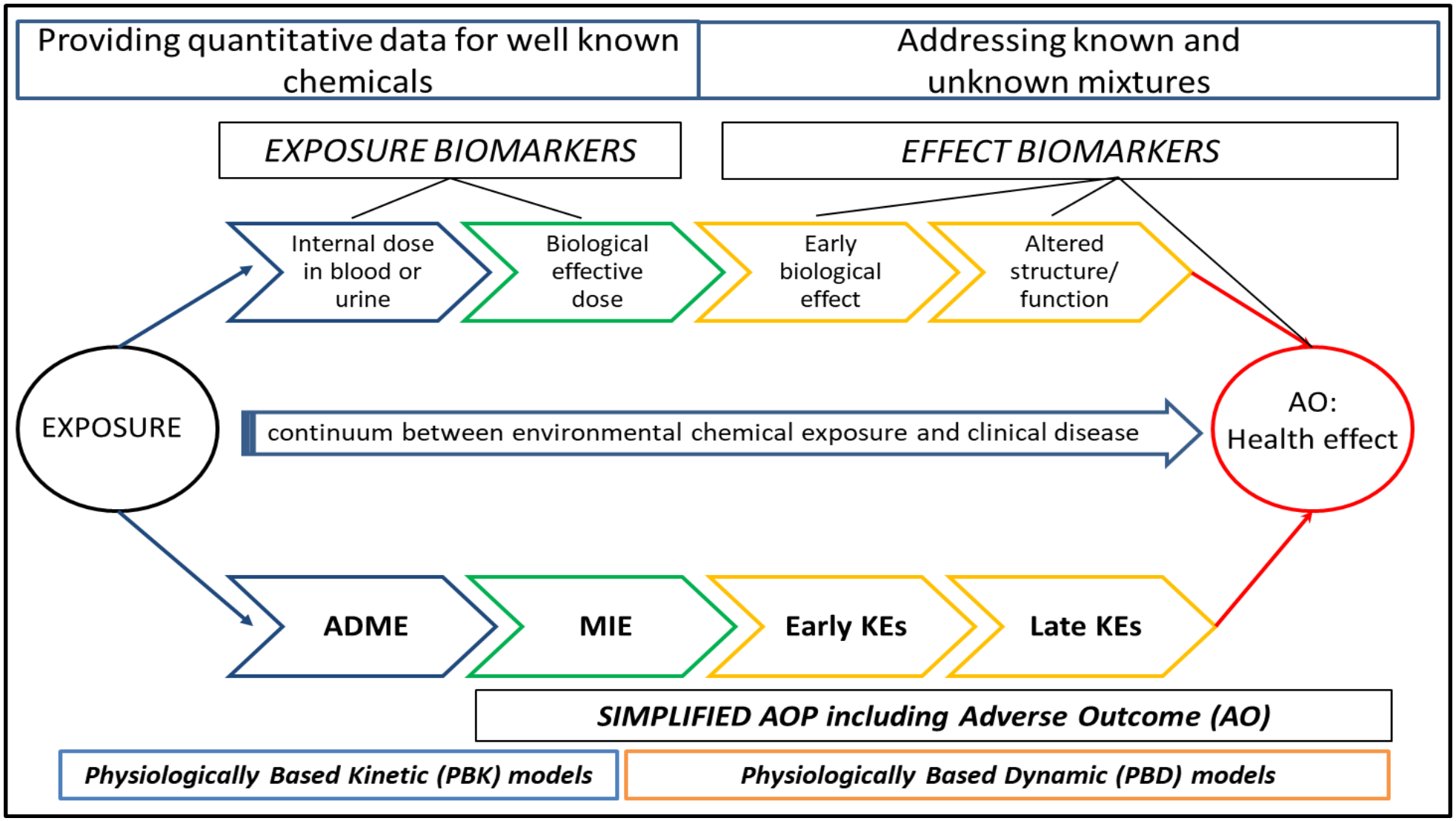
➢**Human Biomonitoring**: regulator aims to protect, humans (general population and workers) against adverse effects of chemical exposures.

➢**Effects-based Environmental Monitoring**: regulator aims to protect wildlife / ecosystems) against adverse effects of chemical exposures.

In both cases:

1) Need to identify what to measure (*Effect-Biomarker*)
2) Need to identify what magnitude of response (or change) is of concern *Effect-Based Trigger (EBT)* or *Occupational Biomonitoring Effect Level (OBEL)* values are necessary.

– We can bridge exposure- and effect-biomarkers



We are ambitious in bridging

Current activity is a **large & ambitious** collaboration of **>90 experts & 23 nations**:

Around 11 effect-biomarkers are characterised

Covering:

- Endocrine Disruption (estrogenicity) (ENV)
- Genotoxicity (HH+ENV) and related aspects
- Oxidative stress (HH)
- Neurotoxicity (NT) & Developmental NT (HH)
- Reproduction toxicity (HH)

- + New drafting group Quality Assessement of Effect Biomonitoring

Previous OECD meeting:

19-20th June in Porto closely linked to ISBM .

Warmest thanks to João PauloTeixeira from INSA and many colleagues for making this possible.

Drafting group compositions

Endocrine Disruption

Dan Villeneuve (US) & Eszter Simon (CH) support by Knut Erik Tollefsen (NOR), Frederic Leusch (AUS)

Further support indicated by:

Magdalena Jagla (CAN), Shiro Kawahara (JPN), Ksenia Groh (CH), Eliana Spilioti (GR), Elke Dopp (DE)…

Genotoxicity & oxidative stress

Bernice Scholten (NL), Stefano Bonassi (IT), Radu Duca (LU), Henriqueta Louro (PT), Robert Pasanen (CH), Nancy Hopf (CH), Kukka Aimonen & Tiina Santonen (FI), Joao Paulo Teixeira (PT), Manosij Ghosh (BE), Susana Viegas (PT), Michael Fenech (AUS)

Further support indicated by:

Laurent Gaté (FR), Ruth Moeller (LU), An van Nieuwenhuyse (LU), Alicia Paini (IT) Simone Schmitz-Spanke (DE), Kyriaki Machera & Konstantinos Kasiotis (GR), Maria Joao Silva (PT), Maria Dusinska (NOR), Kate Guyton (US)…

(Developmental)-Neurotoxicity

Anna Bal Price (JRC), Vicente Mustieles (ES), Robert Pasanen (CH), Christoph van Thriel (DE), Antonio Hernandez Jerez (ES), Andrea Rodriguez-Carillo (BE)

Further support indicated by:

Alicia Paini (IT), Christina Pieper (DE), Devika Poddalgoda (CAN), Kyriaki Machera (GR),…

Reproduction Toxicity

Sophie Ndaw & Nancy Hopf (CH), Laurent Gaté (FR), Rex FitzGerald, Robert Pasanen (CH)

Further support indicated by:

Anna Beronius (SE), Devika Poddalgoda (CAN), Nathalie Bonvallot (FR), Andrea Rodriguez-Carillo (BE), Sylvie Remy (BE),…

Exposure assessment quality principles for occupational effect-biomarker studies

Maryam Zare Jeddi & Jan Urbanus (BIAC); Jörg Rissler (DE)

Further support indicated by:

Susana Viegas (PT), Radu Duca (LU), Sophie Ndaw (FR), Hopf Nancy (CH), Santonen Tiina (FI),Kyriaki Machera (GR), Eliana Spilioti (GR), Adrian Tristram (BIAC) , Craig Sams (UK),, Joao Paulo Teixeira (PT) and ISES HBM experts until May 2024

Focus in hazard assessment: selection criteria

1) Effect-biomarkers representing Key Events (KE) in an AOP

2) Availability of reference compounds which act as prototypical stressor

3) Opportunities to establish quantitative KE/AO relationships for mixture tresholds or risk classes

4) Defining thresholds for human and environmental protection

Applying concepts on selected characterized effect-biomarkers with AOP relevance

Endocrine Disruption-Vitellogenin induction in male fish (ENV)

Endocrine Disruption-Estrogen Receptor activity in water assessment (ENV)

Genotoxicity induction measured via micronuclei in water assessment (ENV)

Genotoxicity measured via micronuclei induction in humans CBMN (HH)

Genotoxicity measured via micronuclei induction in humans in reticulocytes (HH)

Genotoxicity measured via Comet assay (HH)

Oxidative stress measured via GSH/GSSG induction in humans (HH)

NT/DNT measured via BDNF (HH)

NT/DNT measured via Neurofilament light chain measurements (HH)

NT/DNT measured via Neurogranin measurements (HH)

Reproduction toxicity induced via low testosterone levels in male humans (HH)

Targeted interpretation for each EBM is possible

Human Health (HH)	Environmental Health (ENV)	Tier	Level	Meaning if exceeded
OBEL =Occupational Biomonitoring Effect Level	EBT =Effect–Based Trigger value	3	Refined	Health risk indicated
POBEL	P-EBT	2	Provisional	Health risk maybe indicated
ROBEL	R-EBT	1	Reference	Exposure above or below reference level (e.g. > 95%, <5%)
TOBEL	T-EBT	0	Technical	Exposure indicated (e.g. >LOQ or >LOD)

Proposed concept of Occupational Biomonitoring Effect Level (**OBEL**) and for **E**ffect **B**ased **Tr**igger values (**EBT)** allowing their interpretation. Lowest Tier of TOBEL & T-EBT will be improved to a better quantification terminology.

Interpretation according to existing risk assessment standards and data

Provisional Occupational Biomonitoring Effect-Level (POBEL)
or
Provisional Effect-based Trigger value (P-EBT) corresponds to a MoA specific and accepted
Occupational Biomonitoring Level (OBL) or related risk class
or
Environmental Quality Standard (EQS)

Interpretation: At this level a mixture related health risk cannot be excluded.

Interpretation according to existing risk assessment standards and data

A refined OBEL or EBT can be linked directly to an adverse effect-level or risk class for a specific effect-biomarker.

Interpretation:

At this level a mixture related health risk is indicated.

We use existing case studies to provide a proof of concept.

Exposure assessment quality principles for occupational effect-biomarker studies are in prep→ intended as chapter for upcoming guiding principles.

Project timeplan- towards guiding principles for effect-biomarker thresholds

2023:

- **June 2023** 2nd OECD meeting at INSA linked to ISBM
- **September & October 2023** adjusting drafting group work
- Drafting & review by experts **November 2023 → May 2024**

2024:

- Followed by revisions at **3rd Hybrid meeting at 13 & 14th May in BPI in Athens**
- Additional revision step (tbd) of guiding principles
- Review in WPHA/WPEA (tbd)

Expected Finalisation in 2025

Only one conclusion & 3 x harmonisation

More national use of <u>exposure & effect biomonitoring</u> is needed to allow a sufficient protection of workers.

<u>Harmonisation is/will be provided in:</u>

1) Occupational Biomonitoring Guidance finalised in 2022

2) Two follow up publications in prep. close to submission in 2023 or early 2024

3) Practice oriented guiding principles for effect-biomarker mixture assessment are currently under construction for 2025

General discussion

Let us try to use our time effectively. Thanks to numerous motivated colleagues making this progress possible.

Do you have other questions, comments or interest?

Thank you very much for your attention & collaboration

Radu, Robert & colleagues

Later questions are welcome via:
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