DEVELOPMENT OF SCREENING TOOLS FOR THE INTERPRETATION OF CHEMICAL BIOMONITORING DATA

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Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment
May 22-24, 2012, Austin, TX
Workshop 4

American Chemistry Council

Human Biomonitoring

- Measurement of chemicals (or metabolites) in biological media such as blood or urine
- Integrates all exposure sources and routes
- CDC's NHANES now evaluates > 300 substances
- Big Challenge: how to interpret biomonitoring results in a risk-context?
  - It is only for a handful of environmental chemicals, such as lead and mercury, where there are robust datasets and objective medical findings that can relate biomarker concentrations in human populations to potential adverse health effects in people

Reasons for Conducting Population-Based Biomonitoring Studies

- Determine which chemicals get into members of the general population and at what concentrations
- Determine if exposure levels are higher in some groups than in others
- Track temporal trends in levels of exposure
- Assess the effectiveness of public health efforts to reduce exposure
- Establish reference ranges
- **Determine the prevalence of people with levels above known toxicity levels**
- **Set priorities for research on human health effects**

Source: (CDC, 2005)

Existing Chemical Risk Assessment Paradigm

"Point of Departure"

Rat Dose NOAEL/LOAEL

100-1,000

Uncertainty Factors

"Safe" Human Dose – RfD, TDI

Reference Dose or Concentration: "An estimate of an exposure …to the human population (including susceptible subgroups) that is likely to be *without an appreciable risk of adverse health effects over a lifetime*."

http://www.epa.gov/iris/help_gloss.htm#r

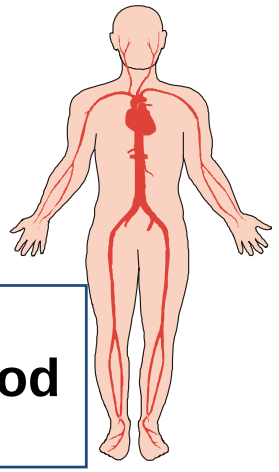
“Biomonitoring Equivalent”

Concentration of biomarker that is consistent with existing exposure guidance or reference values such as RfDs, TDIs, etc.

Rat Dose NOAEL/LOAEL

“Safe” Human Dose – RfD

BE_{RfD} Human Blood Level



Goals of BE Approach

- Leverage and integrate existing datasets and risk assessments
  - Substantial body of data and information
- Provide translational approaches between external and internal dose-based risk assessments
- Enable biomonitoring data to be screened as input to prioritization of research efforts using modern epidemiologic and biological research methods

Biomonitoring Equivalents (BE) Pilot Project Expert Workshop, 2007

- Experts in risk assessment, pharmacokinetics, communication, medical ethics
- Provided guidance on the BE concept, methods, and communication
- Results from pilot project available in *Regul. Toxicol. Pharmacol*., Vol. 51, No. 3, Supplement 1 (2008)
  - Guidelines for Derivation
  - Guidelines for Communication
  - Case Studies

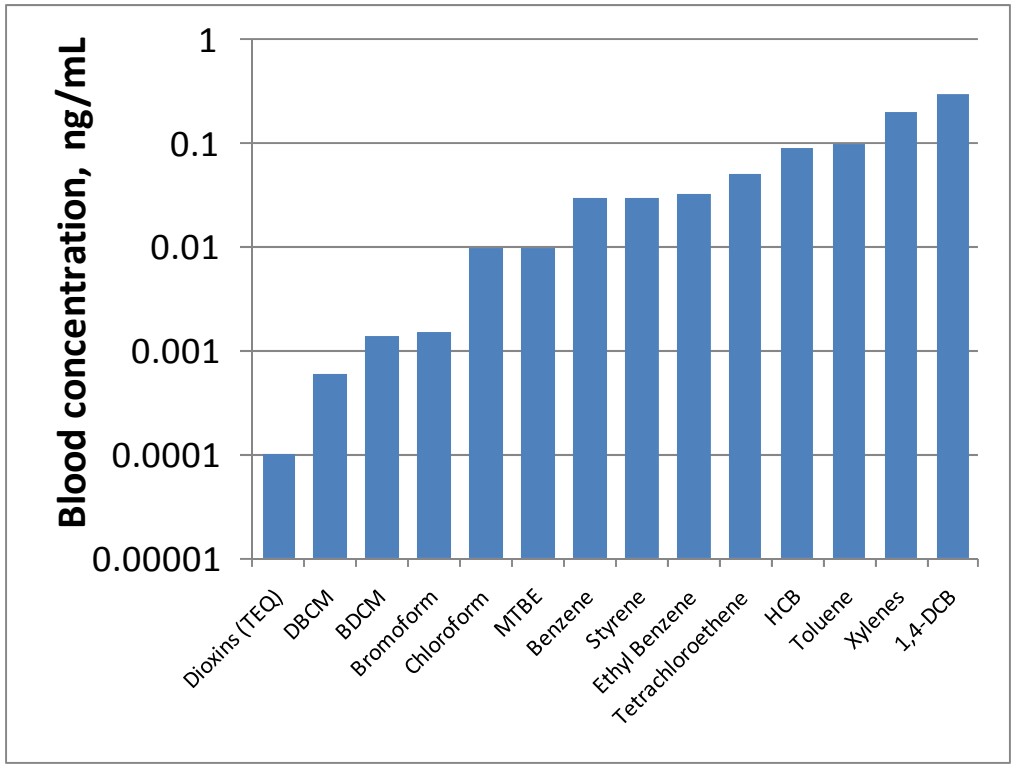
Chemicals with BE Values

Completed and Published

2,4-D	n-Nonane	Dibromomethane
Cyfluthrin	1,1,1-Trichloroethane	n-Hexane
Cadmium	1,1,2-Trichloroethane	1,1-Dichloroethane
Inorganic arsenic	n-Decane	1,2-Dichloroethane
Hexachlorobenzene	1,2,3-Trichloropropane	n-Heptane
Bisphenol A	1,1,1,2-Tetrachloroethane	n-Octane
Triclosan	1,1,2,2-Tetrachloroethane	Acrylonitrile
Diethyl phthalate	1,2-Dibromoethane	Furan
Dibutyl phthalate	Hexachloroethane	Tetrahydrofuran
Benzyl butyl phthalate	1,1-Dichloroethene	1,4-Dioxane
Di-2(ethylhexyl) phthalate	cis-1,2-Dichloroethene	Hexabromocyclododecane
Dioxin TEQ (29 compounds)	trans-1,2-Dichloroethene	Methyl-tert-Butyl Ether (MTBE)
Acrylamide	Trichloroethene	Methyl isobutyl ketone
Chloroform	Tetrachloroethene	Di-isononylphthalate
Bromoform	Benzene	DDT/DDE/DDD
Dibromochloromethane	Toluene	PBDE 99
Bromodichloromethane	Styrene	Deltamethrin
Methylene chloride	Ethylbenzene	selenium
Carbon tetrachloride	Xylenes, mixed	3-PBA

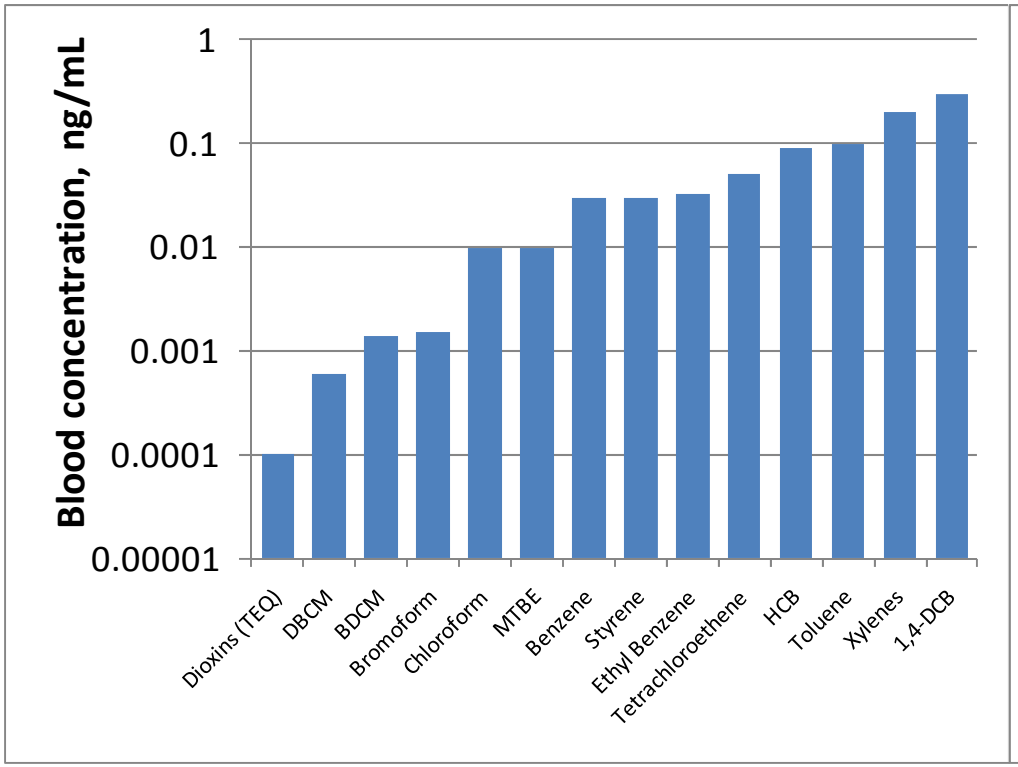
Prioritization Across Chemicals

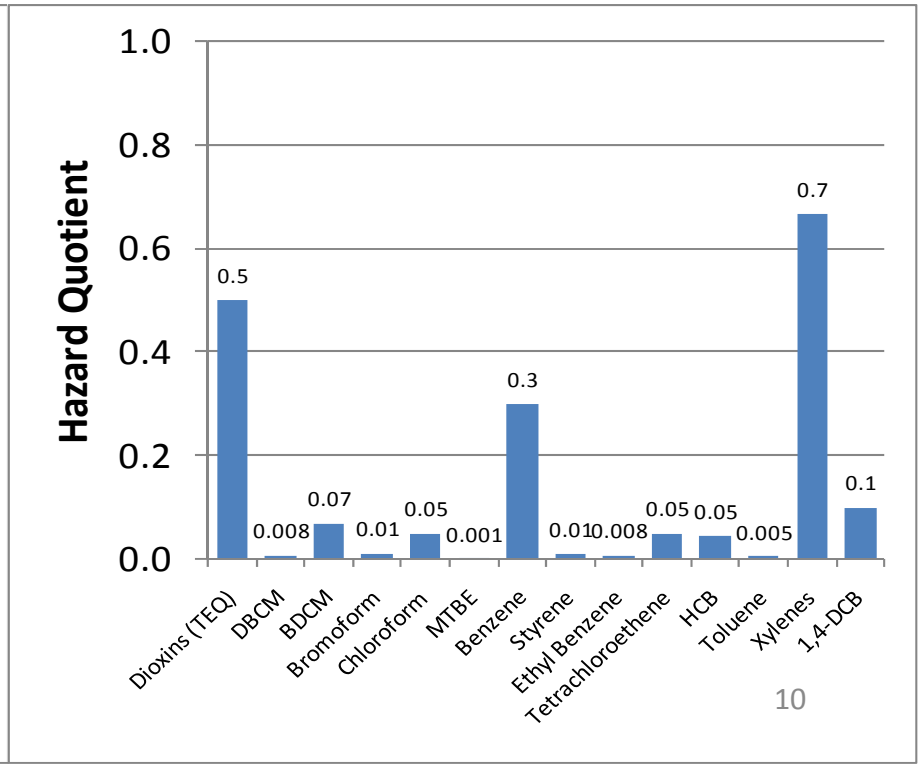
- CDC/NHANES measures >300 chemicals in blood or urine. Which ones are of greatest interest?
- Absolute concentrations tell one story…



Prioritization Across Chemicals (cont'd)

- Hazard Quotients (Biomon. Conc./BE) provides a different perspective
- Its essential to interpret biomonitoring data in a risk context





Limitations Encountered

BE defined as *concentration of biomarker that is consistent with an existing exposure guidance or reference value (e.g., RfDs, TDIs) from authoritative source (e.g., EPA, FDA, Health Canada, EU, etc.)*

But what to do when:

- lack of exposure guidance values (RfD, TDI, etc.) from govt. organizations or outdated values?
- lack of pharmacokinetic data/models to calculate BEs?
- or both (when there's both limited tox info and limited toxicokinetic (TK) info)?

Problem Formulation

- *How can existing data and knowledge of toxicity and toxicokinetics be integrated to enable human biomonitoring results to be interpreted in a health risk context where available information can range from very complete to very sparse?*
- *What would be a consistent and scientifically justified framework and associated decision criteria that could be applied to guide the development of such interpretation tools?*

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Review Article

Development of Screening Tools for the Interpretation of Chemical Biomonitoring Data

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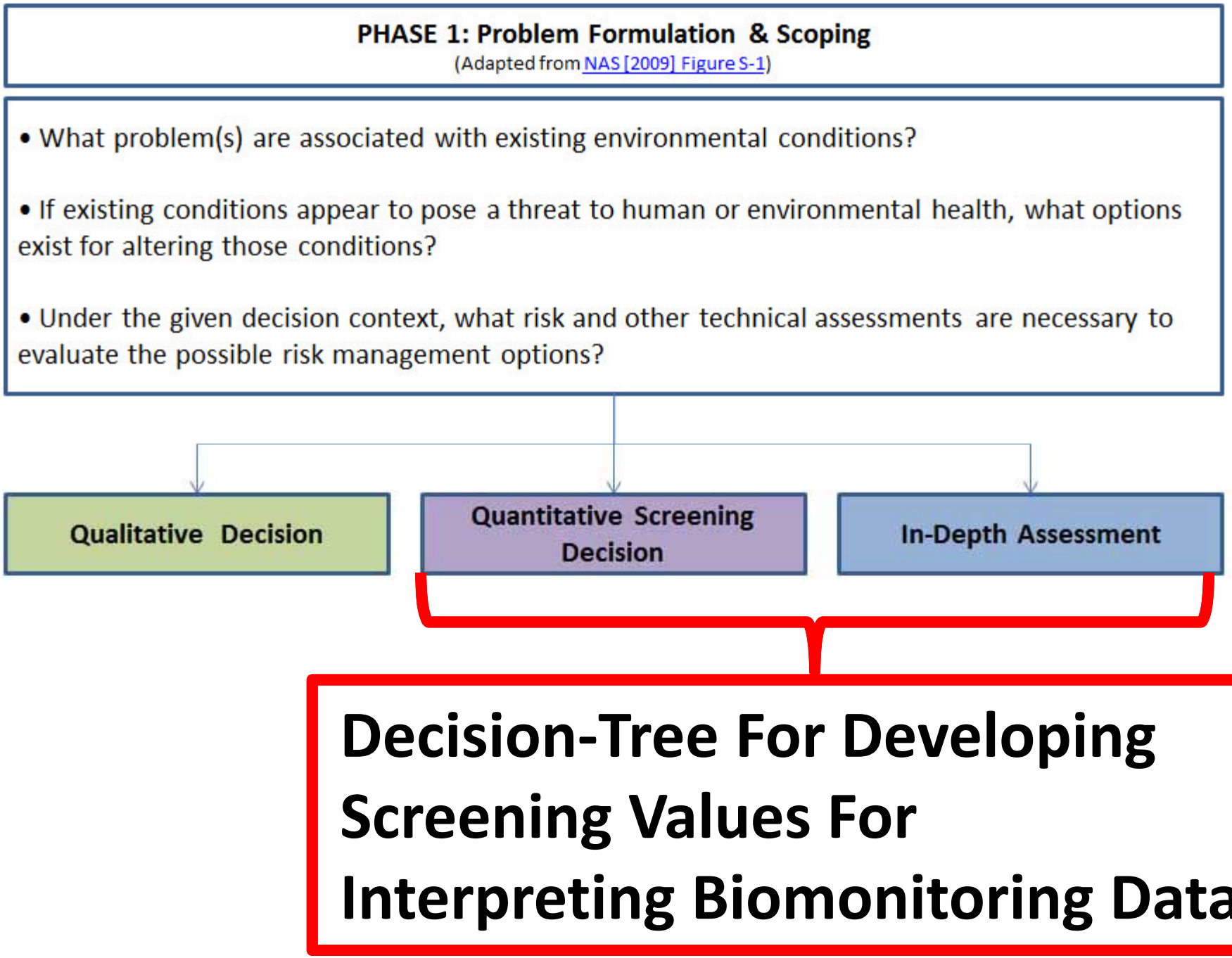
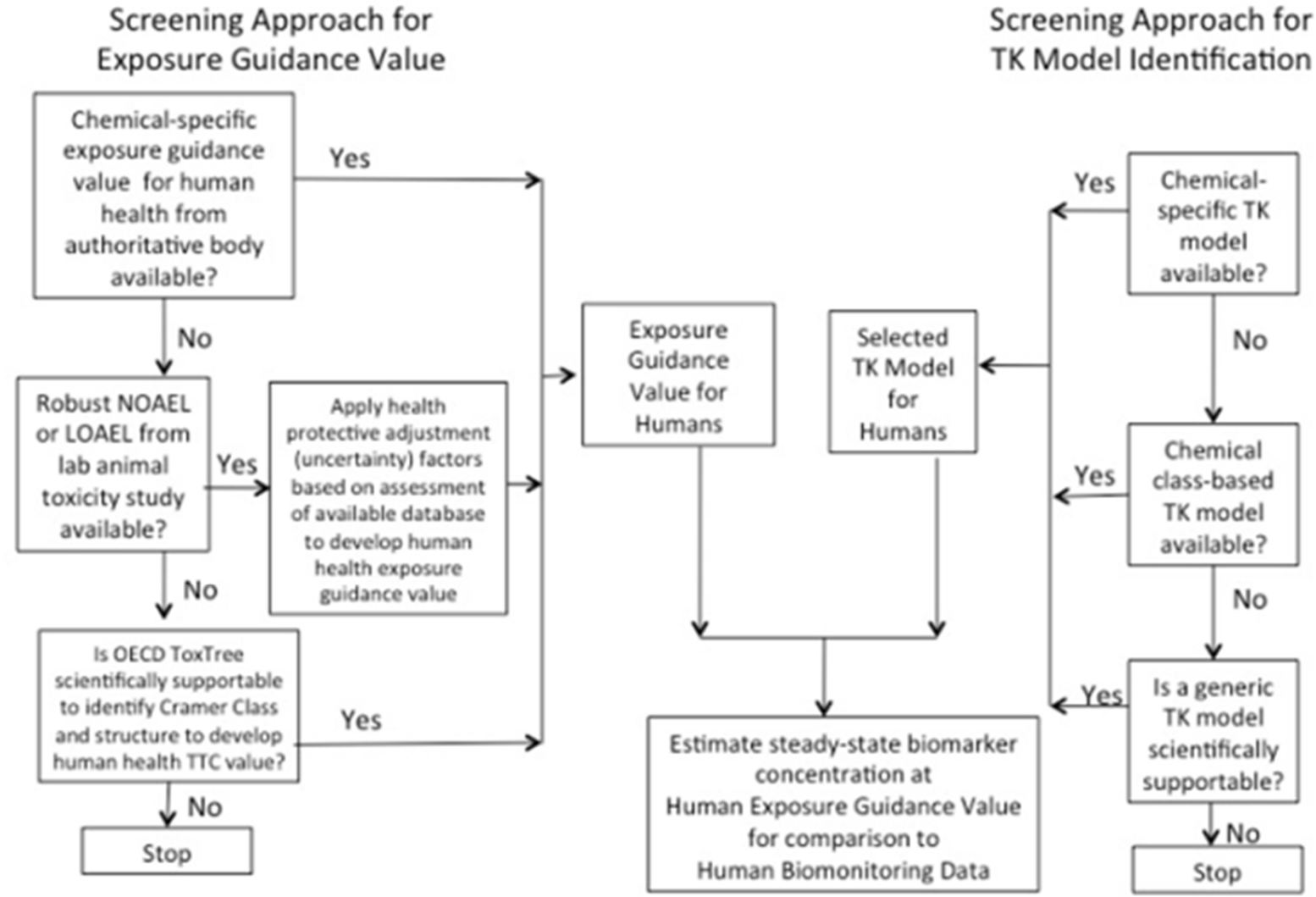
Evaluation of a larger number of chemicals in commerce from the perspective of potential human health risk has become a focus of attention in North America and Europe. Screening-level chemical risk assessment evaluations consider both exposure and hazard. Exposures are increasingly being evaluated through biomonitoring studies in humans. Interpreting human biomonitoring results requires comparison to toxicity guidance values. However, conventional chemical-specific risk assessments result in identification of toxicity-based exposure guidance values such as tolerable daily intakes (TDIs) as applied doses that cannot directly be used to evaluate exposure information provided by biomonitoring data in a health risk context. This paper describes a variety of approaches for development of screening-level exposure guidance values with translation from an external dose to a biomarker


PHASE 1: Problem Formulation & Scoping
(Adapted from NAS [2009] Figure S-1)
• What problem(s) are associated with existing environmental conditions?
• If existing conditions appear to pose a threat to human or environmental health, what options exist for altering those conditions?
• Under the given decision context, what risk and other technical assessments are necessary to evaluate the possible risk management options?
Qualitative Decision
Quantitative Screening Decision
In-Depth Assessment
Decision-Tree For Developing Screening Values For Interpreting Biomonitoring Data

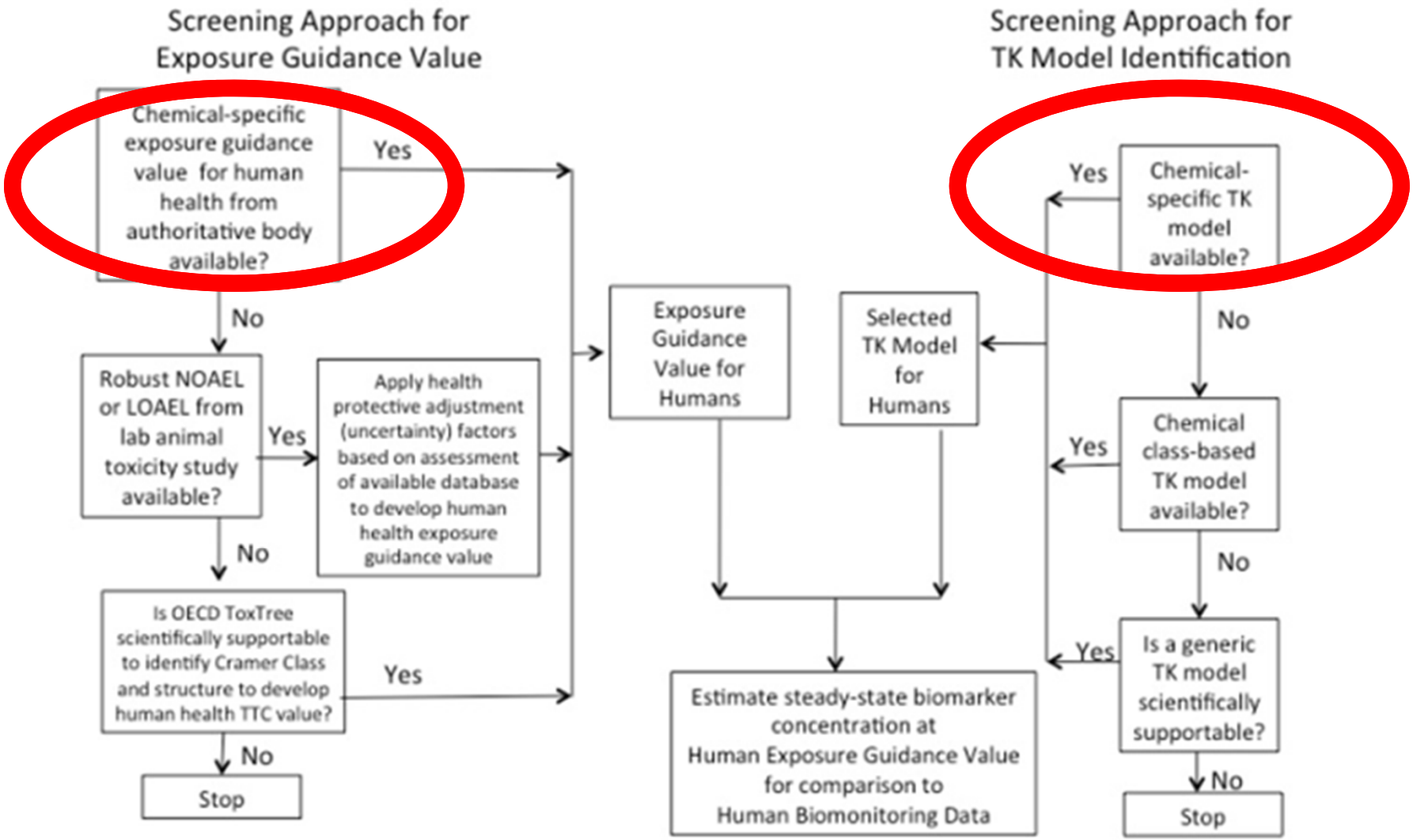
Decision-Tree For Developing Screening Values For Interpreting Biomonitoring Results



Examples

- (1) substances with established government risk assessments (“classical” BE)
- (2) substances with sufficient toxicity datasets but as of yet no government generated (or vetted) risk assessment
- (3) chemical-specific toxicokinetic data or models are lacking
- (4) both toxicity-based guidance values and toxicokinetic data are not readily available
- (5) substances amenable to the generic screening TTC approach for setting conservative tolerable intake rates.

(1) Classical BE



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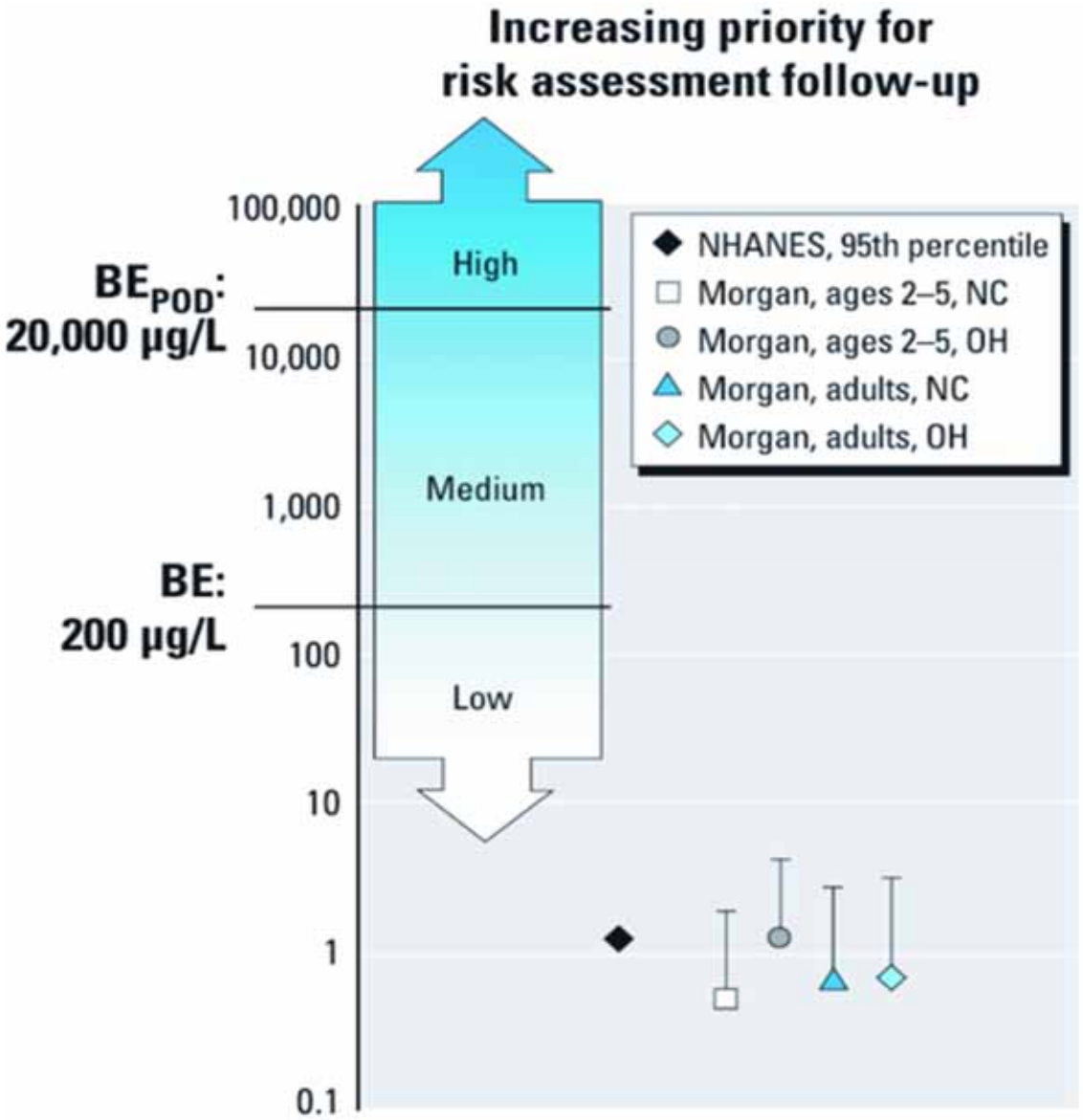
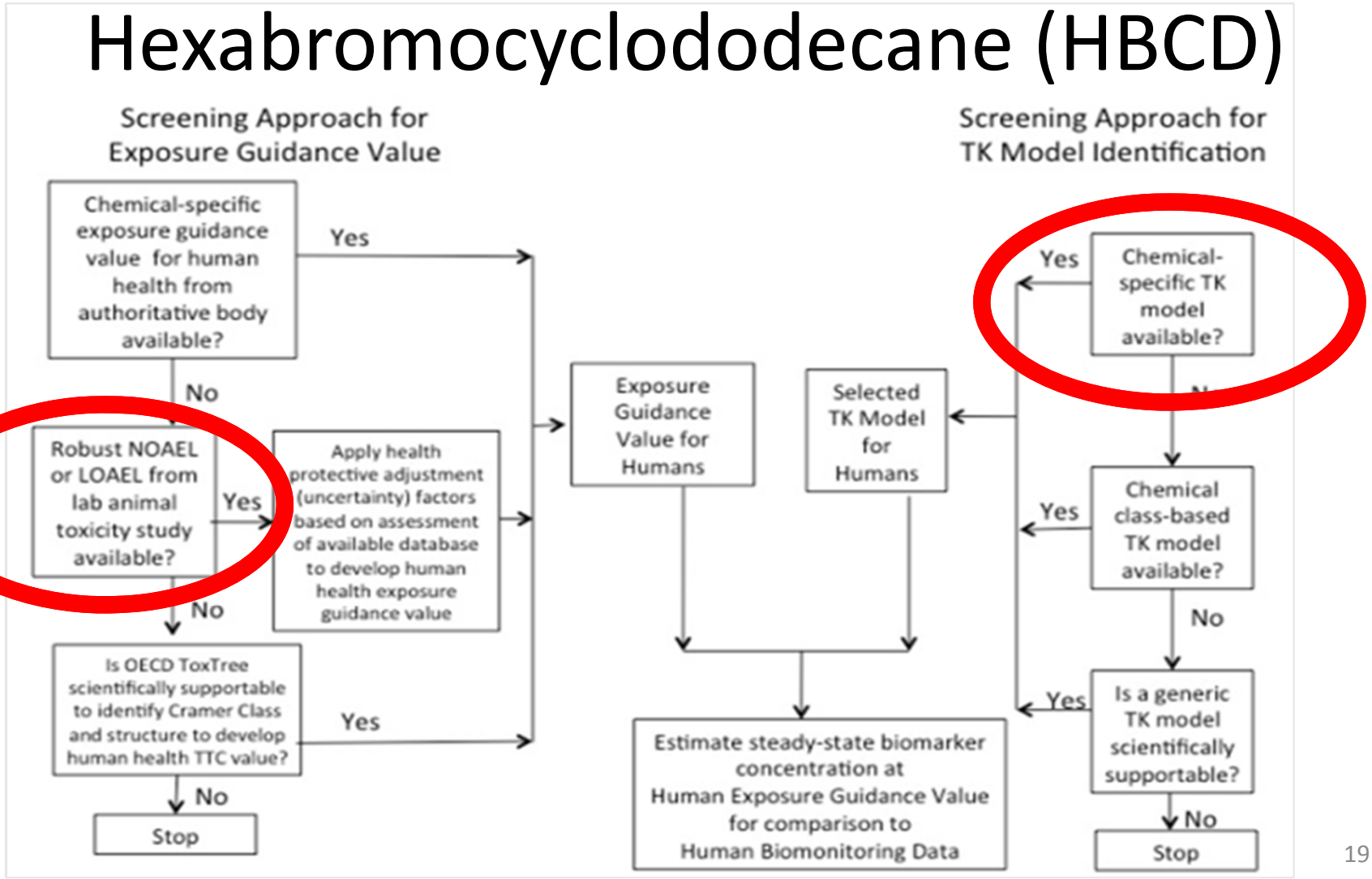


Aylward et al. (2010). Biomonitoring Data for 2,4-Dichlorophenoxyacetic Acid in the United States and Canada: Interpretation in a Public Health Risk Assessment Context Using Biomonitoring Equivalents. Environ Health Perspect 118(2): 177-181.

(2) Sufficient Tox Data
But No Govt Risk Assessment
Hexabromocyclododecane (HBCD)



(2) Hexabromocyclododecane (HBCD)

Table 1: From Aylward and Hays [2011]. Points of departure identified in recent risk assessments for HBCD, with corresponding estimated lipid-adjusted concentrations. Margins of exposure (MOEs) are presented based on comparison of HBCD concentrations in population biomonitoring data to the lipid-adjusted concentrations estimated for the PODs: MOE = POD/[HBCD].

Risk Assessment	Endpoint(s)	POD, administered dose (mg/kg-d)	POD, lipid-adjusted concentrations (ng/g lipid)[a]	MOE at central tendency[b]	MOE at upper bound[b]
EU Draft RAR (2008)	Liver weight in female rats (BMDL for 20% change; van der Ven et al., 2006)	22.9	192,000	192,000	8,000
	Fertility (NOAEL from Ema et al., 2008)	10	121,000	121,000	6,000
HC Draft SLRA (2010)	Fertility and developmental effects (NOAEL from Ema et al., 2008)	10	121,000	121,000	6,000

[a] From regression equation provided in van der Ven et al. [2006] relating liver lipid-adjusted HBCD concentration to administered dose rate at the end of a 28 day administration period in female rats: $C_{lipid} = 33377 * D^{0.55587}$ where C_{lipid} is liver lipid-adjusted HBCD concentration (ng/g lipid) and D is the administered dose (mg/kg-d).

[b] Compared to central tendency or upper bound of general population biomonitoring data (1 or 20 ng/g lipid, respectively). For more details see From Aylward and Hays [2010].

(3) chemical-specific toxicokinetic data or models are lacking Volatile Organic Chemicals (VOCs)

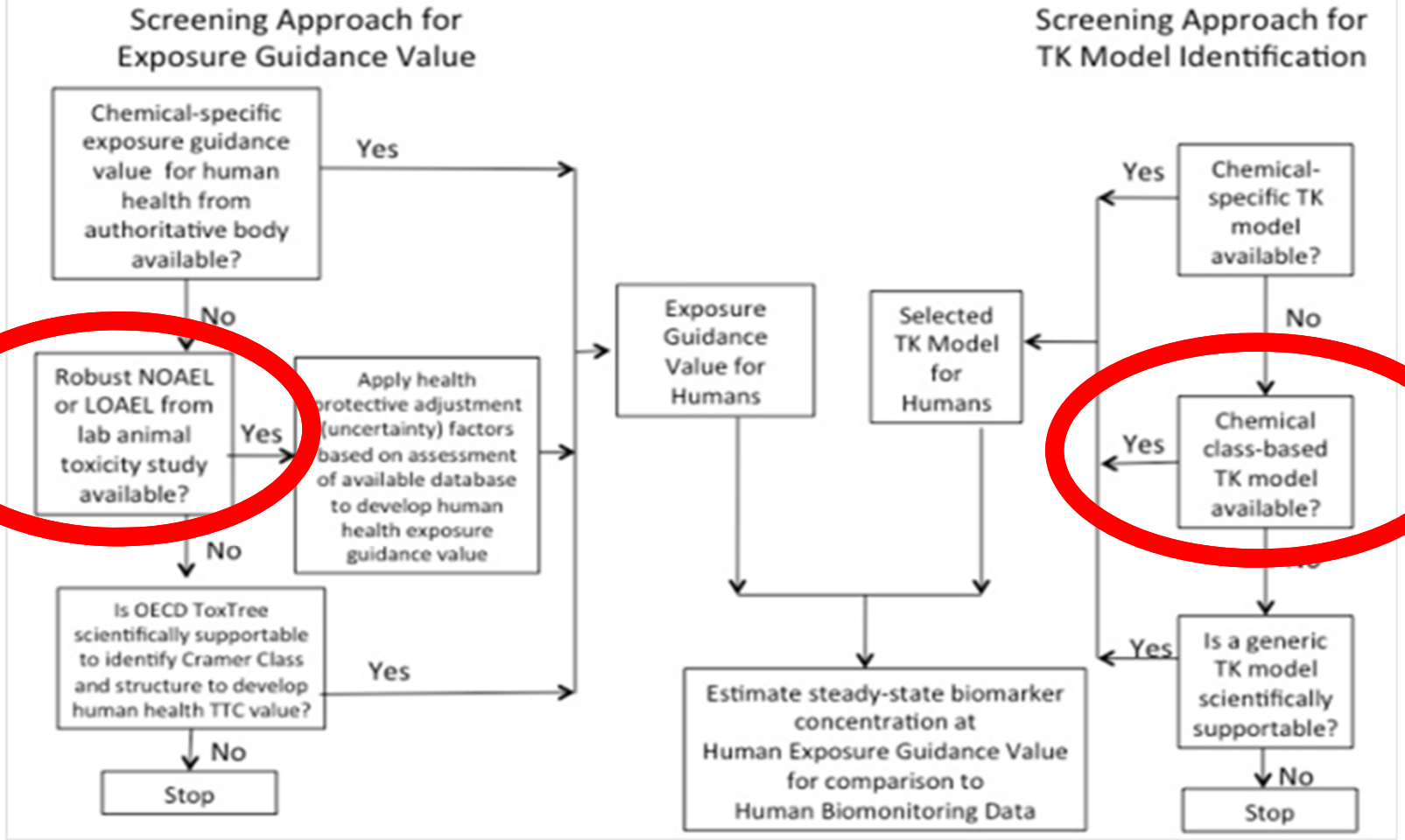


Figure 3: From Aylward et al., 2010b. Estimated steady-state blood concentration screening values associated with oral reference values for 33 compounds with both oral reference values and pharmacokinetic models. Solid line and dotted lines represent the geometric mean and 95% confidence interval on the slope relating steady-state blood concentrations to oral exposure rates for 37 VOC compounds with pharmacokinetic models.

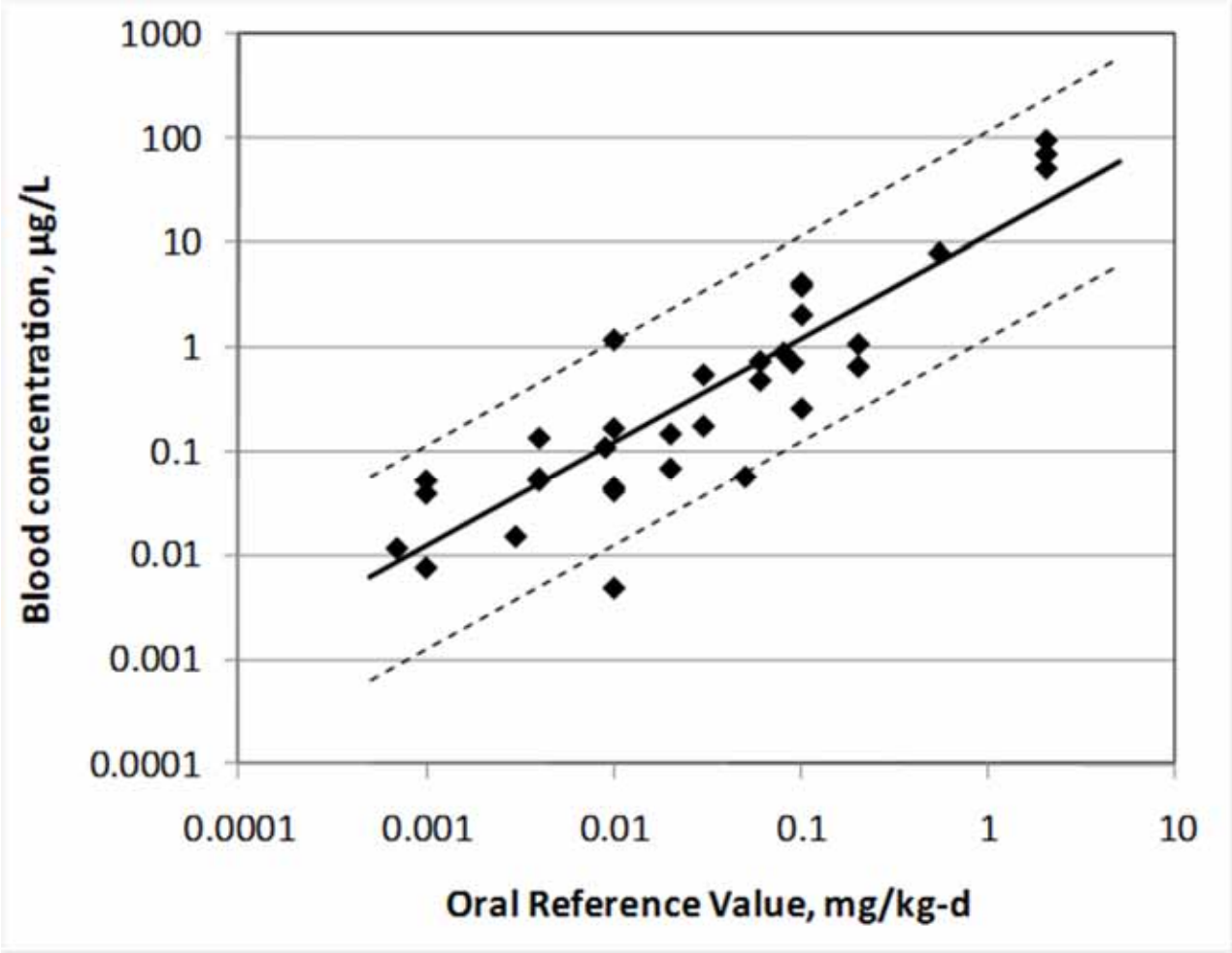


Figure 4: From Aylward et al., 2010b. Estimated steady-state blood concentration screening values associated with inhalation reference values for 23 compounds with both inhalation reference values and pharmacokinetic models. Solid line and dotted lines represent the geometric mean and 95% confidence interval on the slope relating steady-state blood concentrations to inhalation exposure levels for 38 VOC compounds with pharmacokinetic models

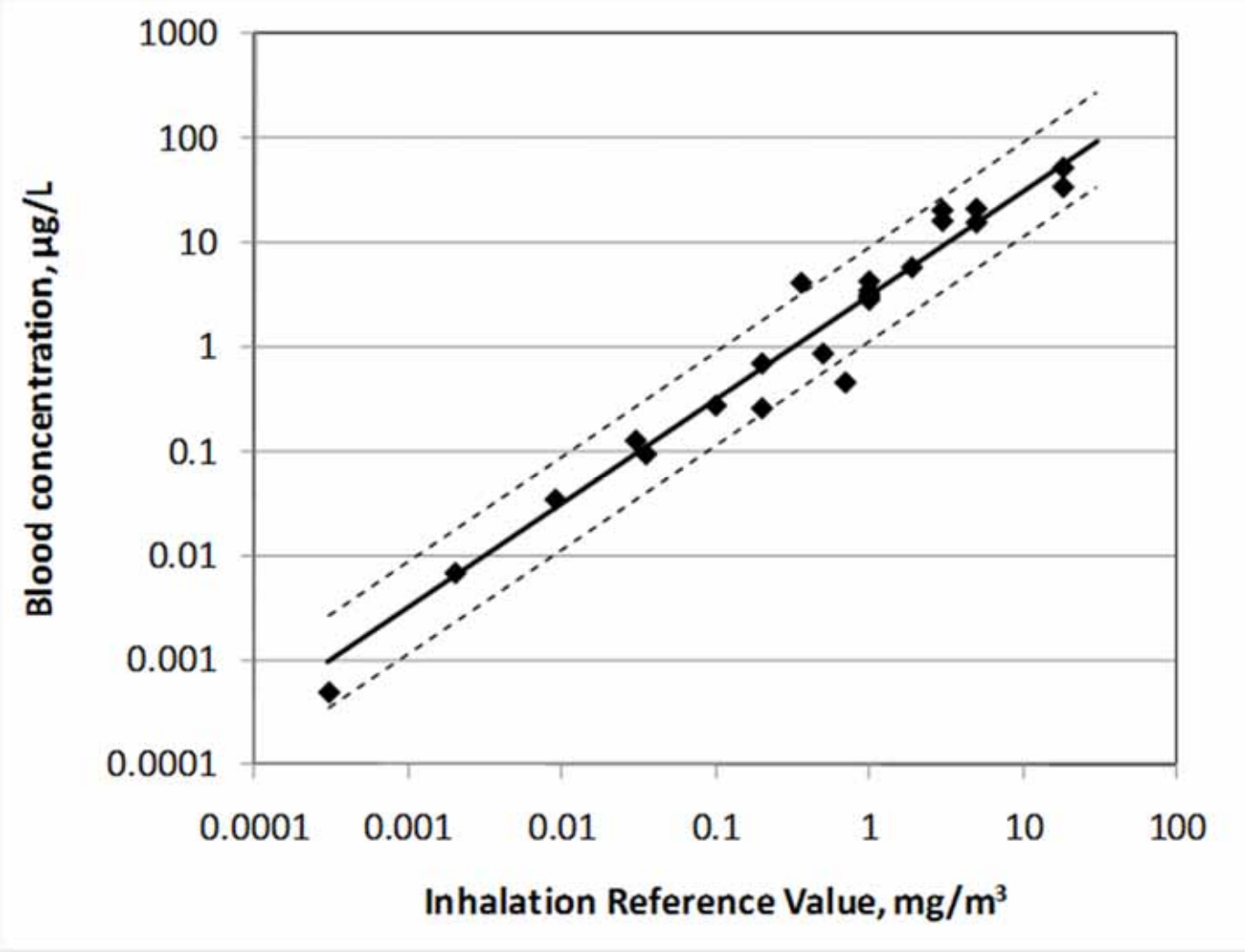


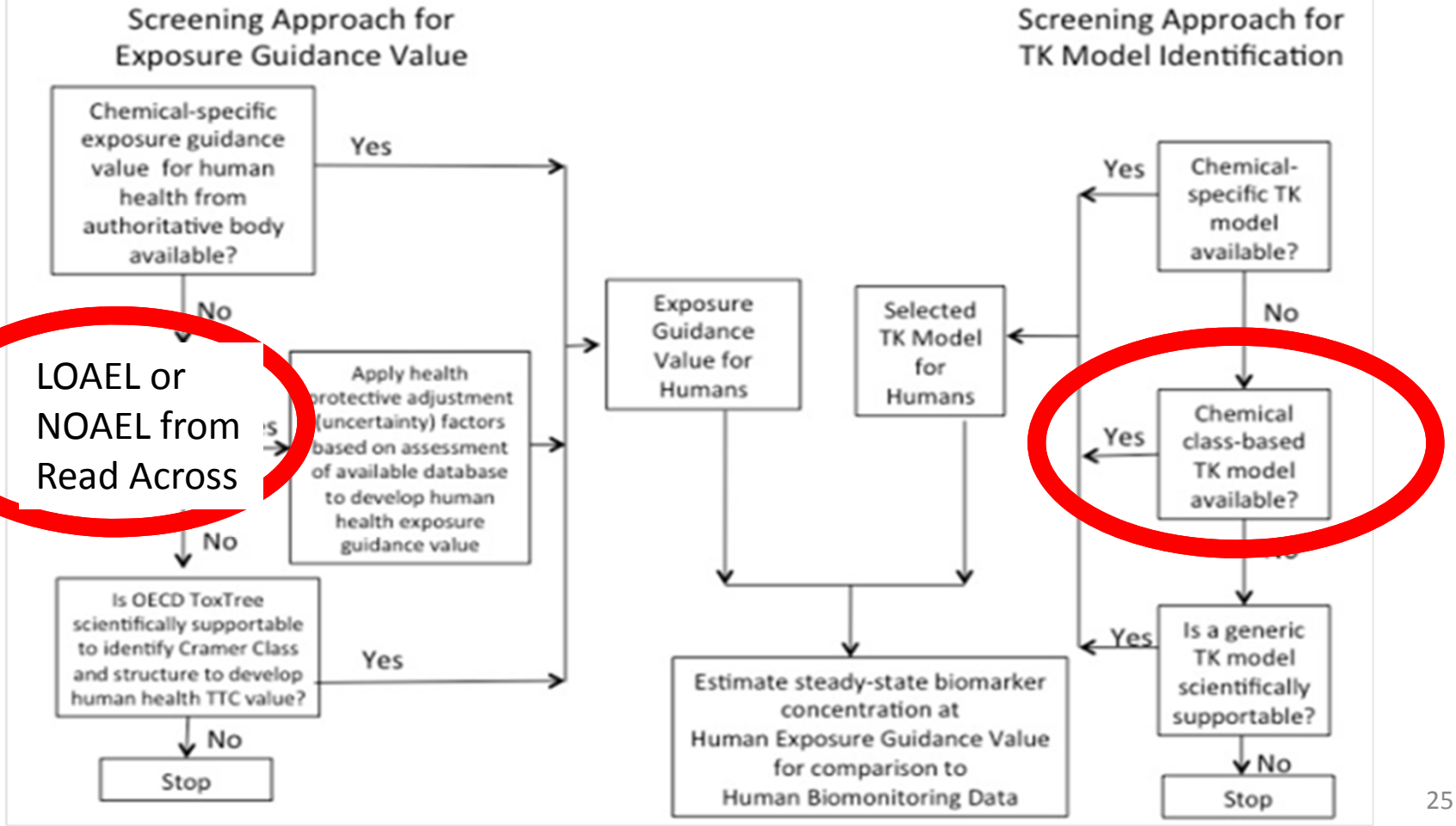
Table 2: From Aylward et al., 2010b. Extrapolated steady-state blood concentration at non-cancer chronic reference exposure levels for compounds with no identified pharmacokinetic model, extrapolated from behavior of the compounds with pharmacokinetic models. A central tendency and range of estimated blood concentrations are presented based on the geometric mean and 95% confidence interval of pharmacokinetic behavior observed among the set of 38 compounds with pharmacokinetic models identified (see Figures 3 and 4).

Chemical	Oral Reference Value (mg/kg-d)	Source	POD	POD Code	Total UF	Extrapolated steady-state blood conc., µg/L (95% CI)	Inhalation Reference Value, mg/m^3	Source	POD	POD Code	HEC POD	Total UF	Extrapolated steady-state blood conc., µg/L (95% CI)
2-Nitropropane	ND						0.02	i	16	L	16	1000	0.06 (0.02-0.2)
1,2-Dichloropropane	ND						0.004	i	12.4	L	1.3	300	0.01 (0.005-0.04)
1,2-Dibromo-3-chloropropane	ND						0.0002	i	0.17	N	0.17	1000	0.001 (0.0002-0.002)
Chlorobenzene	0.02	i	19	N	1000	0.2 (0.02-2)	0.01	HC	341	L	50	5000	0.03 (0.01-0.09)
Isopropylbenzene	0.1	i	110	N	1000	1 (0.1-10)	0.4	i	435	N	435	1000	1 (0.5-4)
Nitrobenzene	0.002	i	1.8	B	1000	0.02 (0.002-0.2)	0.009	i	0.26	B	0.26	30	0.03 (0.01-0.08)
Benzyl chloride	ND						ND						
1,4-Dichlorobenzene	ND						0.8	i	75	N	75	100	3 (0.0-7)
Carbon disulfide	0.1	i	11	N	100	1 (0.1-10)	0.7	i	20	B	20	30	2 (0.8-6)

ND- No data, no reference value found. Column headings are defined in Aylward et al., 2010b;
i, IRIS RfD; ow, EPA Office of Water RfD; h, EPA Health Effects Assessment Summary Tables (HEAST) RfD; R, RIVM TDI. POD, point of departure for derivation of reference value. POD Code: N, no-observed-adverse-effect-level (NOAEL); L, lowest-observed-adverse-effect-level (LOAEL); B, benchmark dose or concentration. HEC POD: human equivalent concentration point

(4) Both tox data and chemical-specific toxicokinetic data or models are lacking and category or class approach can be used

Volatile Organic Chemicals (VOCs)



N-propylbenzene?

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Nitrobenzene	0.002	i	1.8	B	1000	0.02 (0.002-0.2)	0.009	i	0.26	B	0.26	30	0.03 (0.01-0.08)
Benzyl chloride	ND						ND						
1,4-Dichlorobenzene	ND						0.8	i	75	N	75	100	3 (0.0-7)
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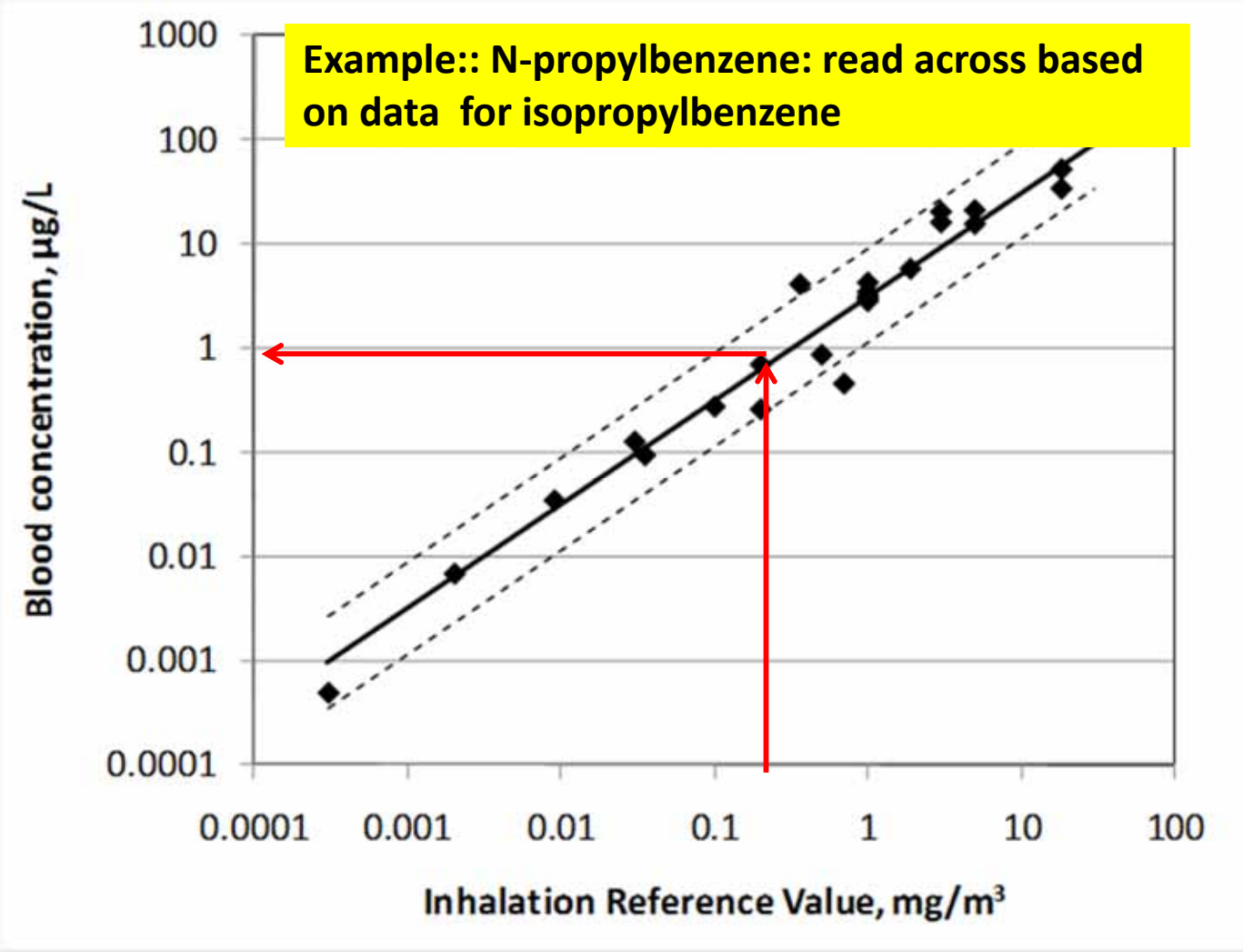
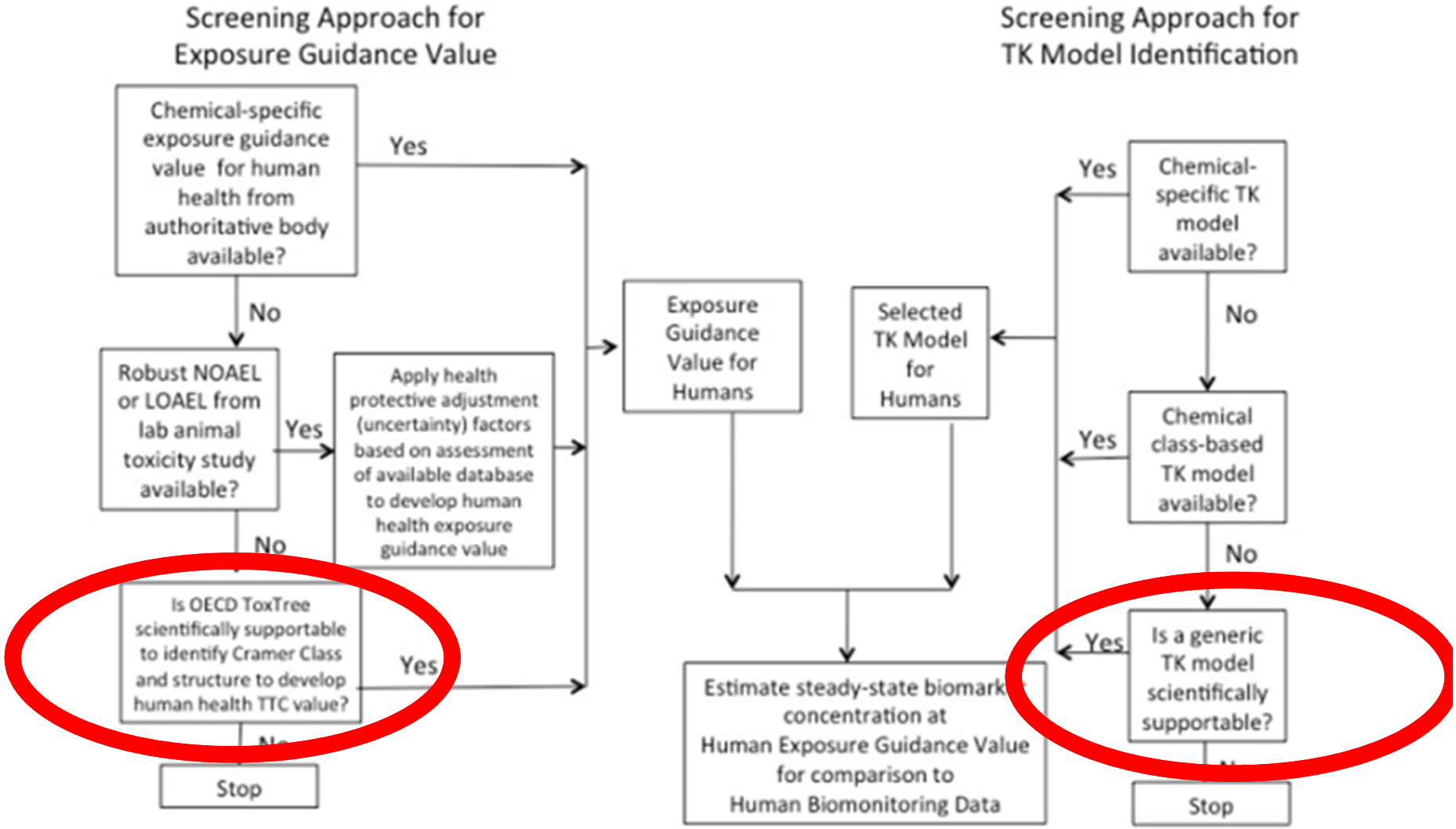


(5) Threshold of Toxicological Concern (TTC)



TTC (continued)

- TTC has been defined as “generic human exposure thresholds for structural groups of chemicals below which no risk to human health is assumed and therefore no further testing is needed”

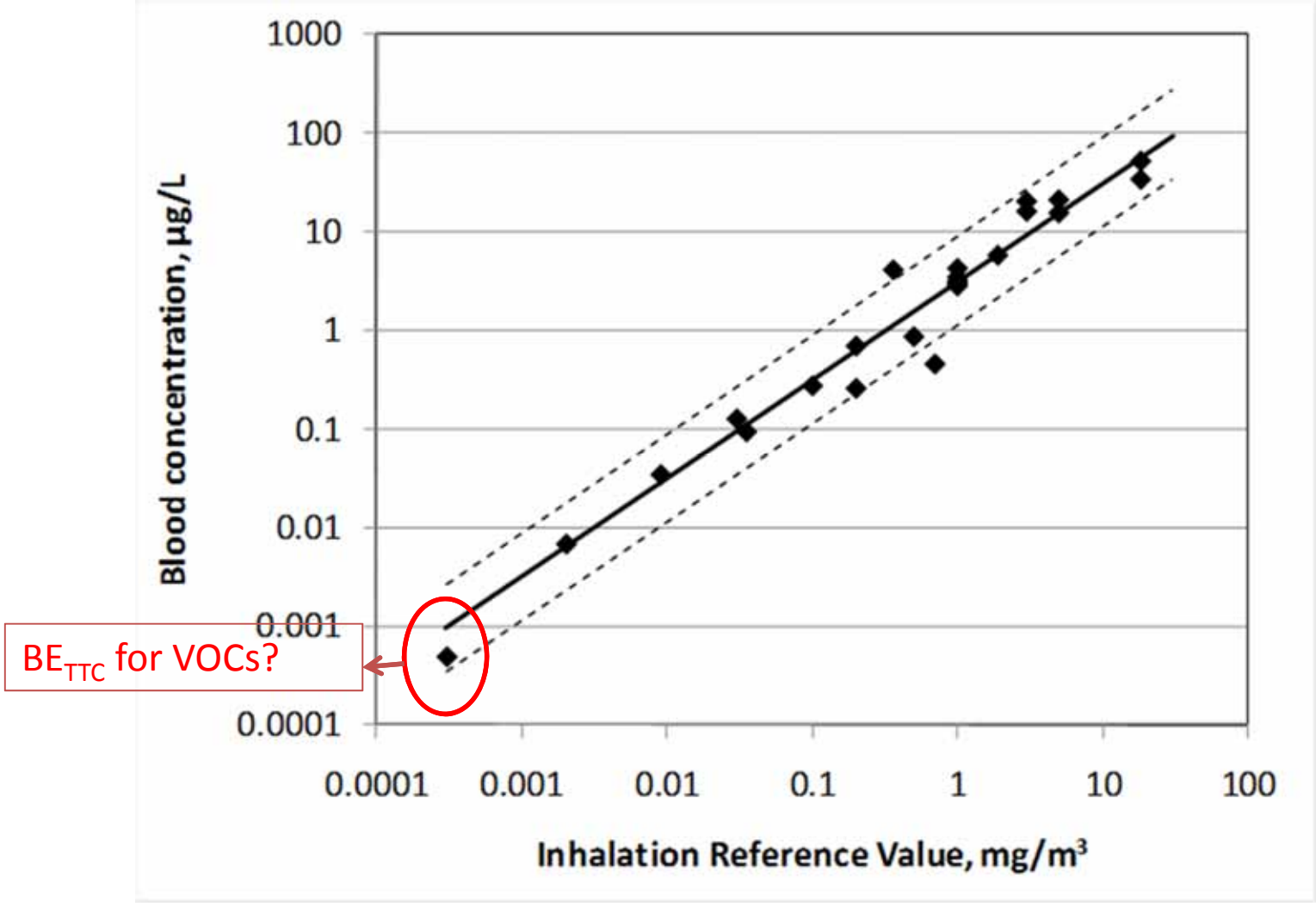
TTC (continued)

- The TTC approach is not a formal SAR or QSAR
- Based on a distribution of the tox potencies structurally similar chemicals
- Structure is evaluated using a decision tree analytic to evaluate functional groups
- Assigned to one of 3 classes:
  - TTC = 0.03 mg/kg/day (Cramer Class I)
  - TTC = 0.009 mg/kg/day (Cramer Class II)
  - TTC = 0.0015 mg/kg/day (Cramer Class III)

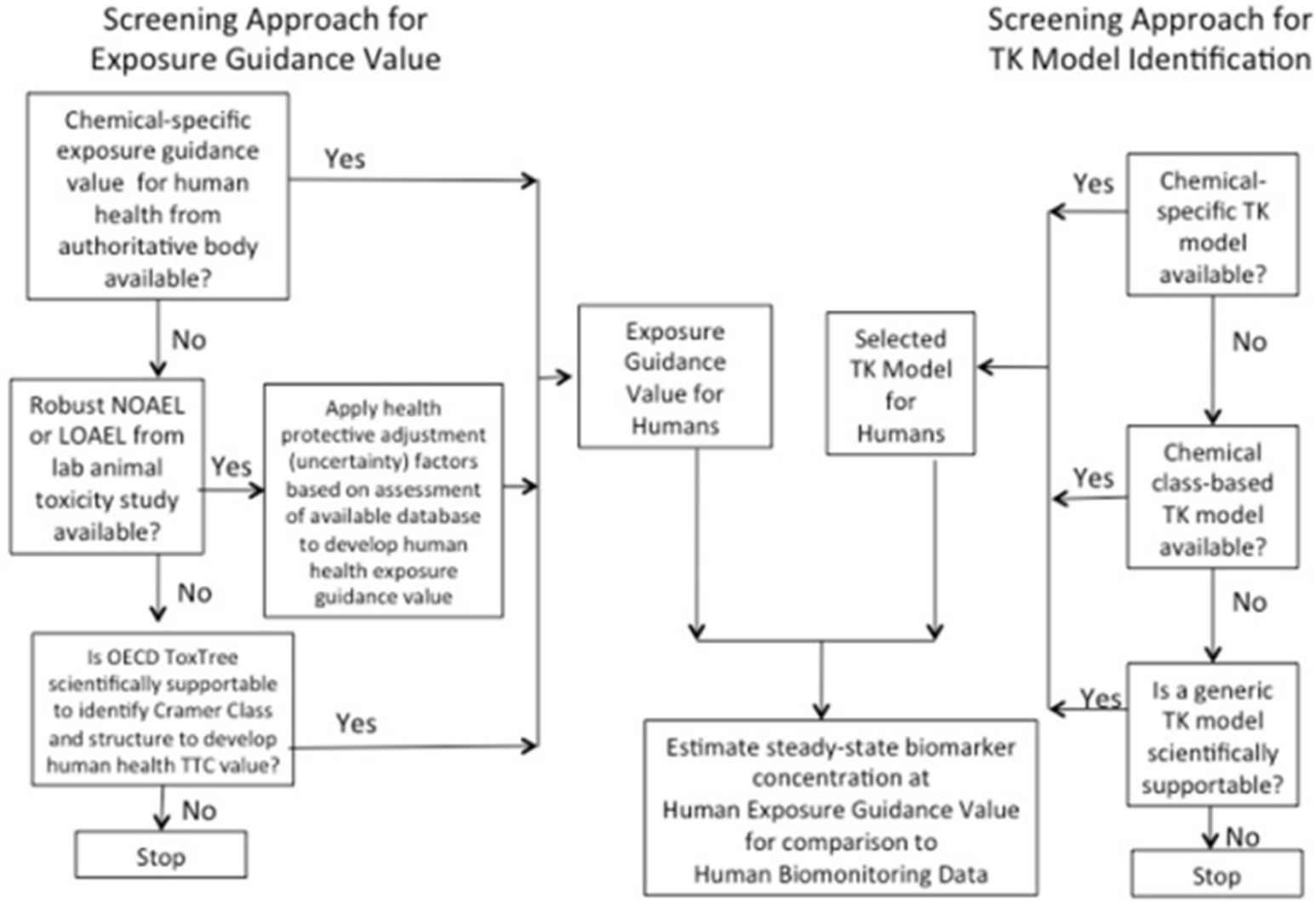
TTC (continued)

- Challenging to convert a TTC value to an internal dose
- For a substance for which a TTC approach is used to drive an external applied “safe dose” its unlikely there will be chemical-specific PK
- So, like the VOC example, a class or category approach for PK would have to be used in TTC cases

TTC Internal Dose for a Chemical Class: Leverage Classical BEs Within a Chemical Class



In Summary


Screening Approach for Exposure Guidance Value
Chemical-specific exposure guidance value for human health from authoritative body available?
Yes
No
Robust NOAEL or LOAEL from lab animal toxicity study available?
Yes
Apply health protective adjustment (uncertainty) factors based on assessment of available database to develop human health exposure guidance value
No
Is OECD ToxTree scientifically supportable to identify Cramer Class and structure to develop human health TTC value?
Yes
No
Stop
Exposure Guidance Value for Humans
Screening Approach for TK Model Identification
Chemical-specific TK model available?
Yes
No
Chemical class-based TK model available?
Yes
No
Is a generic TK model scientifically supportable?
Yes
No
Stop
Selected TK Model for Humans
Estimate steady-state biomarker concentration at Human Exposure Guidance Value for comparison to Human Biomonitoring Data

Confidence in the Different BE Approaches

Higher Confidence

Lower Confidence

(1) Classical BE

(2) Sufficient Tox Data But No Govt RA

(3) Chem-Specific PK Data /Models Lacking

(4) Chem-Specific Tox and PK Data /Models Lacking But Robust Category / Class Data

(5) Threshold of Toxicological Concern (TTC)

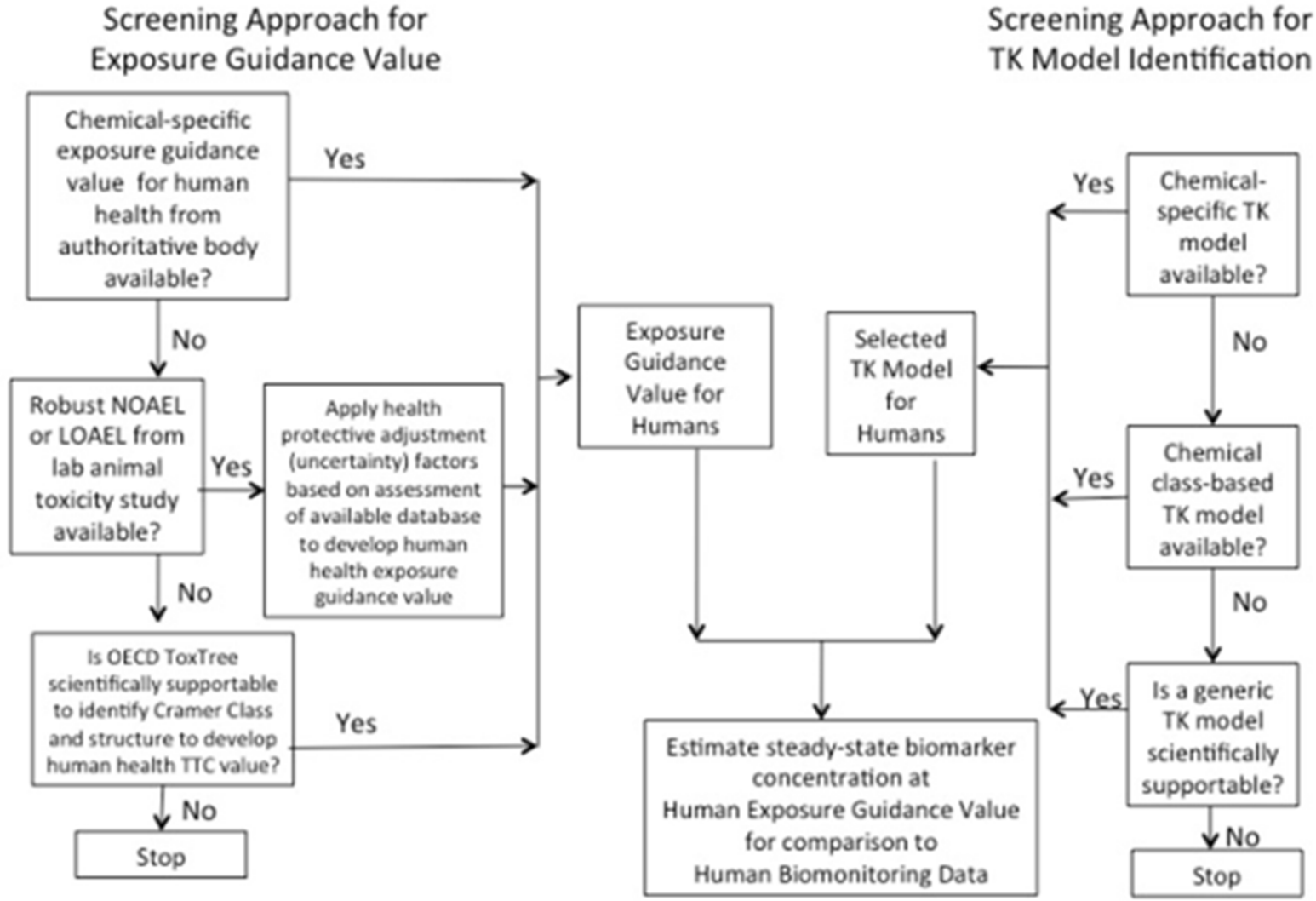
Appropriate Uses and Limitations of BEs

- Extensively discussed in references
- Spot sample collection in biomonitoring studies
- Half lives of substances in relation to sampling frequency
  - For short elimination half-lives, expect considerable variation in concentrations in an individual
  - for such substances: best to use central tendency of measured values in a population-based study for comparing to a BE value (24-h urine composite samples can also minimize this uncertainty.)

BEs Can Be Used With Same Confidence as RfDs/NOAELS for Individuals and Populations

- Neither RfDs nor BEs are medically diagnostic
- RfDs have been used to evaluate potential health risks to both individuals and populations
- BEs and related biomonitoring interpretation tools can be used in a similar manner
- BEs derived using the framework and decision tree presented here are not any different than classical risk assessment approaches used to estimate individual and population risks where external dose benchmarks (e.g., applied dose RfDs, ADIs, (NOAELs/AFs) or TTCs) are used

Conclusion: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Is a generic TK model scientifically supportable?
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Stop
Selected TK Model for Humans
Estimate steady-state biomarker concentration at Human Exposure Guidance Value for comparison to Human Biomonitoring Data

Conclusion

- This Framework provides a consistent and scientifically justified approach for guiding the development of risk-based benchmarks to enable interpretation of human biomonitoring results in a health risk context
  - The Framework provides a path forward to address not only those substances with extensive tox data and solid TK methods but also in instances where a substance has limited tox data and/ or limited TK info