HUMAN BIOMONITORING FOR ENVIRONMENTAL CHEMICALS

National Research Council
Division on Earth and Life Studies
Board on Environmental Studies and Toxicology

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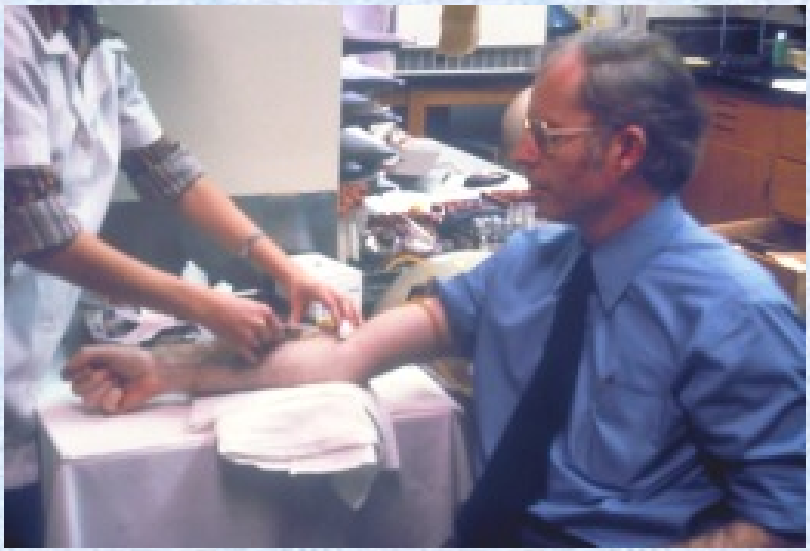
Background

- **Biomonitoring is defined as one method for assessing human exposure to chemicals by measuring the chemicals or their metabolites in human tissues or specimens, such as blood or urine (CDC 2005).**

- **Repeatedly, biomonitoring data have confirmed environmental exposures and validated public-health policies.**



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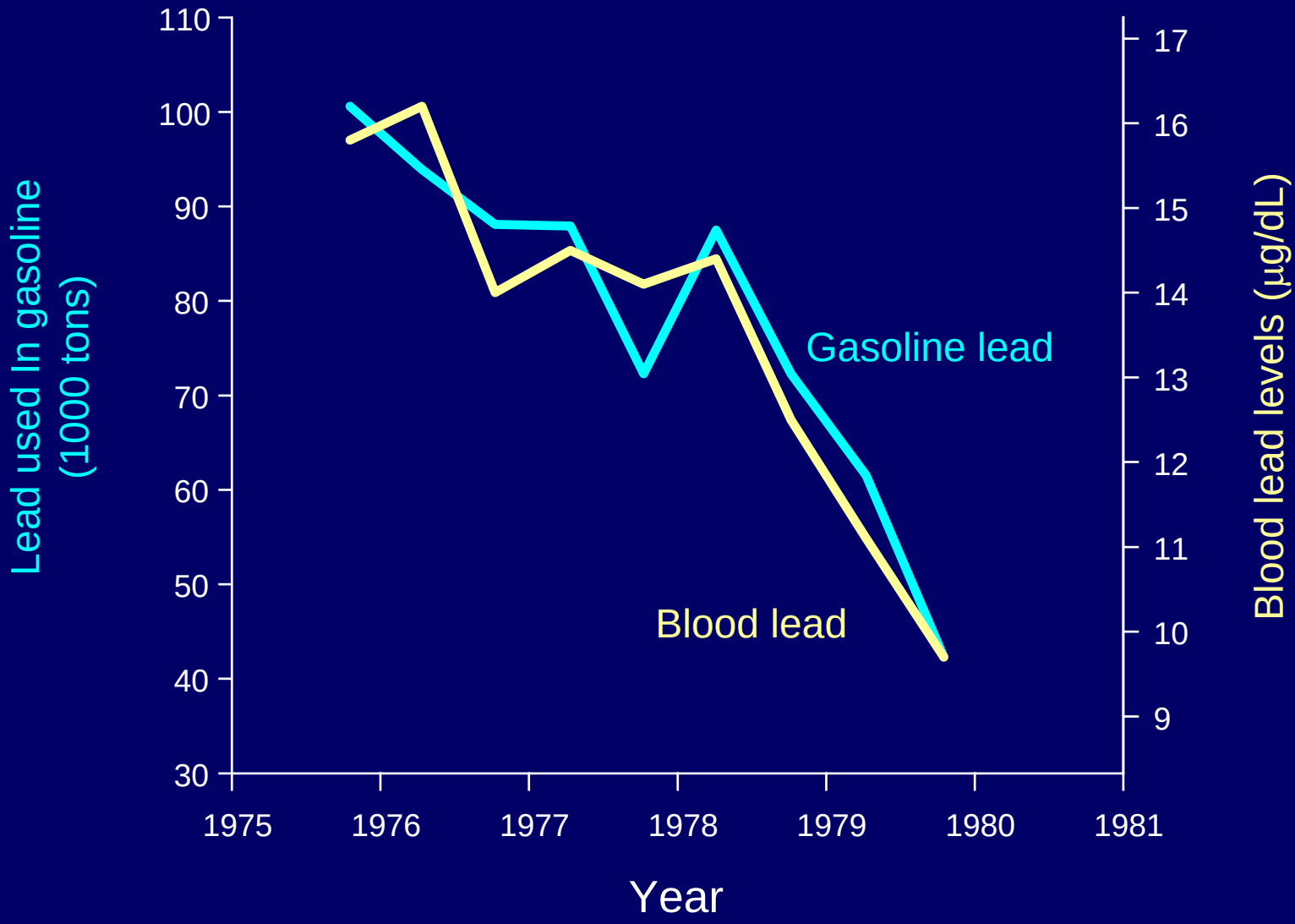
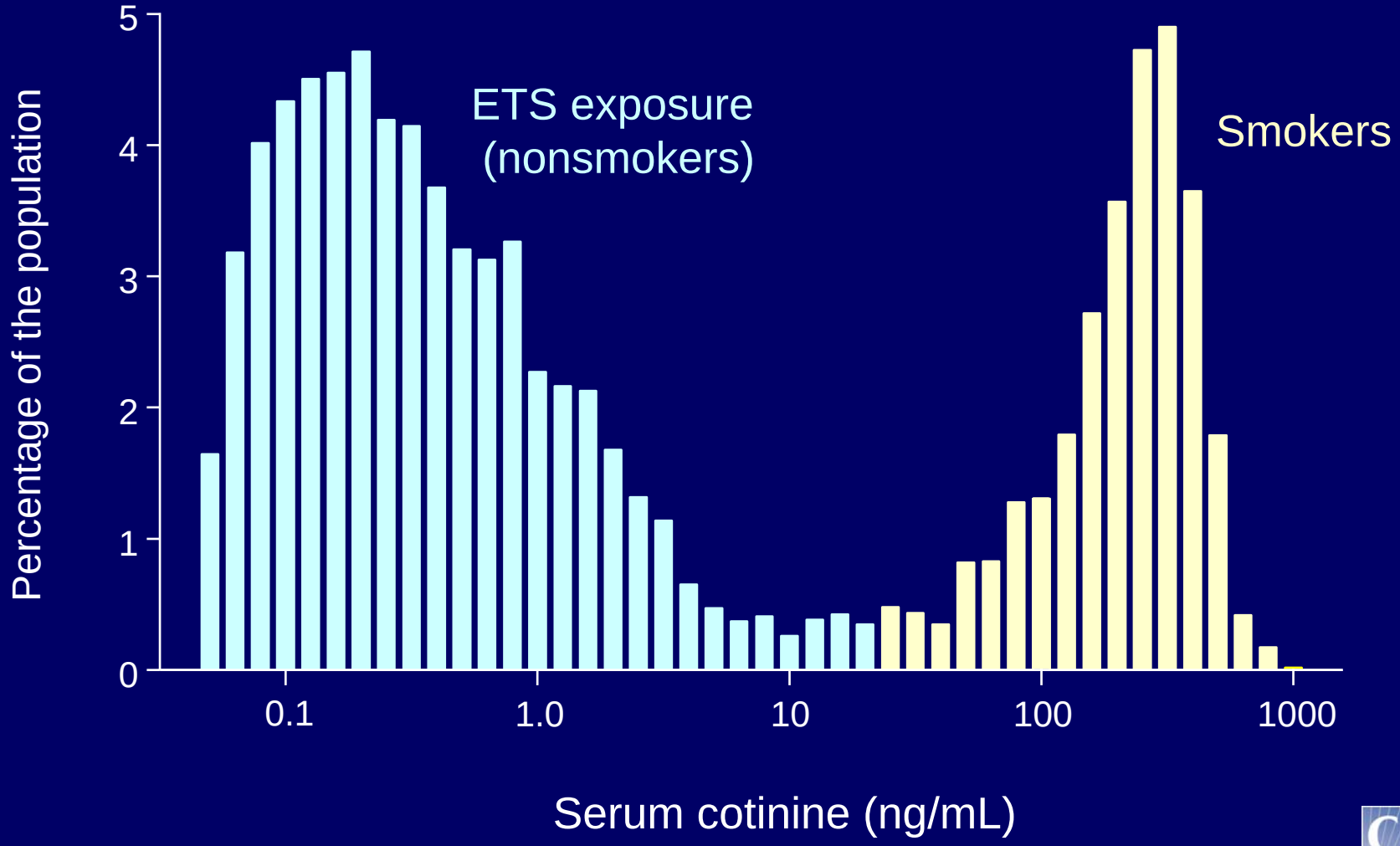
Lead in gasoline and lead in blood

NHANES II, 1976-1980



Exposure of the U.S. population to tobacco smoke: serum cotinine levels (NHANES III, 1988-1991)



Study Motivation

- **The ability to generate new biomonitoring data often exceeds our ability to evaluate the personal or public health implications**
- **Challenges in designing studies, interpretation, ethical and communication issues.**
- **Study was Congressionally requested and funded by EPA and CDC.**

Charge to the Committee

- "…review current practices and recommend ways to improve interpretation and uses of human biomonitoring data…"
- "…identify key principles and uncertainties in estimating and interpreting exposure and health risks from biomonitoring data."

Charge to the Committee

- "…develop an overall research agenda for addressing the uncertainties to improve evaluations and characterizations of health risks and to improve monitoring of changes potentially relevant to public health resulting from environmental policies."

Committee

Thomas Burke (Chair), Johns Hopkins Bloomberg School of Public Health
Mark Cullen, Yale Occupational and Environmental Medicine Program
George Eadon, New York State Department of Health
Peter Farmer, University of Leicester
Gary Ginsberg, Connecticut Department of Public Health
Carol J. Henry, American Chemistry Council
Nina Holland, University of California, Berkeley
Gunnar Johanson, Karolinska Institutet
Branden Johnson, New Jersey Department of Environmental Protection
Dorothy Patton, International Life Sciences Institute
Gerald van Belle, University of Washington
Claude Viau, University of Montreal
Robin Whyatt, Columbia University
Raymond S.H. Yang, Colorado State University

Committee's Approach

- **Focus was on population-based biomonitoring studies: e.g., CDC/*NHANES*, EPA's National Human Exposure Assessment Survey. Consideration also to Europe.**

- **Broad screens raise greatest interpretative challenges**
  - **Widespread low level exposures**
  - **What does it all mean??**

- **Also considered other types of studies:**
  - **Source investigations,**
  - **Occupational investigations,**
  - **Individual risk characterization.**
  - **Regional and state BM efforts**

Where are the Health Reference Levels?

TABLE 1-1 Numbers of Chemicals in *Third National Report on Human Exposures to Environmental Chemicals* for Which Health-Based Values Are Available

148[a]	Number of chemicals sampled by CDC in third national report
25	Number of chemicals for which EPA reference values (i.e., RfCs or RfDs) and/or cancer slope factors are established[b]
23	Number of chemicals for which TLV-TWAs are established
5	Number of chemicals for which BEIs are established
3	Number of chemicals for which RfDs/RfCs, TLVs, and BEIs are established

[a]The CDC measures 148 total analytes; however many are similar compounds that are members of a broader class of chemicals, such as polychlorinated biphenyls, dioxins and furans, organophosphorus pesticides, and heavy metals.

[b]Many of the chemicals do not have specific health-based values, but because many are in similar classes of compounds, alternative approaches to evaluate toxicity, such as toxic equivalency factors, are available.

Source: CDC 2005.

Committee's Evaluation

- **Biomonitoring is a tool with great potential.**
- **The complete potential of this tool has yet to be realized, as the science (epidemiology, toxicology, pharmacokinetic modeling, and exposure assessment) needed to understand the implications of the biomonitoring data for human health is still in its nascent stages.**
- **Scientists, policy-makers, and the public are just beginning to grasp the ethical and communication challenges that the data are creating.**

Finding: No strategy ……

Lacking a coordinated public health-based strategy for selecting chemicals

Selection of Chemicals Often Because:

- There is a method
- Some indication of large scale use
- Some indication of toxicity
- Lack of integrated across-agency approach
  - Allowed impt exposures to go undetected for many years (PBDEs)

Biomarker Development

- Biomarkers arise from
  - Epidemiology studies
  - Analytical chemistry
  - Workplace screening methods
  - CDC efforts to expand capabilities
  - European screening programs
- Not often developed from a pro-active prioritization process

U.S. and European Biomonitoring Efforts

- **Biomonitoring is rapidly developing in the U.S. and Europe with comparable types and numbers of analytes being measured.**

- **Biomonitoring of chemicals in children appears to have high priority in both the U.S. and Europe.**

Roadmap for Addressing Unanswered Questions

- **Framework for Characterizing Biomarkers and Uses of Biomonitoring Data.**
- **Guidelines to ensure the proper conduct of biomonitoring studies**
- **Options for interpreting biomonitoring data**
- **Challenges in communicating results**
- **Research Agenda**
  - Findings and Recommendations

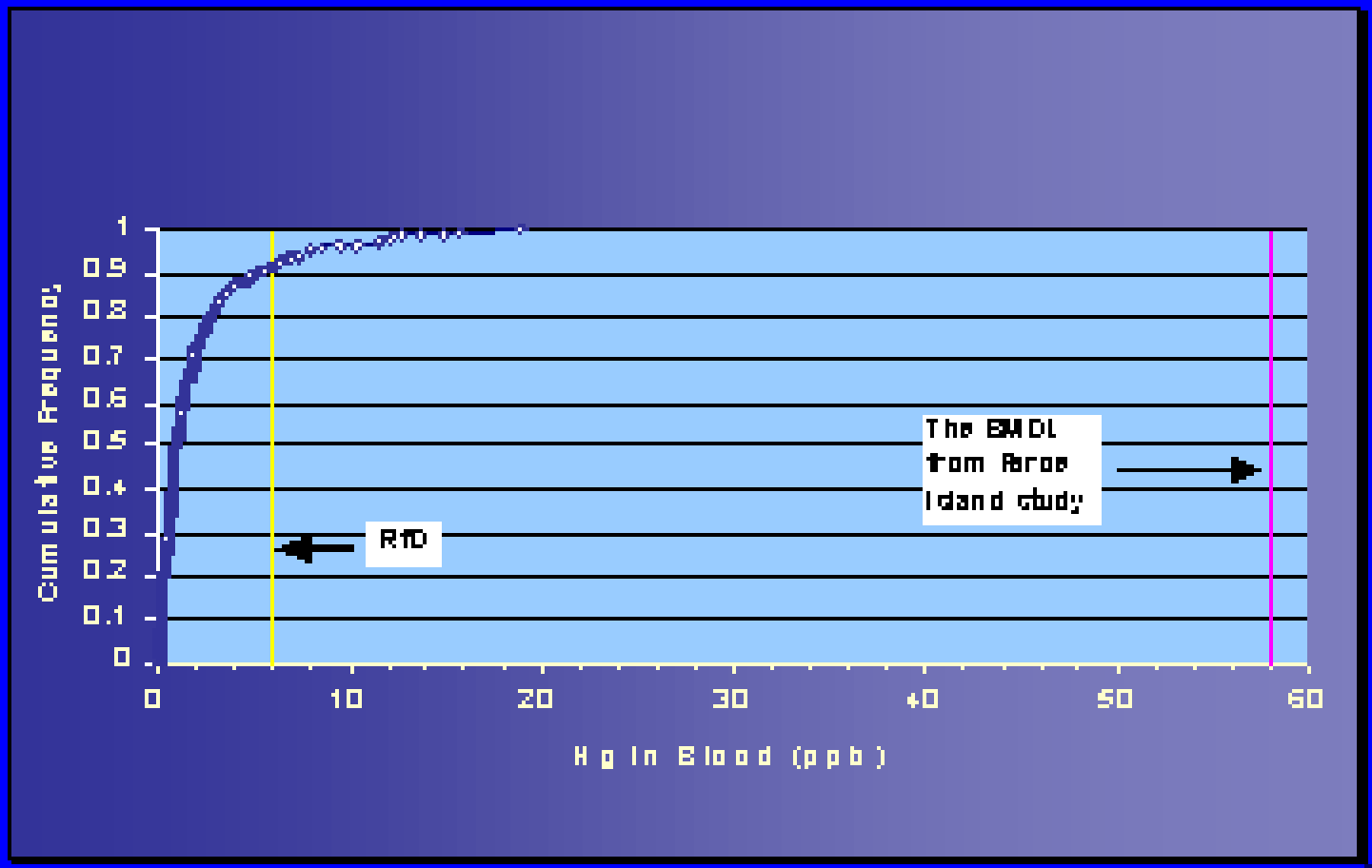
Framework for Characterizing Biomarkers

TABLE 3-1 Framework for Grouping Biomarkers of Exposure[a]

		Biomarker Group						
Properties of Biomarkers		I	II	III	IV	V	VI	VII
Reproducible sampling and analytic method			R	R	R	R	R	R
Known relationship of external dose to [BM] in animals[b]				R				
Known relationship of external dose to [BM] in humans[b]					R		R	R
Known relationship of [BM] to biologic effect in animals							O	
Known relationship of [BM] to biologic effect in humans						R		R
Known relationship of external dose to response in animals							O	
Known relationship of external dose to response in humans							O	
Biomarker informs about	Internal dose		√	√	√	√	√	√
	External dose[c]			√	√		√	√
	Biologic effects[d]					√	√	√
						Potential for risk assessment		

[a]Checkmark in lower portion of table means that biomarkers in group can inform about stated elements of dose and effect.
[b]Implies knowledge of pharmacokinetics of biomarker in relation to exposure to parent chemical.
[c]The relationship between external dose and internal dose may be influenced by metabolic polymorphisms and other factors, including socioeconomic status and racial and ethnic differences.
[d]Biologic effects may include a wide range of observations, from very early biochemical perturbations to clinical signs of alteration of health.
Abbreviations: [BM] = concentration of biomarker; R = required: O = optional (at least one of these is required).

Blood Mercury levels



Biomarker Framework

- Categories indicate interpretative utility
- Categories II to VII generally suitable for BM programs
- Category II – suitable for baseline, status and trends
  - identify emerging exposures and develop research agenda
- Categories II to VII increasing utility to relate internal level to
  - external dose
  - biological effect
- May or may not be desireable to advance from Cat II to VII
  - depends upon level of interpretation needed

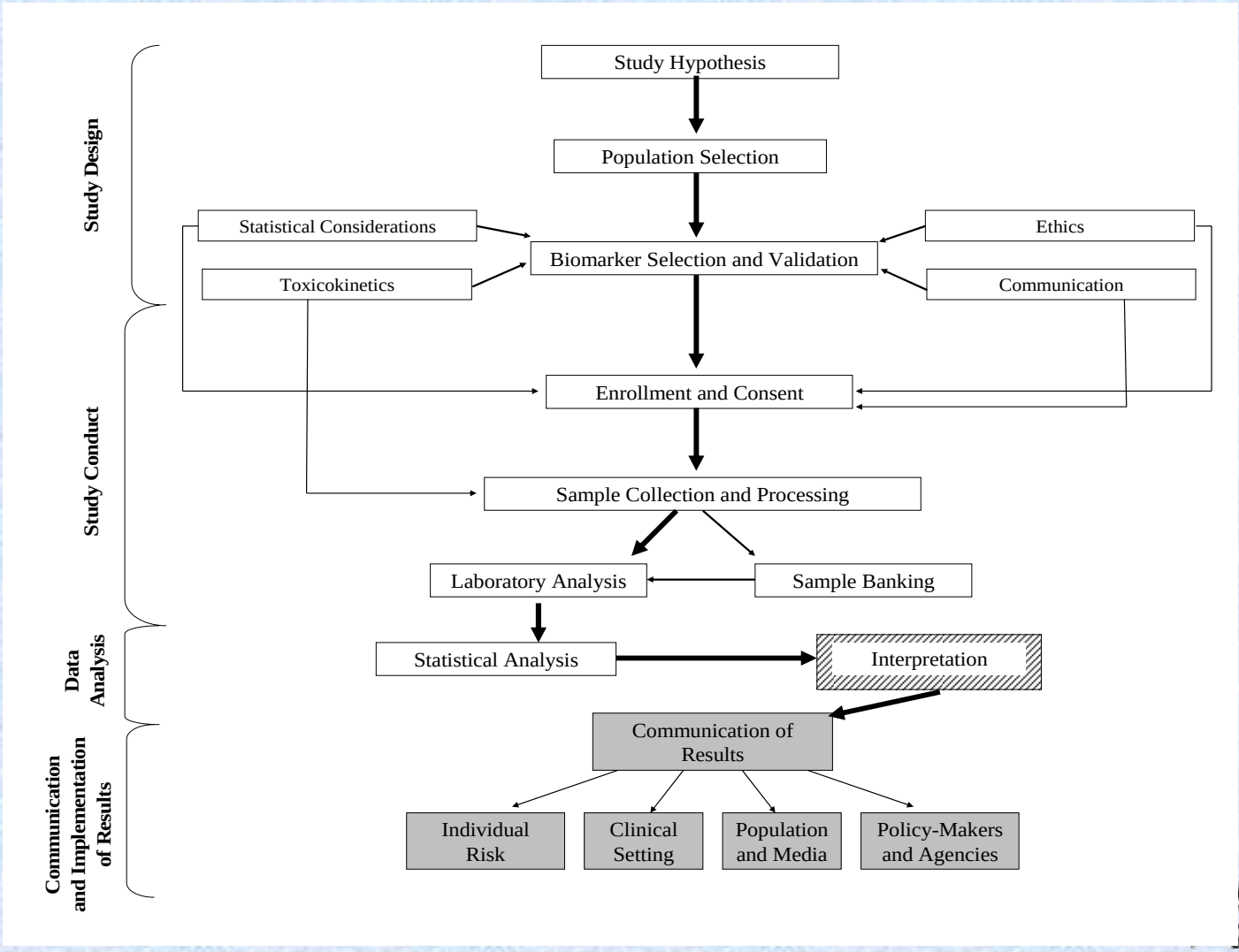
Considerations in the Design of Studies

- The *National Reports on Human Exposure to Environmental Chemicals*, produced by CDC, are based on a representative sample of the population and a large number of chemicals, and they use well-documented analytic techniques. However, not all biomonitoring studies are conducted with the same rigor as the CDC studies.

- The committee discusses scientific practices in biomonitoring (study design, conduct, and analysis).

Considerations in the Design of Studies

FIGURE 4-1 Stages of a biomonitoring study



Considerations in the Design of Studies

- Critical to adhere to statistical principles when sampling populations for valid, representative data
- Collect detailed information on cofactors (e.g., SES, home environment, lifestyle) to facilitate interpreting BM data.
  - Depends to some degree on questions asked
    - e.g, Perfluoro compounds and area of carpeting in home
- Fed agencies such as CDC, NIST could play important roles in improving overall BM data quality
  - Ensure regional, state, university programs at consistent quality

Interpreting Biomonitoring Data

- Biomonitoring data may be interpreted with either descriptive or risk-based approaches.
- Descriptive approaches present a statistical review of the data (e.g., 10^{th}, 25^{th}, 50^{th}, 75^{th}, and 90^{th} percentiles).
- Risk-based approaches use toxicologic, epidemiologic, or pharmacokinetic modeling data to relate biomonitoring data to other measures of toxicity in an effort to evaluate the risk associated with the amount of chemical in the body.

Interpreting Biomonitoring Data

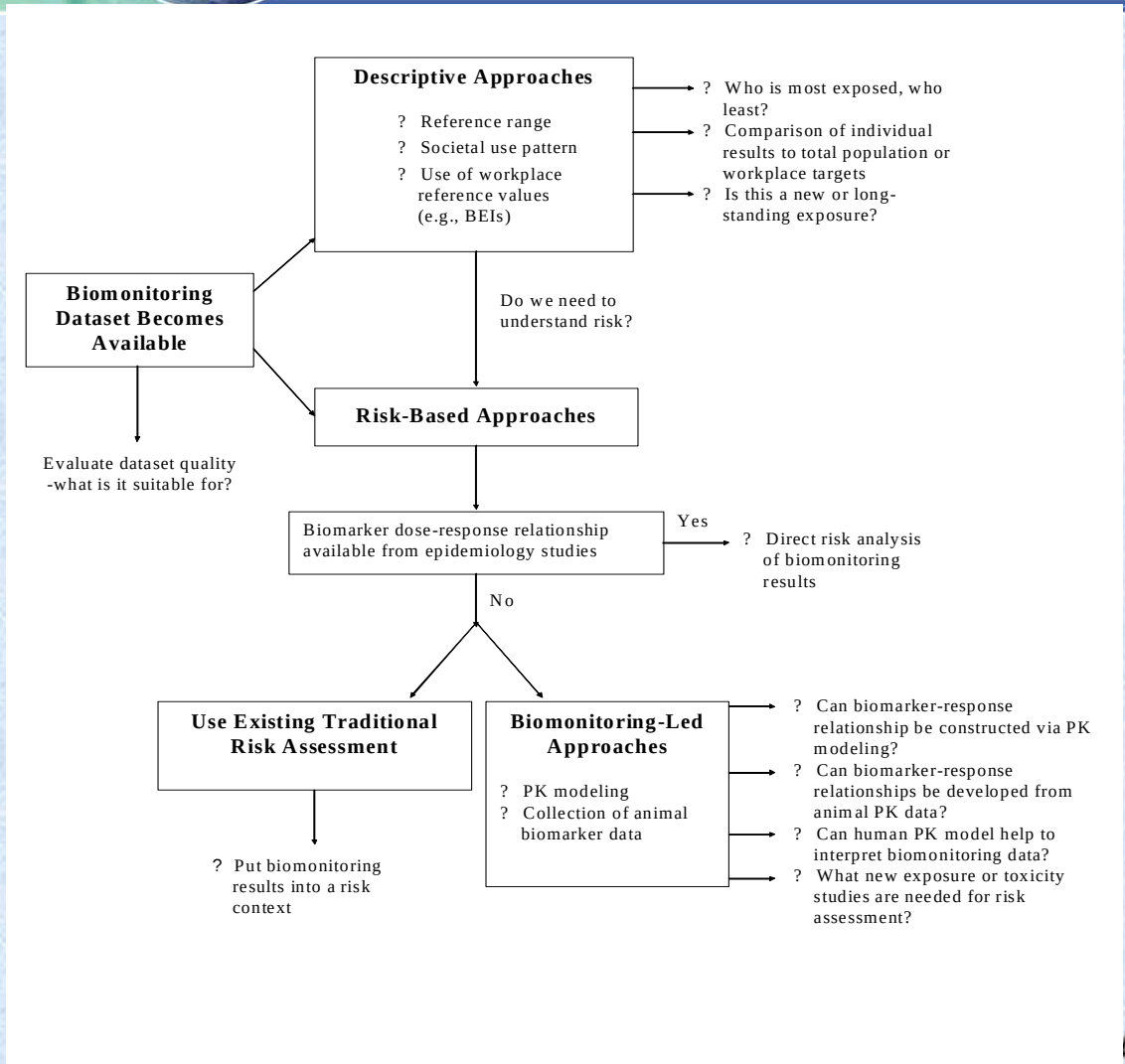


FIGURE 5-1 Overview of interpretive options for biomonitoring data.

Qualitative Approach: Reference Range

- Comparison to workplace BEIs, BATs
  - Not highly relevant to public health
  - If exceed a BEI, generally a risk priority
- Comparison to population exposure stats
  - Where is a given individual in the distribution?
  - Is a community particularly impacted?
  - What is normal? (95^{th}% cutpoint?)

Three Risk-Based Approaches - #1

- **Biomonitoring-based risk assessment**

  - Most straightforward approach.

  - Exp-resp relationships available from epidemiology studies for biomarker in hair, blood, urine, etc

  - Relationships applied directly to new BM data to determine where on the exp-resp curve any person is.

  - Few chemicals are in this data-rich category (e.g., lead and mercury).

Three Risk-Based Approaches - #2

- **Using existing risk assessment for interpreting biomonitoring data**
  - **Interpretation of biomonitoring results can be enhanced by existing RA of a specific chemical.**
  - **Traditional RA cumulates exposure dose & compares with RfD or estimate cancer risk.**
  - **This can be a useful starting point for putting the biomonitoring data into perspective.**
  - **Illustrations of two case studies:**
    - **glyphosate – generally low population risks**
    - **Permethrin – borderline population risks**

Three Risk-Based Approaches - #3

- **Biomonitoring-led risk assessment**
  - **Refers to process where BM data create need for method development to improve RA**
  - **Epidemiological data insufficient**
  - **Toxicology data robust – have animal dose-response**
  - **Need to relate human blood level to animal-based RfD or CSF**
  - **PK modeling the centerpiece**

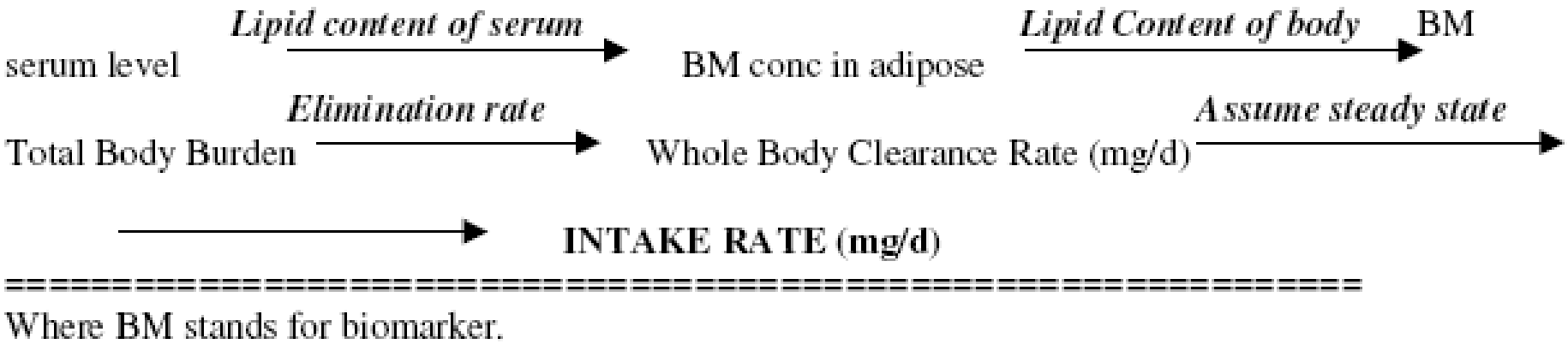
Three Risk-Based Approaches - #3

- **Biomonitoring-led risk assessment (cont)**

- **Pharmacokinetic modeling for estimation of dose**
  - **Forward direction – animal PBPK model to convert dose-response to biomarker-response in animals**
    - **e.g., PFOA**
  - **Reverse direction – human PBPK model to convert biomarker result to intake dose and then risk**
    - **E.g., dioxin, chlorpyrifos, and phthalates.**

Extrapolation to Dose with One Compartment Model for Dioxins

Figure 5-6. Conversion of Biomonitoring Data to Daily Dose Based Upon One Compartment (Body Burden) Model



Where BM stands for biomarker.

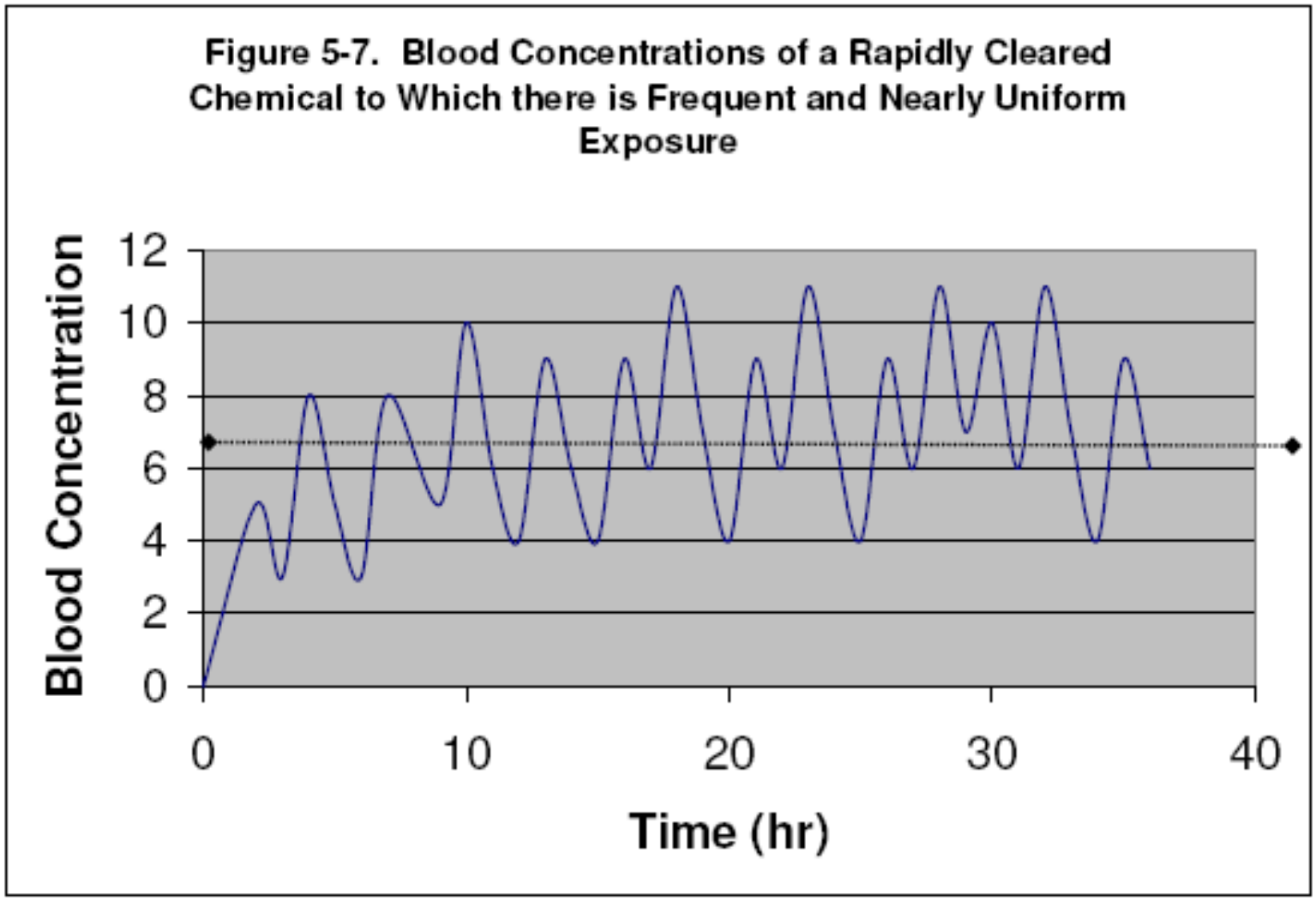


Figure 5-7. Highlighted line (♦--♦) is mean blood concentration across all time points. . Under these exposure conditions, biomonitoring will be within two-fold of mean concentration after the first several hours. A simplifying assumption of pseudo-steady state (mean concentration is approximated by the concentration found at any sampling time) may suffice for estimating exposure dose from blood concentration under these circumstances.

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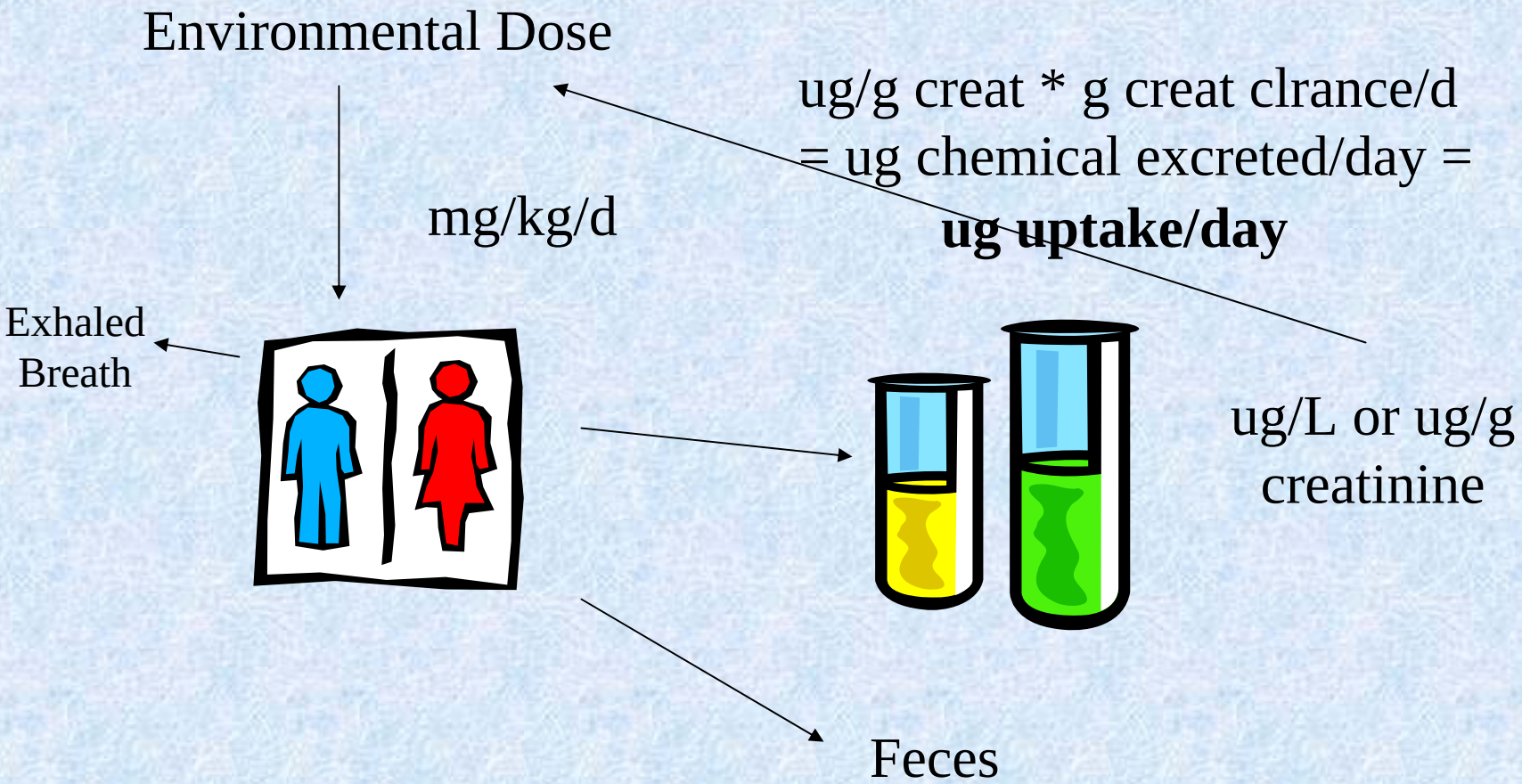
Extrapolation to Dose from Urinary Biomarker



Communicating Results

- **Communication is essential to proper interpretation and use of biomonitoring data.**
- **There is no one recipe for good biomonitoring communications.**
- **Achieving proper communication requires explicit funding, early planning, and empirical evaluation of communication methods and messages.**

Research Agenda

- **To realize the potential of biomonitoring, investment in research is needed to address the critical knowledge gaps that hinder our ability to use biomonitoring data and interpret what they mean with respect to risks of public health.**

- **Recommendations focus not on specific chemicals but rather on methods that can be applied to a broad array of chemicals.**

- **Implementation of research recommendations by federal and state agencies and universities will benefit from an improvement in some parts of our nation's research infrastructure.**

Research Recommendation #1

- **Finding:** Biomonitoring has great value for screening population exposure to many chems

- **Finding:** There has not been a coordinated and consistent public-health-based strategy for selecting how chemicals are included or excluded

- **Finding**: susceptible subpopulations, including infants and children, are generally omitted from these studies.

Recommendation #1: Developing a BM Program

- Agency Coordination
  - EPA/CDC/FDA/CPSC/USDA/NIEHS/NTP
  - Federal / State coordination
    - Leverage research efforts, reduce redundancies
    - Build a body of information meaningful on national and regional level that's useful for:
      - **Status and trends**
      - **Research priorities**
      - **Population risk assessment**

Setting Biomonitoring Priorities

- Evidence of current widespread exposure
  - Exposure to susceptible populations
- Toxic effects of public health concern
- Persistence and projected use pattern
  - Is this an emerging contaminant?
- Untargeted analytes - what else are we finding that is not being identified?
- Early life stage methods development

Research Recommendation #2

- **Finding:** The ability to detect chemicals has outpaced the ability to interpret health risks.
  - BM approaches not well integrated into
    - epidemiology, toxicology, RA

- **Recommendations:**
  - **Increase use of exposure and effect biomarkers in epidemiology studies**
    - **Develop biomarker-effect relationships in humans**
  - **Use biomarkers in toxicology studies**
    - **develop biomarker-response relationships in animals**

Recommendation #2 (cont'd)

- **Expand use of pharmacokinetic models to extrapolate dose**
  - **Key for projecting risk**
  - **Explore variability produced by metabolic diffs, temporal factors**
- **Exposure assessment should be a component of population-based biomonitoring studies**
  - **E.G., NHEXAS**
  - **Allow comparison of forward and backward dose estimates**
- **Reporting of Results**
  - **Provide full range (not just central and upper range)**
  - **Provide indication of multiple contaminants in same individual**

Research Recommendation #3

- **<u>Finding</u>: Effective communication is among the biggest challenges to the future of biomonitoring. Poor communication hampers interpretation and use of the data.**

- **<u>Recommendation:</u> Develop strategies for reporting results at individual, community and population levels**
  - **Consistent terminology and concepts**
  - **Public education and outreach**
  - **Describe exposure reduction options**
  - **Research agenda to include public reaction to uncertainty and risk**

Research Recommendation #4

- **<u>Finding</u>: Biomonitoring research presents a number of ethical concerns about informed consent and the interpretation of results.**
  - **Anonymized samples limit communication of results and potential follow up with study subjects.**
- **<u>Recommendation:</u> There is a need for review of the bioethical issues confronting the future of biomonitoring, including confidentiality, informed consent, reporting of results, and public-health or clinical follow up.**

Recommendation #4 (cont'd)

- **Participants in public-health studies that measure hundreds of chemicals might give "informed consent" only with respect to the general objectives of the study on the grounds that detailed discussion of each biomarker is not feasible. However failing to provide such information raises ethical questions.**

- **Research is needed to identify methods that ethically and practically inform subjects who are participating in biomonitoring studies that measure many chemicals in a single person.**

Infrastructure Needs

- **Current scientific infrastructure is severely limited.**
  - **CDC funded 33 states to plan for BM programs**
  - **Only 3 states funded to implement programs**
    - **Important to identify local/regional exposure and PH issues**
- **Needed improvements in research infrastructure:**
  - **Enhance laboratory capabilities at local level**
    - **Sensitive detection in biological media**
    - **Quality control samples and proficiency programs (NIST)**

Infrastructure Needs (cont)

- **Expand the scope & utility of CDC data**
  - **Only 148 of 1500 priority chemicals sampled for**
  - **Improved reporting of results**
    - **Low end as well as high end of distribution**
    - **Multiple contaminants in single individual**
  - **Expand analysis of infants and young children**
  - **Need information on a greater number of ethnic groups and special populations**
  - **Need BM data for specific geographic locations**
    - **Either expand CDC effort or fund local BM efforts**
      - » **E.g., NYHANES**
- **Maximize utility of collected human samples**
  - **Banking samples for later chemical/biological/genetic analyses**

In Summary…

- **Provides a reference guide for moving the field of biomonitoring forward from the design, to the conduct, interpretation and reporting of biomonitoring results.**

- **To realize the full potential of biomonitoring as an environmental health tool will require:**
  - **Prioritizing biomarkers for development.**
  - **Support of epidemiologic, toxicologic, and exposure-assessment science to interpret biomonitoring data.**
  - **Improved communication of biomonitoring results.**
  - **Review of bioethical issues.**
  - **Enhancement of scientific infrastructure to support regional and research efforts.**

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