

The importance of toxicity thresholds for biomonitoring

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Summary

Environmental chemicals and their breakdown products are always present in our body fluids and tissues. The existence of toxicity thresholds means that before such compounds can be harmful to us, their amounts must be great enough to overcome our body's natural defenses against the thousands of chemicals of all kinds encountered in our everyday existence. The existence of toxicity thresholds means that the presence of such compounds in our bodies does not indicate a health risk as long as the levels are low and below toxicity thresholds. Thus, biomonitoring tells us only which chemicals are in our bodies and the quantities that were found in our tissues. The same holds true for substances detected in cord blood, which is a reflection of the levels of chemicals in the fetus and placenta. Knowledge of toxicological science, including toxicity thresholds, together with the results from ongoing research, allows us to put such findings in context.

Introduction

The purpose of this paper is to discuss the importance of toxicity thresholds for understanding biomonitoring. Biomonitoring is the measurement of chemicals in human biological specimens (such as blood, urine, hair, nails, and breast milk), any breakdown products (called "metabolites"), and any change in certain substances (called "biomarkers") that result from interactions in the body. Biomonitoring tells us the amounts of chemicals that actually get into people from all sources combined, including air, soil, water, dust, and food. Because of this, biomonitoring can provide useful information on how much exposure to environmental chemicals that a person has had. As a result of the availability of biomonitoring techniques, several government agencies in the United States, Canada, and Europe are either currently conducting or planning to conduct large scale biomonitoring programs to gather information on the concentrations of selected chemicals in human samples. Because of such programs, over 300 different environmental compounds have been quantified in human biological samples. However, biomonitoring does not tell us whether or not the chemicals found are causing significant harmful effects in our bodies. That requires data from toxicological studies, including information on "toxicity thresholds."

What is meant by toxicity thresholds?

The toxicity threshold is the exposure level or dose of an agent above which toxicity or adverse health effects can occur, and below which toxicity or adverse health effects are unlikely.

This situation can be portrayed graphically by means of dose-response curves. The region of the dose-response curve that marks the transition from "no-toxicity" to "toxicity" corresponds to the toxicity

threshold – the dose immediately above which responses caused by the chemical begin to manifest themselves and below which no effect occurs (Figure 1).

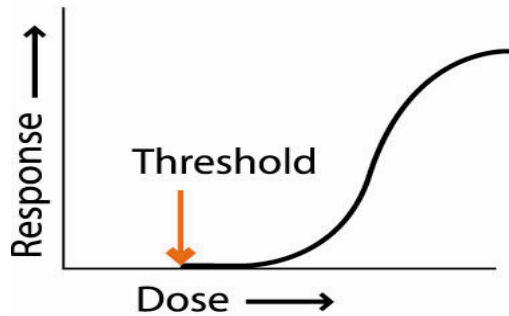


Figure 1. Idealized dose-response curve, showing a toxicity threshold.

The threshold concept provides the basis for determining a “No Observable Adverse Effect Level” or “NOAEL,” which can be used for assigning “safe levels” for exposure. A related term is the “LOAEL” or “Lowest Observable Adverse Effect Level,” the lowest dose at which a harmful effect could be detected in an experiment. For a graphic depiction of the relationship of the NOAEL and LOAEL to the dose-response curve and to the typical range of human exposures, see Figure 2.

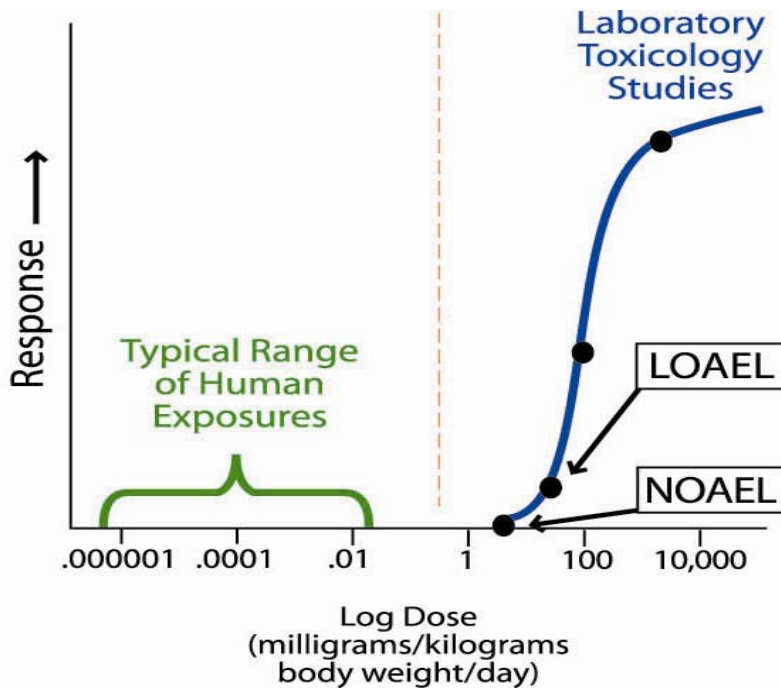


Figure 2. Idealized dose-response curve indicating the NOAEL and LOAEL. The typical range of human exposures is lower than the NOAEL and LOAEL..

As stated by the Centers for Disease Control and Prevention (CDC), the U.S. public health research organization that conducts the national biomonitoring program, “[T]he presence of a chemical does not imply disease. The levels or concentrations of the chemical are more important determinants of the

relation to disease, when established in appropriate research studies, than the detection or presence of a chemical.”¹ To better understand this statement, consider the case of pharmaceutical drugs, where the dose of a drug or its level in the body determines the likelihood of harm. If a patient takes too little of a prescribed drug, it will not have the intended effect. However, if a patient takes too much of a prescribed drug, there can be unintended adverse consequences. The same holds true for the presence of environmental chemicals in our bodies. There exists a dose-response relationship whereby the higher the dose (or concentration of the chemical in the body’s fluids and tissues) the greater the risks of adverse health effects. Conversely, because thresholds for toxicity exist, there is some level at which no response would be expected.

Why do toxicity thresholds exist?

Thresholds for toxicity exist because, up to a certain point, the body can repair damage and detoxify chemicals to which it is exposed. If the exposures get too high, however, the detoxification and repair mechanisms are overwhelmed and toxicity starts to occur. In support of the threshold hypothesis are many observations that some minimum concentration of a toxic chemical or its metabolites must encounter a cellular target before any biologically significant changes take place. Moreover, cells appear to have a remarkable capacity to repair damage caused by foreign chemicals. So until an exposure is reached at which that repair capacity is overwhelmed, there is a very low likelihood that a toxic injury will occur. In addition, there are often large numbers of cells that perform the same or similar functions, and it is likely that their population must be significantly depleted before an adverse effect is seen.

Our very survival has depended on the existence of toxicity thresholds as a practical reality. For virtually every organic substance, there is a finite rate at which it is metabolized. It follows that there must also exist a finite threshold dose rate below which the substance is decomposed, eliminated, or chemically altered so rapidly that it can have no adverse effects. If this were not true, humans could not have survived to the present time, in view of all the things we eat and otherwise encounter in our daily lives. Indeed, every mouthful of food we have ever consumed contained many thousands of kinds of complex molecules whose structure and physiological effects have mostly never been determined, and many of these would be toxic or even fatal in large enough doses.

How well established are thresholds in toxicology?

Much of the evidence in favor of the existence of a threshold dose for chemical toxicity comes from laboratory animal experiments. There are data from many thousands of such experiments in which certain dosages were identified as having no observable adverse effects on health, the NOAEL. These studies demonstrate that if the dose is lowered sufficiently, no toxicity can be observed, regardless of how toxic the chemical may be at higher dosages.² The same also appears to be true for human studies. If human exposures are low enough, it becomes impossible to associate chemical exposure with increases in adverse health effects, no matter how large the epidemiologic study population.

What about cord blood biomonitoring – are there thresholds for developmental effects of environmental chemicals?

There are biological thresholds in utero, just as there are biological thresholds at later life stages. So the principle that CDC states is equally applicable for cord blood biomonitoring results – “The presence of a chemical does not imply disease. The levels or concentrations of the chemical are more important

¹ Centers for Disease Control and Prevention (CDC), Third National Report on Human Exposure to Environmental Chemicals, 2005, Interpreting *Report* Exposure Data: Important Factors , page 4 <http://www.cdc.gov/exposurereport/>.

² Carcinogenicity studies are exceptions to this trend, as test substances cannot be tested at a sufficient range of concentrations and with a sufficient number of animals to determine a NOAEL. Instead, the dose response for carcinogens is assumed to be linear.

determinants of the relation to disease, when established in appropriate research studies, than the detection or presence of a chemical.”³

Exposures that occur during prenatal development may be of heightened concern. Indeed, there are some stages of development where the embryo or fetus is more sensitive than the adult to certain agents. The presence of these “windows of vulnerability” has been well understood for the last 40 years, and chemicals are routinely tested using laboratory animal models that specifically evaluate their potential to impact reproduction or embryonic and fetal growth and development. Thousands of laboratory animal reproductive and developmental studies have been conducted in which toxicity thresholds or NOAELs could be observed.

Once NOAELs are identified, they are used to set exposure limits that protect the developing fetus and neonate. To be on the safe side, exposure limits are typically set one hundred to one thousand times lower than this threshold, which assures a margin of safety. For even the environmental chemicals found in cord blood, detection does not mean that there is a health risk as long as the levels are low and below toxicity thresholds.

Why are toxicity thresholds important to biomonitoring?

Biomonitoring can be useful to:

- 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 trends in levels of exposure over time
- Assess the effectiveness of public health efforts to reduce exposure
- Establish reference ranges for chemicals in the body
- Determine the prevalence of people with levels above known toxicity thresholds
- Set priorities for research on human health effects

As stated by the CDC, “The presence of a chemical does not imply disease. The levels or concentrations of the chemical are more important determinants of the relation to disease, when established in appropriate research studies, than the detection or presence of a chemical.”⁴ The CDC statement is based on the toxicity threshold concept, and the many thousands of laboratory animal studies that support that concept. Thus the existence of toxicity thresholds allows us to put into perspective the findings of biomonitoring studies, including cord blood biomonitoring. This is because of the relationship indicated in Figure 2. Biomonitoring studies typically indicate that environmental chemicals are present at very low levels, generally below one part per million and in the parts per billion, parts per trillion or parts per quadrillion range.⁵ A part per billion is the time equivalent of one second in 32 years, a part per trillion is one second in 32,000 years and a part per quadrillion is one second in 32 million years. These units indicate extremely small quantities. For lead and mercury, two substances for which human safety data are available, biomonitoring levels are generally lower than safe levels. However, comparison of biomonitoring levels with NOAELs from laboratory animal studies has proved more difficult.⁶ Clearly,

³ See citation in note 1 above.

⁴ See citation in note 1 above.

⁵ See for instance the exposure concentrations reported in Centers for Disease Control and Prevention (CDC), Third National Report on Human Exposure to Environmental Chemicals, 2005. <http://www.cdc.gov/exposurereport/>. Note units used in Executive Summary to report results for organic (non-metal) compounds: ng/L (parts per trillion) for PAHs, fg/g (part per quadrillion) for dioxins/furans/coplanar PCBs, ng/g (parts per billion) for other PCBs, µg/L (parts per billion) for phthalates, and ng/g or µg/L (parts per billion) for pesticides/herbicides.

⁶ For a comparison of biomonitoring levels with safety data for three environmental chemicals, see the commentary by Drs. C.A. McKay and J. H. Delgado on the BiomonitoringInfo.org website: <http://www.biomonitoringinfo.org/new/20051128.html>

there is a need for more research, some of which is underway,⁷ to compare biomonitoring results with NOAELs from laboratory animal studies. Nonetheless, the CDC statement and the toxicity threshold data provide an important caution against over-interpretation of the detection of an environmental chemical in the body as indicating a health risk.

⁷ H.J. Clewell, Y.M. Tan, J.L. Campbell and M.E. Andersen, Quantitative Interpretation of Human Biomonitoring Data, *Toxicology and Applied Pharmacology*, vol. 231, pp. 122-133, 2008; *Regulatory Toxicology and Pharmacology*, vol. 51, number 3, supplement 1, Biomonitoring Equivalents: Guidelines and Case Studies, pp. S1-S77, 2008; L.L. Aylward, J.S. LaKind and S.M. Hays, Derivation of Biomonitoring Equivalent (BE) Values for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds: A Screening Tool for Interpretation of Biomonitoring Data in a Risk Assessment Context, *Journal of Toxicology and Environmental Health, Part A*, vol. 71, pp. 1499-1508, 2008.