Environment International 120 (2018) 535–543

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Incorporating regulatory guideline values in analysis of epidemiology data

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ARTICLE INFO

Handling Editor: Lesa Aylward

Keywords:
Environmental chemicals
Mixtures
Cumulative risk assessment

ABSTRACT

Fundamental to regulatory guidelines is to identify chemicals that are implicated with adverse human health effects and inform public health risk assessors about "acceptable ranges" of such environmental exposures (e.g., from consumer products and pesticides). The process is made more difficult when accounting for complex human exposures to multiple environmental chemicals. Herein we propose a new class of nonlinear statistical models for human data that incorporate and evaluate regulatory guideline values into analyses of health effects of exposure to chemical mixtures using so-called 'desirability functions' (DFs). The DFs are incorporated into nonlinear regression models to allow for the simultaneous estimation of points of departure for risk assessment of combinations of individual substances that are parts of chemical mixtures detected in humans. These are, in contrast to published so-called biomonitoring equivalent (BE) values and human biomonitoring (HBM) values that link regulatory guideline values from in vivo studies of single chemicals to internal concentrations monitored in humans. We illustrate the strategy through the analysis of prenatal concentrations of mixtures of 11 chemicals with suspected endocrine disrupting properties and two health effects: birth weight and language delay at 2.5 years. The strategy allows for the creation of a Mixture Desirability Function i.e., MDF, which is a uni-dimensional construct of the set of single chemical DFs; thus, it focuses the resulting inference to a single dimension for a more powerful one degree-of-freedom test of significance. Based on the application of this new method we conclude that the guideline values need to be lower than those for single chemicals when the chemicals are observed in combination to achieve a similar level of protection as was aimed for the individual chemicals. The proposed modeling may thus suggest data-driven uncertainty factors for single chemical risk assessment that takes environmental mixtures into account.

1. Introduction

Human biomonitoring data of mixtures of environmental toxicants, particularly during pregnancy, provide important evidence of exposure to chemicals with purported adverse health outcomes (e.g., endocrine disrupting chemicals; EDCs). However, simply identifying critical mixtures and chemicals that are "bad actors", through epidemiology data, does not adequately inform public health risk assessors about "acceptable ranges" of environmental exposures – which is fundamental to (non cancer) regulatory guidelines and mitigation strategies.

Guideline values, such as the tolerable or acceptable daily intake (TDI/ADI) or reference (RfD) values are important tools for risk assessment of chemicals in the environment, including e.g., contaminants and pesticide residues. These values are generally derived from single chemical experimental toxicity studies and describe a "safe" exposure level of a single chemical to which a person can be exposed each day for a long time (usually lifetime) without suffering harmful effects. It is determined by applying assessment factors (to account for the uncertainty in the data) to point of departures (PODs) such as the highest dose in human or animal studies which has been demonstrated not to cause toxicity (NOAEL) and the lower confidence interval of a Benchmark dose (BMDL) (EPA, 2007). When animal based PODs are used, assessment factors are generally applied to account for (1) differences between the experimental setup and the actual human exposure, e.g. route-to-route extrapolation, subchronic-to-chronic extrapolation, (2) interspecies differences, (3) intra-species differences/

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https://doi.org/10.1016/j.envint.2018.08.039
Received 23 March 2018; Received in revised form 13 August 2018; Accepted 15 August 2018

variability within the human population, i.e. differences between the typical/average human and sensitive humans, and (4) uncertainty in the data, e.g., poor quality data and missing toxicity studies.

Progress in analytical chemistry and toxicokinetic modeling has created possibilities of monitoring toxicants in biological media (i.e., blood, urine, hair, nails, body tissues, fluids and exhaled breath, or the amount of metabolites in tissues and fluids). A first official reference to guidance values for human biomonitoring (HBM) values was made in 1974, and a first set of three so called Biological Limit Values (BLV) (lead, toluene and trichloroethylene), was introduced for occupational settings with the MAK list in 1981 (Bolt and Thier, 2006). The first American Biological Exposure Indices (BEI) report was published by ACGIH in 1984 (ACGIH, 1984).

For environmental exposure to the general public, two main nomenclatures have been concurrently developed but both refer to the guidance values translated to equivalent human concentration levels in blood, urine, or other biological matrices using complex pharmacokinetic modeling. Scientists in the United States have derived so-called biomonitoring equivalent (BE) values (Hays et al., 2007; Aylward et al., 2013). BE values are concentrations of a chemical or its metabolites in a biological medium that is consistent with an existing health-based exposure guideline (Krishnan et al., 2010). Concurrently, the German Human Biomonitoring Commission defined two HBM-values: the HBM-I value is defined as the concentration of a single substance in humans below which no adverse health effect should be expected (i.e., identifying an "acceptable exposure range"); the HBM-II value is defined as the concentration of a substance in human biological material at which (and above) adverse effects are possible, indicating an acute need for reduction of exposure (Angerer et al., 2011; Apel et al., 2016). The evaluation of HBM values is a part of the recently funded HBM4EU, a joint project of 28 countries, the European Environment Agency and the European Commission (https://www.hbm4eu.eu/the-project/).

We note the equivalence of HBM-I and BE values. Both values are generally based on single chemical experimental data from animal studies (i.e., dose response experiments). However, they do not account for exposure to mixtures of similarly acting environmental chemicals. This is a major shortcoming since all available data demonstrate that humans are not exposed to single compounds, but to complex mixtures of numerous molecules (e.g., Crinnion, 2010).

Herein, we propose methods to incorporate this regulatory concept of PODs in human data, somewhat analogous to (unadjusted) BE values and HBM values, into the analysis of mixture related health effects using epidemiological data. Specifically, we propose to estimate guideline values directly in human data with uncertainty factor adjustments made post hoc. To our knowledge such estimates of guideline values from human studies in mixtures has not been previously considered.

We incorporate the concept of "acceptable concentration ranges" of exposure below identified regulatory guideline values (i.e., HBM and BE values are uncertainty adjusted PODs; for convenience, subsequently referred to as HBM values) in regression models using desirability functions (DF) (Fig. 1). DFs are widely used in industry for optimizing processes with multiple responses, where the quality of a product or process with one or more characteristic outside of some "desired" limits are unacceptable (Harrington Jr., 1965; Derringer, 1994; Derringer and Suich, 1980; Shih et al., 2003; Coffey et al., 2007; Costa et al., 2011). However, DFs have not been applied to mixtures of environmental exposures in a regulatory context.

Our objective is to demonstrate simultaneous estimation of "points of departure" values in a new class of models, i.e., "Acceptable Concentration Range" (ACR) models, using maternal concentrations of EDCs from biomonitoring in a pregnancy cohort linked to health effects in the children, i.e., birth weight and language delay at 2.5 years of age. This is a first step in the development of a new class of statistical models that incorporates regulatory guidance concepts into regression models of epidemiology data.

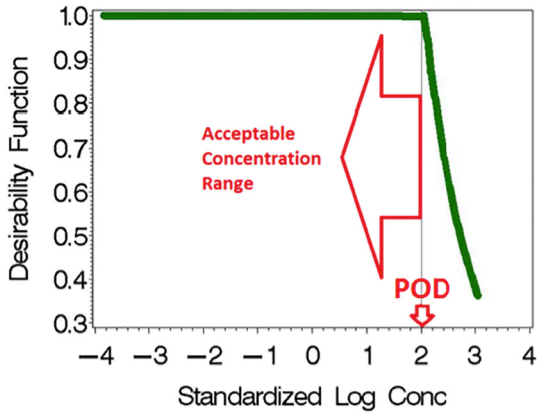

Fig. 1. Linking Desirability Functions ("low is better" shape) to regulatory guidance values.

2. Methods

2.1. Pregnancy cohort study

The Swedish Environmental Longitudinal, Mother and child, Asthma and allergy (SELMA) is a pregnancy cohort study designed to investigate prenatal exposure to environmental chemicals and health outcomes related to growth, developmental and chronic diseases in children. SELMA recruited pregnant women in the county of Värmland, Sweden, between September 2007 and March 2010. Women who could read Swedish and were not planning to move out of the county were recruited at their first antenatal care visit; 8394 pregnant women were identified, 6658 were eligible and 2582 (39%) agreed to participate. The women were enrolled at median week 10 of pregnancy (range week 3–27, where 96% were recruited before week 13 of pregnancy). Detailed recruitment selection criteria and sample collection procedures have been published previously (Bornehag et al., 2012). The Ethics Committee in Uppsala, Sweden approved the SELMA protocol and all participants signed informed consents prior to the start of data collection.

2.2. Outcome variables

Language development is routinely assessed in Sweden when children are 30 months of age. This validated assessment consists of a nurse evaluation and a parental questionnaire on language use. If warranted, the nurse discusses possible referral (to a speech therapist, audiologist, psychologist or pediatrician) with the parent (Mattsson et al., 2001). The questionnaire asks about the number of words the child uses; responses are categorized as < 25, 25–50 and > 50 words. Our primary study outcome is a parental report of the use of 50 words or fewer (yes or no), which we denote here as Language Delay (LD). Data on LD are available from 1113 children. However, with complete case analyses using covariates, the sample size reduced to 840.

Data on birth weight (and gestational age at birth), from the Swedish birth register, are available for 1938 children. However, with complete case analyses using covariates, the sample size reduced to 1323.

2.3. Selection of covariates for analyses

Models for LD were adjusted for child sex and gestational age at birth, maternal education, early pregnancy weight, smoking status, and urinary creatinine to adjust for urinary dilution. Birth weight models also included parity, maternal age and fish intake in the family.