International Journal of Hygiene and Environmental Health 216 (2013) 703–709

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

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

Multiple classes of environmental chemicals are associated with liver disease: NHANES 2003–2004

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A R T I C L E I N F O

Article history:
Received 12 October 2012
Received in revised form 8 January 2013
Accepted 16 January 2013

Keywords:
Biomonitoring
ALT
Liver
Mixtures
Cumulative

A B S T R A C T

Biomonitoring studies show that humans carry a body burden of multiple classes of contaminants which are not often studied together. Many of these chemicals may be hepatotoxic. We used the 2003–2004 National Health and Nutrition Examination Survey to evaluate the relationship between alanine aminotransferase (ALT) and 37 environmental contaminants, comprising heavy metals, non-dioxin-like polychlorinated biphenyls (PCBs), and dioxin-like compounds, using a novel method. Linear regression models were constructed for each chemical separately, then as a class, using quartiles to represent exposure and adjusting for age, sex, race, income, and BMI. We then used an optimization approach to compile a weighted sum of the quartile scores, both within and across chemical classes. Using the optimization approach to construct weighted quartile scores, the dioxin like PCB, the non-dioxin like PCB and metal class-level scores were significantly associated with elevated ALT. A significant interaction was detected between the class-level score for metals, and the score for non-dioxin-like PCBs. When including all chemicals in one model, 3 chemicals accounted for 78% of the weight (mercury, PCB 180, 3,3′,4,4′,5-PNCB) with the remaining 22% associated with 4 chemicals (a dioxin and 3 PCBs). Validation with a holdout dataset indicated that the weighted quartile sum estimator efficiently identifies reproducible significant associations.

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Introduction

Biomonitoring of human tissues and fluids has shown that virtually all individuals, worldwide, carry a "body burden" of synthetic chemicals (Thornton et al., 2002; CDC, 2009). Although the measurement of an environmental chemical in a person's tissues or fluids is an indication of exposure, it does not by itself mean that the chemical or the exposure concentration is sufficient to cause a disease or an adverse effect. However, since humans are exposed to multiple chemicals, there may be a combination effect (e.g., additive and synergistic) on health risks associated with exposure even at low levels (Kortenkamp, 2008). Further, biomonitoring studies show that humans carry a body burden of multiple classes of contaminants, which are often not studied together.Some examples of environmental chemical classes include metals, polychlorinated biphenyls (PCBs) and dioxins. Each is thought to impact human health, and these chemicals are generally ubiquitous exposures. Among the metals, several including cadmium, mercury and lead have been the focus of much research. Cadmium is mainly used in batteries and solar panels, and is also one of the components of cigarette smoke (ATSDR, 2008). Exposure to lead has decreased over time due to removal from gasoline; individuals are still exposed through its presence through automotive and industrial emissions, older paint formulations, ammunition (EPA, 2006), and moonshine (Chisolm, 1971; Needleman, 2004). Mercury is mainly used for industrial chemical production and electronics, but is also present in old thermometers and dental amalgams; for the general population, the main source of exposure is dietary (seafood; Fig. 1) (ATSDR, 1999). Polychlorinated biphenyls (PCBs) and dioxins are persistent organic pollutants (POPs). PCBs are a group of 209 different compounds formerly used in electronic equipment manufacture for their insulative and conductive properties. Although production in the US was banned in 1979 due to health concerns, PCBs persist in the environment, and the main source of exposure for the general population is diet (fish; Fig. 1) (Johnson et al., 2008; ATSDR, 2000). Similarly, dioxins enter the general population almost exclusively from ingestion of food, specifically through the consumption of fish, meat, and dairy products since dioxins are fat-soluble and readily bioaccumulate up the food chain (Schecter et al., 2001).

The liver is the principal organ that detoxifies or excretes a large number of xenobiotics and other foreign substances that enter the body. It therefore follows that long-term environmental exposures

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1438-4639/$ – see front matter. Published by Elsevier GmbH.
http://dx.doi.org/10.1016/j.ijheh.2013.01.005

Fig. 1. Warning sign for contaminated fish.

will lead to chronic intrahepatic exposure to these substances; such chemical exposures may affect not only the expression of genes involved in their metabolism but also other genes which may have either adaptive or harmful consequences. A priori, one may thus hypothesize that chronic environmental exposures may manifest as altered liver function and future liver disease.

In conducting risk assessments, there is an increasing recognition that multiple environmental exposures may impact a common adverse outcome (e.g. liver toxicity). However, classical analytical methods may not be appropriate, due to (1) high dimensional exposure data (relative to number of observations), (2) correlated exposures, (3) low level exposures (particularly multiple compounds below an individual observable effect level, but which in combination produce an observable effect), and (4) differences in potency (i.e. chemicals with the highest body burdens are not necessarily the most potent/toxic). There is a need for straightforward, easily interpretable methods to assess the relationship between relevant environmental exposure profiles and risk of common adverse outcomes.

One study which considered multiple chemical classes in relation to liver function is from Cave et al. (2010). The National Health and Nutrition Examination Survey (NHANES) data were used to evaluate the risk of elevated alanine aminotransferase (ALT, a measure of liver function) and exposure to chemicals in 17 different subclasses. Participants were assigned a rank for each chemical, and these ranks were summed within each of the 17 subclasses. The summed ranks were divided into quartiles; if the test for trend across the quartiles was statistically significant, the chemicals in the subclass were further evaluated in what appear to be single-chemical models. The use of summed ranks (and quartiles of this measure) has the advantage of accommodating relatively low level exposures, as well as potential differences in potency, across chemicals. Although this approach also effectively accounts for all chemicals in a subclass, it is possible that the noise induced by considering only a subclass-level measure (i.e. the summed ranks) in the screening step would mask associations with individual members of the subclass. We propose a weighted quartile score method to represent exposure to multiple chemicals, both within and across classes, and demonstrate the method using epidemiologic data. In the present study, we tested the hypothesis that inter-class mixtures of environmental chemicals/metabolites are dose-dependently associated with increased risk for liver toxicity in the US population.

Materials and methods

We used data from the 2003–2004 cycle of the NHANES for this analysis (CDC, 2008). The NHANES is a cross-sectional, complex sample survey, which is designed to provide a nationally representative sample of the non-institutionalized, civilian US population. Included in these analyses are participants aged 12 years and older, who were included in one of the laboratory assessments of the NHANES. We excluded individuals who were missing information on serum alanine amino-transferase (ALT, used as a measure of liver function), on important covariates including body mass index (BMI), poverty income ratio (PIR) and alcohol intake. Further exclusion criteria were designed to exclude individuals with NAFLD due to identifiable causes (Cave et al., 2010; Clark et al., 2003). Thus, we excluded those who had a positive test result for serum hepatitis B surface antigen or for serum hepatitis C antibody, and women with elevated transferrin saturation (defined as >50%; transferrin saturation was not measured in adult men in the NHANES). We also excluded individuals whose self-reported alcohol intake was high enough, that they may have experienced alcohol-related changes in ALT. This included those with an intake of ≥20 g/day for men or ≥10 g/day for women as assessed by a 2-day dietary recall (all participants included), or who reported regularly having >2 drinks/day for men or >1 drink/day for women (based on the alcohol questionnaire administered to those aged 20 years and older). Finally, those with self-reported liver disease, or who had ALT levels above the 99th percentile of the distribution (>81 U/L) were excluded, on the assumption that these individuals are likely to have frank liver disease and are not representative of the general population with regards to the associations between environmental chemical exposure and liver function. The total 2003–2004 NHANES sample was 10,122 individuals; after the inclusions and exclusions described above, the sample available for these analyses was 1345 individuals (Table 1).

The environmental chemical exposures were grouped into three classes—metals (cadmium, lead and total mercury), co-planar PCBs along with dioxins and furans (PCBs 28, 66, 74, 105, 118, and 156; 1,2,3,6,7,8-HXCDD; 1,2,3,4,6,7,8-HPCDD; 1,2,3,4,6,7,8,9-OCDD; 1,2,3,4,6,7,8-HPCDF; and 3,3′,4,4′,5-PNCB), and non-dioxin-like PCBs (PCBs 44, 49, 52, 87, 99, 101, 110, 138, 146, 149, 151, 153, 170, 177, 178, 180, 183, 187, 194, 196, 199, 206, and 209). Each of these analytes was measured in serum; for PCBs, dioxins and furans, lipid adjusted values were used. We included only analytes detectable in ≥60% of samples. For samples where values