Environmental Research 117 (2012) 90–99

Contents lists available at SciVerse ScienceDirect

Environmental Research

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

Upstream adverse effects in risk assessment: A model of polychlorinated biphenyls, thyroid hormone disruption and neurological outcomes in humans

Amber Wise [a], Fred Parham [b], Daniel A. Axelrad [c], Kathryn Z. Guyton [d], Christopher Portier [b], Lauren Zeise [e], R. Thomas Zoeller [f], Tracey J. Woodruff [a,*]

[a] Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, United States
[b] National Institute of Environmental Health Sciences, Research Triangle Park, NC, United States
[c] Office of Policy, U.S. Environmental Protection Agency (USEPA), Washington, DC, United States
[d] National Center for Environmental Assessment, Office of Research and Development, USEPA, Washington, DC, United States
[e] Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland, CA, United States
[f] Biology Department, University of Massachusetts, Amherst, MA, United States

ARTICLE INFO

Article history:
Received 14 June 2011
Received in revised form
4 May 2012
Accepted 31 May 2012
Available online 7 July 2012

Keywords:
Environmental chemical exposure
Neurodevelopmental outcomes
Polychlorinated biphenyls
Quantitative risk assessment
Thyroid hormone

ABSTRACT

Background: Increasing data on early biological changes from chemical exposures requires new interpretation tools to support decision-making.
Objectives: To test the possibility of applying a quantitative approach using human data linking chemical exposures and upstream biological perturbations to overt downstream outcomes.
Methods: Using polychlorinated biphenyl (PCB) exposures and maternal thyroid hormone (TH) perturbations as a case study, we model three relationships: (1) prenatal PCB exposures and TH changes, using free T_4 (FT_4); (2) prenatal TH and childhood neurodevelopmental outcomes; and (3) prenatal PCB exposures and childhood neurodevelopmental outcomes (IQ). We surveyed the epidemiological literature; extracted relevant quantitative data; and developed models for each relationship, applying meta-analysis where appropriate.
Results: For relationship 1, a meta-analysis of 3 studies gives a coefficient of −0.27 pg/mL FT_4 per ln(sum of PCBs) (95% confidence interval [CI] −0.82 to 0.27). For relationship 2, regression coefficients from three studies of maternal FT_4 levels and cognitive scores ranged between 0.99 IQ points/(pg/mL FT_4) (95% CI −0.31 to 2.2) and 7.6 points/(pg/mL FT_4) (95% CI 1.2 to 16.3). For relationship 3, a meta-analysis of five studies produces a coefficient of −1.98 IQ points (95% CI −4.46 to 0.50) per unit increase in ln(sum of PCBs). Combining relationships 1 and 2 yields an estimate of −2.0 to −0.27 points of IQ per unit increase in ln(sum of PCBs).
Conclusions: Combining analysis of chemical exposures and early biological perturbations (PCBs and FT_4) with analysis of early biological perturbations and downstream overt effects (FT_4 and IQ) yields estimates within the range of studies of exposures and overt effects (PCBs and IQ). This is an example approach using upstream biological perturbations for effect prediction.

1. Introduction

Evolving science has expanded our ability to incorporate relevant and sensitive upstream markers of adverse effects into risk assessment decisions. The U.S. Environmental Protection Agency (USEPA) defines an adverse effect as "a biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge" (US Environmental Protection Agency, 2010). Thus biological perturbations that arise early in the chain of events following chemical exposure can be considered adverse effects by USEPA.

Abbreviations: CI, confidence interval; FT4, free thyroxine; g lipid/L, grams of lipid per liter; IQ, intelligence quotient; ln, natural log; ng/dL, nanograms per deciliter; OH-PCB, hydroxylated polychlorinated biphenyl; PBDEs, polybrominated diphenyl ethers; PCBs, polychlorinated biphenyls; pg/mL, picograms per milliliter; pmol/L, picomoles per liter; std. dev., standard deviation; T3, triiodothyronine; T4, thyroxine; TH, thyroid hormone; TRH, thyrotropin releasing hormone; TSH, thyroid stimulating hormone; TT4, total thyroxine; USEPA, U.S. Environmental Protection Agency

* Correspondence to: Program on Reproductive Health and the Environment, University of California, San Francisco, 330 Broadway St., Suite 1100, Oakland, CA 94612, United States. Fax: +1 510 986 8960.
E-mail address: woodrufft@obgyn.ucsf.edu (T.J. Woodruff).

0013-9351/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.envres.2012.05.013

New approaches are needed to incorporate these perturbations into hazard identification and risk assessment.

A critical part of using early perturbations in hazard identification and risk assessment is an understanding of the relationship between early biological changes and subsequent downstream overt effects. Traditionally, regulatory agencies have based risk assessment decisions on the occurrence of overt effects, such as cancer and neurocognitive deficits. New approaches envisioned for toxicity testing will produce data mostly on relationships between exposures and upstream, or early, indicators (National Research Council, 2007). Further, volumes of early perturbation data are now produced in epidemiologic and toxicology studies. Understanding the quantitative links between early perturbations and downstream overt effects makes it possible to estimate the potential impact and significance of early perturbations by relating their occurrence to events, which are better understood by decision-makers.

Thyroid hormone (TH) disruption is one class of early perturbation which is linked to downstream overt effects, and is amenable to incorporation into risk assessment (Woodruff et al., 2008). Thyroid hormones, including, thyroxine (T_4) and triiodothyronine (T_3), are essential for normal brain development, particularly prenatally (Morreale de Escobar, 2001; Zoeller and Rovet, 2004). TH perturbations in pregnant mothers are associated with neurological deficits in their children, including IQ decrements (Haddow et al., 1999; Oerbeck et al., 2003; Selva et al., 2005). Moreover, numerous environmental chemicals can modulate TH levels (Crofton, 2008; Miller et al., 2009).

We have developed an approach to link early perturbations to downstream overt effects for use in risk assessment. In this paper, we evaluate exposure to TH-disrupting chemicals during the prenatal period and effects on TH disruption as a case study. We chose polychlorinated biphenyls (PCBs), which are associated with altered TH levels and neurological outcomes. We focus here on human data; similar analyses of animal data address incorporating nonhuman perturbation data in risk assessment (Bernal, 2007; Morreale de Escobar et al., 2004; Parham et al., 2012).

2. Background

2.1. PCBs

Our analysis focuses on human exposures to PCBs and circulating TH for several reasons. First, PCBs suppress circulating levels of TH in animals and humans (Langer, 2008; Yang et al., 2010). The presumed mechanism is that these chemicals induce various enzymes that metabolize TH, and thus can reduce levels of T4. (Hood et al., 2003; Liu et al., 1995; Sugatani et al., 2001; Visser et al., 1993). There is enough human data on the relationship between PCB body burden and TH levels humans for modeling. Second, many studies characterize the relationship between PCB body burden and measures of cognitive function (e.g., Stewart et al., 2008), and between TH insufficiency and measures of cognitive function (Zoeller and Rovet, 2004). The literature therefore enables us to use the chain of PCB exposures, TH perturbations, and overt effect (cognitive function) to estimate the relationship between PCB exposure and overt effect as mediated by TH insufficiency. This estimate can be compared to direct estimates of the relationships between PCB exposure and overt effect. Third, the data for other thyroid disrupting chemicals (i.e., brominated flame retardants, perfluorinated compounds, perchlorate) are insufficient to model the chemical–TH relationship, the chemical–IQ relationship, or both. One limitation of choosing PCBs for this case study is that PCBs may influence neurodevelopment through multiple mechanisms, and we do not know the exact contribution of TH perturbations from PCB exposure to neurodevelopmental effects. However, there is a relatively robust database from which to illustrate our proposed approach, which provides data on one of the proposed mechanistic pathways between exposure and overt effects, which informs further applications.

2.2. TH function and role in development

Insufficient levels of TH during development can lead to mild to severe cognitive impairment, neurobehavioral disorders, hypomyelination, and attendant physical impairments and may predispose the individual to other conditions and disease (van der Sluijs Veer et al., 2008; Zoeller, 2005).

The thyroid system is a classic neuroendocrine axis. The hypothalamus releases thyrotropin-releasing hormone (TRH), which acts upon the pituitary gland. In response to TRH, the pituitary releases thyroid-stimulating hormone (TSH) into circulation. TSH controls the thyroid gland's production and secretion of T_4 and, to a lesser extent, T_3. TSH is regulated by the negative feedback action of T_4 on the pituitary. The feedback among the hypothalamus, pituitary, and thyroid maintains the thyroid system's activity within relatively narrow limits (Andersen et al., 2002). Although T_4 is the predominant TH found in serum, T_3 is the active form and is formed primarily by deiodination of T_4 in the target tissue.

The effects of TH on the developing brain are directly related to serum concentrations of T_4 in animal studies; even small reductions in serum TH have effects (Auso et al., 2004; Gilbert and Sui, 2006). Human studies are consistent with these animal studies. The fetus is entirely dependent on maternal THs during the first trimester (Smallridge et al., 2005). Even mild to moderately low levels of T_4 during the first trimester are associated with cognitive deficits in the children (Haddow, 2005; Haddow et al., 1999; Pop et al., 1999, 2003). Also, small deficits in circulating levels of TH are associated with decreased cognitive performance at various times during development and adulthood (Glinoer and Rovet, 2009; Heyerdahl and Oerbeck, 2003; LaFranchi and Austin, 2007; Selva et al., 2005; Simic et al., 2009).

A number of environmental chemicals can disrupt TH levels, and many decrease circulating levels of T_4 (Brucker-Davis, 1998; Howdeshell, 2002). Under normal physiological conditions, a decline in circulating levels of T_4 causes an increase in serum TSH (Burman, 2008). However, there are cases of discordant measures of T_4 and TSH, when T_4 levels can change without changes in TSH. Relying only on evaluation of changes in TSH without consideration of T_4 may underestimate effects. Various chemicals, including PCBs, lower serum total and free T_4 (TT_4 and FT_4) without causing a concomitant increase in serum TSH (Zoeller, 2007).

TH synthesis is iodine-dependent, and about one third of U.S. women have low iodine intake (Caldwell et al., 2005). This at risk population, combined with findings regarding the consequences of small decrements of T_4, and fetal dependence on maternal hormone levels indicate that small, chemically induced changes in T_4 can increase the risk of subsequent neurological events. Compensatory mechanisms may not suffice, and theories for compensation to make up for small changes in T_4 on a population-wide basis lack empirical support.

3. Methods

Fig. 1 shows a diagram of our overall approach, which is to model the relationship between the exposure and early biological perturbations (Relationship 1), and the relationship between the perturbation and overt outcome (Relationship 2), and then to combine the two relationships to determine the