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Short communication

Reconstructing pre-natal and early childhood exposure to multi-class organic chemicals using teeth: Towards a retrospective temporal exposome

Syam S. Andra [a], Christine Austin [a,b], Robert O. Wright [a], Manish Arora [a,b,*]

[a] Lautenberg Environmental Health Sciences Laboratory, Department of Preventive Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[b] Faculty of Dentistry, University of Sydney, Sydney, NSW, Australia

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1. Introduction

Environmental factors are recognized as important determinants of life-long health trajectories (Cohen Hubal et al., 2014; Grandjean and Landrigan, 2006; Manciocco et al., 2014; Sharma et al., 2014). In studying the health effects arising from the interaction of environmental chemicals and human physiology, exposure assessment in most epidemiological studies is limited to a single toxicant or a small group of toxicants. However, humans are exposed to thousands of environmental chemicals which may exert effects jointly that are distinct to their individual effects (Kortenkamp et al., 2007). The "Exposome" concept addresses this issue and encompasses the complete life-long experience of environmental exposures from the pre-natal period onwards (Rappaport, 2011; Vrijheid, 2014; Wild, 2005, 2012). Unlike the human genome, the exposome is dynamic and must be examined at key developmental stages to understand its role in human health. Here, we propose the use of novel tooth matrix biomarkers to capture the composition and timing of the exposome retrospectively.

1.1. Importance of exposure timing

Alongside the growth of the exposome concept, is also the increasing body of evidence that internal and external exposures to chemicals (and their reaction products) exert a variable influence on our physiology at different developmental stages (Selevan et al., 2000). As a consequence, windows of susceptibility exist when vulnerability to environmental chemicals is heightened (Grandjean and Landrigan, 2006). It, therefore, becomes important to look beyond how much exposure has been experienced (i.e. the dose) to also consider the timing of exposure. The pre-natal period is particularly important when considering critical windows. During fetal life and early childhood, the tissues and organs of the body undergo periods of rapid growth, during which a toxic insult or nutrient deficiency can lead to long-term effects (Osmond and Barker, 2000; Selevan et al., 2000). Considering the brain as an example, the complexity of its developmental process underlies its unique sensitivity to the environment. As early as the second week of gestation, the neuro-ontogenic process in humans begins with the folding and fusion of ectoderm to form the neural tube (Tau and Peterson, 2010). The development of the human central nervous system (CNS) involves the production of 100 billion nerve cells and 1 trillion glial cells. These neurons must undergo migration, synaptogenesis, selective cell loss, myelination, and selective synaptic pruning in stages that ebb and flow before development is complete (Faustman et al., 2000). These processes commence early in the first month of gestation and continue well into the second trimester. For example, neuronal migration peaks between gestational weeks 12 and 20 and is largely complete by weeks 26–29 (Tau and Peterson, 2010). Other critical processes in brain development continue post-natally (Andersen, 2003).

Even weak inhibitory or excitatory signals imposed by environmental toxicants during specific CNS developmental stages can alter subsequent processes over-riding a normal growth trajectory towards a maladaptive phenotype. For example, neurotoxic chemicals can lead to permanent reductions in cell number (Bayer, 1989) or altered synaptic architecture (Bressler et al., 1999). In many cases, developmental processes occur sequentially, rather than concurrently; hence the observed specificity of exposure timing on health effects, as exposures

* Corresponding author at: Department of Preventive Medicine, One Gustave L Levy Place, Box 1057, New York, NY 10029, USA.
E-mail address: manish.arora@mssm.edu (M. Arora).

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might affect only a process that is operant at a specific life phase. Thus, *when* a person is exposed to a toxic chemical is as important as the dose. In this regard, our focus is on the pre-natal period because the lack of exposure assessment tools that can directly measure fetal chemical exposure in large population based studies without imposing undue risk on the pregnancy remains an important barrier to environmental health research.

The semi-penetrable nature of the placenta coupled with the increased susceptibility to chemicals makes the pre-natal period of critical interest to the understanding of the fetal environmental determinants of life-long health trajectories. The placenta only partially (and in some cases negligibly) regulates a large number of potentially toxic chemicals. Polybrominated diphenyl ethers (PBDEs) can be transferred to the developing fetus across the placenta (and to children via breast milk) (Lorber, 2008). A prior study has shown almost identical PBDE concentrations in maternal blood collected at delivery and in cord blood, suggesting that the placenta offers limited protection to the fetus (Mazdai et al., 2003). Studies have also shown that bis(4-chlorophenyl)-1,1,1-trichloroethane (DDT) and DDT metabolite levels are higher in fetal circulation than maternal levels (Waliszewski et al., 2001). Similarly, manganese (Mn), an essential metal that can be neurotoxic at high levels, is actively transported across the placenta resulting in higher levels in fetal circulation (Takser et al., 2004).

1.2. Challenges to studying fetal chemical programming

Epidemiologic studies that investigate fetal programming of long-term health trajectories face major challenges when trying to estimate the fetal exposome, and we focus on two barriers that are especially relevant to lower frequency health outcomes. Longitudinal birth cohort studies that collect biomarkers of environmental chemical exposure during pregnancy and then follow offspring into childhood provide the highest evidence study design to assess the impact of exposures during key developmental windows in humans. However, the expense and time required for such studies are major barriers to investigating lower frequency conditions with long latency periods. For example, to determine the fetal origins of a disorder that occurs at a frequency of 1:100 live births, a study would have to recruit 10,000 pregnant women and study the offspring prospectively until a stable clinical diagnosis can be made many years later. This is compounded by another, equally important barrier to uncovering fetal environmental exposures. Even in studies that commence with recruitment of pregnant women, measurements of maternal biomarkers do not necessarily provide accurate measures of fetal exposure for all chemicals. Reliance on maternal biomarkers of fetal exposure fails to account for variability in placental transport and metabolism, potentially overlooking the significant interplay at the maternal–fetal interface. Additionally, in population-based studies it is not feasible to obtain prospective fetal samples without imposing unacceptable health risks to both mother and child. Umbilical cord blood has been successfully collected at birth in epidemiologic studies and has provided valuable exposure information (Aylward et al., 2014; Cooke, 2014; Delvaux et al., 2014; Lin et al., 2013). However, for compounds with a short half-life in blood, cord blood levels can only provide information on the latter part of the third trimester. It is important to consider that even though case–control studies nested within large population cohorts may overcome the first barrier of requiring long-term follow-ups, the absence of a direct fetal measurement would remain a limitation.

To overcome these limitations, researchers have long sought a biomarker that is retrospective, objective, and capable of *directly* measuring fetal exposures to multiple chemicals. For health outcomes that occur at lower frequencies, this biomarker would be applied in population-based case–control designs. Unlike contemporary biomarkers that are cross-sectional, this novel biomarker would provide time-series exposure data similar to that obtained from a longitudinal study, while doing so retrospectively. In this perspective, we discuss a novel dental-matrix based biomarker that brings us closer to this ideal of retrospectively reconstructing the dynamic internal exposome. We provide a conceptual framework for this approach and provide data to support the utility of this biomarker in epidemiologic studies. We place emphasis on case–control studies of lower frequency and rare outcomes with long latency periods where prospective cohort studies would prove inefficient. Our discussion is limited to internal chemical exposures, although some of the concepts we introduce are also relevant to other domains of the exposome.

2. Teeth as a novel matrix for reconstructing the early life exposome

2.1. Aspects of tooth development relevant to this biomarker

Between the 14th to 19th weeks of intrauterine development, the tooth germ enters the advanced bell stage characterized by the appearance of enamel and dentine at the future dentine–enamel junction (DEJ) on the cusp tip (Fig. 1a) (BKB Berkovitz and Moxham, 2009). Subsequently, enamel and dentine deposition occurs in a rhythmic manner, forming incremental lines akin to growth rings in both enamel and dentine (Fig. 1b). At birth, an accentuated incremental line, *the neonatal line*, is formed due to disturbances in the secretory cells during protein

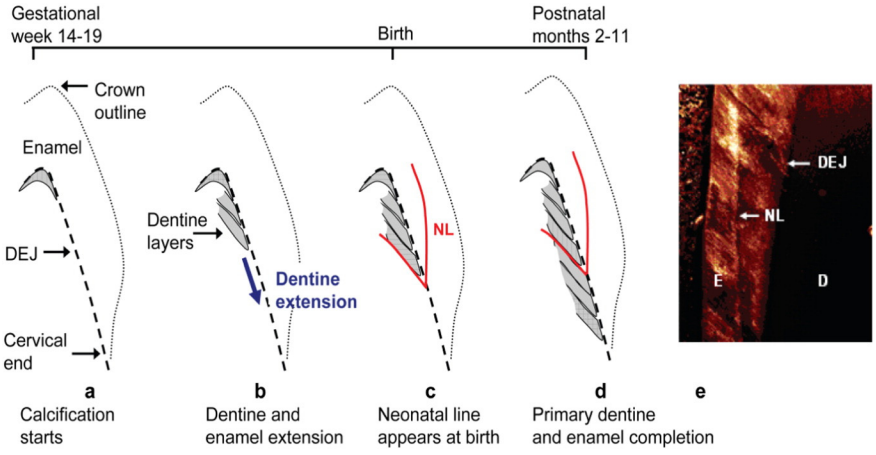

Fig. 1. Schematic of tooth development (Arora et al., 2012). (a) Earliest deposition of dentine (gray area) at DEJ at cusp tip. (b) Continued extension of dentine (and enamel) towards the tooth cervix. (c) Neonatal line (NL), a histological feature, formed at the time of birth. (d) Completion of enamel and primary dentine formations between 2 and 11 post-natal months depending on tooth type. Secondary dentine continues forming at pulpal margin (not shown). (e) Confocal laser scanning micrograph of NL in enamel. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
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