



## A proposal to facilitate weight-of-evidence assessments: Harmonization of Neurodevelopmental Environmental Epidemiology Studies (HONEES)

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### ABSTRACT

The ability to conduct weight-of-evidence assessments to inform the evaluation of potential environmental neurotoxins is limited by lack of comparability of study methods, data analysis, and reporting. There is a need to establish consensus guidelines for conducting, analyzing, and reporting neurodevelopmental environmental epidemiologic studies, while recognizing that consistency is likewise needed for epidemiology studies examining other health outcomes. This paper proposes a set of considerations to be used by the scientific community at-large as a tool for systematically evaluating the quality of proposed and/or published studies in terms of their value for weight-of-evidence assessments. Particular emphasis is placed on evaluating factors influencing the risk of incorrect conclusions at the level of study findings. The proposed considerations are the first step in what must be a larger consensus-based process and can serve to catalyze such a discussion. Achieving consensus in these types of endeavors is difficult; however, opportunities exist for further interdisciplinary discussion, collaboration, and research that will help realize this goal. Broad acceptance and application of such an approach can facilitate the expanded use of environmental epidemiology studies of potential neurodevelopmental toxicants in the protection of public health, and specifically children's health.

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**Abbreviations:** ADHD, attention deficit hyperactivity disorder; CONSORT, Consolidated Standards of Reporting of Trials; HONEES, Harmonization of Neurodevelopmental Environmental Epidemiology Studies; IRIS, Integrated Risk Information System; PCBs, polychlorinated biphenyls; QUADAS, Quality Assessment of Diagnostic Accuracy Studies; US EPA, United States Environmental Protection Agency; STARD, Standards for Reporting of Diagnostic Accuracy; STROBE, Strengthening the Reporting of Observational studies in Epidemiology.

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### 1. Introduction

Pediatric neurodevelopmental disorders have generated substantial attention from the scientific community, the public and media. This high visibility is due in part to an observed increased prevalence of autism spectrum disorders (Rice et al., 2010) and possibly attention deficit hyperactivity disorder (ADHD) (Pastor and Reuben, 2008). Many chemicals are known to be human neurotoxins, at least following acute exposure to adults (Grandjean and Landrigan, 2006). In addition, associations between specific environmental chemicals and neuropsychiatric disorders have been reported (e.g., depression and air pollutants (Szyszkowicz et al., 2009); anxiety and PCB 153 (Plusquellec et al., 2010); ADHD and polyfluoroalkyl chemicals

**Table 1**IRIS chemicals with toxicological reviews.<sup>a</sup>

| No neurotoxicity data in animals or humans                                                                                                   |                                                               |                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|------------------------------------------------------|
| Acrolein                                                                                                                                     | Methylene diphenyl diisocyanate (monomeric and polymeric MDI) | Thallium chloride                                    |
| Bentazon (Basagran)                                                                                                                          |                                                               | Thallium oxide                                       |
| Beryllium and compounds <sup>b</sup>                                                                                                         | Mirex <sup>b</sup>                                            | Thallium selenite                                    |
| 1,3-Butadiene                                                                                                                                | Naphthalene <sup>b</sup>                                      | 1,2,3-Trichloropropane                               |
| Chromium(III), insoluble salts                                                                                                               | Phosgene                                                      | 2,2,4-Trimethylpentane                               |
| Chromium(VI)                                                                                                                                 | Propionaldehyde                                               | Zinc and compounds                                   |
| Ethylene glycol monobutyl ether (EGBE) (2-Butoxyethanol) <sup>b</sup>                                                                        | Thallium carbonate                                            |                                                      |
| No neurotoxicity data in animals; some data in adult humans (mostly positive); no data in children                                           |                                                               |                                                      |
| Chloroform                                                                                                                                   | Hexachlorocyclopentadiene (HCCPD)                             | Thallium nitrate                                     |
| Animal DNT <sup>c</sup> data (all positive); no adult animal data; no adult or child human data                                              |                                                               |                                                      |
| Chlorite (sodium salt)                                                                                                                       | 1,2-Dibromoethane                                             | Perchlorate and Perchlorate salts <sup>b</sup>       |
| 2,2',3,3',4,4',5,5',6,6'-Decabromodiphenyl ether (BDE-209)                                                                                   | Diesel engine exhaust                                         | 2,2',4,4'-Tetrabromodiphenyl ether (BDE-47)          |
|                                                                                                                                              | 2,2',4,4',5,5'-Hexabromodiphenyl ether (BDE-153)              |                                                      |
| Adult animal data; some DNT data, no human data; results in animals are mixed                                                                |                                                               |                                                      |
| Acetonitrile                                                                                                                                 | Cyclohexane                                                   | 2,2',4,4',5-Pentabromodiphenyl ether (BDE-99)        |
| Bromobenzene                                                                                                                                 | Dibutyl phthalate <sup>b</sup>                                | Phenol                                               |
| Cerium oxide and cerium compounds                                                                                                            | 1,1-Dichloroethylene (1,1-DCE)                                | Platinum <sup>b</sup>                                |
| Cis- and trans-1,2-Dichloroethylene <sup>a</sup>                                                                                             | 1,3-Dichloropropene                                           | Quinoline                                            |
| Cumene                                                                                                                                       | Ethyl <i>tert</i> -butyl ether (ETBE) <sup>b</sup>            | Tributyltin oxide (TBTO)                             |
|                                                                                                                                              | 2-Methylnaphthalene                                           | 1,3,5-Trinitrobenzene                                |
| Neurotoxicity testing in adult animals and data in adult humans (all are positive); a few assessments of DNT in animals; no data in children |                                                               |                                                      |
| Acetone                                                                                                                                      | Chlordecone (Kepone)                                          | Nitrobenzene                                         |
| Acrylamide <sup>b</sup>                                                                                                                      | <i>n</i> -Hexane                                              | 1,1,2,2-Tetrachloroethane <sup>b</sup>               |
| Barium and compounds                                                                                                                         | 2-Hexanone                                                    | Tetrahydrofuran <sup>b</sup>                         |
| Benzene                                                                                                                                      | Hydrogen cyanide <sup>b</sup>                                 | Thallium(I), soluble salts                           |
| Carbon tetrachloride <sup>b</sup>                                                                                                            | Methanol <sup>b</sup>                                         | Thallium acetate                                     |
| Chlordane (technical)                                                                                                                        | Methyl chloride                                               | Thallium(I) sulfate                                  |
| Chloroprene                                                                                                                                  | Methyl ethyl ketone (MEK)                                     | Toluene                                              |
| Dichloroacetic acid                                                                                                                          | Methyl isobutyl ketone (MIBK)                                 | 1,1,1-Trichloroethane                                |
| Dichlorobenzenes <sup>b</sup>                                                                                                                | Methyl methacrylate                                           | Vinyl chloride                                       |
| 1,4-Dioxane <sup>b</sup>                                                                                                                     | Pentachlorophenol <sup>b</sup>                                | Xylenes                                              |
| Data in children                                                                                                                             |                                                               |                                                      |
| Neurodevelopmental outcomes observed (congenital anomalies)                                                                                  | Case reports in children identified effects on nervous system | Neurodevelopmental testing was conducted in children |
| Chlorine dioxide                                                                                                                             | Boron and compounds                                           | Methyl mercury                                       |
| Trichloroacetic acid <sup>b</sup>                                                                                                            | Bromate                                                       | Perchloroethylene <sup>b</sup>                       |
|                                                                                                                                              | Chloral hydrate                                               | Trichloroethylene <sup>b</sup>                       |
|                                                                                                                                              | Hydrogen sulfide                                              |                                                      |

<sup>a</sup> To facilitate consistency of comparison across chemicals, this evaluation includes only those substances for which an IRIS Toxicological Review was available on the IRIS website (U.S. EPA, 2010a); it is not a comprehensive list of neurotoxic environmental chemicals. Thus, a number of important chemical assessments that include neurodevelopmental testing in children (e.g., lead, PCBs, some pesticides) are not included in the list.

<sup>b</sup> External review draft.

<sup>c</sup> DNT = developmental neurotoxicity.

(Hoffman et al., 2010); ADHD and PCBs and lead (Eubig et al., 2010); autism and pesticides (Roberts et al., 2007)).

In spite of the growing concerns about perturbations in neurodevelopment that may be associated with environmental exposures, few environmental chemicals are regulated on the basis of neurodevelopmental outcomes. A review of the U.S. Environmental Protection Agency (US EPA) Integrated Risk Information System (IRIS) database illustrated the limited impact of studies assessing neurodevelopmental endpoints in children have had on the characterization of hazards resulting from early life stage exposures to environmental toxicants. The IRIS database is a publicly available peer-reviewed source of toxicological information maintained by the US EPA National

Center for Environmental Assessment (NCEA) for over 550 environmental chemicals (U.S. EPA, 2010a). For those chemical assessments that were issued in 1997 or later (a total of 85, listed in Table 1), detailed hazard and dose response information is provided in a "Toxicological Review," thereby allowing an examination of the use and influence of neurobehavioral data in oral and inhalation reference value derivation. Out of the 85 assessments examined, 19 had no neurotoxicity data in either animals or humans, 24 had animal but not human neurotoxicity data, and 33 had adult human neurotoxicity data (30 of which were supported by animal data). Only 9 of the 85 IRIS toxicological databases that were examined included any information on neurotoxicity in children, and of those only 3 reported

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