

CEFIC Long-Range Research Initiative Request for Proposals (RfP)

Title and Code Number:

Review of neurodevelopmental function tests in children – EMSG54

Background

Neurodevelopmental disorders are a wide range of disorders including learning disabilities, autism, mental retardation, low intelligence, slow motor development, learning deficits and attention deficit hyperactivity disorder (ADHD). These disorders can have a great impact on the lives of affected children, their families and society.

Children's health in relation to chemical exposures has been a topic that has received significant interest. The Voluntary Children's Chemical Exposure Program (US EPA 2000) and the European action plan developed through SCALE (EU Commission 2004) are examples of this increased interest. To a certain extent, this has been triggered by recent publications in the scientific literature claiming that chemical exposures during pregnancy are playing a significant role in the reported increased incidence of neurodevelopmental disorders. A widely quoted article in the Lancet by Grandjean and Landrigan claims that these neurodevelopmental disorders are likely to be causally associated with exposure to industrial chemicals (Grandjean/Landrigan 2006). The authors also claim that the window of exposure *in utero* more strongly determines this neurodevelopmental toxicity than the actual dose. They claim that probably in excess of 1000 chemicals have been shown to be neurotoxic in laboratory studies. The authors speak of a pandemic of neurodevelopmental toxicity from industrial chemicals and foresee that large-scale prospective epidemiological studies such as birth cohorts will be especially informative about neurodevelopmental disorders in children. The claims made by Grandjean and Landrigan appear not to be based on reliable findings from epidemiological studies. They merely speculate that the developing human brain is inherently more susceptible to toxic agents than the adult brain.

However, recent literature reviews in Europe as well as the United States concluded that reliable and consistent data on associations between chemical exposures and neurodevelopmental disorders is generally lacking. An ECETOC review of the literature on the role of chemicals in trends in children's health concludes on the topic of neurodevelopmental disorders that increased survival of pre-term deliveries in western society should be taken into account in the evaluation of time trend analysis of these disorders (ECETOC 2005). A similar conclusion was drawn in a report commissioned by the American Chemistry Council (ACC 2002). Some epidemiological studies report associations between *in utero* exposure to chemicals and neurodevelopmental disorders. For instance Garry *et al.* report an increased prevalence of attention deficit disorders in children of pesticide applicators with self reported exposure to phosphine (Garry, Harkins *et al.* 2002). However this study, as do many other studies, suffers from a lack of an *a priori* specific hypothesis and a reliable diagnostic test to independently establish the presence of the neurodevelopmental disorder under investigation.

Clearly other factors can play a role in the incidence of neurodevelopmental disorders, such as the social milieu, lifestyle factors such as smoking and alcohol consumption (Dietrich, Eskenazi *et al.* 2005). As was pointed out by Grandjean and Landrigan, the emerging birth cohorts and the National Children's Health study in the United States, provide excellent opportunities to study the potential associations between exposure to chemicals and neurodevelopmental disorders in children. These studies can strongly benefit from the application of reliable testing methods to determine the presence of neurodevelopmental disorders and from defining an *a priori* specific hypothesis to be

tested. This hypothesis to be tested should be based on knowledge about the most likely neurodevelopmental disorder that can be expected to be associated with a specific chemical. In addition, it should also *a priori* define the most relevant biological time window for exposure to exert its effect.

In summary, there is concern that exposure to chemicals may be associated with neurodevelopmental disorders. Prospective studies, including birth cohort studies form an excellent opportunity to study these potential associations. However, these studies can strongly increase in quality if reliable validated testing methods are used to determine the presence of neurodevelopmental disorders, and they can strongly increase their weight of evidence if *a priori* specified hypotheses in terms of exposure, relevant time window, confounders and adverse effect are formulated.

References:

- ACC (2002): A primer on environmental risk factors and the nervous system. American Chemistry Council, Arlington, VA, USA.
- KN Dietrich, B. Eskenazi *et al.*, Principles and practices of neurodevelopmental assessment in children: lessons learned from the Centers for Children's Environmental Health and Disease Prevention Research, *Environ Health Perspect* **2005**, 113, 1437-1446.
- ECETOC (2005): Trends in Children's Health and the Role of Chemicals: State of the Science Review, Brussels.
- VF Garry, ME Harkins *et al.*, Birth defects, season of conception, and sex of children born to pesticide applicators living in the Red River Valley of Minnesota, USA, *Environ Health Perspect* **2002**, 110, Suppl 3, 441-449.
- P Grandjean, PJ Landrigan, Developmental neurotoxicity of industrial chemicals, *Lancet* **2006**, 368, 2167-2178.

Objectives

The objectives of this RfP are:

1. To better understand the tests which are currently available to objectively determine the major endpoints covering neurodevelopmental effects in children including the age period in which these tests can reliably be applied and compare the test characteristics such as sensitivity, specificity and overall validity.
2. To summarize and assess the currently available evidence for associations between environmental stressors and neurodevelopmental disorders in children, building on the conclusions drawn from objective #1.
3. To identify and describe other potential risk factors such as socio-economic status, smoking and drinking habits, viral infections, etc. that have been reported to be associated with neurodevelopmental disorders and how they can be best accounted for in epidemiology studies.
4. Develop a set of quality criteria for epidemiological studies of associations between chemical exposures and neurodevelopmental disorders in children which would minimize the chance of false positive and false negative study results.

In these objectives it should be kept in mind that the neurodevelopmental tests are likely to be applied in field studies and as such must maintain their reliability if applied in the homes of study participants or in the form of questionnaires. Other circumstances, such as sample size requirements may also provide indications for which neurodevelopmental

disorders can be adequately studied in prospective epidemiological studies including birth cohorts.

In case of positive associations between exposure to chemicals and neurodevelopmental impairment follow-up investigations could be proposed. An additional option might be the validation of one or several specific neurodevelopmental tests provided the literature review shows that a given test is particularly suitable to study a sentinel neurodevelopmental disorder in a cohort of children.

Scope

1. Provide a critical review of the currently available testing methods for neurodevelopmental disorders in children and their potential for application in epidemiological studies.
2. Provide a critical review of the available evidence on neurodevelopmental disorders in children and their association with chemical exposure, and identify the critical or key effects and appropriate time windows for exposure and response measurement.
3. Provide guidelines and quality criteria for epidemiological research in the area of neurodevelopmental disorders and exposure to chemicals.
4. The option of organizing a workshop among experts in the area of neurodevelopmental testing and its application in environmental epidemiology is recognized and inclusion in the project is welcomed.

Short interim reports on progress are required at 3 to 6-monthly intervals. It is expected that the findings will be developed into a peer reviewed publication, following presentation at a suitable scientific conference.

Cost and Timing

Budget in the order of €175,000
Start in 2008, duration up to 12 months