

Neurodevelopmental Toxicity Risks Due to Occupational Exposure to Industrial Chemicals during Pregnancy

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Abstract: Exposure to neurotoxic chemicals is of particular concern when it occurs during early development. The immature brain is highly vulnerable prenatally and is therefore at risk due to occupational exposures incurred by pregnant women. A systematic search of the literature has been performed with emphasis on epidemiological studies on female workers and the neurodevelopment of their children. The majority of recent occupational studies focused on organic solvents and pesticides, which were associated with neurobehavioral impairments in the progeny. Additional evidence on environmental exposures demonstrates the vulnerability of the developing brain to substances like lead and methylmercury. Despite the evident hazards involved, the number of occupational cohort studies carried out in this field is very low. However, the lack of evidence for assumed neurotoxicants should not divert the attention by occupational health researchers and practitioners from the need to protect pregnant workers. Due to the vulnerability of the brain during early development, a precautionary approach to neurodevelopmental toxicity needs to be applied in occupational health.

Key words: Occupational health, Pregnancy, Industrial chemicals, Organic solvents, Pesticides, Neurodevelopment, Silent pandemic of developmental toxicity, Review

Introduction

The human brain is the most complex human organ with its sophisticated functions and ability to control behavior, learning, talking, memorizing, organizing, listening, performance of routine skills and interaction with one's social environment. For this reason, the brain is also a highly vulnerable organ, and a damaged brain cannot function optimally¹. Neurotoxic hazards can cause injury to the brain, especially if exposures happen during the early developmental period². Among documented hazards are certain industrial chemicals, tobacco smoke, alcohol and certain drugs, as well as maternal stress. If the developmental processes in the immature fetal ner-

vous system are harmed, the effects are likely to be lasting and possibly permanent, whether subclinical deficits in mental abilities or more severe behavioral disorders^{2–8}). The social consequences of developmental neurotoxicity include an increased likelihood of school failure, diminished economic productivity, and increased risk of anti-social and criminal behavior²).

Occupational medicine has traditionally studied the neurotoxic and other adverse consequences in the workers themselves^{9, 10}). Ample evidence exists for adults in regard to the neurotoxic effects of metals (such as lead and mercury), polychlorinated biphenyls (PCBs), and many pesticides, solvents and other industrial chemicals^{2, 9–14}). However, studies on neurodevelopmental consequences in children born by pregnant workers exposed to the same industrial chemicals so far have been much less intensely pursued¹⁵). Millions of women have joined

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the work force during recent decades. A large proportion are of a reproductive age, and female employees often continue working throughout their pregnancy^{1,2,16}. Attention has been paid to the possible reproductive toxicity risks, such as birth defects, but a recent literature review concluded that the existing studies showed ambiguous findings due to methodological and design problems¹⁷. Assessment of neurodevelopment may require many years of follow-up and is therefore even more difficult to document. Evidence on the consequences of industrial chemical exposures among pregnant workers is therefore rather scant, despite the magnitude of this public health concern². Improved insight into developmental neurotoxicity is crucial, because these effects may occur at exposure levels that are lower than existing occupational exposure limits, which aim at protecting the nervous system of the adult workers themselves^{2,18,19}.

The purpose of this review is to examine the occupational health evidence in regard to the vulnerability of the developing nervous system and to outline the developmental neurotoxicity risks in offspring of female workers exposed to neurotoxicants.

Prenatal vulnerability of the developing brain

During intrauterine development, the human brain follows a unique timeframe of intense and complex processes. The human brain must develop from a strip of cells along the dorsal ectoderm of the embryo into a complex organ consisting of billions of precisely located, highly interconnected, and specialized cells, with the major part of this impressive development taking place during the intrauterine period. However, the intricacy of these closely interlinked processes also predisposes this organ to injury from toxic agents that may interfere with minute, but essential steps in brain development. If these complex processes are halted or disturbed, there is a little potential for later repair, and the functional consequences can therefore be permanent^{2,20,21}.

The placenta may provide some protection, but many industrial chemicals like pesticides, organic solvents or metals, such as lead and mercury, can cross the placenta and concentrate in the fetal nervous system, sometimes in even higher concentrations than in the maternal organism²². Some of these chemicals are lipophilic and therefore are likely to be retained in organs with higher lipid concentrations, such as the brain²³. The fetal blood-brain barrier is unlikely to provide protection against industrial chemicals, and the same applies to immature detoxification mechanisms^{2,24}.

The combination of all these features makes the fetal period a critical window of vulnerability to environmental hazards that can impact optimal brain development,

thereby leading to impairment of behaviors and skills, including cognitive abilities and social competences that are further developed and fine-tuned during childhood and adolescence^{1,2}.

Review Strategy

Epidemiological studies focused on occupational exposure to industrial chemicals and subsequent neurodevelopmental consequences in the offspring were identified by using PubMed and PSYCHinfo literature data bases. The language was not specified, although English was preferred. The following keywords were used: occupational exposure, work exposure, job exposure, industrial exposure, pregnancy, prenatal, uterine period, behavior, neurobehavior, neurodevelopment, cognitive abilities, and mental health. We first used these terms separately and in a second step we combined them (i.e., occupational exposure + neurodevelopment). We otherwise followed the same search strategy described in a previous review². Reference lists in the articles selected were also scrutinized to identify older studies that might satisfy the search criteria. For each article, the following information was abstracted: location, type of study, study period, population, child age, type of exposure, exposure measurements, covariates, outcome scales, and effects studied. Through this systematic search, a total of 15 papers^{23,25–38} were identified that fit the above criteria (Table 1). Each of these studies is reviewed below.

Organic Solvents

Organic solvents encompass a large number of different chemicals that include widely used compounds such as toluene and trichloroethylene. Their chemical structure can be classified as aromatic, aliphatic, hydrocarbons, halogenated compounds, alcohols, and other solvents^{25,26}. They are lipophilic and are mostly known to be neurotoxic from acute poisoning cases and occupational studies in adults with chronic exposure². Seven epidemiological studies have assessed the neurodevelopmental consequences in children of workers with solvent exposures during pregnancy (Table 1)^{23,25–30}.

Most reports describe small nested case-control studies that generally used structured questionnaires to assess exposures, with specific questions about timing (weeks of gestation), duration (hours/week) and protective equipment. The women were exposed within permissible workplace limits, thereby likely preventing toxic effects in the workers themselves. The age of the children examined ranged from 6 months to 8 yr, with a large age disparity in each study sample. All studies applied adjustments for appropriate covariates in the analysis. The results showed negative associations between the report-

Table 1. Main characteristics of the reports in the different publications of occupational exposure to industrial chemicals during pregnancy and neurodevelopmental toxicity at different ages

Ref.	Loc.	Type of Study	Study period	Popul.	Child. Age	Type of Exp.	Exp. Measurement	Covariates	Outcome Scales	Effect studied
Eskenazi 1988 ²³⁾	Yale	Nested Case-control study matched for race, marital status, age and age of her child.	1980–1982	82 (41/41)	3, 1–3,9 yr	Organic solvents	Structured questionnaire assessing the Estimated Exposure Index including info. about: Length (weeks) and duration (hours/week) of exposure in pregnancy; proleptic barriers; adverse symptoms. They also classified them by solvent chemical structure: aromatic, aliphatic, hydrocarbons, halogenated compounds, alcohols, polyaromatic hydrocarbons, ketones, glycols and esters, or multi-exposure. But no power to assess individual effects.	Home environment and parenting, smoking and alcohol use during pregnancy, civil status, maternal age, race, education, occupational status, breastfeeding, gravity, birth order, infant sex	McCarthy Scales; Conner's Parent Scale National Institute of Mental Health Childhood Personality Scale-Revised	No differences between exposed and controls in any neurobehavioral area assessed.
Till 2001a ²⁵⁾	Toronto	Nested Case-control study matched by child's age, gender, ethnicity and SES.	1992–1996	61 (33/28)	3–7 yr	Organic solvents	Structured questionnaire, assessing the Estimated Exposure Index including info. about: Length (weeks) and duration (hours/week) of exposure in pregnancy; proleptic barriers; adverse symptoms. They also classified them by solvent chemical structure: aromatic, aliphatic, hydrocarbons, halogenated compounds, alcohols, polyaromatic hydrocarbons, ketones, glycols and esters, or multi-exposure. But no power to assess individual effects.	Alcohol, smoking or other recreational drug during pregnancy, marital status, education, ethnicity, age, occupation, The Hollingshead Four Factor Index of Social Status, family functioning, breastfeeding duration, developmental milestones, child gestational age and head circumference, child age, and growth	Developmental Neuropsychological Assessment (NESP); Peabody Picture Vocabulary Test (PPVT-III); a Test of auditory receptive language; the Expressive One-Word Picture Vocabulary Test (revised) (EOWPVT-R), a test of expressive language ability; Pegboard and Matching subtests of the Wide Range Assessment of Visual Motor Abilities (WRAVMA); Child Behavior Checklist (CBCL); Continuous Performance Task (CPT)	Graphomotor ability (-) Receptive and Expressive language (-) Impulsivity by false positive in CPT (+) General behavioral problems (+) The associations with language and graphomotor domains showed a dose response pattern: no exp., middle exp., highly exp.
Till 2001b ²⁶⁾	Toronto	Nested Case-control study matched by child's age, gender, ethnicity and SES.	1992–1996	59 (32/27)	3–7 yr	Organic solvents	As above	Maternal alcohol use, smoking or other recreational drug during pregnancy, marital status, education, ethnicity, age, occupation, The Hollingshead Four Factor Index of Social Status, family functioning, breastfeeding duration, developmental milestones, child gestational age and head circumference, child age, and growth	Color vision by Minimalist Test; Visual Acuity by Cardiff Cards	Tritan color vision (-) Visual acuity (-) No dose-response pattern found.
Till 2005 ²⁷⁾	Toronto	Nested Case-control study	1999–2003	48 (21/27)	6–40 months	Organic solvents	As above	Maternal smoking or other recreational drug during pregnancy, education, ethnicity, age, occupation, The Hollingshead Four Factor Index of Social Status, breastfeeding duration, child age, birth weight and gestational age, child gender, age during testing, and growth	Contrast Sensitivity using Sweep Evoked Potentials (VEP); chromatic and achromatic mechanisms using Transient (VEP)	Contrast Sensitivity (-) red-green color abnormalities (+) Dose-response association in grating acuity.

Ref.	Loc.	Type of Study	Study period	Popul.	Child. Age	Type of Exp.	Exp. Measurement	Covariates	Outcome Scales	Effect studied
Laslo-Baker 2004 ⁽²⁸⁾	Toronto	Nested Case-control study matched by child sex and age, maternal age, socio-economic status and smoking during pregnancy.	1989–1998	64 (32/32)	3–8.9 yr	Organic solvents	Reported info of specific type of organic solvents involved, type of occupational setting, duration of exposure in pregnancy, any adverse symptoms, type of protective gear used, and other safety feature	Maternal IQ (Wechsler Abbreviated Scale of Intelligence), gender, age, maternal age, education, socioeconomic status, and parity, length of breastfeeding, Apgar, birthweight, gestational age, height and weight at time of testing, head circumference, milestones, occupational and domestic exposure to lead and mercury	Wechsler Preschool and Primary Scale of Intelligence (WPPSI); Wechsler Intelligence Scale for Children (WISC); Preschool Language Scale; Clinical Evaluation of Language Fundamentals; Beery-Buktenica Developmental Test of Visual-Motor Integration; Grooved Pegboard Test; CBCL; Conner's Rating Scale-Revised; Behavioral Style Questionnaire	Only with case control differences: Motor functioning (–) Short term auditory memory (–) General verbal information (–) Behavior (–) Attention (–) Hyperactivity (–)
Ratzon 2004 ⁽²⁹⁾	Israel	Historical Cohort, matched by gender and sex with controls. Nested case-control study?	1990–2001	80 (40/40)	5–13 yr	Organic solvents; anesthetic gases	Working hours	Gestational age, birth weight, Apgar at 1 min and 5 min. Controls matched by maternal professional characteristics, gender and age. Mother's age, education level	WPPSI; WISC-R; The Bruiniks-Oseretsky Motor Test; The Parent-Teacher Questionnaire (DSM-III-R); Developmental Background Questionnaire	Only with case control differences and hours working: Fine and Gross motor (–) Inattention-Hyperactivity (+)
Perrin 2007 ⁽³⁰⁾	Israel	Population-based cohort	1964–1976 /1998	88, 829	adults	Organic solvents in dry cleaning since the 1950	Questionnaire: If parents worked as dry cleaners.	Paternal age, father's social class, duration of marriage, rural residence, religion, ethnic origin, parental immigration status, offspring birth order, sex, birth weight and month of birth.	Psychiatric diagnosed of schizophrenia in the hospital.	RR: 3.4 (+)
Gullette 1998 ⁽³¹⁾	Mexico	Case-control Study	1990–1995?	50 (33/17)	48–62 months	Organo-chlorines and Organophosphates	Maternal blood samples during pregnancy and breast-milk	Diet, number of pregnancies and any related complications, the types and frequency of family illness, obstetrical and lifestyle history	Rapid Assessment Tool Playing with the Child (RATPC), motor and mental assessments	Creative in the play (–) Gross and fine motor skills (–) Memory (–) Drawing (–)
Young 2005 ⁽³²⁾	California	Population-based birth cohort of low-income population of which substantial proportion are agricultural workers	1999–2000	381	≤62 d	Organophosphates	Six organophosphates metabolites in maternal urine during prenatal and post-delivery interviews	Maternal education, marital status, parity, country of birth, poverty, smoked during pregnancy, alcohol use during pregnancy, caffeine use during pregnancy, cesarean delivery, general anesthesia, breastfeeding, infant sex, birth weight and gestational age.	Brazelton neonatal Behavioral Assessment Scale (BNBAS)	Abnormal reflexes for all metabolites (+) No association found only taking into account postnatal metabolites.
Eskenazi 2007 ⁽³³⁾	California	Population-based birth cohort of low-income population of which substantial proportion are agricultural workers	1999–2002	356	6–24 months	Organophosphates	Six organophosphate metabolites in maternal urine during prenatal and post-delivery interviews Metabolites specific to malathion and chlorpyrifos	Maternal verbal abilities, HOME, maternal symptoms of depression, maternal education, marital status, parity, country of birth, poverty, smoked during pregnancy, alcohol use during pregnancy, caffeine use during pregnancy, cesarean delivery, general anesthesia, breastfeeding, infant sex, birth weight and gestational age, lead, DDT, DDE, B-HCB, HCB, PCBs in prenatal blood samples.	Bailey's Scales; CBCL	Mental development (–) Pervasive Development Disorder (+) Particularly dimethyl-phosphate metabolites No associations with metabolites specific to malathion and chlorpyrifos

Ref.	Loc.	Type of Study	Study period	Popul.	Child. Age	Type of Exp.	Exp. Measurement	Covariates	Outcome Scales	Effect studied
Grandjean 2006 ⁽⁴⁵⁾	Ecuador	Case-control, cross-sectional study		72 (37/35)	7-8 yr	Organophosphates	Prenatal exposure by reported questionnaire Current exposure by six organophosphate metabolites in children's urine	Stunting, gender, school grade, housing, running water at home, sewage drainage, at home, number of meals, protein-rich diet, number of siblings, delivery at home, maternal smoking during pregnancy, maternal alcohol use during pregnancy, maternal age, race and education	Simple reaction time; Santa Ana Dexterity Test; Stanford-Binet Copying Test; WISC-R Digit Span	Prenatal exposure: Visuospatial performance (-) Current exposure: Simple Reaction time (+) Systolic blood pressure (+)
Handal 2007 ⁽³⁵⁾	Ecuador	Ecological and cross-sectional study comparing three communities	2003-2004	142	24-61 months	Organophosphates	Questionnaire: Mother currently work in flower industry, mother worked in flower industry during pregnancy, father currently work in flower industry, pesticides on domestic crops, pesticides in home, child plays outdoor ≥ 5 h/d, child plays with irrigation water.	Stunting, daycare, child's daily activities, stimulation at home, maternal age, education, ethnicity, predominant language, income, housing construction, paternal education	Ages and Stages Questionnaire (ASQ) Beery-Buktenica VMI developmental test for assessing visual motor integration	Maternal prenatal and current exposure to pesticides via work: communication (+) problem solving (+)
Handal 2008 ⁽³⁶⁾	Ecuador	Cross-sectional study	2003-2004	121	3-23 months	Organophosphates Carbamates	Questionnaire: working to the flowering industry during pregnancy	Stunting, daycare, child's daily activities, stimulation at home, maternal age, education, ethnicity, predominant language, income, housing construction, paternal education	Ages and Stages Questionnaire (ASQ) Targeted Developmental Tests (motor, bi-manual coordination and visual acuity)	Motor skills (-) Visual acuity (-)
Eskenazi 2006 ⁽³⁷⁾	California	Population-based birth cohort of low-income population of which substantial proportion are agricultural workers	1999-2002	330	6-24 months	1,1,1-trichloro-2,2-bis (p-chlorophenyl) ethane (DDT) 1,1-dichloro-2,2-bis (p-chlorophenyl) ethylene (DDE)	Maternal blood samples during pregnancy	Maternal verbal abilities, HOME, maternal symptoms of depression, country of birth, poverty, smoked during pregnancy, alcohol use during pregnancy, caffeine use during pregnancy, cesarean delivery, general anesthesia, breastfeeding, infant sex, birth weight and gestational age, organo-phosphates (Ops), Lead, beta-hexachlorobenzene (B-HCB), hexachlorobenzene (HCB), Polychlorinated Biphenyls (PCBs) in prenatal blood samples.	Bailey Scales, at 6, 12, 24 months of age.	DDT: 12 month-Mental Developmental Index (MDI) (-) 24 m-MDI (-) 6 m-Psicomotor Developmental Index (PDI) (-) 12 m-PDI (-) DDE: 6 m-PDI (-)
Fenster 2007 ⁽³⁸⁾	California	Population-based birth cohort of low-income population of which substantial proportion are agricultural workers	1999-2002	303	≤62 d	DDT DDE	Maternal blood samples during pregnancy	Maternal education, marital status, parity, country of birth, poverty, smoked during pregnancy, alcohol use during pregnancy, caffeine use during pregnancy, cesarean delivery, general anesthesia, breastfeeding, infant sex, birth weight and gestational age, OPs, cad, B-HCB, HCB, PCBs in prenatal blood samples.	Brazelton neonatal Behavioral Assessment Scale (BNBAS)	No association found

ed prenatal exposure and several outcomes in six of the seven studies (Table 1). The developmental areas affected were motor and verbal skills, visual-motor and memory functions, attention-deficit-hyperactivity behaviors and visual functions (color discrimination and acuity). Two studies (from the same research group) described a significant dose-response pattern in visual acuity, and visual-motor and verbal skills. The exposure gradient was based on an index that combined several factors, including magnitude and duration of the exposure and the use of protective equipment^{25, 27}.

Lastly, a short report described a large population cohort study carried out in Israel (Table 1), where the prevalence of schizophrenia diagnosis from hospital data was compared between adults, whose parents had worked as dry cleaners, and those without such exposure. The results showed a three-fold higher risk in the exposed group³⁰. While this group was primarily exposed to perchloroethylene, exposures encountered in other studies involved several solvents, often present as mixtures. Although attribution is therefore problematic, evidence related to toluene sniffing during pregnancy supports the notion that neurotoxic solvents may have serious adverse effects on the developing brain².

Organophosphate pesticides

The organophosphates are commonly used as insecticides in agriculture³³. These substances inhibit the enzyme acetylcholinesterase, which hydrolyses the neurotransmitter acetylcholine in both the peripheral and the central nervous system. Acute pesticide neurotoxicity is well known from occupational exposure studies, poisoning events, and suicide data in adults². Developmental neurotoxicity may be caused by similar mechanisms, which may lead to more permanent effects, as acetylcholine has crucial functions during brain development^{2, 33}.

Two cohort studies (from the same research group) were based on an agricultural worker population in California^{32, 33}. The authors studied the effects of prenatal exposure to organophosphates, as assessed by maternal urinary excretion of pesticide metabolites. The results showed negative associations between the prenatal exposure and abnormal reflexes in the infant, as determined by the Brazelton Neonatal Behavioral Assessment Scale³². At ages 6–24 months, the results showed lower mental development on the Bailey Scales and higher pervasive disorder scores on the Child Behavior Check List questionnaire, as compared to unexposed controls³³. These results were independent of other potential neurotoxics measured, such as lead, dichlorodiphenyltrichloroethane (DDT), and PCB, in blood samples (Table 1).

Additionally, four cross-sectional studies^{31, 34–36} were carried out in Ecuador and Mexico, where mothers work-

ing in agriculture or flower production were exposed to pesticides during pregnancy, while comparison groups were similar but not exposed to pesticides. The findings showed lower motor skills, communication and problem solving abilities, creativity, and lower visual acuity at age 6–61 months in infants with prenatal exposure. In older children at age 8 yr, Grandjean *et al.* (2006)³⁴ reported lower visuospatial performance in prenatally exposed children and an additive effect of stunting (Table 1).

In all of these studies, the exact identity of the pesticides is unclear, as exposures involved mixtures of substances. From the evidence available, the organophosphates are likely the causative substance, as also supported by experimental studies². Although many different compounds were involved, they may share toxic mechanisms in regard to developmental neurotoxicity³⁹.

Organochlorine Pesticides

DDT is a neurotoxic, lipophilic and an environmentally very persistent agent used worldwide as agricultural insecticide and against mosquito species that transfer malaria^{37, 38}. The Stockholm Convention on Persistent Organic Pollutants, ratified in 2004, intends to phase out all uses of DDT. However, some countries are permitted to continue using DDT for indoor malaria control^{37, 38}.

Two cohort studies (carried out by the same research group) fit the criteria for this literature review^{37, 38}. Additionally, they were based on an agriculture population in California. Using the same study design as for organophosphates, the authors studied the association between neurodevelopmental outcomes and the maternal blood concentrations of DDT and its metabolite DDE during pregnancy. The results showed that neonatal behavior was not affected³⁸, but mental and motor developments were negatively associated with DDT exposure during infant ages³⁷ (Table 1). Although DDE showed similar associations and may be considered neurotoxic, these associations may also reflect the current or previous presence of the parent substance DDT.

Industrial chemicals in environmental epidemiology

Lead, methylmercury, arsenic, and PCBs are examples of other industrial chemicals that have been studied in environmental epidemiology in regard to neurotoxic effects in prenatally exposed children. To our knowledge there are no recent occupational studies on these substances based on exposed pregnant workers. Their industrial use or production is prohibited (PCBs) or has been severely restricted (lead, mercury), although their persistence in the environment remains a major reason for concern². Prospective studies have documented that low-level exposures to lead, methylmercury, and PCBs can impair the neurobehavioral development in chil-

dren^{2-5, 40}). The effects appear to be permanent, as suggested by the absence of any recovery from previously incurred deficits in prospective studies³⁻⁵). The dose-response association patterns for methylmercury and PCBs indicated much stronger effects of prenatal exposures than postnatal ones, while prenatal lead exposures seemed to have less impact than the much higher postnatal exposures²).

Evaluation of the Evidence

This review highlights the scarcity of scientific literature on pregnant workers exposed to hazards that can affect the neurodevelopment of their children. In general, the majority of the existing studies are based on small samples and nested case-control designs. The chemical substances studied fall into two major groups, i.e., organic solvents and pesticides. Among the latter, most studies addressed organophosphate insecticides, while two population-based birth cohort studies examined the effects of DDT³¹⁻³⁸). Studies on solvents often concerned mixed exposures^{23, 25-30}). We were unable to identify any recent occupational studies relating prenatal exposures to mercury, lead, arsenic and PCBs to neurodevelopment outcomes as parallel to the substantial evidence from environmental epidemiology²). The occupational studies identified show negative consequences of prenatal exposures to the industrial chemicals studied (Table 1)^{23, 25-38}).

The occupational studies on organic solvents used standardized questionnaires, where an industrial hygienist identified the jobs associated with the likely exposure to these compounds. Three of the studies further calculated an exposure index from the information reported by the mother herself²⁵⁻²⁷). These exposure measures are crude proxies that may relate poorly with actual exposures. They are likely affected by low precision and low specificity, as compared to prospective data that include biological monitoring or air concentration measures. These limitations generally cause a bias toward the null and will result in an underestimation of the true dose-effect relationship. Another factor of concern is the disparity of the children's ages at clinical examination, sometimes ranging between ages 3 to 7 yr, thus adding variability to the outcome scores obtained from different age-appropriate psychometric instruments. Despite this important source of variability, the results showed several consistencies regarding the neurobehavioral areas affected, i.e., visual functions, motor and verbal skills and attention-deficit-hyperactivity behaviors. Still, the specific neurotoxic causation and pathogenesis are unknown due to the frequent occurrence of mixed exposures in these studies (Table 1). Nonetheless, toluene is a solvent with known developmental neurotoxicity caused by maternal toluene

sniffing during pregnancy²).

One cohort study reported that organic solvents used in dry cleaning occupations were associated with an increased risk of schizophrenia in the offspring. This report was unable to separate maternal and paternal exposures and the timing in relation to the pregnancy, but it provides suggestive evidence on the consequences of organic solvent exposures for the workers' offspring in relation to psychiatric outcomes at adult age³⁰). The evidence from these studies on the solvents mentioned is highly relevant, as female workers may be exposed to several organic solvents that occur in products used, e.g., by hair dressers or dry cleaners, and perhaps in trades and professions with increasing numbers of females, such as chemists, biologists or artists²⁸). A large number of solvents are known to be neurotoxic in adults²).

Globally, over US \$30 billion are spent every year on pesticides, one third of it in the developing world³⁶). Organochlorine pesticides (and other persistent chemicals, such as PCBs) have been banned, but the neurotoxic effects remain significant from an environmental perspective, when the compounds are persistent and accumulate in food chains^{37, 38}). From an occupational health perspective, the pesticides of greatest current relevance in regard to neurotoxicity risks are the organophosphate insecticides, which are widely used²). In countries like Ecuador, where the flower industry is a main source of income, the use of organophosphates causes widespread exposures to the work force, approximately half of which is women in reproductive age groups³⁴⁻³⁶).

Organophosphates inhibit cholinesterase, thus resulting in cellular deficits in developing brains, particularly in regions rich in cholinergic projections^{41, 42}). The best method to measure organophosphate exposures is by analyzing the urinary excretion of organo phosphate metabolites, with appropriate adjustment for creatinine, while taking into account age, sex, height, and weight⁴³). High day-to-day variability may render a single sample unreliable as indicator of exposure levels during pregnancy³³). Such imprecision will tend to bias the results toward the null. Nevertheless, two cohort studies found consistent results using this approach with two sets of samples, one during pregnancy and the other in connection with the post-delivery interview. The findings showed negative associations with neonatal reflexes and 24-month mental development, particularly with the pre-parturition urine concentrations^{32, 33}). The findings relating to neonatal reflexes are of interest, as this outcome would be thought to be less influenced to the family socio-environment and perhaps more sensitive to toxic effects³²). The strength of these two studies is that the organophosphate effects were adjusted for possible effects of other industrial neurotoxicants, notably lead and DDT. Concomitant expo-

tures to multiple compounds is common concern, and such an adjustment is important to disentangle their specific effects^{4, 32, 33, 37, 38}).

Two other case-control studies were based on questionnaire reports on prenatal exposure and referred to mixtures of pesticides, predominantly organophosphates. Despite this methodological weakness, consistent findings were reported in relation to the impairment of motor and communication skills, problem solving and visual acuity^{35, 36}. Of particular interest is the recent case-control study in school-age children from Ecuador, the only one based on subjects at this age so far, where possible effects of prenatal and current exposures were examined. Prenatal exposures were based on maternal questionnaires and the current exposures on the children's urinary excretion of organophosphate metabolites. Different neuropsychological functions seem to be affected, perhaps because different neurotoxic mechanisms are involved during early development and at school age: visual-spatial performance was highly sensitive to the former and simple reaction time to the latter³⁴. Overall, the evidence of prenatal vulnerability to organophosphate pesticides seems quite clear, although specific compounds have not been identified. More cohort studies will be needed to ascertain if different mixtures of pesticides are associated with different types and relative severities of effects.

Occupational health perspectives

Among more than 1,000 industrial chemicals known to be neurotoxic in experimental studies, 201 are known to be neurotoxic to humans, from clinical and epidemiological evidence. However, only five of them -arsenic, lead, methylmercury, toluene and polychlorinated biphenyls (PCBs)- are regarded as documented causes of human neurodevelopmental toxicity². This evidence puts into perspective the paucity of studies on the neurodevelopmental consequences of maternal occupational exposures. Figure 1 illustrates how historical evidence on poisoning cases first demonstrated toxicity also in the offspring, while the fifteen reports identified in the present study have extended the curve and shown adverse effects in larger numbers of children at lower levels of occupational exposures.

This evidence must be considered in light of the experimental documentation on neurotoxic potentials of many industrial chemicals and the environmental epidemiology studies of adverse effects in children prenatally exposed to toxicants at much lower levels than those encountered at work². Current occupational exposures at levels deemed to be safe to adult workers are therefore highly likely to contribute to the 'silent pandemic' of developmental neurotoxicity².

The substantial vulnerability of the developing brain

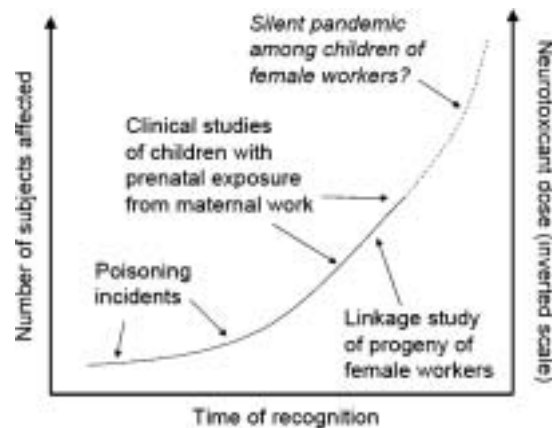


Fig. 1. For occupational exposures to neurotoxicants that may harm the fetus, the evidence at first dealt with acute adverse effects at high doses, but was later followed by studies of case series and linkage of epidemiological evidence on developmental toxicity.

These more recent studies refer to successively lower doses, to which childhood populations of increasing magnitude are exposed. As with the evidence on environmental exposures to neurotoxicants, an unrecognized pandemic may well exist, where the developing brain is harmed by occupational exposures to female workers at concentrations that are deemed safe to the mature brain. Revised from reference 2.

and the severe consequences of developmental neurotoxicity suggest that occupational health must recognize a responsibility to help prevent such adverse effects from happening. The 201 chemicals already recognized as human neurotoxicants should be considered potentially hazardous to pregnant workers. Despite the lack of occupational epidemiology studies in this field, exposures that are not considered to be toxic in adults may still be harmful to fetal neurodevelopment. This issue is of substantial concern in modern occupational health practice, since women are integrated into the workforce, and many spend the major of their pregnancy at work, thereby potentially exposing their fetus to neurotoxic mixtures of industrial chemicals²⁸).

Although developmental neurotoxicity, once it has happened, may not be reversible, it is, in theory, entirely preventable. An important prerequisite would be testing industrial chemicals before allowing them to be marketed. Still, current legislation only requires such testing in rare and specific cases and not as a general condition. Of the thousands of chemicals used in commerce, fewer than half have been subjected to even token laboratory testing for toxicity^{2, 44}, and only a small fraction has been tested for any kind of neurotoxicity, including crude measures, such as brain weight and morphology^{2, 45, 46}. However, more than one thousand chemicals are known to be neurotoxic in experimental models, and these results should be wisely considered as an indication of a serious hazard to the brains of the next generation. The absence

of any toxicity in the mother and other adult workers is no guarantee that the fetal brain is well protected²).

A precautionary approach should therefore lead to strict regulation, with the understanding that it could be relaxed later on if subsequent documentation shows that the risk is less than anticipated. The vulnerability of the human nervous system during prenatal development, and the importance of optimal brain development for the welfare of the next generation, would suggest that the protection of the developing brain against neurotoxic chemicals should be a paramount goal of occupational health.

Conclusions

This review covers the background information and the modest epidemiological evidence on occupational exposures of female workers to industrial chemicals and the consequences in regard to the child's neurodevelopment. The majority of the occupational studies identified aimed to assess organic solvents and organophosphate pesticide effects in the offspring, and consistent neurobehavioral impairments were reported. The evidence suffers from a variety of shortcomings and sources of imprecision. These problems would tend to cause an underestimation of the true extent of the risks. The overall experimental and epidemiological evidence suggests that the substantial vulnerability of the developing nervous system to low concentrations of neurotoxic chemicals should lead to a strengthened emphasis on protection of pregnant workers and women in general against substances that may cause harm to the fetus. A precautionary principle in regard to neurodevelopmental toxicity should therefore be applied in occupational health, and this issue should also attract more research, preferably with a focus on exposure assessment and valid outcome measures in prospective study designs. While preventive measures should not be delayed, research is needed to improve our understanding of the mechanisms involved and help in identifying the best means of protecting future generations against a silent pandemic of developmental neurotoxicity.

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