Occupational exposure and defects of the central nervous system in offspring: review

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Abstract

A study of published work was carried out in a search for evidence of a causal role for parental occupational exposure in the origin of structural and functional defects of the central nervous system (CNS) in children. Studies that consider this topic are scarce and mostly refer to broad categories of exposures and effects. Non-occupational studies referring to environmental exposure of humans and studies on experimental animals were also reviewed. The studies on animals provided straightforward evidence about morphological and behavioural abnormalities resulting from some agents used occupationally. The studies on humans yielded a scala of defects that could be ascribed to exposure to high doses of various agents in the environment. Evidence for a causal role of occupational exposure has not been found, but a highly probable influence on the developing CNS is hypothesised for lead, methyl mercury, and ionising radiation. Parental occupational exposure to cadmium, organic solvents, anaesthetics, and pesticides may also play a part in causing defects of the CNS. Well designed future research is needed to test the above hypotheses.

The effects of occupational exposure on the nervous system of workers have gained increasing attention over the past 20 years. Exposure to heavy metals and organic solvents in particular have been shown to cause functional disturbances in both the peripheral nervous system (PNS) and central nervous system (CNS). As the developing CNS is more susceptible to exogenous influences than the mature nervous system,^{1,2} parental occupational exposure in the pre

and postnatal periods has been associated with defects of the CNS in offspring. Exposure to teratogens in the embryonic period may lead to structural malformations or to functional defects of the CNS at low doses. Fetal and postnatal exposure may affect the further growth and development of the CNS, mainly resulting in functional disturbances.¹⁻⁴ Moreover, exposure to genotoxic chemicals and ionising radiation before conception may cause alterations in genetic material, ultimately expressed as structural or functional defects of the CNS in offspring.^{1,7,8} Evidence for these teratogenic effects is fairly strong for certain medical drugs, ionising radiation, and environmental pollutants accidentally occurring in high doses.^{6,9,10} Effects of occupational exposure on the CNS in offspring, however, have rarely been described.

The aim of the present review was to find indications for a causal role of parental occupational exposure in the origin of defects of the CNS in children. To this end, publications on the teratogenic effects of agents used occupationally were extensively evaluated. Both structural and functional disturbances in the developing brain were considered.

Material and methods

To evaluate all the relevant publications, a search was conducted on occupational and also environmental exposure associated with defects of the CNS in children and in experimental animals. An online computer search on MEDLINE from 1981 to and including 1989, with the keywords (congenital) CNS diseases or abnormalities, behaviour, and mental retardation in association with teratogens, radiation, and environmental pollution or exposure produced a large number of original articles and reviews. Additional papers were traced through the references listed in the reviews and by browsing through the major journals on occupational and environmental health. A selection was made from more than 300 publications in accordance with the following inclusion criteria:

The paper referred to agents used in occupational settings.

Indications of structural or functional defects of the CNS in offspring were described in relation to prenatal or postnatal exposure.

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No major sources of bias were present in the study.

The paper contained sufficient information to warrant conclusions.

Eighty four original articles and 37 reviews were selected. Only 35 papers, however, described a relation between certain occupations or occupational exposure and defects of the CNS; the other papers referred to studies on environmental exposure or to animal models; a great deal of caution is required when extrapolating from studies on laboratory animals to the human brain. Among the studies on humans, clinical series and case reports also have limited value for the estimation of effects and the effects of occupational and environmental exposure are best evaluated by epidemiological studies.¹¹ Despite the lack of comparability between studies, all the papers that meet the criteria described above were included in the review. For most studies published before the 1980s, information from previously published reviews was used. All the papers were critically evaluated and the relative value of their results is discussed below. For the most important groups of agents the available evidence is summarised in the table. Finally, an appraisal is made of the influence of parental occupational exposure on the developing CNS.

Teratogenic influences on the central nervous system

The developing brain is at high risk of being affected by teratogenic agents because of its long lasting sensitive period, which extends from the beginning of organogenesis to the neonatal and infantile period; the vulnerability of undifferentiated neural cells; and lack of reproductive capacity of cerebral neurons.² Teratogenic insults during the early embryonic period may cause gross structural malformations of the brain, such as anencephaly, meningocele, and hydrocephalus. During the developmental period, teratogens influence the formation and maturation of the neuronal and glial network by enhancing cell death and affecting proliferation, migration, and differentiation of cells, modifying the formation of neurites, synapses, and receptors; or causing hormonal and neurotransmitter disturbances. This influence can result in deficiencies in the number of cells, minute defects in brain architecture, or altered chemical composition of fetal brain tissue culminating in permanent functional disorders.^{1-3 5 6 12} The most susceptible period is between 10 and 18 weeks of gestation during which intensive neuronal proliferation takes place,¹³ but the development of the brain extends into the neonatal and early childhood period. The time of exposure determines the nature of the abnormality, which depends on the specific CNS structures damaged.^{2 3 12} Long term as well as brief exposure may pose a threat to the fetal brain,^{2 9} at doses that inflict only minor or transient damage to

the CNS of the adult¹ and which are far below the threshold limits for major malformations.^{5 12} During pregnancy, the placenta and the blood brain barrier of the fetus can be permeated by virtually any type of substance and the fetus can even concentrate teratogens.^{6 9} In the postnatal period, exposure to agents which concentrate in maternal milk can be substantial.¹⁴ Parental exposure to teratogenic agents preconception may cause genetic damage or other disturbances, which can be reflected in defects of the CNS in offspring.^{1 7 8} It is often difficult to assess whether prenatal or postnatal exposure or exposure preconception should be held responsible for a particular teratogenic effect.

Defects of the central nervous system and parental exposure

Publications on occupational exposure and reproductive defects have been reviewed many times, but effects on the CNS in offspring have only rarely been described.¹⁴⁻¹⁷ Some epidemiological studies related malformations of the CNS in general to mothers who were sales workers,¹⁸ industrial or construction workers,¹⁹ or who were employed in manufacturing industries.²⁰ Moreover, an association was found between brain tumours in children and mothers exposed to chemicals, and fathers exposed to solvents and paint,^{21 22} working in the aircraft industry,^{22 23} or in the printing, chemical, or petroleum industries.²⁴ The same applied to fathers working in industries with exposure to ionising radiation,²⁵ in agriculture, in metal related jobs, or in the construction industry.²⁶ The results for the fathers refer to exposure preconception but exposure during gestation and lactation—for instance, when fathers bring home soiled clothing—cannot be ruled out. Effects of specific occupational exposure on the developing brain were not described in these studies. In other (non-occupational) studies, indications of defects of the CNS in offspring were found after parental exposure to lead, mercury, cadmium, organic solvents, anaesthetics, pesticides, and ionising radiation. The available evidence for effects of these agents is reviewed in the sections below.

LEAD

Lead is a widely used industrial chemical. Occupational exposure to inorganic lead occurs in lead smelters, construction works, plastics production, jobs with paint and dyes, and in the printing, ceramics, galvanic, and electrotechnical industries. Inhalation of lead fumes and dust is the main route of exposure in adults, but ingestion might also occur. Organic lead is a major component of petrol, which can be inhaled as well as absorbed by the skin—for example, by workers in petrol stations and policemen working in polluted urban areas. Lead can easily pass the placenta and the blood brain barrier and it

accumulates in brain tissue as well as in breast milk.^{14 27 28} It may affect the fetal CNS by a direct toxic effect on neurones, inhibition of enzymes, or other biochemical changes.^{29 30} Studies in animals have shown gross and microscopic cerebral lesions in different species of animals exposed prenatally to lead,^{30 31} and behaviour and learning ability was shown to be impaired in other studies.^{32 33} Neurological deficits can also result from postnatal exposure, through breast feeding for example.³⁴

In studies on humans, no gross structural malformations of the CNS were found in relation to exposure to lead. Studies on behavioural effects, however, are numerous. Prenatal exposure to lead was related to minor malformations,³⁵ mental retardation,^{29 36 37} and impaired cognitive development.³⁸ Postnatal exposure and exposure to low lead concentrations in young children, often measured as the concentration of lead in blood or teeth, have been associated with impaired cognitive and behavioural functioning.^{39 44} It is also possible that the association can be reversed and functionally handicapped children may have a higher lead intake than healthy children.⁴⁵

No studies were found that reported a relation between occupational exposure to lead and defects of the CNS in offspring. Animal experiments, however, and environmental studies on lead pollution provided substantial evidence that exposure to lead may affect the CNS both prenatally and postnatally. It may be hypothesised, therefore, that parental occupational exposure to lead could have adverse effects on the developing brain.

MERCURY

Compounds of mercury can be divided into organic, inorganic, and metallic mercury. Methylmercury is used in fungicides, wood and paper preservatives, and in the pharmaceutical industry together with other organic mercury compounds. In occupational situations, intake occurs through inhalation and skin contact.^{27 28} Methylmercury passes easily through the placenta and accumulates in brain tissue. A reduction in brain size and disturbances in the cerebral architecture due to interference with neuronal growth and migration underlie the effects on the developing CNS.^{37 46 47} Biochemical disturbances have also been found in studies on animals.^{48 50}

Evidence for a teratogenic role for methylmercury in defects of the CNS dates back to 1953, when a disastrous outbreak of methylmercury poisoning occurred in Japan. Children of mothers who ate contaminated fish were born with fetal Minamata disease, a complex of neurological symptoms including cerebral palsy, ataxia, pathological reflexes, disturbed psychomotor development, and mental retardation often accompanied by microcephaly.⁵¹ Comparable symptoms were described in

cases of acute prenatal exposure to methylmercury in Iraq.⁵² Studies with animals have shown the same defects with additional exencephaly, hydrocephalus, and behavioural disturbances. The effects of methylmercury on the fetal CNS of humans and animals have been extensively studied and reviewed.^{37 46 53 57} Differences in the intensity and duration of exposure and the stage of gestation at which exposure occurs, define the extent of the effect. Postnatal exposure to methylmercury through lactation may result in high tissue concentrations, but the infantile brain seems to be less vulnerable than the fetal brain.^{37 46}

So far, occupational exposure to methylmercury has not been studied in relation to defects of the fetal CNS. Although the concentrations that reach the fetus or infant may be lower than in the above mentioned studies on humans, effects on the CNS certainly cannot be excluded.

Inorganic mercury compounds are sometimes present in pesticides and antiseptics and are used in the electrical appliance and paint industries. After inhalation or ingestion by the mother, they are rapidly dissolved in blood and deposited in the placenta. As a result, normal growth and development of the fetus may be reduced. Abnormal behavioural patterns have been observed in experimental animals. The full effect of inorganic mercury on the fetal CNS is as yet unknown, however.^{53 58}

Exposure to metallic mercury vapour may occur in the production of medical and scientific instruments, in the chemical and electrotechnical industries, in laboratories, and in dental surgeries.^{27 28 56} Although it crosses the placenta rapidly and accumulates in the fetal brain, only a few studies have been carried out on the prenatal effects of mercury vapour.³⁷ Two cases of severe congenital brain damage after occupational exposure to mercury vapour have been reported.⁵⁹ Because of nervous excitability in adults, an exposure limit of 0.01 mg/m³ instead of 0.05 mg/m³ is recommended for pregnant women.⁵⁸ Both inorganic and metallic mercury can be transferred through breast milk and be accumulated in the infant. Therefore, it also seems justified to expect effects on the CNS after exposure during the postnatal period.^{37 46}

CADMIUM

Exposure to cadmium is associated with modern industrial processes such as the manufacture of batteries, alloys, paints, pesticides, plastics, and electroplating. Inhalation is the primary route of industrial exposure; smoking also makes a relatively large contribution to the body burden of cadmium.^{27 28} The placenta acts as a partial barrier to cadmium by accumulating it, but a small amount, nevertheless, reaches the fetus. It is also transferred to neonates through lactation. Some studies on animals reported exencephaly because of incomplete

closure of the neural tube, or more insidious effects, such as increased vacuolation, haemorrhage, and behavioural and learning deficits.^{5 55 60} There are no data available on the effects of prenatal or postnatal exposure to cadmium in humans, but in an epidemiological study, Marlowe *et al* found an association between mental retardation and raised concentrations of cadmium in hair in school age children.⁴¹ This indicates that cadmium may cause gross malformations as well as subtle behavioural effects, possibly mediated by the alteration of neurotransmitter systems.⁶¹

The main effect of exposure to cadmium is retardation of fetal growth, probably caused by changes in the structure of the placenta and a reduction in uteroplacental blood flow.^{5 14 37} This may be critical for the CNS, which is incapable of compensating for decrements in growth once the neural cells have matured.⁶⁰ It is not possible to conclude whether any of the above mentioned effects can result from actual occupational exposure levels because of the imperfect information to date.

ORGANIC SOLVENTS

Organic solvents are widely used in industry for cleansing, degreasing, extraction, and as chemical intermediates. They are also used in laboratories and medical occupations and as components in paint, printing ink, and pesticides. Inhalation and absorption through the skin are the two major routes of exposure. Most solvents can pass the placental barrier; they are stored in fatty tissue and are excreted in breast milk.^{14 27 28} No environmental studies or studies on experimental animals showed a relation between exposure to solvents and gross defects of the CNS. A few studies indicated subtle behavioural and biochemical effects in laboratory animals.⁶²⁻⁶⁴ Case reports were found on children with delayed development, microcephaly, and mental retardation resembling the fetal alcohol syndrome after toluene inhalation abuse by the mother.^{65 66}

Several studies have been published on the neurobehavioural effects of occupational exposure to solvents in adults but studies on fetal or postnatal exposure are scarce and most of them fail to establish a relation with defects of the CNS. Maternal laboratory work was associated with an increased frequency of all congenital malformations in four studies.⁶⁷⁻⁷⁰ A relation between defects of the CNS and exposure to organic solvents during the first trimester of pregnancy was found in one case-referent study in Finland, with an odds ratio (OR) of 5.5.⁷¹ When the study was extended for three more years, the association vanished.⁷² A recent study also failed to show an association between exposure to low concentrations of organic solvents in industry during gestation and adverse neurodevelopmental outcomes.⁷³ A study based on occupational titles in

Denmark showed that malformations of the CNS were related to fathers exposed to solvents (OR = 2.8) and employed as painters (OR = 4.9).⁷⁴ This result is indirectly supported by the association demonstrated between painting and exposure to solvents and brain tumours in children.^{21 22}

There is little evidence that structural or functional defects of the CNS are due to parental occupational exposure. The number of studies is, however, small and the group of organic solvents represent a wide range of different agents. Bearing in mind the well known neurobehavioural effects on the mature nervous system, organic solvents may be regarded as potentially hazardous agents for the developing brain.

ANAESTHETIC GASES

The effects of anaesthetic gases such as halothane and nitrous oxide on reproductive outcome have been of great concern to anaesthesiologists, operating room personnel, surgeons, dentists, and dental assistants for many years. The studies on this topic have been reviewed before.^{11 14 55 75-77} Various effects were reported including an increased frequency of congenital malformations; defects of the CNS were not mentioned separately, but one study showed a concentration of anomalies in the brain and possibly impaired intellectual development in children.⁷⁸ This result was supported by studies on animals in which neurobehavioural changes were seen after prenatal and postnatal exposure to inhalant anaesthetics.⁷⁹⁻⁸¹ The published material does not allow conclusions to be made about the potentially harmful effects of anaesthetic gases on the CNS in the fetus and infant.

PESTICIDES

Occupational exposure to pesticides mainly occurs through inhalation and skin contact during production, formulation, and agricultural usage. Pesticides can be divided into insecticides (organophosphates, such as parathion and malathion and cyclic chlorinated pesticides such as DDT), herbicides (for example 2,4-D and 2,4,5-T), halogenated aliphatic pesticides used as fumigants (for example, methylbromide) and fungicides (mostly mercury compounds).^{14 27 28} Studies with experimental animals encompassing several insecticides suggested fetotoxic effects at high doses, and altered learning patterns and behavioural effects at concentrations below those experienced in occupational exposure.^{9 14 55 82} Prenatal exposure of rats to low concentrations of 2,4,5-T also led to long term effects on behaviour,^{83 84} and exposure to the fungicide benomyl caused cranio-cerebral malformations.^{85 86}

Studies on reproductive outcome in humans referred particularly to parental exposure to herbicides.^{87 88} Several studies suggested a possible increase in birth defects but a greater occurrence of

malformations of the CNS was not found. One case report described a child with severe mental retardation that may have been related to parental exposure to 2,4-D.⁸⁹ No clear associations were found between congenital malformations and exposure to dioxins,^{90 91} agricultural workers,^{92 93} or exposure to other pesticides.^{11 14} High concentrations of some insecticides are excreted in maternal milk but no effects were described in breast fed infants.¹⁴ Studies on laboratory animals suggested that various pesticides have teratogenic effects on the developing CNS but studies on humans were inconclusive regarding the risks of parental occupational exposure. The effects of exposure to low doses of pesticides in humans are difficult to investigate, however, because of the problem of finding pesticide free control populations.⁹

OTHER OCCUPATIONAL CHEMICALS

Among the heavy metals, occupational exposure to arsenic could be seen as possibly teratogenic to the CNS, in addition to lead, mercury, and cadmium. A few studies on animals described congenital abnormalities including exencephaly.⁵⁵ In studies on humans conducted in the vicinity of a metal smelter in Sweden,¹⁴ increased frequencies of congenital malformations were found but defects of the CNS were not specified. Arsenic may not have been the only substance responsible for these findings.

In the plastic and rubber industry, some agents, such as vinyl chloride, styrene and chloroprene, are suspected of being teratogenic, but contradictory reports about the occurrence of defects of the CNS in offspring¹⁴ do not allow us to draw conclusions.

Effects of polychlorinated biphenyls (PCBs) used in the manufacture of plastics, condensers, and batteries, have been described for both prenatal and postnatal exposure. Behavioural and developmental abnormalities after transplacental exposure were found in animals^{94 95} and children.^{96 97} The transfer of PCBs through breast milk, however, is probably more important than placental transfer.^{9 14} Breast fed children showed higher serum PCBs and some neurological impairment.^{98 99} A similar association was suggested between polybrominated biphenyls (PBBs) and developmental abilities in children.¹⁰⁰ A relation with parental occupational exposure to PCBs or PBBs has not been described, but cannot be ruled out.

RADIATION

Exposure to ionising radiation is an issue in many occupations, not only in nuclear power plants and radiography departments in hospitals, but also in the construction industry, the chemical and pharmaceutical industries, in food processing, and in research. Ionising radiation is known to cause genetic defects, but it may also exert a direct effect on the

fetus leading to microcephaly, mental retardation, and growth retardation.^{101 102} The most relevant information on prenatal exposure in humans was found in studies on the survivors of the atomic bombs in Japan.¹⁰³⁻¹⁰⁶ Obvious relations were found between the above mentioned effects and exposure to doses of over 50 rad. The most radiosensitive period seems to be between eight and 15 weeks of gestation, the period in which rapid proliferation and migration of neuroblasts occurs. If the fetus is exposed to ionising radiation before week eight or after week 20 of gestation, only minor effects on the CNS are to be expected.¹⁰¹ These results were confirmed in studies on experimental animals¹⁰⁷ in which gross malformations of the CNS¹⁰⁸⁻¹¹⁰ and behavioural effects were also found.^{111 112} The behavioural changes were associated with low doses of ionising radiation. Indications of effects of low doses on the developing CNS were reported for humans after diagnostic or therapeutic irradiation of the mother during gestation,¹¹³⁻¹¹⁵ although recent studies on exposure to environmental radiation failed to show any increase in congenital malformations.^{116 117} Postnatal exposure to ionising radiation was associated with impairments in the CNS in only one study.¹¹⁸ Reports of studies on parental occupational exposure have not been found, but the available evidence indicates that effects on the fetal CNS are possible, even at low levels of ionising radiation.

Studies of the effects of non-ionising radiation, such as microwaves and radio frequencies, on humans did not show any CNS or other congenital defects. Behavioural changes were found in rats after prenatal radiation with microwaves.¹¹⁹⁻¹²¹

Summary and conclusions

The effects of exposure to agents used occupationally on the developing CNS are summarised in the table. On the basis of the information available (number and quality of studies combined with the results) a classification is made into obvious, probable, and possible effects. "Negative" studies were not taken into account in this review. For most agents, a number of studies with experimental animals have been performed, which provide relatively straightforward evidence regarding both morphological and behavioural abnormalities. High levels of exposure were often used in these studies, however, and the reliability of extrapolation to defects in the CNS of humans is questionable. Studies on humans include epidemiological surveys, large case series, and also single case reports that mostly refer to environmental "accidents" with exposure to high doses. Few epidemiological studies were found and some showed methodological shortcomings. The case reports only gave tentative indications of defects; larger case series were more informative in this respect. The results from the different types of study, which often yielded

Summary of effects of prenatal and postnatal exposure on developing brain, classified as obvious, probable, or possible

Exposure category	Period (pre or postnatal)	Effects in experimental animal studies		Effects in environmental studies		Effects in occupational studies	
		S*	F*	S*	F*	S*	F*
Lead	pre	++	+	±	++		
	post				++		
Methylmercury	pre	++	++	++	++		
	post						
Other mercury	pre		±			±	
	post						
Cadmium	pre	+	+				
	post				±		
Organic solvents	pre		+		±	+	
	post						
Anaesthetics	pre		+			±	±
	post		+				
Pesticides	pre	++	++		±		
	post						
PCB or PBB	pre		+		+		
	post				+		
Ionising radiation	pre	++	++	++	++		
	post				±		

++ = Obvious; + = probable; ± = possible.

*S = Structural CNS defects; F = functional CNS defects.

†Including paternal exposure and brain tumours.

contradictory or inconsistent information, are weighted in the classification in the table. Studies on occupational exposure were scarce and most of them addressed congenital malformations as such, sometimes highlighting defects of the CNS. Unfortunately, a broad range of exposures or occupations were often evaluated, making these studies inconclusive.

Despite the large number of papers addressing this subject in general, there is no direct evidence that defects of the CNS in offspring are associated with parental occupational exposure during gestation. The information obtained from non-occupational studies, in which a scale of structural and functional defects of the CNS were found, is inadequate to form sound conclusions about occupational exposure, but some hypotheses may be formulated. A causal role of parental occupational exposure in the origin of defects of the CNS is:

probable, for lead, (methyl) mercury, and ionising radiation;

possible, for cadmium, organic solvents, anaesthetics and pesticides;

not to be excluded, for other chemicals and non-ionising radiation.

There are still large gaps in our knowledge on the influence of parental occupational exposure on the developing CNS that call for well designed future research. So far, most studies have referred to broad categories of exposure and effects, which usually lead to misclassification obscuring any possible evidence of an association. Future research should focus on relating specific exposures to specific effects, with the emphasis on the validity of estimation of exposure

and assessment of outcome. The available evidence at this moment stresses the urgent need to test hypotheses regarding a causal role of parental occupational exposure to the agents described above in the origin of defects of the CNS in offspring.

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- 2 Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. *N Engl J Med* 1976;294:687-90.
- 3 Weinstein L, Swartz MN. Pathogenic properties of invading micro-organisms. In: Sodeman WA Jr, Sodeman WA, eds. *Pathologic physiology: mechanisms of disease*. Philadelphia: W B Saunders, 1974:457-72.