Technical Working Group on priority diseases, subgroup neurodevelopmental disorders

Draft Baseline Report on
Neurodevelopmental disorders in the framework of the European Environment and Health Strategy
(COM(2003)338 final)
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This report reflects the opinions of the members of the Working Group and it highlights the different opinions where appropriate. It should not be considered as an official statement of the position of the European Commission.
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SUMMARY

Environment and Health Strategy
The EU Environment and Health Strategy puts an emphasis on improving understanding of the links between environmental factors and key diseases and conditions. Neurodevelopmental disorders has been identified as a priority disease, together with childhood cancers and respiratory diseases, asthma and allergies. As a first step to come to policy recommendations on indicators and priority diseases a baseline report was drawn up.

In this part of the base-line report on neurodevelopmental disorders an overview is given on present knowledge on diseases, environmental factors, exposure and strength of evidence.

Neurodevelopmental disorders
Recent data confirm for EU the apparent increase of ADHD (Attention Deficit Hyperactivity Disorder), Autism and neurobehavioural problems reported in the US. However it is hard to say whether such increase is due to broader diagnostic criteria or to environmental factors. In Europe the percentage of children with neurodevelopmental disorders is between 3-8%.

To study environmental risk factors they are divided in three groups:
1. Voluntary exposure
2. Involuntary exposure
3. Therapeutic exposure

Voluntary and therapeutic exposures are addressed not extensively, because the risks of alcohol, smoking and drugs for the developing brain are well recognized. Therapeutic exposure like anticonvulsants, steroids, diethylstilboestrol and radiation are addressed briefly. Effects in these two groups of exposure can be a warning, because mechanisms of actions can be the same as for other environmental factors.

The involuntary exposure is the most important group to address the environmental risk factors and possible effects on neurodevelopment.

The following groups or substances in the table are studied and the evidence of links with neurodevelopmental disorders in children are given in different levels:
- Level 1: Reliable studies (based on human data) linking one or more neurodevelopmental disorders to a group or a substance (high relevance).
- Level 2: Animal studies show link (reasonable). *Animal or in vitro studies that report effects on mechanisms known to be in common with humans.
- Level 3: Only assumptions, hypotheses and single case reports.
<table>
<thead>
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<td>Cadmium</td>
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<td>DES</td>
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<td>Radiation</td>
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<td>X</td>
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</tbody>
</table>

¹ Only one study [Guillette et al., 1998 for OPs; Dorner and Plagemann for OCs, 2002]
² One single publication each for humans and animals.

**Specific substances**

PCBs, dioxins, lead and mercury are proven to be neurotoxic in humans. Background levels of PCBs and dioxins in several parts of Europe in 1990-1992 had negative effects on neurodevelopment. Levels are decreasing, but still too high. The tolerable daily intake (TDI) for dioxins and dioxin-like PCBs is set to 2 picograms per kg bodyweight per day. During pregnancy the foetus is exposed to nanograms through the placenta. His daily exposure is many times more than the TDI. When the baby is growing...
prenatal and postnatal, the exposure tapers down to levels between 100 and 300 picogram per kg bodyweight per day in the breastfeeding period.

PBDEs are also presumed to be neurotoxic (proven in animal studies) and are increasing in breast milk.

The pesticides are divided in 4 groups. Neurotoxic effects in humans are described for organochlorine compounds and chlorpyrifos. And there are a lot of the animal data on neurotoxic effects. Exposure to a mixture of pesticides shows a negative influence on neurodevelopment in one study under Mexican children (neuropsychological problems) and one in Canada in relation to the spraying of trees (spina bifida and stillbirths rate). Animal studies underline the possible synergistic and also antagonistic effects of pesticides.

Solvents do not seem to pose a risk for human neurodevelopment according to current knowledge. Given the widespread exposure, however more research is needed, as for high exposures both to ethanol and toluene severe congenital syndromes have been described.

Lead is proven to be neurotoxic to humans. Recent studies to the effects of lead in humans underline that a safe (exposure) level cannot be defined. Therefore exposure should be as low as possible. It appears likely that some sub-populations may be at particular risk of lead exposure from older houses, and these should be identified and cleaned. More data on levels in Europe are necessary and are underway.

Mercury is well known to have neurodevelopmental effects, though some studies are contradictory. The current levels of tolerable intakes are already targeted for pregnant woman.

Other neurotoxicants like Cadmium, Aluminium, Manganese, Arsenic, Monosodiumglutamate, Formaldehyde are not known to cause neurodevelopmental disorders in general in the European population, but may do so in specific situations and need further research.

Gaps in knowledge.
Gaps in knowledge relate to different issues. In general they concern:
- Trends in environmental exposure;
- Trends in internal exposure;
- Data on neurodevelopmental disorders (e.g. trends);
- Effects of mixtures and cocktails;

Recommendations for monitoring and research
- Prospective study to intra-uterine growth retardation and environmental influences in different European countries to:
  1. Preconceptual situation in the mother (T4, lead, mercury, stress-score, PCBs, Dioxins, smoking, alcohol, drugs, folic acid status, toxoplasmosis titre);
2. Obstetric history (optimality score Touwen) and blood samples of the mother;
3. Placenta: levels of pollutants;
4. Baby: birth weight, length and head circumference, biomarkers of internal exposure to environmental chemicals;

- For "level 2" substances and exposures research or assess whether the results can be transferred to humans (comparison of study and actual human doses), eventually repeat animal research with doses similar to human exposures or do studies in human populations, whether the animal study results can be reproduced in humans.
- Use validated and reproducible methods only. If validated methods and instruments are lacking, there is an urgent need to develop such.
- The present incidences of CNS disorders/malformations that may be indicators of developmental neurotoxicity need to be better monitored within the EU.
- The levels of putative toxic agents in food and in breast milk also need to be monitored in a harmonized way.
- Assess trends in environmental exposures all over Europe (e.g. "Umweltsurvey" in Germany).
- Use existing large collectives (e.g. Faroes, Seychelles, Seveso) to check for incidence of neurodevelopmental disorders.
- The reasons for the different outcomes of different studies on mercury should be clarified.
- Given the contradictory results e.g. cadmium and manganese in hair and neurodevelopmental disorders internal exposures and neurodevelopmental outcomes should be studied.
- Establish trends in neurodevelopmental disease (childhood disability) using the international classification of functioning, disability and health (ICF).
1 INTRODUCTION

1.1 General introduction

The EU Environment and Health Strategy puts a particular emphasis on improving understanding of the links between environmental factors and key diseases and conditions. This document is part of the report that the Technical Working Group on Priority Diseases prepares in support of the European Commission’s SCALE initiative. It is based on Scientific evidence, focused on Children, meant to raise Awareness, improve the situation by use of Legal instruments and ensure a continual Evaluation of the progress made.

The objective of the work of the Technical Working Group on neurodevelopmental disorders has been to assess the overview on neurodevelopmental disorders in relation to environmental factors. The mandate and terms of reference of the TWG-ND are given in the Annex as well as the participants for this TWG-ND.

1.1.1 Structure of the report

This part of the baseline report on neurodevelopmental disorders is composed of three parts: voluntary, involuntary and therapeutic exposures of environmental risk factors. This is followed by background information, programmes, gaps in knowledge and recommendations. At the end of the report the conclusion stated. The references can be found at the end of this report.

The baseline report gives an overview of the existing state of knowledge and activities, and observes problems and deficits of current activities. Furthermore it gives recommendations for EU activities.

1.1.2 Resources

The TWG ND has representatives from 9 countries – covering existing EU members and acceding states and northern and southern member states, industrial organisations, citizen’s organisations, the research community, the WHO and various European Commission services.

The individuals on the TWG-ND have expertise in the fields of: occupational medicine, environmental medicine, clinical toxicology, developmental psychobiology and behavioural teratology and neonatology, pediatrics, environmental hygiene and pediatric neurology.

The organizations represented have access to work carried out for/by: the WHO, the EC (DGs ENV, SANCO, RTD, JRC and the EEA), industry, public health authorities, and international research work carried out under academic or intergovernmental programmes.
1.2 Introduction to the neurodevelopmental disorders report

Neurodevelopmental disorders are disabilities in the functioning of the brain that affect a child’s behaviour, memory or ability to learn. They include mental retardation, dyslexia, attention deficit hyperactivity disorder (ADHD), learning deficits, autism and autism-like disorders, affecting between 3-8 % of the children in USA and Europe [Weiss and Landrigan, 2000]. Recent epidemiological data seem to indicate that for at least two of these disorders (autism and ADHD) the prevalence rate has increased in the last two decades [Gurney et al., 2003; Charman, 2002]. Although such increase may reflect increased awareness of these disorders and broader diagnostic criteria, there is general concern on the possible implication of environmental factors in the etiology of neurodevelopmental disorders.

For most of neurodevelopmental disorders characterised by cognitive and behavioral deficits the neural basis and the etiology are still poorly understood [Murphy et al., 1998]. A large number of environmental factors have been implicated as causes, in addition to the genetic components of the disorders. The nervous system is in fact vulnerable during development to a wide range of environmental factors and agent. Maternal stress during pregnancy, exposure to neurotoxicants in the prenatal/postnatal phase, or poor psychosocial environment are all factors that may affect the correct development of brain functional circuitries, particularly when acting on a vulnerable genetic background [Schroeder, 2000]. Rodier et al. (1996) reported that some forms of autism might arise from toxic insult. Thalidomide and valproic acid effects during a specific time window (neurulation) are an example of critical gene-brain-environment interaction that can affect neurobehavioural development. Furthermore, the kind of damage that may occur depends upon a variety of factors, including the stage of development, the particular agent/environment factor and magnitude, route and duration of exposure. Nervous system damage may be characterised by anatomical, neurochemical, behavioural and/or cognitive deficits. In some cases behavioural and cognitive alterations may be the only marker of effect accessible and thus would be important for risk assessment.

Due to their multicausal etiology, identification of causative factors for neurodevelopmental disorders is a difficult task. One must consider the crucial role of socioeconomic variables in exacerbating or compensating for the potential adverse effects of environmental contaminants. In human studies, exposure to mixtures of chemicals or to different risk factors makes it difficult to isolate the contribution of the different chemicals/factors to the aetiology of the disease.

In addition specific tests for neurodevelopment, e.g. learning and memory, are required in the first tier of toxicology studies for the majority of chemicals [Hass, 2003]. Thus, for many potentially hazardous compounds introduced in the environment, the risk of adverse effects on the developing brain is presently unknown. Finally, though epidemiological studies carried out mainly in the US indicate a significant association between child’s neuropsychological outcome and exposure to some neurotoxicants (lead, methylmercury and PCBs), their mechanisms of toxicity are far from being fully understood.
In this report we have studied the possible exposures that might negatively influence neurodevelopment. Exposures are divided in:
1. Voluntary exposure
2. Involuntary exposure
3. Therapeutic exposure

This report gives a review of available knowledge on the environmental influences and neurodevelopmental outcome, and is intended to be a basis for decisions upon actions.
2 VOLUNTARY EXPOSURE

2.1 General

Socio-economic factors
Many factors influence brain development and maturation. Environmental chemicals act in the context of other major influences, probably the most significant of which are the child’s social interactions (home and school environment) and general physical development (influenced by breast feeding and nutritional adequacy of diet). Social context can either exacerbate or protect against early developmental risks. There are studies showing that an optimal socioeconomic environment can compensate for the effects of low-level exposure to lead, while the effects of alcohol on cognitive function are the same irrespectively on the socioeconomic context. It is likely that the positive effects of an optimal social environment will depend on the type of endpoint more affected by a specific neurotoxicant [Jacobson and Jacobson, 2002]. Such interactions can be complex, but even simple additive effects can have serious consequences, as when a drop in IQ as a result of developmental neurotoxicity occurs in a population that already has a low baseline IQ due to social disadvantage, thereby needing remedial education [Gee, 2003].

Because of these non-chemical factors, most epidemiological studies of the influence of environmental chemicals have needed to make corrections for parental education level or family income in order to prevent socio-economic factors acting as confounders [Kotimaa et al., 2003]. Whilst exposure to many chemical agents is spread relatively evenly across the population, some chemical exposures such as lead or cigarette smoking [Joossens, 1999], [Dewan et al., 2003] show a significant linkage to lower socio-economic status. This association between chemical and socio-economic influences requires a sophisticated analysis to determine the relative importance of the individual adverse factors, but only those studies, which have made such an analysis, can be considered valid.

Recognized hazards
In addition to involuntary exposures to environmental chemicals that may have an adverse effect on neurodevelopment, there may also be significant exposures that are voluntary on the part of the mother. The most notable of these are cigarette smoking and alcohol consumption. These are already widely recognised as hazards during pregnancy, and will therefore be only briefly mentioned here.

Protect the child (recommendation):
Although many women do reduce alcohol consumption and smoking during pregnancy [Waterson et al., 1990], alcohol and smoking still represent an important cause of neurodevelopmental problems, and their control must therefore remain an important element in any EC policy to protect the developing child.
2.2 Smoking

Smoking during pregnancy is clearly associated with risk of low birth weight for gestational age [Dickute et al., 2002] especially in teenage mothers [Dewan et al., 2003] and a dose-response relationship can be shown for both low birth weight and spontaneous abortion [Ernst et al., 2001]. Smoking leads both to foetal nicotine and carbon monoxide exposure, and maternal smoking during pregnancy was associated with hyperactivity in 8-year-old children even after allowance for socio-economic status and maternal alcohol use [Kotimaa et al., 2003]. The situation is less clear for environmental tobacco smoke exposure though: a survey of epidemiological studies providing no clear indication of a neurodevelopmental effect of paternal prenatal or postnatal smoking [Eskenazi and Castorina, 1999].

The prevalence of smoking amongst women generally was increasing in Portugal, Spain, Italy, Greece, Luxemburg and Austria in 1995; and in the United Kingdom the proportion of women smoking during pregnancy rose from 27% in 1992 to 32% in 1996 [Joossens, 1999] a percentage as in The Netherlands and Denmark. Across Europe, the proportion of 15-16 year olds reporting smoking within the last month ranged from 16% (Cyprus) to 67% (Greenland), with a mean of 37% [Hibell et al., 1997]. Risk communication and taxation can be effective however, and in Sweden the proportion of pregnant women who smoked fell from 31% in 1983 to 15% in 1997 [Joossens, 1999].

2.3 Alcohol

Alcohol consumption during pregnancy is strongly associated with reduced birth weight [Dickute et al., 2002] and alcohol consumption during pregnancy at a mean level of 3 drinks per day results in a marked decrease in the cognitive ability of the pre-school children [Larroque and Kaminski, 1998]. Whilst higher levels of consumption cause the severe foetal alcohol syndrome [Warren et al. 2001] lower levels can lead to more subtle neuropsychiatric effects [Streissguth and O’Mally, 2000]. Direct measures of foetal behaviour have shown effects of maternal alcohol consumption at the level of 3-6 units per week [Little et al., 2002], although it is not clear if these have long-lasting consequences.

Consumption of alcohol in the UK has been reported at 60-70% of pregnant women, with 15% drinking more than 14 units per week [Alcohol Education and Research Council, 2003]. The European Survey Project on Alcohol and Drugs found that amongst 15-16 year olds generally, 62% had consumed alcohol within the last month [Hibell et al., 1997]. This figure ranged from 36% in Macedonia to 85% in Denmark. In general in Europe in 30% of all pregnancies alcohol is consumed and about 10% are heavy drinkers who consume more than 80 grams alcohol per day [Zetterstrom, 1994]. This amount means a high risk of growth retardation and cranio-facial abnormalities and mental retardation. Detection of these heavy drinking mothers is difficult, since most deny it.
2.4 Hard drugs and cannabis

In the Netherlands about 20,000 people are addicted to hard drugs like heroin and about 200 children are born each year to drug-addicted women. In a follow-up study of 168 such children about 80% of the mothers used heroin or methadone or both and about 20% used other psychoactive drugs. There was a high percentage of premature birth between 32-36 weeks and more than twice as many babies were small for date. Length, weight and head circumference were less than normal at one year of age. They were neurologically retarded but not severely so. At the age of five neuromotor development was normal, but cognitive functioning was reduced. The children were also more active than normal. At the age of ten total IQ was significantly lower than normal, especially verbal IQ. Behavioral problems were increased and social capabilities were lower than normal [Sri Soepatmi, 1992; van Baar & de Graaf, 1994; Verdoux, 2002]. Cannabis use causes no known adverse effects in pregnancy. However there is some evidence that use in adolescence can facilitate the manifestation of schizophrenia in predisposed subjects [Smit et al., 2003].
3 INVOLUNTARY EXPOSURE

3.1 General

In order to facilitate an overview assessment of the strength of evidence, that exposure to a particular substance is correlated to neurodevelopmental disorders, a level of evidence has been assigned.

Reliable studies (based on human data) linking one or more neurodevelopmental disorders to a group or a substance prompt the assignment of level 1.

Animal- or in vitro studies that report effects on mechanisms known to be in common with humans will be assigned to level 2 with an asterisk*. Other animal or in vitro-experiments will be assigned to level 2.

Only assumptions, hypotheses and single case-reports are considered to be of level 3 evidence. And the same applies for single studies never corroborated by other ones.

The tables must not be read without the subchapters, as controversies and rationales for assigning the levels and asterisk (*) will be explained there.

The assigned levels of evidence will have consequences for our recommendations. Level 1 groups or substances will need priority and something should be done to decrease exposures or to protect the individual otherwise, and the same for level 2 asterisk. If in level 2 only animal data are available, for which it is not clear, whether they can be transferred to humans, further research should be done.

For level 3 groups or substances there are no useful data, the accusations of disturbance of neurodevelopment being only hypotheses or assumptions. In a rank of priority such substances or influences do at present not prompt further actions. Research can be considered, if resources allow.

During pregnancy congenital infections can result in brain damage. Examples are the congenital rubella syndrome, congenital toxoplasmosis, congenital lues, and congenital infection with listeria monocytogenes. And also meningitis in infancy can be related to severe brain damage. These diseases due to viruses, bacteria and parasites are not addressed in this report.
3.2 PCBs and dioxins, PBDEs, Pesticides, Solvents

Table level of evidence substance linked to neurodevelopmental disorders

<table>
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<th>Substance</th>
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<td>SEE BELOW*</td>
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<tr>
<td>Solvents</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Formaldehyde</td>
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<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Level 1: Human studies (high relevance)
Level 2: Animal studies show link (reasonable) *Animal of in vitro studies that report effects on mechanisms known to be in common with humans
Level 3: Case histories and (logical) assumptions

Table level of evidence pesticides linked to neurodevelopmental disorders

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<th>Pesticides</th>
<th>Level 1</th>
<th>Level 2</th>
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<td>X*</td>
<td>X</td>
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<td>Pyrethroids</td>
<td></td>
<td>X</td>
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</tr>
<tr>
<td>Dithiocarbamates</td>
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</tbody>
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*Only one study [Guillette et al., 1998 for OPs; Dorner and Plagemann for OCs, 2002]

3.2.1 PCBs and dioxins

Polychlorobiphenyls (PCBs) can have adverse effects in human beings as became already clear in 1930 [Koppe and Keys et al, 2001]. The UNEP Washington Declaration in 1995 acknowledged the problem and agreed the need to act on PCBs in use. Manufacturing was prohibited in the 1980s. [Koppe et al., 2001]. Longnecker compared PCB 153 levels in serum, collected around 1990, in different countries as a marker of levels [Longnecker et al, 2003]. Results are:

<table>
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<tr>
<td>England</td>
<td>78</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>100</td>
</tr>
<tr>
<td>Faroe islands</td>
<td>450</td>
</tr>
<tr>
<td>Inuits (Canada)</td>
<td>100</td>
</tr>
<tr>
<td>Massachusetts (USA)1</td>
<td>40</td>
</tr>
<tr>
<td>Massachusetts (USA)2</td>
<td>30</td>
</tr>
</tbody>
</table>

Studies in Europe and in the USA revealed negative influences on growth in general. [Patandin et al., 1999; Patandin et al, 1998; Fein et al., 2003]. Lower IQ, psychomotor
retardation and hyperactivity are described in relation to background levels [Koopman-
Esseboom et al, 1994; Jacobson et al., 1996; Walkowiak, et al., 2001]. In the Rotterdam
cohort the development at eighteen months of age, measured with the Bayley Scale, was
neither affected by PCB and dioxin exposure, nor by feeding type [Koopman-
Esseboom, 1995]. However in this same cohort, at the age of four a four-point decline in
IQ in relation to maternal PCBs was found [Patandin et al., 1999].
Influence on the sexual development of the brain in utero was found in the Dutch cohort
with both PCBs and dioxins [Vreugdenhil et al., 2002]. Recently neurophysiologic
effects of prenatal PCB exposure were described by Vreugdenhil in the Rotterdam
cohort: a prolongation of the P300 latency measured by an auditory evoked response,
known to be related to cognitive functioning [Vreugdenhil et al, 2003]. Levels of PCB
in the Dutch studies were in the range of 2.21 ng/g/plasma (PCB 118, 138, 153, 180).
In contrary in the Faroese study no effects were found of PCBs on neurodevelopment,
although levels are four times higher than in The Netherlands [Grandjean, 1997]. An
explanation can be that in this study the effects of methylmercury are overriding the
PCB-effects, according to Grandjean.

Conclusion is that levels of PCBs in combination with the dioxins have been too high in
most parts of Europe when last assessed, since at levels in the USA, only one third of
those in Europe, negative effects on neurodevelopment are already found [Darvill et al.,
2000].

Lower levels of thyroxins (T3 and T4) were found in mothers with the higher PCB-
levels (> 3 ng/g plasma) in the perinatal period [Koopman-Esseboom et al., 1994]. In
this aspect it might be interesting that lower levels of thyroxin in early pregnancy (under
the tenth percentile in this group) are related to retarded psychomotor development in
their children [Pop et al., 1999].

Dioxins
In most parts of Western Europe and the USA background levels of PCBs are always
combined with dioxins. It is not clear if the mechanism causing neurodevelopmental
disorders is a combined effect of PCBs and dioxins and neither is known if the
damaging effect is directly on the neurons and myelination or indirectly through a
disturbed thyroxin metabolism or testosterone metabolism or both. In animal studies
dioxin is facilitating the effect of Phenobarbital [Dees et al., 1982]. Combination of the
two chemicals PCBs and dioxins might be an important hazard in relation to the
chemicals alone. Dioxins can have either an agonistic or antagonistic effect depending
on the type of thyroxin receptor [Ilsen et al., 1996; Vulsma, 2000].

Few prospective studies in mother-baby pairs are done exclusively to dioxins. Only the
Amsterdam and Rotterdam cohorts are examples [Koopman-Esseboom, 1995; Pluim et
al. 1992]. A follow-up at the age of 8-12 years in the Amsterdam cohort
neurophysiologic studies revealed a prolonged latency and decreased amplitude of the
N200 component in the EEG elicited by a visual oddball stimulus, and the same for the
P300 component. This is also described in the Attention Deficit Hyperactivity Disorder
(ADHD). The increased latencies are probably related to a defective myelination. A
lower number of neurons or an unwanted spreading of the activation causes the decrease in amplitude [ten Tusscher, 2002].

In the same cohort an association with behavioural problems, more aggression, more social problems and anxious-depressed feelings are found with higher prenatal- and postnatal dioxin exposure (dioxin levels in breast milk 8.74 to 88.80 mean 34.6 ng ITEQ dioxin/kg milk fat) [ten Tusscher, 2002].

Levels of dioxins and furans decreased in the years 1988 to 1998 by 50 % in the Netherlands and were in 1998 19.7 WHOTEQ dioxin ng/kg milkfat. The same levels are measured in France. In Sweden the levels were in that year 14.7ng/kg milkfat [Zeilmaker et al., 2002]. Ninety percent of the PCB- and dioxin exposure is through animal food (in Holland 17% is due to dairy products, 18% to industrial fats and oils, 27% by animal products, 5% by eggs, 26 % by fish, and 7% by vegetable products. For dioxins the exposure is more through dairy products and less through fish) [Bakker et al., 2003]. The tolerable daily intake for dioxins and dioxin-like PCBs is now 2 picograms/ kg bodyweight / per day in Europe. For the UK population average daily intakes are 1.8 picograms TEQ per kilogram of bodyweight [SCOOP report, 2000]. As much as 36% of UK adults, and most children, may exceed the TDI in their daily diet. The TDI is too high for pregnant women. Neurotoxic effects are found in children with background levels of 30 ngr ITEQ dioxin per kilogram milkfat. During pregnancy and breast feeding the TDI is exceeded many times. The exposure in early pregnancy is in nanograms, the same as in the mother. After birth, in the breast-feeding period, the levels are tapering down, when the baby is growing, until levels of 100 – 300 picogram/day. In conclusion dioxins are dangerous neurotoxicants, because relatively low levels, like the background level in the Netherlands of 29ng/kg milkfat (range 8.7-88.8) are already toxic for the brain.

3.2.2 PBDEs

Polybrominated diphenyl ethers (PBDEs) are used as flame retardant additives in household goods, computers and textiles. From the commercial product the tetrabromodiphenyl ether (PBDE-47) is the congener found in environmental and human samples, followed by the penta- and hexabromodiphenyl. This flame retardant now in use since 20 years is found in breast milk in increasing amounts. In a study in Sweden the median PBDE fresh weight concentrations in maternal and cord blood plasma and in breast milk are respectively 24, 4.3 and 75 pg/g wet weight. Still 60 times lower than the PCB-levels, but increasing [Guvenius et al, 2003]. In California and Indiana 3-10 times higher levels are detected as in Sweden. The exposure is most likely through inhalation of household and office goods treated with PBDEs. A high correlation is found between PBDEs in maternal plasma and in fetal plasma. The danger of this flame retardant is considered to be a possible effect on thyroxin metabolism. No relation is found in the Indiana study in 9 mother-baby pairs with either T4 or T3 levels. Unfortunately TSH (thyroid stimulating hormone) was not
measured and the numbers are small [Mazdai et al, 2003]. So far no adverse effects in human children are described in relation to current background levels. But in vitro studies reveal a binding of p-Hydroxy-Bromo-Diphenyl-Ethers to a human thyroxin receptor [Marsh et al., 1998]. In animals PBDEs can cause delayed onset of puberty, decreased sperm counts, hearing impairment, hearing loss and disruption of the thyroid hormone metabolism at levels 10 to 20 times higher than doses found in humans. There is recent evidence that perinatal exposure to PBDE 99 (0.6, 6 and 30 mg/kg/day) induces hyperactivity in mice [Branchi et al., 2002].

3.2.3 Pesticides

We refer to the 2001 Report of European Commission on “Monitoring of pesticide residues in products of plant origin in the EU, Norway, Iceland and Liechtenstein”, that assessed the pesticide residues in fruit, vegetables and cereal products. EU monitoring data indicate that levels of pesticides in food have remained stable over the last 5 years. In line with this report, the four classes of pesticides more frequently found in food will be reviewed, namely organophosphorous pesticides, organochlorine pesticides, pyrethroids and dithiocarbamates.

Organophosphorous pesticides (OP’s)

OPs are widely used as general-purpose insecticides and agricultural and horticultural pesticides. OP’s have diverse effects on the peripheral and central nervous system due to their ability to inhibit acetylcholinesterase (AChE) and neurotoxic esterase (NTE). Inhibition of AChE produces the signs seen in mammals following acute poisoning. These include excessive urination, lachrymation, diarrhoea, muscular twitching, weakness and convulsions with death usually caused by respiratory paralysis. Inhibition of the membrane-bound protein NTE can result, after a single dose, in a delayed polyneuropathy for some neurotoxic OP’s only.

Following a single dose of a neurotoxic OP there is rapid inhibition of NTE. The percentage inhibition and, thereby the degree of phosphorylation of NTE is highly correlated with the initiation of OP delayed neuropathy (not all OP’s that inhibit NTE cause neuropathy, but all those that cause neuropathy inhibit NTE).

Low-level chronic exposure of infant and children to OP may occur by diet and/or by contact with indoor and outdoor polluted environment. In particular it has been suggested that in infants with high mouthing behaviour, exposures can exceed five times the Not Observed Effect Level (NOEL) after a standard home application of chlorpyrifos (CPF), due to persistent accumulation of CPF on residential surfaces and toys [Gurunathan et al., 1998; Lu and Fenske, 1998; Fenske et al., 2000]. These data prompted the U.S. Environmental Protection Agency to revise their risk assessment for CPF [EPA, 2000].

Several European and US studies have provided an indication of internal exposure levels to OPs. Many studies have looked at dialkylphosphate metabolites in urine samples, which are specific to OPs as a class [Heudorf and Angerer, 2001; Heudorf et al., 2003; Aprea et al., 2000; Loewenherz et al., 1997; Lu et al., 2001; Adgate et al.,
2001; Whyatt and Barr, 2001; Fenske et al., 2002). Overall, these data show that infants and children can be exposed to levels of OPs higher than those of adults in the general population. In the German study, they may exceed the acceptable daily intake values, which range from 4 µg/kg up to 20µg/kg/body weight [Heudorf et al., 2003]. However, it is not clear, whether the urine excretion is due to uptake of active substances or of inactive metabolites present in food, which are excreted as such. Epidemiological studies are on the way in the US to analyse the possible association between exposure to OPs and adverse neuropsychological outcome in exposed children. So far, there is only one study carried out in Mexico showing that children exposed to supposedly subtoxic concentrations of pesticide mixtures have significant neurobehavioural deficits as compared to children in the same community who do not have pesticide exposures [Guillette et al., 1998], which is discussed below.

Epidemiological studies did not show reproductive or developmental adverse health effects for low-doses exposure to OPs in humans [Savitz et al., 1997; Garcia et al., 1998; Mc Connell et al., 1999; Arbuckle et al., 2001], though there is animal data in the literature showing the neurotoxic effects of OP pesticides on the fetus, neonates and adult animals [IEH, 2002]. Among OPs, CPF is the most extensively studied. Developing rodents are markedly more sensitive to the lethal effects of high doses of methylparathion and CPF [Pope et al., 1991], while lesser or no age-related differences are apparent when considering non-lethal endpoints (such as in vivo AChE inhibition) and repeated lower level exposures [Maurissen et al., 2000; Zheng et al., 2000].

Both in vivo and in vitro studies have shown that CPF at doses (1-5 mg/kg) that do not produce overt systemic toxicity and that causes only minor (20%) inhibition of AChE exerts disruptive effects on neural cell development. Repeated CPF administration during the neonatal phase affects DNA synthesis, gene transcription, cell differentiation and synaptogenesis [Dam et al., 1998; Crumpton et al., 2000; Roy et al., 1998; Dam et al., 1999; Lassiter et al., 2002]. Delayed neurotoxic effects have been reported, indicating altered noradrenergic and dopaminergic function at adulthood in neonatally treated rats [Slotkin et al. 2002]. Recent data by Qiao et al. [2003] indicated a wide window of vulnerability of the developing brain to CPF, extending from prenatal through postnatal periods. Prenatal exposure targets are preferentially neural cells, whereas postnatal exposure affects gliogenesis and glial cell differentiation [Garcia et al., 2002]. Behavioural effects of neonatal CPF exposure at the same range of doses reported above include delay in reflex development and in locomotor activity in immature rats [Carr et al., 2001; Dam et al., 2000], learning deficits at adulthood [Jett et al., 2001] and altered social behaviour in juvenile mice [Ricceri et al., 2003]. Two rat studies showed no learning deficits following perinatal CPF exposure [Maurissen 2000a] and no cognitive effects when CPF was repeatedly administered in the adult animals [Maurissen, 2000b]. A further study showed no decrease of brain or red blood cell AChE in pups, while in the rat dams significant inhibitions were found at 1 mg/kg/day CPF from gestation day 6 to postnatal day 10 [Mattson et al., 2000]. Animal studies indicate that neural systems further from the cholinergic one might be affected by low-level developmental exposure to CPF and possibly other OPs. In this respect, some authors have suggested that AChE inhibition may be inadequate as the only parameter to predict vulnerability to OPs during brain development [Dam et al.,
1999; IEH, 2002]. Still, AChE inhibition remains the most sensitive macromolecular target of OP exposure [Monnet-Tschudi, 2000].

**Organochlorine pesticides (OC’s)**

OCs are extremely persistent compounds and they accumulate in the adipose tissue. The use of some has been banned (as for DDT) or restricted (heptachlor) in US and EU countries, but other OC’s (lindane, dieldrin, methoxychlor and endosulfan) are currently in use for agricultural and medical purpose. Some organochlorines have been targeted for global elimination under the recently signed Stockholm Convention on Persistent Organic Pollutants (POPs). Significant residues of OCs, including DDT, are found in vegetables, seafood, and dairy products [US Food and Drug Administration, Total diet study, 2000]. Furthermore, as a persisting environmental contaminant, DDT exposure may also co-vary with PCBs and other agents.

Acute actions of lindane and heptachlor at perilethal doses include excitation, hyperstimulation, and convulsions [Fendick et al., 1990]. OCs alter GABAergic neurotransmission in the brain, acting as antagonists in the chloride channel within the GABAa receptor [Abalis et al., 1986]. They appear to affect other neurotransmitter systems, such as noradrenaline, serotonin and dopamine.

Neonates can be exposed to OCs by breast milk, infant and children by diet. 43 of 113 samples (38%) of fat from children living in farm areas in southeastern Spain were positive for one or more organochlorine insecticides [Olea et al., 1999]. Human breast milk in Lower Saxony (Germany) contains organochlorine residues but all but 2/159 cases below the tolerable concentration [Raum et al., 1998] Organochlorines were found in neonates’ adipose tissue before the first uptake of food in Germany, indicating in utero exposure to these compounds [Teufel et al., 1990].

Organochlorines have clear adverse developmental effects in animal studies, but effects in humans have not been investigated. There is one study from Hawaii in which residents were exposed to high levels of heptachlor epoxide (up to 1.2 µg/g fat) in the milk supply in 1980-1982. No statistically significant increase in birth defects was noted, but delayed adverse effects were not monitored [Baker et al., 1991]. Moser et al. [2001] exposed rats perinatally to heptachlor, at doses (0.03 mg/kg/day) that reproduced in the rat dam milk the human milk values found in Hawaii in 1981. Rat offspring showed neurochemical and persistent behavioural changes, including delay in reflex development in males, altered GABAergic transmission, slower acquisition of a spatial task and impaired recall if treated until postnatal day 42, not if treated until day 21, whereas passive avoidance learning was unaltered.

Prenatal exposure to dieldrin (1 mg/kg) induced persistent behavioral alterations at adulthood in the offspring, with respect to locomotor activity and exploratory behaviour [Castro et al., 1992], and perinatal exposure to endrin (1.5 mg/kg/day) and chlordane (0.1, 0.5 and 5 µg/kg/day from gestation day 4 to postnatal day 80) causes neurobehavioural alterations [Cassidy et al., 1994; Gray et al., 1981]. Cassidy et al. suggested that low-level prolonged exposure to chlordane masculinized sexually dimorphic functions and behaviors by mimicking sex steroids and/or changing their levels. At this doses females had improved spatial abilities, however. A significant
positive correlation was observed between total DDT contents in human milk in 1984/85 and the percentages of backward school children in 1994/95 in Federal States of Germany [Dorner and Plagemann, 2002]. As for delayed effects, evidence suggest that exposure to OCs might have a role in the etiopathogenesis of Parkinson’s disease [Oertel et al., 1996; Semchuck et al., 1993].

**Pyrethroids (PyrS)**

PyrS are synthetic insecticides derived structurally from the natural pyrethrin, largely used in agricultural, veterinary and household pest control. PyrS are neurotoxic and have a direct excitatory effect on central nervous system. Type I pyrethroids produce reflex hyperexcitability and fine tremor. Type II pyrethroids produce salivation, hyperexcitability, choreoathetosis, and seizures (acute effects for a dose range 10-200 mg/kg). Acute intoxication by ingestion at peri-lethal dose levels produces EEG abnormalities in the CNS and PNS as well as cardiovascular effects [Soderlund et al., 2002]. PyrS act on voltage-sensitive sodium channels in neurons thus modifying neuronal excitability and neurotransmitter release at synapses [Soderlund et al., 2002]. Low-level chronic exposure of infant and children to PyrS may occur mainly by diet, by contact with indoor environment and by inhalation after domestic application. Two German studies have looked at metabolites of PyrS in urine samples from children and adolescents [Heudorf et al., 2003; Heudorf and Angerer, 2001], finding that levels were lower than the corresponding ADI (10 µg/kg up to 50 µg/kg body weight for the different PyrS).

Developmental neurotoxicity of PyrS has been assessed only in animal models. The studies from Eriksson’s group reported immediate and delayed effects on muscarinic cholinergic receptors in the mouse neocortex after neonatal oral pyrethroid exposure at a dose of 0.7 mg/kg daily for 7 days [Eriksson and Nordberg, 1990; Eriksson and Fredriksson, 1991; Ahlbom et al., 1994]. Behavioural effects resulted mainly in hyperactivity and impaired habituation [Eriksson and Nordberg, 1990]. Other authors could not replicate these findings [Tsuji et al., 2001]. Neonatal exposure to DDT increases neurochemical and behavioural sensitivity to PyrS in adult mice [Johansson et al., 1995]. An effect of permethrin at a single dose of 3mg/kg on nigrostriatal dopaminergic pathways has also been observed in adult animals [Pittman, et al., 2003]. As a whole, the relevance of adverse effects of pyrethroid in animals to human studies is at present unclear.

**Dithiocarbamates**

Dithiocarbamates are largely used in agriculture mainly as fungicides. Dithiocarbamates may decompose into a number of compounds, such as imidazole and ethylenthiourea that can be toxicologically important. Muscle twitch and paralysis (movement disorders) are the prevailing symptoms in chronically exposed animals and humans. The neurotoxic action of dithiocarbamates may be related to their metal-chelating properties [Miller, 1982]. Interference with cholinergic neurotransmission has been recently postulated [Marinovich et al., 2002]. In vitro studies reported altered transport of the excitatory neurotransmitter glutamate in rat cortical vesicles with Ki of 0.27 to > 1000 µM [Vaccari et al., 1999].
The source of human exposure probably is mainly the diet. Measures of internal exposure exists only from occupational exposure.

Reproductive effects in rats consist in somatic and skeletal malformations in the offspring upon exposure of pregnant rats to very high doses. Weak neurotoxic effects have been reported only in adult animals [Konno, 2003], while demyelination was observed in newborn mouse cerebellum in vitro [Kim and Rizzuto, 1975]. In rats, high levels of dithiocarbamates (500-1500 mg/kg) produce an increase in thyroid weight and in thyroid-stimulating hormone [Kackar et al., 1997]. Dithiocarbamates have been reported to cause a redistribution of heavy metals, e.g., lead and cadmium, in the brain [Oskarsson, 1984].

3.2.4 Solvents

Alcohol (ethanol) also is a solvent, and there are numerous reports on neurodevelopmental effects of alcohol. It outweighs by far any evidence for effects of other solvent [see above].

In humans certain solvents, mainly toluene, can cause a „fetal toluene syndrome“, which resembles very closely the fetal alcohol syndrome with malformations and developmental disorders [Toutant, 1979; Hersh, 1985; Hersh, 1989; Pearson, 1994; Jones, 1998; Scheeres, 2002; Costa, 2002]. However, it is caused only by abuse of toluene as a sniffing drug.

Literature on other solvents in humans is contradictory. No effects of relatively low maternal solvent exposure during pregnancy were seen [Eskenazi, 1988]. In children of mothers exposed to organic solvents during pregnancy at age 3-7 years some tests showed a poorer outcome in selective aspects of cognitive and neuromotor functioning [Till, 2001]. A shortcoming of the studies is, that exposures were assessed without actual measurements.

Animal experiments (rats) are scarce and available only for single solvents. No significant effects of trichloromethan (by gavages at 31.3 mg/kg/day during the whole reproduction period) could be seen [Burkhalter 1979]. For perchloroethylen inhalation (900 ppm) effects were seen, if the mothers were treated during days 7-13 of gestation but if treated on days 14-20 the pups performed better. A similar test at the permissible occupational exposure limit (100 ppm) showed no significant difference between treated and control animals [Nelson 1980]. For ethoxyethanol inhalation (100 ppm days 7-13 as well as 14 -20) effects were seen [Nelson 1981]. 2-Methoxyethanol inhalation at the occupational exposure limit (25 ppm) resulted only in significant differences in avoidance conditioning, if the mothers had been treated during day 7-13 of gestation [Nelson 1984] and later only high doses induced effects in one single test, whereas all other were normal [Nelson 1989].

An overview of similar experiments with 13 industrial alcohols revealed sporadic behavioral and neurochemical deviations, but no consistent pattern for any of the alcohols [Nelson 1990]. For polyoxyethylene (10) nonylphenyl ether (NP-10), a surfactant and solvent (2 and 20 mg/kg/day by injection during gestation and lactation), no neurodevelopmental effects could be seen [Aso, 1999].
Taken together there are but few indications of neurodevelopmental effects of the tested solvents in animals. A possible mechanism for the minute effects seen would be a neurochemical alteration in brain [Nelson, 1980; Nelson, 1981; Nelson, 1984].

Exposure data for the population can be derived from environmental surveys as done in Germany (http://www.umweltbundesamt.de/survey/). Sources of solvents are - as in the studies cited - occupational exposures. In much lesser amounts environmental exposures result from e.g. exposures to fuels, paints, some disinfectants, glues. Indoor renovations can result in short-term exposures to volatile organic substances (VOC), to which many solvents belong.

3.2.5 Formaldehyde

Formaldehyde is a neurotoxic substance, which is used as glue for wooden panels for furniture. In the textile industry Formaldehyde is used in the production of fire-resistant tissue. Impairments of attention and memory have been associated with formaldehyde exposure [Lezak, 1995]. But this is controversial [Cripe and Dodrill, 1988]. Because it is so widely used in buildings and furnishings material and in household products, formaldehyde in vapour or derivative form is often present in home environments [Schenker et al., 1982]. Laboratory animals exposed steadily for three months to somewhat higher than normal levels of formaldehyde incurred brain damage particularly involving the parietal cortex [Fel'dman and Bonashevskaya, 1971]. Both acutely and chronically, persons exposed to formaldehyde have complaints implicating the central nervous system, such as headache, dizziness, irritability, memory problems, and sleep disturbances [Report on the Consensus Workshop on Formaldehyde, 1984; Olsen et al., 1982; both in Lezak, 1995]. The mechanism of the neurotoxicity of formaldehyde has not yet been identified. However formaldehyde cross-links proteins, DNA and unsaturated fatty acids. This high affinity for these chemicals suggests a rapid interaction with cells after inhalation or ingestion. This suggests that low levels of formaldehyde should be able to reach the nervous system.
3.3 Metals and food additives

### Table level of evidence substance linked to neurodevelopmental disorders

<table>
<thead>
<tr>
<th>Substance</th>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
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<tr>
<td>Mercury (Hg)</td>
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<tr>
<td>Manganese</td>
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<td>Aluminium</td>
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<td>Cadmium</td>
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<tr>
<td>Arsenic</td>
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<td>X</td>
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<tr>
<td>Food additives (monosodiumglutamate)</td>
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<td>X</td>
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</table>

- **Level 1**: Human studies (high relevance)
- **Level 2**: Animal studies show link (reasonable)
- **Level 3**: Case histories and (logical) assumptions
- *(one single publication each for humans and animals)*

#### 3.3.1 Lead

The neurotoxicity of lead exposure through the mother and in infancy and childhood is since long known as it is the negative impact of lead on children’s IQ. Recently studies on the effects of lead in humans underlines that there cannot be defined a safe level in children. Even lower than 3 µg/dl effects can be expected [Canfield et al., 2003]. Lead levels in mothers are also very important during gestational age. Lead mimicks Calcium and can disturb many important basic biochemical processes for instance in mitochondria leading to apoptosis of the cell. A direct interaction with glutamatergic transmission has been reported, as well as interferences with both cholinergic and catecholaminergic functions.

In adults effects of lead on the brain are found in the endothelium of the blood brain barrier, in astrocytes and oligodendrocytes, and the prefrontal cortex is damaged by lead. In monkeys following moderate exposure (steady-state PbB 11-13 µg/dl) unusual behavioral pattern of response is observed [Lidsky and Schneider, 2003]. In lead exposed children increased distractibility, inability to inhibit inappropriate behavioral response and perseveration in behaviour, that is no longer appropriate, is found. These signs are the same as found in ADHD. The effect on IQ is dose related and significant [Lidsky and Schneider, 2003]. In girls blood lead concentrations of 3 microgram/dl are correlated with delayed puberty and growth [Selevan et al., 2003].
**Behaviour**

Needleman draws the attention to behavioural abnormalities like antisocial and delinquent behaviour caused by lead toxicity [Needleman et al., 1996], though without reported measured bone lead levels. Later publications showed a bone lead level of 11 ppm in delinquents compared to 1.5 ppm in controls [Needleman et al., 2002]. Also neuropsychological studies are showing a decreased auditory sensitivity in children and decreased visuomotor performance in preschool children. Further on increased latencies of brain stem evoked responses in P300 component are described [Finkelstein et al., 1998].

In Europe levels went down since 1970 after the lowering of lead in fuel. Levels in different countries of Europe were between 5-60 µg/dl in 1984-1989 [Winneke et al., 1990]. But in France the levels in certain parts of the population living in old housing painted with lead-containing paint like in the city of Lyon the levels are still high and not much influenced by the lowering of lead in fuel [Huel et al., 2002]. A further source of lead is water piping with lead pipes.

A review is written by Philip Grandjean on lead as a neurotoxicant in a combined report of WHO and EEA [Grandjean & White, 2002]. A study by Perrone et al. [1999] found high lead concentrations in children and adolescents living in urban areas in the south of Italy (more than 10 µg/dl). In children living in the neighbourhood of a ceramic workshop exposure can be were about 10 µg/dl [Abbriti et al., 1992]. Lead can be measured in blood, hair and dentine; in general levels in dentine correlate more with neuropsychological scores.

Data on levels in Europe are scarce, though e.g. the last ‘Umweltsurvey’ in Germany (1998) reported a mean of 3µg/dl blood in the population, and a survey in children is underway in Germany. In Paris a new study will start [personal communication Georges Salines, Nat. Institute for Public Health Surveillance (Institut de Veille Sanitaire Paris)].

### 3.3.2 Mercury

There are recent reports on mercury [COT, 2003; EU, 2001; UNEP, 2002; WHO, 2003].

The central nervous system is the most sensitive target for elemental mercury. Effects on behaviour and learning at concentrations of 0.05 to 1.8 mg/m³ during gestation were seen in animal experiments [WHO, 2003], but exposure is low, as recent ongoing studies like the EMECAP project show [L. Barregaard, personal communication]. Dental amalgam is an important source for elemental mercury. The gastrointestinal absorption is low (possibly below 0.01%). Inhalation of vapours can be dangerous [EU, 2001; UNEP, 2002].

For inorganic mercury compounds there are no publications on neurodevelopmental effects [WHO, 2003].

The main concern is methylmercury from fish, to which elemental and inorganic mercury are transformed by microorganisms in the environment. It passes both the placenta and the blood-brain barrier, thus exposures during pregnancy are of high
concern. Methylmercury in pregnant women’s diet appears to have subtle, persistent effects on the children’s mental development [NRC, 2000 in UNEP 2002]. Studies in the Faroe Islands with maternal methylmercury uptake from whale meat in concentrations of up to 2 mg/kg [US EPA, 2001b in UNEP 2002], showed neuropsychological deficits at 7 years [Grandjean, 1977 in UNEP 2002]. Attention, memory, and language were affected most. There was a parallel exposure to PCBs, but this did not change the results for methylmercury much [Grandjean, 2001 in UNEP 2002].

A study on the Seychelles Islands (exposure to fish with mean methylmercury levels of 0.2-0.3 mg/kg) did not show effects on developmental tests [Axtell, 2000; Crump, 2000; Davidson, 1998; Davidson, 2001; Myers, 2000; Palumbo et al., 2000, all in UNEP 2002].

A New Zealand study showed effects on mental development correlated to maternal hair-mercury of about 9 µg/g [US EPA, 2001b in UNEP 2002]. The studies from the Faroes and the Seychelles are contradictory. Though both studies are considered to be scientifically valid and without flaws, conclusions were based only on the Faroes study [US EPA, 2001 in EU 2001].

Recent experiments from a single working group with the application of methylmercury (0.375 mg/kg/day) and mercury chloride (0.8 mg/kg/day) during pregnancy and lactation resulted in an increased number and easier kindling of (epileptic) seizures in young [Szasz, 1999; Szasz, 2002]. The study design involved first setting a surgical damage to the brain and then applying a substance causing seizures. It is unclear, whether this model can be extrapolated to humans, for which there are no such results or epidemiological studies known.

The mechanism of mercury toxicity is not clear. Degeneration due to nerve fiber damage or neuronal cell death [Nagashima, 1997] is discussed, as is a pathway involving generation of free radicals ultimately leading to cell death [EU, 2001] and inhibition of protein synthesis, disturbance of neurotransmitter function, oxidative stress and excitotoxicity [Sanfeliu, 2003]. Interestingly gender differences in methylmercury toxicity have been described [Rossi, 1997], and a further possible mechanism seems to be involvement of the dopaminergic system [Daré, 2003]. In addition oxidative stress could play a role, as in vitro experiments have shown [Daré, 2000]. Doses used in these studies were 0.5 mg/kgb.w./day, but additionally apomorphine or d-amphetamine were given for testing, so that the results do not refer to methylmercury alone.

It is possible to estimate safe mercury doses in human diet [UNEP, 2002] ranging from 0.3 to 1 ppm (mg/kg) in fish. In an ongoing multicenter study in Italy, consumption of large fish (tuna) had a negative effect, whereas consumption of small fish less contaminated with mercury had positive effects, probably due to other contents of these fish [Carta, 2003; Lucchini, 2003]. Indications of similar positive results were seen in other studies [Daniels, 2002].

A safe daily intake was estimated to be 0.1µg/kg body weight per day [UNEP 2002]. This value is regarded as appropriate for Europe, too. It is mainly relevant for fertile women, and includes an uncertainty factor [EU, 2001].
The PTWI\(^1\) was set recently by the JECFA\(^2\) at 1.6 µg/kg/week taking the Faroes and Seychelles studies into account and targeting it for pregnant women and the foetus. The value would correspond to a daily intake of 0.23µg/kg body weight.

WHO estimated the daily intake of methylmercury in the general population to be 2.4 µg/d [WHO 1990], which for a 60 kg woman would correlate to 0.04µg/kg body weight per day. However, in Europe population groups can have a higher intake [EU, 2001]. Exact daily intake values are well known for many foods and countries and have been related in recent publications [UNEP, 2002].

Limited evidence suggests that diet and nutrition may potentially reduce or enhance the toxicity of mercury this influencing study outcomes [UNEP, 2002]. In vitro experiments have shown that glutathion, cysteine, selenite and vitamin E protected CNS cells against methylmercury toxicity [Sanfeliu, 2001].

### 3.3.3 Manganese

Manganese (Mn) is an essential element, but may become neurotoxic at high levels. Recent reports of high Mn levels in hair of children with neurodevelopmental deficits suggest that these deficits could be due to Mn-induced neurotoxic effects on brain dopamine systems, although the mechanism is not well understood. In contrast in autistic children significantly lower levels of Mn in hair were found [Wecker et al., 1985]. Infant formulas contain considerably higher concentrations of Mn than human milk. Thus, formula-fed infants are exposed to high levels of Mn at a time when Mn homeostasis is incompletely developed.

Little is known about the potential health effects that may result from long-term exposure to manganese at relatively low concentrations. With the prospect of more intensive use of MMT (methylcyclopentadienyl manganese tricarbonyl), a manganese-containing anti-knock agent, which improves octane rating in unleaded gasoline [Hinderer, 1979] and leads to increase manganese emissions in the atmosphere, the metal has attracted environmental attention [Normandin and Hazell, 2002].

Observations suggest that dietary exposure to high levels of Mn during infancy can be neurotoxic to rat pups and result in developmental deficits [Tran et al., 2002].

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\(^1\) Provisional tolerable weekly intake  
\(^2\) Joint Expert Committee on Food Additives and Contaminants of the WHO and the Food and Agriculture Administration
3.3.4 Aluminium

The data situation for aluminium is controversial.

Injections to pregnant rabbits resulted in improved learning of the young at low doses (25 µM/kg and 100 µM/Kg Al lactate) and decreased learning at high doses (400 µM/kg), which were fatal in 58% [Yokel, 1985]. At 400 mg/kg aluminium (Al) effects on learning and locomotion were found [Muller, 1990]. Very few significant effects on learning were seen with a single dose (1800 mg/kg aluminium chloride) to pregnant rats, with 900 mg/kg there were no significant effects [Misawa, 1993]. Effects on learning were seen with injections (200 mg/kg/day Al sulphate or 2.5, 5, 10 and 10 mg/kg/day Al lactate) [Santucci, 1994; Gonda, 1996; Gonda, 1997; Alleva, 1998]. With application by drinking water (750, 1000, or 1250 mg/l Al sulphate) to mice from different genetic strains, learning effects were mice strain dependant [Alleva, 1998]. An aluminium rich diet during gestation and to day 35 (100, 500, and 1000 µg/g) resulted in effects on learning and in addition on motor testing only in the higher dose groups [Golub, 2001]. Effects on motor development were seen at doses of 500 and 1000 µg/g diet, though the results were not consistent [Donald, 1989].

In 2-day-old rabbits an injected dose of 3µM (Al tartrate) killed most animals, at 2 µM no difference in learning and memory was seen [Petit, 1985]. The postpartal application of 100mg/kg/d aluminium in drinking water to male rats did not results in significant effects on behaviour [Colomina, 2002].

A suggested mechanism is a decrease in the number of synapses in the hippocampus [Colomina, 2002].

No data for the aluminium uptake in children could be found. The uptake in adults is up to 14 mg/day (or 0.2 mg/kg/day at 70 kg body weight) [WHO, 1994]. The suggested ADI (acceptable daily intake) is 1 mg/kg/day [Wang, 1994]. These levels are far below the doses used in the animal studies.

Taken together some data show an effect of aluminium on neurodevelopment in rodents, however, very high and sometimes lethal doses were used [Petit, 1985; Yokel 1985], and the pathway of application with single high-dose injection is irrelevant for humans. Lower doses of aluminium had no significant effects, nor had postpartal exposures. Even positive effects were seen at low doses. Human studies could not be located. Thus evidence for neurodevelopmental effects of aluminium in low doses in humans is currently lacking.

3.3.5 Cadmium

Lead and cadmium (Cd) co-vary closely in human tissue [Winneke, 1983]. There are elder studies on hair analyses and behavioral aspects in children old enough for IQ testing. No conclusion is possible regarding neurodevelopment. An overview of 51 studies on hair analyses reports a finding of elevated cadmium in gifted children, though
most studies correlated elevated cadmium to behavioral disorders [Rimland, 1983], but there are also studies in autistic children showing decreased cadmium [Shearer, 1982; Wecker, 1983].

Animal studies in rats are contradictory. Injections (0.15 mg cadmium/kg/day during gestation and lactation) resulted in significantly slower learning in the young [Winneke, 1983], or (0.2, 0.62 and 2.0 mg/kg Cd chloride during gestation days 7-15) in significant alteration of all behavioural aspects only for medium and high doses, without a significant effect for the low-dose [Lehotzky, 1990]. This was partly confirmed after daily injection (0.075 and 0.225 mg/kg Cd chloride during gestation), but with differences between genetic lines [Pelletier, 1991].

Cadmium in drinking water (17.2µg/ml 90 days before and during gestation) caused reduced activity, but no effects on CNS function [Hastings 1978], or (4.2 and 8.4 µg/ml during gestation) hyperactivity in newborns, lower activity at 60 days, and developmental delay [Ali, 1986]. The combination in drinking water of 10mg/l cadmium acetate and 300mg/l lead acetate during gestation and lactation provoked an increased anxiety-like behavior in the offspring, but causes cannot be discriminated [Leret, 2003].

Inhalation (0.02 and 0.16mg/m³ Cd oxide) prior to and during gestation showed a dose-dependent reduction of behavioural performance [Baranski, 1983]. Single dose injection of 1, 2, 3 or 4mg/kg on infant days 5 or 6 resulted in high mortality in the higher regimens, whereas only males showed hyperactivity after 1 and 2mg/kg [Holloway, 1988]. However, such applications bear no relevance for human exposure.

Taken together animal experiments show effects for Cd by drinking water, inhalation and injection with contradictions for activity, but for higher doses only – a repeated injected dose of 0.2 mg/kg did not cause significant effects.

Suggested mechanisms involve dopaminergic and serotoninergic alterations in the hippocampus [Leret, 2003], or antimetabolic effects interfering with the absorption of zinc, iron, copper, and calcium, and decreasing the concentration of copper and iron transporting proteins in blood [Capel, 1981; Holloway, 1988; Pelletier, 1991; Liu, 1995].

Food is the main source of cadmium for non-smokers. Smoking leads to a significant additional cadmium uptake. The daily uptake of cadmium from food is estimated to be at about 10-25 µg/kg in the adult general population in Europe, but at up to 400 µg/kg in heavily contaminated areas [WHO, 1992], far lower than the study doses.

3.3.6 Arsenic

For arsenic and neurodevelopment disorders, there is one single publication finding arsenic in urine elevated in 6/10 autism spectrum children compared to healthy controls [Lonsdale 2002]. In rats effects on locomotor activity and alteration in spatial learning
have been seen at 36.7mg/l, as (as sodium arsenite) in drinking water either from gestation day 15 or lactation day 1 for 4 months [Rodriguez, 2002]. However, even in heavily contaminated areas like Bangladesh, the maximum concentrations in drinking water are 1.66mg/l [Tareq, 2003]. In Germany the limit value for drinking water is 10µg/l. In this respect, no risk seems to be present in Europe.

3.3.7 Monosodiumglutamate

For one single food additive there are elder reports from one author, which indicate the possibility of behavioural changes (learning deficits) in rats after application of monosodiumglutamate via drinking water to rats during the 2nd and 3rd third of pregnancy [Frieder, 1984]. However, the doses were extremely high at 10g/kg b.w.

Mechanisms suggested are cholinergic and adrenergic changes in certain brain areas, albeit with sex differences [Frieder, 1987].

A further publication described effects on neurotransmitters, neuropeptides, and binding sides in certain brain regions, but at very high levels of 4g/kg body weight in rats [Meister, 1989]. Even for the authors the relevance for human exposures is not great [S.Ceccatelli, personal communication].

Surprisingly, especially in regard of the wide spread use of MSG in food, no further publications could be found, and the Frieder results have never been corroborated by other authors. Thus the evidence is very low and the results have to be regarded with caution.

3.4 Stress, noise, not considered substances

| Table level of evidence substance linked to neurodevelopmental disorders |
|-----------------------------|-----------------|------------------|
|                             | Level 1 | Level 2 | Level 3 |
| Stress                      | X       |         |        |
| Noise                       | X       |         |        |
| Not considered substances   |         |         | X       |

Level 1: Human studies (high relevance)

Level 2: Animal studies show link (reasonable) *Animal of in vitro studies that report effects on mechanisms known to be in common with humans

Level 3: Case histories and (logical) assumptions

3.4.1 Stress

Stressful experiences during pregnancy can contribute to poor pregnancy outcome. Early pregnancy (the first trimester) is the most vulnerable period. Maternal stress can be divided in psychosocial stress, strenuous physical activity, and fasting or food deprivation and all three are independent risk factors.
A physiological role is probably played by the production of the neuropeptide corticotrophin-releasing hormone (CRH) under the influence of mental stress. This hormone activates the pituitary gland to produce ACTH and this hormone elevates the cortisol level. Depending on the chronicity of the stressor the increase in CRH production and the elevation of the cortisol level may cause impaired fetal growth in the first half of pregnancy when a detoxifying enzyme in the placenta is not yet formed. Negative influences of cortisol on the immune system can also be responsible for early preterm delivery through infection. The two problems caused by stress are preterm delivery and growth retardation. Both can have negative influences on neurodevelopment [Hobel and Culhane, 2002; Low et al., 1992].

**Poor nutrition as a stressor**

Nutrition can be poor in quantity or quality. Interesting is the suggestion that during early pregnancy a deficit of omega-3-fatty acids is responsible through a defective brain lipid metabolism for an increased vulnerability to depression in the offspring [Mischoulon and Fava, 2003]. That oligodendrocyte dysfunction and defective myelination may play a role in schizophrenia and bipolar disorders is plausible [Tkachev et al., 2003]. The Dutch Hunger Winter studies are a good example for the consequences and the outcome later in life of food deprivation in early pregnancy. In this studies the cohort conceived during the height of the famine, so in early pregnancy, is the most vulnerable group. Perinatal mortality is increased and so is the number of congenital malformations like spina bifida and anencephaly. There is a peak in schizophrenia in the babies born in November 1945, so conceived in the spring, when problems were the most severe [Susser and Lin, 1992]. At birth the head circumference is smaller. At the age of fifty their lipid profile is more atherogenic, there is more coronary disease, more prevalence of obstructive airway disease, and more obesity in the 50-year old women. The persons of this group feel significantly less healthy [Ravelli, 1998; Roseboom et al., 2001; Roseboom, 2000].

One must realize that the mothers were not only deprived of food, but were also living under stressful war conditions. Both quality and quantity of food are important for the prevention of neurodevelopmental disorders in the baby and child.

**Stress of low social economic status**

There are strong social class gradients in health including perinatal outcome and later neurodevelopmental disorders [Kliegman, 1992]. Living in a stressful criminal neighbourhood in itself is a risk factor to deliver a low birth weight baby at risk, independent of individual level poverty and other risk factors [O'Campo, 1997].

### 3.4.2 Noise

The overview of research on the health effects of children’s exposure to noise has shown that noise may result in auditory as well as non-auditory effects of significance for children’s health and quality of sleep, well being and learning capability. Children’s
hearing, language development, motivation, short and long term memory, and children’s ability to solve complex tasks can be affected by noise.

Studies on the effect of environmental noise on the foetus are difficult due to methodological problems. Pre-term babies have shown noise-induced effects on disturbed sleep and effects on auditory perception and emotional development. The noise event in neonatal intensive care units and incubators are sufficiently loud to affect sleep. Knowledge suggests that stimulation by the auditory environment plays a role in emotional development. The impaired sound quality implies for the pre-term infant difficulties in subtly discriminating the voice of mother or caretakers.

Preschool children and schoolchildren show cognitive effects and stress-related somatic effects due to noise. In this latter group we see effects on the neuroendocrine indices of chronic stress in children (e.g. aircraft noise close to airports). Negative relationships have been shown between chronic noise exposure and delayed acquisition of reading skills in young children. Several studies have examined links between noise exposure and attention deficits. The results are mixed. Reading, long-term memory and learning in children are particularly sensitive to noise. These effects seem to depend on the way information is stored and reorganized in memory and learning [Passchier – Vermeer, 2002].

3.4.3 Not considered substances

**Thallium**

For thallium, which is a known neurotoxin, though mainly for the peripheral, not the central nervous system, no data could be found in the peer-reviewed literature indicating a correlation to neurodevelopmental effects in humans.

**Food additives**

Though there is an intense discussion on a possible correlation between food additives and attention deficit hyperactivity disorder (ADHD) in childhood [Carter, 1993; Boris, 1994; Story, 1998; Kidd, 2000; Schnoll, 2003], there are no results suggesting a correlation between maternal ingestion of food additives during pregnancy or breast feeding and ADHD in peer-reviewed literature.

There is one possible exception – monosodiumglutamate, which is discussed above.

**Acrylamide**

Recently it has become obvious, that acrylamide is found in significant concentrations in certain foods. It is not an artificial addition, but is formed from proteins (asparagine) and sugars (glucose, fructose) at certain preparation temperatures e.g. in cookies, bread and especially French fries (3.6 mg/kg), but also in coffee and cocoa.

As acrylamide is known neurotoxicant, which also exerts neurobehavioural effects [Daniel and Evans, 1985; Rafales et al., 1982], and it’s neurotoxic ranking is above methylmercury and lead [Pryor and Uyeno, 1983], it is surprising, that only a single publication on developmental neurotoxicity could be found. Application by gavage of 5,
100, 15 and 20 mg/kg body weight acrylamide to rats from gestation day 6 to lactation day 10 resulted in neurobehavioral alterations (motor activity and auditory startle response) seen at 15 mg/kg, while the pups at 20 mg/kg were dead. A clear no-observed effect level (NOEL) thus is 10 mg/kg/day, and developmental neurotoxicity only occurs at doses, which are maternally toxic [Wise et al., 1995]. To put this in relation to human exposures: exposure should be minimized for food containing 1mg/kg acrylamide or more [http://www.verbraucherministerium.de/English/pk-acrylamide-in-foods.html]. For a 60 kg woman, this would mean an uptake of such a ‘risk’ food in an amount of 600 kg per day even for the no-effect level of 10 mg/kg/day. So no risk is imminent from acrylamide for neurodevelopment.

**Low SES**

Low Social Economic Status (SES) is seldom the only factor that influences neurodevelopmental disorder. In studies it is a known confounder.
4 THERAPEUTIC EXPOSURE

The medicaments most studied in pregnancies, because of possible negative effects on the developing child are:
- Anticonvulsant drugs
- Glucocorticoids
- Di-ethyl stilboestrol (DES)
- Radiation

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Level 1: Human studies (high relevance)
Level 2: Animal studies show link (reasonable) *Animal of in vitro studies that report effects on mechanisms known to be in common with humans
Level 3: Case histories and (logical) assumptions

4.1 Anticonvulsants

About one in two hundred pregnancies are in an epileptic woman, who needs anticonvulsants. Meadow published in 1968 the first article that cleft lip and palate occurred more often in children of mothers with epilepsy [Meadow, 1968]. After a few years of strong opposition against this fact a number of publications confirmed Meadow’s findings [Annegers et al., 1974; Koppe et al., 1973]. Epileptic women on anticonvulsants run an increased risk to have children with congenital anomalies such as heart defects, cleft lip and palate, neural tube defects, urogenital defects, skeletal abnormalities, facial dysplasia, cerebral pathology and mental retardation [Hanson and Smith, 1975]. Also genital malformations like hypospadias, epispadias, bifid scrotum and micropenis are described [Dessens et al., 1994; Dessens, 1996]. At long term follow-up more cases of transsexualism and gender dysphoria are found [Dessens et al., 1999]. Spatial abilities as a marker of cognitive function were decreased [Dessens et al., 1998; Hanson & Smith, 1975].

Barbiturate-induced disturbances in brain development can be caused by two different mechanisms:

1) Influences on electrical transmission, inhibiting the formation of new synaptic connections.

2) Enhanced metabolization in the liver of important hormones (e.g. T4, oestrogen’s and testosterone) and vitamins like vitamin K, A, and D.

If only one medicament is used the risk is lower than after a mixture of anticonvulsants. Exposure to carbamazepine, phenobarbitone, valproate and dilantin was associated with...
a high rate of anomalies (58 %), not explainable by any single drug or drug level. Malformations consist mainly of heart defects, cleft lip + palate, and dysmorphia syndromes + retardation. When only carbamazepine and/or valproate was used the number went down significantly and the pattern changed to spinal dysraphism and glandular hypospadias [Lindhout et al., 1985]. Newer medicaments are not yet evaluated for their teratogenic effect in humans.

4.2 Glucocorticoids

As medicament glucocorticoids are used in pregnancy because of maternal diseases like idiopathic trombocytopenia, malignant diseases, asthma or as a prevention of the Idiopathic Respiratory Distress Syndrome in threatening pretem labour for the baby. It is one of the few pharmacologic agents that can have a positive effect on cognitive function in the baby.

However depending on the dose there are also adverse effects described. The most well known effect is the inhibition of growth. After long-term use in pregnancy both placenta and baby are smaller, but the baby shows catch-up growth after birth in the following years [Koppe et al., 1977]. Rats exposed in utero to glucocorticoids are more sensitive to oxidative stress in later life [Canlon et al., 2003; Ahlbom et al., 2000]

In newborn animals reports of impaired central nervous system development after treatment in the neonatal period are published and impairment of brain growth especially of the cerebellum is mentioned and this was associated with decreased performance in tests of fine motor control (4-60 mg/kg dexamethasone). Also effects on the immune system are described. And cleft lip and especially palate are known as the congenital malformation caused by glucocorticoids given to the mother in a high dose in the first trimester. A review of these findings in animal models and in humans is published in a report of the consensus development conference on the Effects of Corticosteroids for fetal maturation on Perinatal Outcomes [Slotkin, 1994].

After short-term use in pregnancy (one course of 2x 12 mg betametasone) for the prevention of IRDS no effects on physical and psychological development were seen after follow-up at the age of 10-12 years [Schmand et al., 1990], [Smolders-de Haas et al., 1990]. After more courses smaller head circumference is found as is also seen after a high dose postnatal in the treatment of bronchopulmonary dysplasia.

4.3 DES

There is evidence that antenatal Di-Ethyl-Stilboestrol (DES) have resulted in primary mental abnormalities. Developing brain cells have oestrogen receptors and they play a role in neural development. It seemed likely that DES influenced the sexual dimorphism of the brain with consequences for the behaviour of the children. Antenatal exposure to DES might result in “feminization” of males and “virilization” of females and DES daughters were a little more masculine than their unexposed sisters [Hines and Shipley,
Other psychiatric disorders described are profound weight loss, indicative of anorexia nervosa, and depression [Bernheim, 2003; Gustavson et al., 1991].

4.4 Radiation

The risk of malformation will depend on the period of organogenesis at the time of irradiation and is probably especially high during the most active phase of cell multiplication and differentiation of structures being developed [EC, 1998].

Ionizing radiation to the developing brain has been shown to result in decreased cognitive function [EC, 2001], although the lowest doses that affects cognitive function yet has to be defined. Children exposed in utero as a consequence of the atomic bombs in Hiroshima and Nagasaki experienced an increased prevalence of mental retardation and reduced school performance [EC, 2001]. The highest risk of damage to the frontal lobes was seen at a gestational age of 8-15 weeks, the time of rapid proliferation of neurons and neuroblast migration from the cerebral ventricles to the cerebral cortex, although no significant effect on cognitive ability was seen at a fetal dose-range below 100-200 mGy [EC, 2001].

No studies have evaluated the possible adverse cognitive effects of low doses of ionizing radiation, defined as <100 mGy, to the developing brain [EC, 2001].

The underlying mechanisms by which ionizing radiation causes brain damage are still largely unknown, although reduced neuronal migration, cell death, and decreased perfusion have been suggested [EC, 2001]. Prenatal irradiation of the rodent brain [Reyners et al., 1994] produced alteration in the patterns of cell proliferation and migration in the neuroepithelium. This leads to long-term morphological changes such as reduction of brain weight. Even 60 mGy was shown to be effective in producing diminution of the diameter of the parietal cortex. Among the effects of prenatal irradiation on the animal’s adult behaviour, the final output of brain function, spatial memory appeared to be the most vulnerable to prenatal irradiation.

Values of intelligence quotient (IQ) lower than expected were reported in some children exposed in utero at Hiroshima and Nagasaki [EC, 1998]. The data are consistent with general downward shift in the distribution of IQ with increasing doses. It is assumed that this shift is proportional to dose. Another finding is the dose-related increase in the frequency of children classified as « severely retarded » and microcephalic. The number is small, but the data indicate an excess probability of severe mental retardation of 0.47 at 1 sievert. The effect was observed following exposures in the 8th to 15th week after conception, and is less marked following exposures in the period from the 16th to 25th week and has not been observed for other periods of pregnancy [EC, 1998].
4.5 Multiple factors / cocktails

Neurotoxic risks to the fetus and/or infant include a wide variety of agents: microbiological agents, radiations or chemicals present in the mother, the environment or indoors.

In a recent background paper of EEA, nr 5, an approach to Multi-causality in Children’s Health is made [Gee, 2003]. Addressing childhood IQ and Multi-causality an interesting paper is referred [Weiss, 2000]. The conclusion of that paper is that the number of risk factors and their cumulative effects, rather than any particular risk factor, determined overall IQ and social competence. As risk factors only socio-economic ones were taken into account, like for instance high maternal anxiety, minimal maternal education, single parenthood, disadvantaged minority and stressful life events, not environmental neurotoxicant exposures.

In analogy to this findings of multicausality are the findings in the use of antiepileptic drugs and their teratogenic property. A mixture of antiepileptic drugs turned out to be much more teratogenic than the use of a single anticonvulsant drug [Lindhout et al., 1985].

In the field of pesticides also the publication of the Mexican children are an example. They were neuropsychologically affected after exposure to a mixture of pesticides. But there are no measurements of levels in the children [Guillette et al., 1998]. In vitro studies corroborate these findings [Axelrad et al., 2002; Axelrad et al., 2003]. The authors state that their finding applies for some, but ‘by no means all, environmental agents’.

Testing all possible multiple exposures that occur at the moment is impossible and very few data are available on the potential health effects of mixtures of chemicals [Carpenter et al., 2002].

Also the combination of PCBs and dioxins are in most aspects an example of synergistic effects on IQ and behaviour [Chen et al., 1992; Guo, 1999; Patandin, 1999]. In animal studies dioxin is facilitating the effect of phenobarbital, and many PCBs are phenobarbital-like [Dees et al., 1982].

The paper by Guillette et al. [1998] carried out in Mexico evidenced that children exposed to different environmental pollutants in their resident area had lower neuropsychological outcome that children living in less contaminated areas. However, in human studies is difficult to isolate the contribution of the single compounds to the adverse health effects. Experimental studies clearly indicate that different chemical compounds can act synergic, additive or antagonistic on the developing brain [Axelrad et al., 2003]. More animal studies are needed in these fields, also in a regulatory perspective.
5 BACKGROUND INFORMATION

5.1 Development of the brain

The human nervous system develops over a very long period of time extending from the embryonic period through puberty. The primary event is the formation of the neural plate from the ectoderm, between 15 and 17 days after fertilization. The neural plate folds to form the neural tube, which is completed by day 26. Cells formed during this period of rapid proliferation migrate to a different position where they differentiate into neurons and neuroglia. In the human foetus, cell migration is nearly complete in the neocortex and in most of the brain by the sixth month of gestation. During the remainder of intrauterine development neurons differentiate and connect with each other, and these two processes (differentiation and synapse formation) continue for several years postnatal [Rice and Barone, 2000]. Neuronal differentiation requires both dendritic development and axonal growth. The phase of synaptogenesis starts when neurons reach their final targets. There follows a period of adjustment affecting both the number of projecting cells and the number of synapses they retain. These adjustments generally involve a substantial degree of cell death by apoptotic mechanisms. In this developmental phase, both endogenous (neurotrophic factors, neurotransmitters, hormones) and environmental factors concur to influence the fine match up between pre- and postsynaptic neurons. Myelination begins around the four month of gestation [Paus et al., 1999] and around thirty weeks of gestation the brain growth spurt starts. The peak of the growth spurt is around birth and then the growth slows down in early childhood, and continues to progress through adolescence [Paus et al., 1999; Dobbing, 1974].

5.2 Time windows/mechanisms (general)/ vulnerability

Brain develops through several interactive and temporally overlapping stages [Rice and Barone, 2000]. Exposure to toxicants at any point during brain development may result in aberrant neural structure or function. The endpoints affected and the severity of the outcome may vary depending on the timing and duration of exposure. Toxic disruption of early maturational events such as neurulation is more likely to result in neural tube defects or major malformation (i.e. anencephaly, spina bifida). Toxic interference with later developmental events results more commonly in cytoarchitectural and molecular alterations, which are expressed as behavioural dysfunction. In this case, the effects produced are less easily associated with narrow periods of heightened vulnerability. As a matter of fact most neurally active agents are able to disrupt development at multiple time points. This is the case for lead and ethanol, which can interfere with cell migration, synaptogenesis and myelination. The organophosphorous pesticide chlorpyrifos may affect proliferation in the prenatal stage but also myelination when exposure occurs in the late neonatal phase [Garcia et al., 2003]. Furthermore, different brain areas mature at different times, and behaviour mediated by different brain systems would be disrupted by insult at different times during development. Thus the window of greatest vulnerability to a specific neurotoxicant may
vary with the behavioural end point under examination. Altogether, it is conceivable that protracted exposure to low doses of neurotoxicants, as it is the case for environmental agents, induces perturbation of multiple maturational events. It is important to recognize that developmental exposure to certain agents may also increase vulnerability to later environmental challenges (stress, ageing, exposure to toxicants).

5.3 Diseases due to neurodevelopmental disorders

Abnormal development of the nervous system can result, depending on the time of the insult, in malformations e.g. spina bifida and anencephaly, diseases like autism and schizophrenia, and other functional abnormalities like Attention Deficit Hyperactivity Disorder (ADHD), severe behavioural problems like transsexualism or delinquent behaviour, depression and more subtle disorders like a lower IQ, language difficulties, less spatial capabilities, gender dysphoria and slightly abnormal behaviour like being more timid or more aggressive. Two conditions ADHD and Autism will be discussed more extensively because there is the impression of an increase of these two disease entities in the last two decades in relation to environmental influences.

**Attention Deficit Hyperactivity Disorder (ADHD)**

Joe Biederman, a psychiatrist of Harvard Medical School is an expert in the field of ADHD. He makes the diagnosis on the basis of anamnesis of parents and teachers. That makes the diagnosis arbitrary. Six of the following items must be positive during more than 6 months and must be there before the age of seven in school and at home:

**Shortness of attention:**
- No attention for details or makes mistakes carelessly
- Span of attention is short in playing or tasks
- Seems not to listen when he/she is spoken to.
- Doesn’t do what you say or is not finishing tasks
- Difficulties in organizing tasks and activities
- Avoids or hates tasks that needs longer attention like homework from school
- Loses often things
- Easily distracted by external stimulation
- Is very forgetful in daily tasks

**Hyperactivity**
- Moves often with hands and foots or cannot sit still
- Stands up when he/she is expected to sit
- Is running around and climbs on everything
- Has difficulties in quiet playing or relaxing activities
- Is often busy and goes on and on
- Talks without stopping

**Impulsiveness**
- Answers before the question is ended
- Difficulties in waiting in his / her turn
- Often disturbs somebody else’s jobs or is intrusive

Normally the hyperactivity becomes less after the age of twelve, the attention deficit is very persistent. Only 10% has a complete remission, 60% keeps persistent in some items and 30% is the same in adulthood.

The prevalence of the disease is between 5-10 percent. A relative high percentage of the ADHD children can become depressive in later life. Stress is a risk factor for both diseases.

MRI in ADHD children has revealed that the brain volume is 3% less than normal. And it is assumed that the problems result from a disturbance early in the development. There is strong evidence of a genetic component and some life style factors have been found to cause behavioural problems that are hallmarks of ADHD. Possible gene-environment interactions in ADHD are an important direction for future research. There are some parallels between characteristics of ADHD and the behaviour of monkeys exposed during development to lead or PCBs. It has not been suggested that ADHD is caused exclusively by neurotoxic agents from the environment, but rather it has been postulated that environmental neurotoxicants may contribute to the prevalence of ADHD.

Both a prolongation of the latency (defective myelination) and a decreased amplitude (less number of neurons) of the P300 is found in ADHD children, the same abnormalities we also found in children exposed to high background levels of dioxins in the Netherlands [ten Tusscher, 2002] and to PCBs [Vreugdenhil, 2003]. In an autosomal disease of the thyroid hormone receptor resulting in a thyroxin-resistance children also develop ADHD. They are less intelligent, have language disorders and a smaller corpus callosum (less myelination), which is known to result in visuo-motor disabilities. The reason why a lot of children are treated with Ritalin, a dopamine re-uptake inhibitor is that often a higher activity of the dopamine transporter is found. Current evidence implicates multiple factors in the etiology of ADHD. Depending on the nature of the study, heritability has found to be between 50-80%. Most recent evidence indicates that ADHD symptoms have a central nervous system basis. There now exists a range of neuropsychologic, electrophysiologic, and neuro-imaging studies that have shown fairly consistent differences in prefrontal cortical, parietal, and basal ganglia functioning associated with ADHD symptomatology. In addition, there now have been a number of candidate gene studies exploring the dopamine transporter (DAT1) or dopamine receptor (DRD4) genes, each of which has now had several independent replications (Swanson et al., 1998). While these studies generally indicate an association with ADHD and specific polymorphisms, effects are quite small. It is likely that a host of other genes are involved, and that specific components or combinations of environmental forces are necessary to switch on these genes and lead to the expression of the full phenotype.

**Autism**

The incidence of autism or autism spectrum disorders seems to have increased in the last two decades. This can be due to better diagnosis and/or a shift in the definition of autism, and not to a real increase. Autism has now a prevalence of one in 1000 children...
and those with autism spectrum disorders are estimated to be one in 200 in the US and probably the same in Europe [Fombonne et al., 1999].

The disturbance of brain organization following an insult occurs probably early in pregnancy, a sensitive period as is seen in the Dutch Hunger Winter studies [Ravelli, 1998; Roseboom, 2000]. That the first trimester is a sensitive period is corroborated by the fact that in a group of thalidomide victims autistic children are found in a high prevalence in the group with external ear malformations. The external ear is formed 49 days after conception.

Head circumference is diminished at birth or can be normal, however there is an abnormal brain growth, not uniformly distributed in the following one or two years. The hypothesis is that otherwise normal processes switches on too early or too strongly and shuts of too late, a process controlled by genes. It is hypothesized that some children, or better their genes make them more susceptible than others to damage by environmental agents.

Leo Kanner was the first to describe autism in 1943 followed in 1944 by the Austrian pediatrician Hans Asperger, who describes the “Asperger syndrome”. In autism 4x more boys than girls are involved and in Asperger’s syndrome it is 10x more.

Signs of autism:
• Starts in toddlers
• No pointing by one year
• No babbling by one year; no single words by 16 months; no two-word phrases by 24 months
• Any loss of language skills at any time
• No pretend playing
• Little interest in making friends
• Extremely short attention span
• No response, when called by name; indifference to others
• Little or no eye contact
• Repetitive body movements, such as hand flapping, rocking
• Intense tantrums
• Fixations on a single object, such as spinning fan
• Unusually strong resistance to changes in routine
• Over sensitivity to certain sounds, textures or smells.

Signs of Asperger’s:
• Diagnosed at age six or older
• Difficulty making friends
• Difficulty reading or communicating through nonverbal social cues, such as facial expressions
• No understanding that others may have thoughts or feelings different from his or her own
• Obsessive focus on a narrow interest, such as reciting train schedules
• Awkward motor skill’s
• Inflexibility about routines, especially when changes occur spontaneously
• Mechanical, almost robotic patterns of speech
• The signs are persistent and debilitating
In the cohort of 44 children controlled at the age of 8 to study effects of background exposure to dioxins in the perinatal period there is one case of Asperger syndrome. MEG- and EEG studies gave chaotic results and were not included in the statistical analysis of the group. In this small group of children it can’t be said that the illness has anything to do with the dioxin exposure [tenTusscher, 2002].

5.4 Trends in neurodevelopmental disorders

The question if there is a real increase in neurodevelopmental disorders in the last decades cannot be answered. Recent data confirm for the EU the apparent increase in ADHD, Autism and neurobehavioural problems as reported in US, as stated above. However it is hard to say whether such increase is due to broader diagnostic criteria or to environmental factors. To discover trends in neurodevelopmental disorders one might study the number of congenital malformations, since diagnosis in these cases is less controversial. An example is e.g. the rise in spina bifidas and stillbirths in New Brunswick in Canada in relation to spraying of the trees. Seven pesticides categories were considered: fentrothion formulations, aminocarb formulations, other forest insecticides, herbicides with some phenoxy-component, herbicides with only phenoxy, chlorinated herbicides and nonchlorinated herbicides. The first three categories were recorded according to mass (kilogram of active gradient per county), and the remainder was based on area (number of hectares sprayed per county). [White et al., 1988]. Another indication in general is the rise in Hypospadias and environmental factors are discussed [Dolk, 1998]. If Hypospadias is caused by a hormonal disruption (lower testosterone due to an enhanced metabolism in the liver after induction of enzymes) than this same disruption can have negative effects on brain development. This means that a good registration of congenital anomalies can be very helpful in detecting increases or clusters of negative environmental influences on the brain.

It is worth noting that there are sound data showing that specific environmental factors (alcohol, maternal smoking, psychopharma, lead, methylmercury and possibly PCBs) after brain and behavioural development at different degree of severity. It is possible that a large proportion of neurodevelopmental disabilities with no apparent genetic bases and unknown etiology are caused or at least triggered by environmental chemicals. In this respect, even in the absence of a clear increasing trend for these disorders, the search for potential causal links between adverse neurobehavioural outcome and environmental factors should be pursued.


6 GAPS IN KNOWLEDGE

6.1 General

Gaps in knowledge relate to different issues. In general they concern:
- Trends in environmental exposure
- Trends in internal exposure
- Data on neurodevelopmental disorders (e.g. trends)
- Effects of mixtures and cocktails

It is unclear whether environmental exposures are on the rise or not. If they are decreased or decreasing, it will be difficult to assume their causation of increasing neurodevelopmental disorders, with the exception of the delayed effect of the persistent ones. An example would be lead, which should find a correlate in decreasing signs and symptoms in areas where levels went down.

In general there is scarcity of data concerning measures of internal exposure to pesticides in the EU. We don’t know what the sources of real exposure are in addition to the dietary exposure: is exposure to polluted indoor environment (i.e. house dust, toys, contaminated floors/carpets etc.) relevant for Europe too?

Very few prevalence data for neurodevelopmental disorders in Europe are available.

Furthermore the eventual effects of mixtures and cocktails are widely unknown.

6.2 Gaps in knowledge relating to single or groups of substances

Besides more general gaps in knowledge there are also gaps defined for specific substances. They are mentioned below.

PCBs, dioxins and PBDEs

A number of human studies have shown associations between exposure and neurobehavioural effects, and tolerable daily intake values have been set for dioxins and dioxin-like PCBs. Epidemiological studies in Europe and in the USA are in agreement. In the Faroes studies different results are obtained. In the Faroes studies is co-exposure to organic mercury present in the same food sources, so the relative contributions of the individual agents to biological effects is not always clear. More follow-up studies are needed.

Pesticides

Organophosphorous pesticides have not in general been found to produce developmental neurotoxicity at levels not causing overt maternal toxicity, but chlorpyrifos is an exception. It is not clear if the developmental effects of chlorpyrifos (at exposures above the MRL) are produced by other organophosphates. Organochlorines such as DDT have clear adverse developmental effects in animal
studies, but effects in humans have not been investigated thoroughly. As a persisting environmental contaminant, DDT exposure may also co-vary with PCBs and other agents. Adverse effects of pyrethroids have been seen in animal studies by one research group, but not others. The relevance of these to human studies is at present unclear. Many regulatory studies of pesticides will have provided information on their potential for developmental neurotoxicity, and this information should be integrated with published information before conclusions are drawn about their safety.

There is a lack of epidemiological studies linking biomarkers of exposure to Organochlorine pesticides either to adverse health effects or to altered neurodevelopment in children.

There is a scarcity of exposure data of Pyrethroids in foetus, infants and children. There are limited studies on neurobehavioural neurotoxicity in animal models.

There is a lack of exposure data in general populations on dithiocarbamates. A complete characterization of the neurotoxicity mechanisms of these compounds is lacking. There are no data available on developmental neurotoxicity in vivo.

Finally, pesticides such as organochlorines and dithiocarbamates could act on the developing nervous system by interfering with neuroendocrine mechanisms, in addition to their direct effects on the brain. This issue needs further investigation.

**Solvents**

Gaps in knowledge are exact assessment of solvent exposures in human beings, especially in pregnant mothers. What is more, evidence found in animal experiment relates to exposures in the range of and above occupational exposure limits, and cannot be extrapolated to environmentally relevant low doses.

**Metals and organometals**

Lead is a well-recognized developmental neurotoxicant for which no safe exposure level can at present be defined, but lead exposure of populations in the EU is not well characterised at present.

There are few gaps in knowledge for methylmercury, however, it is important to clarify the differences between the outcomes in the two large recent studies (the Seychelles and the Faroes). A possible explanation is the difference between constant intake of less contaminated fish on the Seychelles and intermittent intake of highly contaminated whale meat on the Faroes. In addition the results on mercury and seizures should be assessed and possibly the experiments should be repeated.

Gaps in knowledge for cadmium refer mainly to human studies, which will have to account for smoking as confounder. Animal experiments show some contradictory results and only at high doses.
Food additives
There is little evidence to support suggestions of harmful effects of food additives other than glutamate. Monosodium glutamate can have adverse effects in developing animals, and the relevance of these to human exposures is uncertain.

Therapeutic agents
Some drugs have the potential to produce developmental neurotoxicity, as does neonatal radiotherapy, but these are well-recognized adverse effects.

Mixed exposures
In the absence of understanding of the mode of action of most developmental neurotoxicants, and the similar effects produced by exposures to different agents at similar developmental stages, it would be prudent to assume that they may show additive behaviour, though there is also proof of synergistic and antagonistic behaviour. More research on mode of action may highlight particularly harmful combinations of agents. Also smoking and alcohol can influence levels of neurotoxicants in adults.

6.3 Risks and benefits

Breast milk
Much larger quantities of PCBs are transferred to the infant via breast-feeding than prenatally across the placenta. However, Patandin et al. [1999] found in the Dutch cohort of exposed children that the association of prenatal PCB exposure and negative cognitive outcome was statistically significant only for the non-breast fed children. A recent study by Jacobson and Jacobson [2002] confirmed such effects in a US cohort of exposed children. One possible explanation for this pattern is that certain nutrients in breast milk might attenuate adverse effects of PCBs on neural development. Alternatively (or concomitantly) breast-feeding mothers provide more intellectual stimulation to their children. Thus breast-feeding might be an indicator of the quality of the social environment.
7 PROGRAMMES AND STUDIES ON THE WAY

7.1 European programmes/studies

Eurocat is an European network of population-based registries for the epidemiological surveillance of congenital anomalies that started in 1979. The network covers different regions in European counties. Some countries are better covered than others. The network is based on data obtained after confirmed consent of the parents. This means a high dropout rate. To find a trend is more difficult and anonymous registrations can give more information, when e.g. an easy recognizable malformation as spina bifida of cleft lip and/or palate is used as a marker. Both the specific registration of Eurocat and the more sensitive anonymous registrations need more support.

For Eurocat the project leader is Prof. Helen Dolk
Room 15E12, University of Ulster, Newtonabbey, Co Antrim, Northern Ireland BT37 QQB

A project on Developmental neurotoxicity of PBDE mainly in animal models has been carried out within the Vth Framework (PBDE-NTOX; QLK4-CT-1999-01562).

7.2 Studies on the way

Pesticides (Organophosphorous): A US study to evaluate the association between methylparathion exposure by illegal spraying in Mississippi and Ohio and neurobehavioural development in children 6 years of age or younger, is on the way [Zeitz et al., 2002]. Also US study (CHAMACO) to assess the extent of children’s low-level exposure to pesticides and associated health effects, included neurodevelopmental functioning and behavioural problems, can be expected [Eskenazi et al., in press, 2004].

ANEMONE: Assessment of Neurobehavioural Endpoints and Markers of Neurotoxicant Exposures. http://www.anemone-project.dk. The project aims at a) improving methods for assessment of hazardous exposures and for early detection of adverse effects on cognitive functions, and at b) applying these methods in determining developmental risks due to contaminated seafood.

Alspac. The Avon longitudinal study of parents and children. J. Golding, M. Pembrey, R. Jones (Golding et al., 2001)
8 RECOMMENDATIONS

8.1 Recommendations for research

Prospective study to intra-uterine growth retardation (between P2.3 and P10 of birth weight) and environmental influences in different European countries to:

2. Preconceptional situation in the mother (T4, lead, mercury, stress-score, PCBs, Dioxins, smoking, alcohol, drugs, folic acid status, toxoplasmosis titre);
3. Obstetric history (optimality score Touwen) and blood samples of the mother;
4. Placenta: levels of pollutants;
5. Baby: birth weight, length and head circumference, biomarkers of internal exposure to environmental chemicals;

For "level 2" substances and exposures (see above) research or assess whether the results can be transferred to humans (comparison of study and actual human doses), eventually repeat animal research with doses similar to human exposures or do studies in human populations, whether the animal study results can be reproduced in humans.

Use validated and reproducible methods only. If validated methods and instruments are lacking, there is an urgent need to develop such.

8.2 Recommendations for research to specific agents

Lead
The hazard presented by environmental lead exposure is well recognized, and it is currently not possible to set an acceptable daily intake. Hence lead exposure should be as low as possible. It appears likely that some sub-populations within Europe may be at particular risk of lead exposure from older houses or water piping, and these should be identified and their exposures reduced.

Mercury
The reasons for the different outcomes of different studies should be clarified.

Other metals
Given the contradictory results e.g. cadmium and manganese in hair and neurodevelopmental disorders internal exposures and neurodevelopmental outcomes should be studied.
PCBs, dioxins and PBDEs
Research is needed to clarify the relative contribution of these classes to adverse effects in children. Existing cohorts should be followed-up at later ages (puberty, reproductive age). Exposure should be safe for the baby during pregnancy and lactation.

Pesticides
The extent to which the neurodevelopmental effects of chorpyrifos may extend to other organophosphates needs to be determined in animals. The mechanism of developmental neurotoxicity of organochlorines such as DDT needs to be determined. The reproducibility of the developmental neurotoxicity reported for pyrethroids in mice needs to be determined in the light of contradicting studies.

Organophosphorous: 1) Effects mediated by novel mechanisms not directly related to AChE inhibition and possible identification of novel markers of neurotoxicity in animals and humans; 2) Quantification of internal exposure of children to OPs and assessment of the relative contribution of the sources of exposure [see Minnesota Children’s Pesticide Exposure Study, Quackenboss et al., 2000]; 3) Assessment of polymorphisms in gene for serum paraoxonase (PON1), the enzyme responsible for the metabolism of Ops in the serum, in general population, in relation with differential susceptibility to Ops neurotoxicity.

Organochlorines: 1) Mechanisms of developmental neurotoxicity; 2) Endocrine-disrupting activity of organochlorine and their synergy with PCB effects in animals and humans, 3) Quantification of biomarkers of internal exposure in women (breast milk), foetus (meconium), neonates, infants and children and follow-up studies.

Pyrethroids: 1) Mechanisms of Pyrs neurotoxicity in developing CNS: are there different sites of action for different Pyr types? 2) More internal exposure data in children also considering synergies between mixtures of compounds.

Dithiocarbamates: 1) Measurement of biomarkers of exposure in general population, also considering ETU metabolite; 2) Assessment of potential adverse effects on neurodevelopment associated to interference with thyroid function; 3) Metal-chelating properties of dithiocarbamates and susceptibility to neurotoxic effects of metals in animal models.

8.3 Recommendations for monitoring exposure and trends in diseases

Neurodevelopmental disorders and toxicant exposures
Demographic trends emphasize the need for universal studies that encompass the components of the international classification of functioning, disability and health (ICF) to measure childhood disability. This can be used in surveillance, screening and evaluation [Simeonsson et al., 2003]. It is important to establish trends in disease
incidence in order to examine the correlations between this and putative toxicant exposures. It might be feasible to assess the incidence of neurodevelopmental disorders like ADHD, autism, or Asperger’s syndrome in large cohort already examined, like the Faroe and Seychelles Islands groups.

The present incidences of CNS disorders/malformations that may be indicators of developmental neurotoxicity need to be monitored within the EU.

The levels of putative toxic agents in food and in breast milk also need to be monitored.

In summary:

- Assess incidence rates of neurodevelopmental disorders.
- Compare old and new incidence rates based on identical case definitions.
- Assess trends in environmental exposures all over Europe (e.g. "Umweltsurvey" in Germany).
- Use existing large collectives (e.g. Faroes, Seychelles, Seveso) to check for incidence of neurodevelopmental disorders.
9 CONCLUSIONS

In this baseline report the current knowledge on environmental risk factors and neurodevelopmental disorders is compiled and analyzed. It aims to give an overview of current knowledge on neurodevelopmental disorders and environmental influence.

The (central) nervous system is very vulnerable during development to a wide range of environmental factors and agents both preconceptional, during the different stages of pregnancy and postnatal, during growth until adolescent age. In these stages voluntary, involuntary and therapeutic exposure are relevant.

The voluntary exposure consists of socio-economic factors, which plays an important role in both a exacerbating and protecting way. Recognized hazards are alcohol, smoking and drugs. Although this voluntary exposure on the part of the mother play a role in neurodevelopment of the child, the emphasis in this report lies with the involuntary exposure.

The involuntary exposure is indicated for the relevant substances/factors:

- PCBs,
- Dioxins,
- PBDEs,
- Pesticides,
- Solvents,
- Formaldehyde
- Monosodiumglutamate
- Metals,
- Stress and
- Noise

PCBs, dioxins, lead and mercury are proven to be neurotoxic in humans. Background levels of PCBs and dioxins in several parts of Europe in 1990-1992 had negative effects on neurodevelopment. Levels are decreasing, but still too high. The tolerable daily intake of 2 pgr WHOTEQdioxin /kg bw/day is based on animal data and maybe all right for adults. However human data have to be taken into account to protect the foetus and the baby.

PBDEs are also presumed to be neurotoxic (proven in animal studies) and are increasing in breast milk.

The pesticides are divided in 4 groups. Neurotoxic effects in humans are described for organochlorine compounds and chlorpyrifos. And there are a lot of the animal data on neurotoxic effects. Exposure to a mixture of pesticides shows a negative influence on neurodevelopment in one study under Mexican children (neuropsychological problems) and one in Canada in relation to the spraying of trees (spina bifida and stillbirths rate).
Animal studies underline the possible synergistic and also antagonistic effects of pesticides.

Solvents do not seem to pose a risk for human neurodevelopment according to current knowledge. Given the widespread exposure, however more research is needed, as for high exposures both to ethanol and toluene severe congenital syndromes have been described.

Lead is proven to be neurotoxic to humans. Recent studies to the effects of lead in humans underline that a safe (exposure) level cannot be defined currently. Therefore exposure should be as low as possible. It appears likely that some sub-populations may be at particular risk of lead exposure from older houses, and these should be identified and cleaned. More data on levels in Europe are necessary and are underway.

Mercury is well known to have neurodevelopmental effects, though some studies are contradictory. The current levels of tolerable intakes are already targeted for pregnant woman.

Other neurotoxicants like Cadmium, Aluminium, Manganese, Monosodiumglutamate, Formaldehyde and Arsenic are not known to cause neurodevelopmental disorders in general in the European population, but may do so in specific situations and need further research.

Therapeutic exposure by anticonvulsants, steroids, and events like radiation and stress, cause known neurodevelopmental disorders. A study on these medicaments might help to explain findings or can be warnings for other environmental factors.

There are sound data that specific environmental factors (alcohol, maternal smoking, psychopharmaca, lead, methylmercury, PCBs and dioxins) alter brain and behavioural development at different degrees of severity either alone or in concert with each other. It is possible that a large proportion of neurodevelopmental disabilities with no apparent genetic bases and unknown etiology are caused or triggered by environmental chemicals. In this respect, even in the absence of a clear increasing trend for these disorders, the search for potential causal links between adverse neurobehavioural outcome and avoidable environmental factors should be pursued. However this may by no means lead to a reduction of effort put into a further decrease of known influences.

Gaps in knowledge relate to different issues. In general they concern:
- Trends in environmental exposure;
- Trends in internal exposure;
- Data on neurodevelopmental disorders (e.g. trends);
- Effects of mixtures and cocktails;
- Recommendations for research, monitoring exposure and trends in neurodevelopmental disorders are given above (8).
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ANNEX I MANDATE OF THE SUB-GROUP NEURODEVELOPMENTAL DISORDERS


Introduction
The EU Environment and Health Strategy puts a particular emphasis on improving understanding of the links between environmental factors and key diseases and conditions. For the first cycle, three priority disease areas have been identified: childhood cancers, neurodegenerative diseases, and respiratory diseases, asthma and allergies. The underlying environmental factors, determinants and risks, which contribute to these diseases, are similar. Moreover, in addressing the diseases and developing actions in the Community framework, a similar set of instruments is being used.

The development of indicators and the identification of priority diseases is closely linked. The work on European Health and Environment indicators will therefore take place as part of the developing European health information system.

Work on these issues will therefore be taken forward in an integrated way. One overall group on ‘Indicators and priority diseases’ will be created to ensure that synergies between the different areas are properly explored. The meetings will include breakout sessions to discuss specific issues related to the different subject areas (see specific sub-mandates).

Tasks
In all areas set out below, a similar structure of work will be pursued:

Step 1: definition of the baseline
The WG should first provide a Baseline Report (end of December 2003) on indicators and on the priority diseases, including:

- An overview of the existing state of knowledge and activities, including an appraisal of problems and deficits of current activities
- Advantages of developing work at EU level;
- Requirements for EU activities;
- Assess the adequacy/scope of proposed actions/priorities

Step 2: establishment of options for action & recommendations

On the basis of the outcome of the previous tasks, the Working Group will then establish options for action and recommendations for the Commission’s “AP 2004-2010”.

Links with other TWGs should be ensured in step 1 as well as in step 2.
Introduction
The developing nervous system is particularly vulnerable very early in life to damaging effects of exposure to specific contaminants such as lead, methylmercury and polychlorinated biphenyls (PCBs). A child can absorb as much as 50% of the lead present in food, while an adult takes up only 10%\(^3\). Exposure to such substances has been associated with developmental disabilities in the form of physical, cognitive, sensory and speech impairments, including in particular learning disabilities and intellectual retardation. Prevalence rates are up to about 10% in certain populations. When incurred early in life such developmental effects are likely to be permanent.

Problems identified
Improve understanding of the links between environmental factors and neurodevelopmental disorders in children, and to develop specific actions, which could be taken up in the first cycle of the European Environment and Health action plan.

Objectives/Tasks of the Group
Step 1: definition of the baseline
The Group will first define a baseline including:

- Providing an overview of relevant epidemiological studies or programmes in the Member States and Acceding Countries investigating neurodevelopmental disorders and their relationship with environmental factors
- Identifying data gaps in knowledge regarding environmental exposures and neurodevelopmental disorders.
- Assessing the identification of unrecognised causal links between environmental agents and neurodevelopmental disorders.
- Identify ways to improve the understanding of the effect of neurotoxicants on neurodevelopmental disorders

The result of this first step is a « Baseline Report » to be presented by the end of December 2003.

Step 2: establishment of options for action & recommendations
On the basis of the outcome of the first step, the Group will then:

- Establish options for actions and recommendations for the Commission’s “AP 2004-2010”. In particular proposals for:
  - Preventive actions
  - The establishment of monitoring/epidemiological surveillance programmes in areas at risk
  - Gaps in knowledge

\(^3\) United States Environmental Protection Agency (US EPA) estimates in 1986
Each recommendation or option presented will be accompanied by a justification of the choices, the practicability, the estimated impacts and costs involved, the time lines and the interlinkages with other measures or policies.

The links with other TWGs (e.g. dioxins, heavy metals) and the work in other sub-groups of the indicators and priority diseases group should be ensured.
## ANNEX 2 MEMBERS OF THE SUB-GROUP NEURODEVELOPMENTAL DISORDERS

### Members (participating in the writing of the baseline report)

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### Members contributing

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The post addresses and email addresses of the members of the TWG Neurodevelopmental disorders can be found at: [www.rome-conference.org](http://www.rome-conference.org)
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<td>Peter van den Hazel, Dorine Kolkman</td>
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