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# Executive summary

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## Questions about early exposure to substances

We are exposed to a large number of substances that are present in our environment on a daily basis. In order to prevent or limit as much health damage as possible, these exposure levels are measured or estimated, and acceptable limits are defined. This is all the more important where exposure prior to birth and in very early life is concerned, when vulnerability to lasting health damage is often the greatest. Countless delicate, fundamental developmental processes take place at that time.

There is clear evidence from the fields of toxicology, pharmacology and epidemiology that the risk associated with exposure to substances is greatest during the prenatal phase. That is the reason for remaining vigilant and regularly mapping the state of scientific knowledge. Upon the request of the secretary of state for Infrastructure and the Environment, a specially appointed Committee of the Health Council investigates how clear the evidence is for health damage due to prenatal exposure to certain substances found in the environment. Additionally, the Committee will examine whether current scientific evaluations frameworks are sufficiently equipped to identify health damage due to prenatal exposure to substances.

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## Relationships between exposure and health effects

For which health effects is there evidence for an association with prenatal or early postnatal exposure to substances via the mother? In order to address this question, the Committee examined four types of health effects and classified the level of evidence as *proven*, *likely*, or *possible*, depending on the availability and quality of primarily epidemiological and additionally toxicological data.

First, exposure to certain levels of PCBs and PBDEs appears to negatively impact thyroid function. The Committee considers this relationship to be *proven* for PCBs and *likely* for PBDEs. There is no proof that this also results in health damage later in life, although there are indications this is the case.

Second, a relationship between prenatal exposure to dioxins and dioxin-like PCBs and reduced function of the immune system is considered to be *proven*. Whether perfluorcarbon compounds have the same effect is considered *likely*.

Third, there are effects on the nervous system. Individual effects are not always easily identified, as the nervous system is a system with a great deal of interconnected, related processes. However, when studies examining partial effects are considered together, the relationships between effects on the nervous system and prenatal exposure to lead, methylmercury, PCBs and dioxin-like substances and organophosphates are considered to be *proven*. The Committee considers the level for a relationship with DDT/DDE, PBDEs and perfluorcarbon compounds *likely*. The judgement regarding phthalates, cadmium and bisphenol A (BPA) is: *possible*.

Finally, in the category ‘other effects’, there is a *proven* association between lower birth weight and prenatal exposure to PCBs. For lead, the relationship between prenatal exposure and cardiovascular effects is qualified as *possible*. The same holds true for the relationship between prenatal exposure to BPA and growth retardation.

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## Health effects in the Netherlands

The most important instrument for limiting prenatal and postnatal risks is reducing maternal exposure to specific substances. Therefore, the Committee provides an overview of the substances that may have resulted in health effects via prenatal exposure or breastfeeding, and of current health effects. The Committee begins with the substances for which the causality discussed above is considered *proven*.

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## Lead

Despite a significant reduction in exposure to lead in the 1980s and 1990s, significant health damage may still be expected. Although it may only amount to a small reduction in IQ on an individual level, the population effects may still be undesirable. Furthermore, there is a group of children with additional exposure, namely whose mothers resided in a house with lead pipes during the pregnancy, and if they live in such a house themselves as a newborn.

## Methylmercury

Another substance for which there is clear evidence for effects of prenatal exposure on the nervous system is methylmercury. This consists of a negative influence on the development of cognitive, motor and visual function in the child. In our country, these effects may still occur in exceptional circumstances, particularly if pregnant women eat a lot of tuna or other large fish that are at the top of the food chain.

## PCBs and dioxin-like substances

The demonstrated effects of PCBs and dioxin-like substances due to prenatal exposure are effects on the thyroid gland, the immune system and the nervous system. There is also an association with low birth weight. In our country, exposure to these substances has dropped significantly over the past decades. Although absorption of these substances from food and the environment is now almost always below the recommended limit for adults in the Netherlands, the long half-life in humans and the environment means there are continuing worries about the extent of prenatal exposure and exposure via breastfeeding. Effects may therefore still occur at current levels of exposure.

## Organophosphates

Recent Dutch research shows that exposure concentrations in our country, though they are dropping, currently remain much higher than the measured concentrations in foreign studies at which effects on the neurological development of children were seen. Exposure is expected to drop further in the near future.

The Committee concludes the following regarding substances for which causality is considered *likely*.

### DDT/DDE

The presence of DDT and DDE in the Netherlands has dropped significantly over the past decades. Although foreign research has shown there is a possible link to permanent negative effects on mental development in children, such an effect is unlikely at current levels of exposure in Western Europe.

### PBDEs

A Dutch study found neurotoxic effects of prenatal exposure to PBDEs. There are also indications for effects on the thyroid gland. Use of PBDEs was banned in 2006, with the exception of the most highly brominated compound. However, the long half-life means the effects may continue to occur for some time. Exposure via food and breast milk will also only drop slowly.

### Perfluorcarbon compounds

The concentrations of perfluorcarbon compounds measured in the blood of adults in the countries around us is consistent with the range of exposure concentrations related to effects on the immune system in epidemiological studies. The use of perfluorcarbon compounds has been reduced significantly, but these substances also have long half lives, and effects may therefore persist for some time.

Regarding substances for which causality is considered *possible*, the Committee concludes the following.

### Phthalates

In 2008, the EU regulated the use of a number of phthalates, and exposure levels will have dropped since then. However, recent Dutch research shows that exposure concentrations are still comparable to the concentrations seen in a number of foreign cohorts, which found associations with neurological development. Newborns admitted to intensive care units are a particular risk group. It is possible that the use of phthalates in medical applications has resulted

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in high exposure levels and thus to health effects. The use of phthalates for medical applications has since been reduced.

### Cadmium

Levels of cadmium in the urine of mothers of a group of children in whom a foreign study found health effects, is consistent with the levels of cadmium in the urine of adults in the Netherlands with the highest values (95<sup>th</sup> percentile). It is therefore possible that prenatal exposure to cadmium may lead to effects on the nervous system in the children of women in that group.

### Bisphenol A (BPA)

Comparison of BPA concentrations in the urine of Dutch pregnant women with concentrations at which associations were found with effects on behaviour and growth retardation shows that such effects may have been or may still be present in our country. In the EU and a few other countries, baby bottles made with BPA may no longer be used as a precaution. However, this measure has no effect on exposure during the prenatal phase. Recent scientific research, however, does raise concerns about the risk of prenatal exposure.

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### The bottom line

The judgements on possible relationships between exposure to substances early in life and certain kinds of health effects are summarized in the first four columns of the table. The next four columns show the results of health effects that may have occurred in our country, current health effects, the effects of reduction measures and possibilities for further reduction.

According to the Committee, a number of substances still pose a problem, even though exposure to them has been dropping for decades. The latter is good news and a success in terms of policy, but should also be seen as an encouragement to continue along this path. As more epidemiological research into effects becomes available, the causality of the relationships in question may potentially be better assessed. After all, confirmation or rejection of causal relationships between other substances and health effects sometimes took a long time. Furthermore, these effects are often subtle and can only be determined at a higher age. The Committee would like to emphasize that there are other substances that may have health effects in practice, but that we are unaware of because there is (currently)

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*Table* Evidence for a causal relationship between prenatal and postnatal exposure to substances and the occurrence of four categories of effects. The adjoining columns indicate whether these effects have been observed (in epidemiological studies in the Netherlands) or are likely (based on comparison of exposure in the Netherlands with epidemiologic research performed abroad or based on comparison with reference values), presently (defined as between 2004 and now) or in the past (prior to 2004) in the Netherlands. The final two columns indicate whether government interventions have resulted in a reduction of exposure, and whether there are still possibilities for reducing exposure further.

	Effects on the endocrine system (H3) <sup>a</sup>	Effects on the immune system (H4) <sup>a</sup>	Effects on the nervous system (H5) <sup>a</sup>	Other effects (H6) <sup>a</sup>	Effects in the Netherlands in the past: observed or likely? (H7) <sup>b</sup>	Effects in the Netherlands in the present (from 2004): observed or likely? (H7) <sup>b</sup>	Policy to reduce exposure successful? (H7) <sup>c,d</sup>	Possibilities for further reduction of exposure (H7) <sup>e</sup>
Lead			proven	possible	yes	yes	yes	limited
Methylmercury			proven		yes	uncertain	yes	limited
PCBs and dioxin-like substances	proven	proven	proven	proven	yes	yes	yes	no
Organo-phosphates			proven		yes	uncertain	yes	yes
DDT and DDE			likely		yes	no	yes	no
PBDEs	likely		likely		yes	uncertain	yes	limited
Perfluorcarbon compounds		likely			yes	uncertain	yes	limited
Phthalates			possible		uncertain*	uncertain*	yes	yes
Cadmium			possible		uncertain*	uncertain*	yes	limited
Bisphenol A			possible	possible	uncertain*	uncertain*	limited	yes

a levels of evidence 'proven', 'likely' and 'possible' are defined in section 2.2.

b 'yes': exposure within the range observed in epidemiological studies in which negative effects were seen; 'no': exposure below the range observed in epidemiological studies in which negative effects were seen; 'uncertain': exposure is unclear; uncertain\*: exposure within the range observed in epidemiological studies in which negative effects were seen, but causality is *possible* at best.

c 'yes': exposure levels have dropped; 'limited' there is no policy for protection during the prenatal phase; 'no': there is no policy.

d it should be noted that lowering exposure levels does not rule out the presence of effects.

e 'yes': reduction is possible and/or (illegal) uses can be reduced further; 'limited': this substance may still be present in consumer products in people's homes; 'no': there are no background residues.

a lack of research available. All the more reason to closely monitor the quality of risk assessment.

## Quality of the risk assessment

The assessment framework is a preventive strategy that allows denying potentially problematic substances access to the market. The initial assessment framework for chemical substances is based largely on toxicological research.

Within the context of the European chemicals directive REACH (Registration, Evaluation, Authorisation and restriction of Chemicals), the Committee recommends introducing the so-called EOGRTS (*Extended One Generation Reproduction Toxicity Study*), as defined by the OECD (Organisation for Economic Co-operation and Development), in 2011. The Committee previously published an advisory letter on this subject. The ‘*extended*’ refers to, among other things, endpoints for prenatal exposure that are relatively sensitive, namely endocrine, neurotoxic and immunotoxic effects of exposure during development. Introduction of EOGRTS reduces the risk of a substance that is potentially harmful in this phase of life slipping through the cracks of the testing procedure. Furthermore, the Committee feels the current assessment framework in REACH is lacking in vitro tests. In vitro studies allow investigation of a number of subtle effects on specific developmental processes that are not clearly expressed in animal studies. Aspects including stem cell differentiation and epigenetic effects are also important.

However, this is not a solid guarantee. Certain relevant effects may not become visible in animal studies, for example, because they are rare or only manifest very late in life. Additionally, the fact many substances are allowed onto the market without extensive toxicological testing procedures, while epidemiological data are also lacking, remains a problem.

Therefore, it is possible that we may face a few unpleasant surprises in the future. Taking this into consideration, the Committee recommends setting up a *post marketing surveillance* system, analogous to that in place for medicinal products. Elements that may play a role are new data on mechanisms of action – the substance proves to be more risky – and new applications of the substance – exposure is higher than expected or affects high-risk groups.

This may be a reason to closely monitor use of the substance or perform further or more in-depth epidemiological research. Hopefully, this will allow any health damage that occurs to be discovered sooner and enable earlier policy-level interventions.

