
Executive summary

Dutch study poses questions for Health Council

It is estimated that half a million workers in the Netherlands are regularly exposed to organic solvents. Some examples of well-known solvents are toluene, styrene, xylene, benzene and turpentine. These are widely used for degreasing and diluting, and are found in such products as ordinary paints, car paints, stains, and glues. Solvents evaporate, so those who work with these products tend to inhale them.

It is known for a long time that inhaling organic solvent fumes may impair people's health. In recent years, occupational exposure to these solvents has been linked to various effects. The most well-known and best documented effect is the occurrence of chronic toxic encephalopathy (CTE), also known as organic psycho syndrome (OPS). This involves serious damage to the nervous system, resulting in memory disorders, impaired concentration, mental inertia, fatigue, headache, irritability and depression. In addition, it is known that exposure to certain organic solvents (such as benzene) can cause cancer.

Less is known about possible effects on reproduction. In 1999, that topic was at the centre of a commotion, following the publication of a Dutch study in men who had been examined at a fertility clinic. This study found that exposure to organic solvents appeared to be linked to reduced sperm quality. The results of this study led to questions being asked in the Dutch parliament. The results of another Dutch study were published in 2005. These results suggested that expo-

sure to solvents might cause birth defects among the children of professional painters.

In 2005, these two Dutch studies caused the State Secretary for Social Affairs and Employment to seek the Health Council's advice about the possible effects on reproduction of occupational exposure to organic solvents. The following questions were submitted to a specially appointed committee:

- Is there any evidence that occupational exposure to organic solvents can produce effects on reproduction?
- Is there a known mechanism of action that could explain these possible effects?
- Do the limit values* that currently apply to various organic solvents provide protection against effects on reproduction?

The Committee uses the term “reproductive disorders” to refer to any problems that may arise in connection with fertility, pregnancy, and development of the offspring.

Half of the available research is useable

Requests for advice are answered by assessing and weighing up the results of scientific research. One key finding is that, while there are many publications dealing with the effects of occupational exposure to solvents on reproduction, only a few of them can be used for answering the committee's questions. For example, exposure to solvents is often difficult to quantify. One of the major problems is that, in nearly every case, the employees in question are exposed to mixtures of different solvents. Furthermore, workers in many industries also come into contact with other substances (such as metals), which can sometimes cause reproductive disorders. In such cases, it is no longer possible to identify the relation between exposure to a given solvent and the occurrence of reproductive disorders. In spite of the efforts of research workers in recent years, very little is known about the composition of the mixtures used by people in the course of their work, and about the concentrations of the individual solvents to which they are exposed.

A second problem is that effects can occur at many different phases in the reproductive cycle. This may involve effects on sperm, ova, ovaries, and menstruation, as well as the occurrence of miscarriages, birth defects, and problems

* The 2005 request for advice refers to the MAC values (Maximum Allowed Concentrations). In 2007, these values were substituted by public and private occupational exposure limits.

in the child's psychomotor development. These effects all involve different mechanisms and, in all probability, a range of different causes. Therefore, for all studies it is essential to draw a distinction between the different effects and to define each effect accurately.

Finally, there is often no information available about the timing of exposure, even though this is thought to be one of the critical factors in causing toxic effects on the reproductive system. For example, effects of exposure at an early stage of pregnancy can differ from those resulting from exposure at a later stage.

As a result of these weaknesses, the quality of much epidemiological research is too poor to enable judgments about the reported links between exposures and reproductive disorders. After evaluating the available studies, the committee has rejected more than half of them. This still left well over 80 studies which did meet the quality criteria.

Effects on reproduction were identified for a number of solvents and situations

Exposure to some ethylene glycol ethers impairs male fertility

After examining studies in human subjects, the committee found indications that exposure to various ethylene glycol ethers (EGEE* and EGME**) may impair male fertility. This has been confirmed by experimental animal studies.

Workers exposed to ethylene glycol ethers include those carrying out painting or maintenance work, and those employed in the semiconductor industry. Studies of employees in the painting and maintenance trade show weak indications for an increased risk of fertility problems in men, depending on the level of exposure (probably to ethylene glycol ethers). The introduction of appropriate regulations caused exposure levels to these glycol ethers in Dutch companies to fall markedly in recent years. In addition, a switch was made from using ethylene glycol ethers (such as EGEE and EGME) to using other less harmful glycol ethers. However, recent exposure data are not available. For this reason, the committee cannot exclude the possibility that employees in some sectors may still be at risk for harmful effects on reproduction as a result of exposure to these ethylene glycol ethers.

* EGEE: Ethylene glycol ethyl ether or 2-ethoxyethanol.

** EGME: Ethylene glycol methyl ether or 2-methoxyethanol.

Exposure of pregnant women to some ethylene glycol ethers increases the risk of spontaneous abortions and birth defects

Exposure of pregnant women to ethylene glycol ethers may lead to reproduction toxic effects. Epidemiological studies give indications for an increased risk of spontaneous abortions and malformations after exposure to EGME and EGEE. In addition, experimental animal studies convincingly demonstrated that exposure to ethylene glycol ethers gives causes harmful effects during and after pregnancy (ranging from foetal death to birth defects).

Ethylene glycol ethers are primarily used in the semiconductor industry. Human studies in this industry also provide indications for an increased risk of such effects. Here too, exposure levels have fallen substantially, but the committee cannot exclude the possibility that there are still companies where the airborne concentrations of these substances could exert an effect on the development of the progeny.

Exposure of pregnant women to tetrachloroethylene (PER) and xylene may increase the risk of miscarriage

The committee concludes that there are weak indications that exposure to tetrachloroethylene (PER) and xylene in pregnant women increases the risk of spontaneous abortions. Experimental animal studies also show that exposure to these solvents may harm the unborn foetus. However, the evidence is not strong enough to confirm the epidemiological data.

Exposure to PER is mainly found in dry-cleaning shops (chemical laundries). Studies carried out among employees of dry-cleaning shops and laundries in the 1980s confirm the perception that there might be an increased risk of miscarriage, probably due to exposure to high concentrations of PER. However, PER exposure levels have dropped so markedly in recent years that the committee does not expect current exposure levels to lead to effects on reproduction.

Exposure to xylene mainly occurs in printing companies and in the petrochemical industry. Because the subjects in the available studies were simultaneously exposed to other solvents, the committee is unable to determine whether there is still an elevated risk for those who are currently employed in these industries.

Exposure of men and pregnant women to toluene increases the risk of spontaneous abortion

The committee concludes that there are indications from studies in human subjects that exposure of pregnant women to toluene increases the risk of spontaneous abortion. There are also weak indications for an increased risk of childhood leukaemia. Data from experimental animal studies do not confirm a possible link between exposure to toluene and the occurrence of spontaneous abortions. However, the evidence in these studies is limited and not sufficient for definite conclusions.

Aside from exposure to xylene, those working in printing companies and in the petrochemical industry may also be exposed to toluene. The committee concludes that there are weak indications that pregnant female employees working in printing companies or the petrochemical industry who are exposed to agents such as toluene, amongst others, have an elevated risk of reproductive disorders. As these women are also exposed to other solvents (e.g. xylene and styrene), it is impossible to determine which proportion of that risk can be attributed to toluene.

It is not just the exposure of pregnant women that may have implications for the offspring. There are also weak indications that if men are exposed to toluene (during painting and maintenance work, for example) prior to conception, their partner is at increased risk of a spontaneous abortions.

No details are available concerning the current concentrations of toluene. Accordingly, the committee is unable to determine whether there is still an increased risk of spontaneous abortions in these industries.

The effects of many solvents are still poorly understood

Information concerning the effects of exposure on reproduction is only available for a small fraction of the total group of organic solvents (toluene, xylene, styrene, acetone, ethylene glycol ethers, tetrachloroethylene, benzene and methylene chloride). For a large group of organic solvents (such as N-methylpyrrolidone, butanol, isopropanol, 2-butoxyethanol and many others) no epidemiological or other research has been carried regarding their effects on reproduction. Although people are regularly exposed to these solvents in practice, the committee cannot make any statements concerning the effects of occupational exposure on reproduction.

Even in the case of those solvents for which data are available, the issue is far from cut and dried. Sometimes, the results are very limited or contradictory.

Therefore, it is impossible to draw any conclusions with regard to these solvents, either.

Current limit values cannot be assessed

Do the limit values which currently apply to various organic solvents in the workplace offer sufficient protection against effects on reproduction? Based on the data which has been examined, the committee is unable to answer this question from the State Secretary. By definition, a health-based recommended occupational exposure limit protects employees (and their offspring) against *all* adverse health effects arising from occupational exposure to substances. Therefore, when determining the health-based recommended exposure limits, the effects on reproduction must also be taken into account. But that would require relevant data to be available, and that is often not the case.

Since the introduction of the new Working Conditions Act on January 1, 2007, both public and private limit values have to be pegged at the same level as the health-based recommended occupational exposure limit. Toluene, acetone, xylene, benzene, and some glycol ethers are examples of solvents which are subject to a legally binding limit. In the case of most other solvents, the social partners (employers and trade union confederations) are responsible for deriving of safe limit values.

The committee therefore believes that if an epidemiological study identifies effects on reproduction, it is important to determine the type and concentration of the solvents to which the individuals in question have been exposed. If these details are lacking, it is impossible to determine whether the identified effects on reproduction are due to exposure at a level above the existing limit values, or that the existing limit values simply do not provide sufficient protection.

Better exposure data are needed to identify the potential risks

For a number of solvents (ethylene glycol ethers, toluene, xylene and tetrachloroethylene), there are (weak) indications that exposure may cause reproductive disorders. However, up-to-date data concerning exposure in various branches of industry are not publicly available. Therefore, the committee recommends the following for these substances:

- first, identify those types of industry in which exposure to these solvents still takes place
- next, produce quantitative data on the exposure levels of the individual solvents for those types of industry in which exposure is likely.

Improved data accessibility is also required

For most solvents, little or no exposure data are available. In the Netherlands, most exposure measurements are done at the behest of individual companies, which means that the data are often not publicly available. Therefore, the committee recommends that a national database be created in which all exposure data could be collected. The systems currently in use in Great Britain or Germany could serve as an example.

In addition, the committee established that current registration systems for recording birth defects also have their limitations. Therefore, the committee also recommends the creation of a single national registry which would incorporate and integrate all existing registers.

Furthermore, if it were possible to link these two databases (for exposure and for effects), numerous opportunities would be provided to investigate risks in the workplace more effectively than is currently possible.