

Toxicology Topics in Brief

Reproductive Risks of Chemicals at Work

Reproductive hazards of chemicals in the workplace are taken into account when the obligatory COSHH assessments are made. Similarly, there may be additional risks for new and expectant mothers at work which need to be reflected in a special risk assessment.

Legislation relating to the control of reproductive risks from chemicals at work merges into broader aspects of employment law which are not the subject of this document. Furthermore, moral and emotive issues are significant in this area. Changes in fertility treatments continue to be a rapidly developing subject and the authors recognise that it may be necessary to revise this document further in due course in the light of new knowledge and legislative changes.

General Considerations

The reproductive hazards of a chemical can affect men, women, the foetus and postnatal development. However such hazards have been demonstrated for relatively few chemicals, and even fewer chemicals have been shown to be of high potency. While caution in dealing with any chemical is always required there is no reason to think that reproductive risks from exposure to chemicals at work are other than very small if adequate precautions are taken.

As indicated above, this document deals only with occupational exposure to chemicals and it must be recognised that there are many other potential sources of exposure (e.g. “DIY”, gardening, domestic cleaning agents). This document is not intended to cover substances deliberately administered for therapeutic purposes, although our knowledge of some reproductive effects has arisen in this way. Nor does this document deal with ionising radiations or micro-organisms, both of which can affect the reproductive system.

Recent trends in human fertility are indicative of a possible decline in normal reproduction, and suggest, but do not prove, that exposure to environmental chemicals and drugs, and possibly trace hormonal residues in drinking water, may contribute to this decline. Most recently there has been significant attention given to Endocrine Disrupting Chemicals (EDCs), which are suspected of causing adverse effects due to their effects either directly or indirectly on the hormonal systems.

Reproductive hazards from chemicals have much in common with other forms of chemical toxicity (although in general there are fewer data), and, as with any other toxic effect, the degree of response depends on the dose or exposure; this controls the risk. Thus harmful exposure is likely to occur only if substances are ingested, inhaled or absorbed through the skin in sufficient quantities. Similarly, “lifestyle factors” (e.g. diet and smoking) and genetic predisposition may affect any reproductive risk to an individual from a particular chemical. Also, it is important to realise that there is a natural background of reproductive abnormalities quite independent of any occupational chemical exposure.

Possible Reproductive Effects of Chemicals

The causes of adverse effects on the human reproductive process are very varied and, on the whole, poorly understood. Hereditary factors are usually accepted as being responsible for a large proportion of reproductive malfunction. Environmental and lifestyle factors, including exposure to natural and synthetic chemicals, drugs, ionising radiation and alcohol consumption are also contributors but the magnitude of each contribution is unknown. Other factors also need to be considered, such as changes in reproductive behaviour. Some of the possible reproductive effects seen can at least in part be associated with having children later in life (both mothers and fathers being older than in the relatively recent past) and also having fewer children.

Reproduction is a complex, multi-stage process covering pertinent events between the development of germ cells in both male and female, starting early in life right through to the status of the offspring as a healthy sexually mature adult. Interference at any of these stages may cause adverse effects, collectively described as “reproductive impairment”. It is difficult to estimate the overall rate of reproductive impairment in the “normal” human population. This is because figures quoted for specific types of impairment are often incomplete and, in particular, because most spontaneous abortions occur very early and may be perceived as late menstruation. However the following estimates have been suggested for a “developed” society:

- 8 to 15% of couples seek treatment for clinical infertility.
- More than one-third of early human conceptions and 10 to 15% of recognised pregnancies are terminated by spontaneous abortion usually between the 7th and 12th weeks of pregnancy.
- The number of babies born with birth defects varies according to social class/income level and geographical location. However, it is estimated that, on average, about 16 – 17% of live births have major or minor malformations after one year.
- Anecdotal evidence of increased intersex and hormonal insensitivities which result in reproductive incapability.

Birth defects are abnormalities of structure, function or metabolism present at birth that result in physical or mental disability or fatality. Birth defects are the leading cause of death in the first year of life. Both genetic and environmental factors can cause birth defects although the causes of about 60% to 70% are currently unknown. Globally about 150,000 babies are born each year with birth defects, as are about 3% of live births in the USA. Considering just genetic defects these reportedly range from 39.7 per 1000 live births in high-income regions up to 82 per 1000 live births in low-income regions. That is roughly 1 in 25 (4%) to 1 in 12 (8%). Much of this incidence of birth defects is not attributed to chemical exposure but to other causes.

A relatively small number of chemical, physical and biological agents have been linked to specific effects. Of all the chemical substances and mixtures which are commercially available, few, other than drugs, pesticides, food additives and new industrial chemicals have been evaluated for reproductive effects. Guidance may be derived from the safety data sheets or the hazard statements or precautionary statements on the label.

In the main, adverse reproductive effects of chemicals have been identified by direct practical experience from either accidental occupational exposure or as side effects of therapeutic drugs. Thalidomide is the classic example. Exposure is often difficult to identify or quantify and, of course, once discovered or suspected cannot be subject to experimental examination. Experimental animal studies, on the other hand, have identified a number of unrelated chemicals that cause various adverse reproductive effects. While these results are likely to be used for regulatory or labelling purposes to indicate a potential hazard, the predictability of risk to humans arising from exposure to these substances is much more limited because animal models often do not mimic the relevant human biology, and there can be considerable differences in absorption, metabolism and genetic variability between humans and other species.

Adverse effects on reproduction may be chronic, arising from exposures long before pregnancy, as well as the more obvious acute effects. Advances in techniques and our expanding knowledge of genetics means that far more is known about individual susceptibilities to chemicals, and this includes the risks to reproductive health.

Many associations between chemical exposure and reproductive effect are based on limited evidence. There is extreme difficulty in many cases in developing satisfactory cause and effect relationships in humans or in quantifying exposures. Estimates of the extent of particular influences may vary widely from source to source. It is against this background that the general question of the reproductive hazards of chemicals must be set.

Earlier studies focused mainly on the possible association between exposure of the mother to chemicals during pregnancy and subsequent birth defects, especially anatomical abnormalities in the offspring (e.g. thalidomide and diethylstilboestrol). More attention is now paid to effects resulting from exposure of either parent at other stages of the reproductive process or even earlier in life.

Reproduction may be subdivided into germ-cell development, pre-natal and postnatal stages. For ease of presentation reproductive hazards may be considered in terms of possible end points in these various stages.

Toxic Effects on the Human Male Reproductive System

Chemicals that target the male reproductive system may affect male reproductive organ structure, spermatogenesis, androgen hormone secretion and accessory organ function, if either the dose and/or exposure is sufficient.

Some examples of chemicals which have been implicated in affecting the human male reproductive system are:

- The nematocide DBCP (1, 2-dibromo-3-chloropropane), ethylene oxide and chlordecone (infertility).
- Kepone (chlordecone) and carbon disulphide (reduced sperm counts).
- Lead and epichlorohydrin (sperm abnormalities).
- 1,2-Dibromoethane, cadmium, *m*-dinitrobenzene and ethylene glycol monomethylether (reduced fertility).
- Carbon tetrachloride (hormonal changes).

In addition, mention must be made of substances which are not normally thought of as “chemicals”. Alcoholic drinks are a well-known cause of impotence in men and reduced sperm counts have been imputed to marijuana smoking.

Finally, compounds with oestrogenic (feminising) effects may interfere with the reproductive process by reducing libido or affecting sex hormone balance while neurotoxic substances may affect coital ability.

Toxic Effects on the Human Female Reproductive System

Chemicals that target the female reproductive system can cause a wide variety of adverse effects, including changes in sexual behaviour, onset of puberty, cyclicity, fertility (oogenesis or ovulation), implantation, gestation time, pregnancy outcome, lactation and premature menopause. All these adverse effects can disrupt a woman's ability to reproduce successfully if either the dose and/or exposure is sufficient.

Some examples of chemicals which have been implicated in affecting the human female reproductive system are:

- Lead - menstrual disorders and infertility.
- Carbon disulphide, mercury, and polychlorinated biphenyls (PCBs) - cause irregularities in the menstrual cycle.
- Vinclozolin, procymidone and linuron, some phthalates, arsenic, toluene and some other organic solvents and endocrine disrupting chemicals (foetal abnormalities).
- Nitrous oxide at concentrations considerably above the occupational exposure limits (reduced fertility).

Toxic Effects in the Pre- and Peri-Natal Periods

The pre-natal period comprises pre-implantation, embryonic and foetal stages. The pre-implantation phase lasts about two weeks and chemical toxicity at this stage usually leads to the death of the developing organism so that an abnormal foetus does not develop. The next phase, when the basic development of organ structures takes place, lasts broadly from days 20 to 55. This is a period of particular vulnerability to insults leading to morphological defects. These may be severe enough to cause embryonic death or may be manifest at term as birth defects. Within this general developmental timescale individual organ systems have their own periods of particular vulnerability, and these have been well documented. After the 7th or 8th week of pregnancy the major processes are tissue development, functional maturation and continuing growth. Toxic effects during this period may lead to retardation of growth or functional disorders. The foetus (i.e. after 7-8 weeks) is more resistant to lethal effects than the embryo but severe toxic chemical insults can lead to stillbirths. Thus the most important phase of pregnancy for induction of birth defects may be before the pregnancy is recognised, and risk assessments must take account of this effect.

The placenta prevents the passage of some substances to the foetus and acts to metabolise other chemicals absorbed by the mother. The end products of this metabolism are usually less toxic than the original compounds; this is not invariably so and some chemicals may be activated to more toxic metabolites. The development in the foetus of enzyme systems for metabolizing foreign chemicals is slow and is not complete till long after birth. Examples of materials which may exert toxic effects in the pre-natal phase are methylmercury compounds (CNS effects) and some heavy metals (embryotoxic).

The best known examples of toxicants (teratogens) associated with a range of developmental abnormalities are:

- Thalidomide prescribed for morning sickness which, taken in the first trimester, caused gross malformations, largely shortening of limbs (phocomelia) and ears.
- Diethylstilboestrol (DES) which was prescribed to pregnant women to prevent miscarriage. It was also used to stop breast milk and to inhibit growth in young girls. It was subsequently found to cause clear-cell adenocarcinoma of the vagina and cervix in women who had been exposed *in utero*. Also, DES increases the risk of testicular cancer in males exposed *in utero*.

Other substances known to be teratogenic in humans include:

- Alcohol. Heavy alcohol consumption by pregnant women is associated with adverse effects upon offspring. Known as foetal alcohol syndrome, this is characterised by facial, limb and cardiovascular abnormalities, growth retardation and CNS dysfunction.
- PCBs have been associated with malformations and other effects in children.
- Angiotensin converting enzyme inhibitors (ACE Inhibitors) are potent anti-hypertensive drugs associated with, inter alia, foetal toxicity including intrauterine renal insufficiency.
- Cigarette smoking is associated with low birth weight, shortened gestation and increased perinatal mortality.

- Cocaine use during pregnancy has been associated with abruptio placentae, prematurity, foetal loss, decreased birth weight, microcephaly, limb defects, urinary tract malformations, and poorer neurodevelopmental performance.
- Hydantoins (phenytoin and trimethadione) have been associated with a recognisable pattern of malformation termed the foetal hydantoin syndrome. The clinical features include craniofacial dysmorphology.
- Lithium treatment for bi-polar disorder may rarely produce heart defects in the foetus during the first trimester. However the risks are generally considered lower than with other drugs for this condition.
- Sodium valproate in the first trimester is associated with, *inter alia*, neural tube defects.

Other compounds which may be teratogens include D-penicillamine, methimazole and diazepam.

Toxic Effects in the Post Natal Period

Development of the nervous, immune, endocrine, reproductive and metabolising systems continues after birth. Some chemicals absorbed by the mother are excreted in breast milk, unchanged or as metabolites. Hence the opportunity for toxic insult to the newborn baby by those chemicals is significant following sufficient exposure. Heavy metals, PCBs and PBBs have all been associated with this route of exposure.

Conclusions

The identification of the reproductive effects of chemicals and their dose-effect relationships is in many respects a rapidly developing science. However it has many features in common with other forms of chemical toxicity. Detailed assessment of risk requires reliable, high-quality data covering exposure and outcome. Except in a very few cases such data are not available.

Reproductive effects are only one of the potential risks to health that have to be controlled in the workplace. In general it is desirable that legislation to control the use of chemicals at work should so far as is practicable protect against adverse reproductive effects by controlling and minimising exposure, and hence risk.

Women of child-bearing age are often considered a group of particular concern in relation to chemical reproductive hazards requiring special provisions. However it is clear from the information above that the possibility of adverse pre-conception effects exists at any time in either sex, and not just during pregnancy. More importantly there may be adverse effects before pregnancy is recognised, or during breast feeding after the pregnancy. Of particular relevance here is that a woman is born with all the eggs needed for her child-bearing lifetime. Moreover, fertility treatment has extended the age range of women potentially at risk and introduced possible donors who may have been previously exposed to chemicals. It is thus important that, as far as practicable, adequate protection be afforded to all persons at risk at work. This must be a standard feature of all COSHH hazard assessments, as set out in the HSE publication "COSHH Assessments; a step-by-step guide to assessment and the skills needed for it". This all important COSHH assessment to evaluate risk is a vital part of any risk assessment for chemicals which may affect reproduction as with all toxic hazards and is paramount in controlling exposure to hazards of this type at work. Where appropriate, occupational exposure limits should be, and normally are, set so as to take account of known reproductive effects.

For additional reassurance some organisations offer pregnant employees the opportunity to work away from chemicals during part or all of their pregnancy, but clearly this should be in addition to the above safeguards.

Except for those chemical groups where there are regulatory requirements for reproductive toxicity testing (e.g. pharmaceuticals, pesticides and food additives, there is a shortage of information on reproductive effects of many substances. Registration under the UK and EU REACH Regulations of existing and new chemicals requires an assessment of reproductive hazard for all chemicals manufactured or imported in quantities > 10 tonnes/year,

either a weight of evidence approach using existing information, or the conduct of experimental studies (reproductive toxicity screen, and developmental/reproductive toxicity at higher tonnages). It is to be hoped that advances in knowledge will lead to a better understanding of which chemicals may affect reproduction, and of the relevant dose-response relationships, and hence to a consequent improvement in risk assessment and control.

The main way that chemicals can be identified as being a possible risk to reproduction in the workplace is via their classification and labelling. This is based on the GHS system which is implemented in the UK and EU as the CLP Regulations, currently based on the EU Guidance. The three main classifications which indicate a need to manage the risk from possible exposure, are those for Germ cell mutagens, Carcinogens and specifically for Toxicity to reproduction.

Further Reading

Casarett and Doull's Essentials of Toxicology 2010 2nd ed. Klaassen C D, Watkins J. McGraw-Hill Publishing Co. 459 pages ISBN: 007162240

ECHA (European Chemicals Agency). Guidance on the Application of the CLP Criteria. Version 5.0, July 2017. https://echa.europa.eu/documents/10162/2324906/clp_en.pdf/58b5dc6d-ac2a-4910-9702-e9e1f5051cc5?t=1499091929578

Genius S. J. Mini-Review, Developments in Reproductive Medicine, Human Reproduction, 2006, 21, (9), 2201-8

HSE (UK Health and Safety Executive). COSHH Assessments; a step-by-step guide to assessment and the skills needed for it. <https://www.hse.gov.uk/coshh/riskassess/index.htm>

International Programme on Chemical Safety 2001 Environmental Health Criteria No. 225. Principles for evaluating health risks to reproduction associated with exposure to chemicals. <http://www.inchem.org/documents/ehc/ehc/ehc225.htm>

March of Dimes <http://www.marchofdimes.com>

Principles and Methods of Toxicology 2008 5th ed. Hayes AW Ed. Taylor & Francis Inc. 2270 pages ISBN: 100: 84933778

Schardein J L. 2000 Chemically Induced Birth Defects, 3rd ed. New York: Marcel Dekker, Inc., xiv, 1109 pages, ISBN 0824702654

Annex: Details of GHS Classification and Labelling relevant to the identification of chemicals known to represent a possible risk to human reproduction.



To identify those substances that can represent a reproductive risk in the workplaces the classification and labelling of the substance is the main starting point. The GHS system as implemented in the EU and UK under the REACH regulations and CLP regulations has specific classifications for hazardous substances which are specifically a risk for reproduction (Toxic to Reproduction). Also there are those whose classification which not specific to toxic effects on reproduction but which do also pose a possible risk to reproduction due to their hazardous properties, such as Carcinogens and Mutagens.

In the UK, the application of the Classification and labelling of chemicals currently still directs you to the EU Guidance on the Application of CLP criteria (see link below) in this document it details the criteria for classification and labelling for Germ Cell Mutagenicity, for Carcinogenicity and for Toxicity to reproduction, both effects on reproduction directly and also on developmental toxicity (adverse effects specifically on the foetus). The primary way to identify such substances with potential to cause risks too reproduction in the workplace is via the pictograms and Hazard statements that should appear on the labels.

Germ Cell Mutagens

Germ cell mutagens are substance which if they can reach the gonads (the testis and the ovaries) could cause mutations in the germ cells (the sperm and the eggs). This could result in cancer but they could also cause adverse reproductive effects such as effects on fertility and developmental toxicity in the foetus.

3.5.4.1. Pictograms, signal words, hazard statements and precautionary statements

Annex I: 3.5.4.1. Label elements shall be used in accordance with Table 3.5.3, for substances or mixtures meeting the criteria for classification in this hazard class.		
<i>Table 3.5.3</i>		
Label elements of germ cell mutagenicity		
<i>Classification</i>	<i>Category 1 (Category 1A, 1B)</i>	<i>Category 2</i>
<i>GHS Pictograms</i>		
<i>Signal Word</i>	<i>Danger</i>	<i>Warning</i>
<i>Hazard Statement</i>	<i>H340: May cause genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)</i>	<i>H341: Suspected of causing genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)</i>

Carcinogens



Carcinogens are another class of substances which may possibly pose a risk to reproduction, in particular those which are considered to be genotoxic carcinogens. These have the potential in addition to causing cancer in the parent to also adversely affect a foetus.

3.6.4.1. Pictograms, signal words, hazard statements and precautionary statements

Annex I: 3.6.4.1 Label elements shall be used in accordance with Table 3.6.3, for substances or mixtures meeting the criteria for classification in this hazard class.

Table 3.6.3

Label elements for carcinogenicity

Classification	Category 1 (Category 1A, 1B)	Category 2
GHS Pictograms		
Signal Word	Danger	Warning
Hazard Statement	H350: May cause cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H351: Suspected of causing cancer (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)

Toxicity to Reproduction



The category of substances which are of specific concern for their risk to reproduction are those specifically classified as Toxic to Reproduction, this includes both adverse effects on fertility in either males or females but also adverse effect on the foetus during pregnancy or during lactation.

3.7.4.1. Pictograms, signal words, hazard statements and precautionary statements

Annex I: 3.7.4.1. Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 3.7.3.

Table 3.7.3

Label elements for reproductive toxicity

Classification	Category 1 (Category 1A, 1B)	Category 2	Additional category for effects on or via lactation
GHS Pictograms			No pictogram
Signal Word	Danger	Warning	No signal word
Hazard Statement	H360: May damage fertility or the unborn child (state specific effect if known)(state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H361: Suspected of damaging fertility or the unborn child (state specific effect if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H362: May cause harm to breast-fed children.

© 2023 Royal Society of Chemistry Toxicology Interest Group. All Rights Reserved.

This text was originally produced by a working party of the Environment, Health and Safety Committee (EHSC) of the Royal Society of Chemistry. This updated version was prepared by the RSC Toxicology Group Committee in September 2023. This document does not represent an official opinion or policy position of the Royal Society of Chemistry. The information in this publication is intended to be an introduction into this topic and is not exhaustive, and was correct at the time of publication. The RSC Toxicology Group Committee accepts no liability for actions taken on the basis of the information in this document.

For more information on the RSC Toxicology Group, please visit <https://www.rsc.org/membership-and-community/connect-with-others/through-interests/interest-groups/toxicology/>