

1. Introduction

The purpose of this Note is to provide clarification of some of the complex and potentially emotive issues surrounding the subject of reproductive hazards, and hence risks, from chemicals at work. It is concerned only with known and suspected potential effects on human reproduction. It should be emphasised that the risk from exposure in the workplace, as opposed to lifestyle choices, is minimal. The Note is not intended to provide data on individual chemicals; such information may be available from other sources (see 'Further Reading').

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 Note. Moral and emotive issues are significant in this area, especially now that there are more women in the workplace, and more mothers return to work after childbirth. Changes in fertility treatments continue to be a rapidly developing subject and the Working Party recognises that it may be necessary to revise this Note further in due course in the light of new knowledge and legislative changes.

2. 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 Note 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 Note 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 Note deal with ionising radiations or micro-organisms, both of which can affect the reproductive system.

Recent trends in human fertility suggest 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. This possibility can only be evaluated by further research work.

Reproductive hazards from chemicals have much in common with other forms of chemical toxicity (although in general there are less data), and, as with any other

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The EHSC welcomes comments on this Note. Please send them to the Committee Secretary:
Environment, Health and Safety Committee
Royal Society of Chemistry
Burlington House
Piccadilly
London
W1J 0BA

Tel: +44 (0) 207 440 3337
Fax: +44 (0) 207 437 8883
Email: ehsc@rsc.org

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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.

3. 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 "life-style" 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.

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 are fatal. 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%). The country with the lowest level of birth defects is France. 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, as for example with diethylstilboestrol, 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 adverse reproductive effects of various sorts. 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 are 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 (vide infra – 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 drink is a well-known cause of impotence in men and reduced sperm counts have been imputed to marijuana smoking.

Finally, compounds with oestrogenic (feminizing) 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-natal and perinatal 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 but 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 the 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
- hydantoin (phenytoin and trimethadione) have been associated with a recognisable pattern of malformation termed the foetal hydantoin syndrome. The clinical features include craniofacial dysmorphism
- 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 postnatal 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 new-born baby by those chemicals is significant following sufficient exposure. Heavy metals, PCBs and PBBs have all been associated with this route of exposure.

4. 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 *inter alia* against adverse reproductive effects by controlling and minimising exposure, and hence risk.

Women of child-bearing age (the definition of which has become much more extended recently) 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 most substances. Registration of existing and new chemicals requires an assessment of reproductive hazard for all chemicals > 10 tpa, 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.

5. Glossary

CNS	central nervous system
COSHH	Control of Substances Hazardous to Health Regulations
Endocrine	a system of glands in the body that produce the hormones responsible for regulating growth and sexual function
Germ-cell	any of the embryonic cells that have the potential to develop into spermatozoa or ova
Hazard	a hazard is something with the potential to cause harm
HSE	Health and Safety Executive
Oogenesis	process by which mature ova are produced in the ovary
Risk	a risk is the likelihood of a hazard being realised
Spermatogenesis	the process by which mature sperm develop from germ cells within the testis
Teratogen	an agent that has the potential to cause birth defects (non-heritable genetic mutations or malformations) through interference with normal embryonic development if exposure of the foetus occurs at a critical time in pregnancy

6. 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

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

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>

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

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

Environment, Health and Safety Committee *Note on COSHH in Laboratories* 2008

Environment, Health and Safety Committee *Note on Pregnant Workers, Chemicals and the Law* 2010

Environment, Health and Safety Committee *Note on Harmful Effects of Chemicals on Children* 2010

Note was prepared by a Working Party of the RSC Environment, Health and Safety Committee.

The members of the Working Party were: Dr I Wrightson (Chairman), S J Cooper, Dr M Crookes, Dr N King, Dr P Lewis, J Larner, Dr D H Lohmann, Dr C Maxwell, D M Sanderson, Dr C Watts, P Jackson and Dr S Lipworth (Secretary).

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