MRC Reproductive hazards, carcinogens and mutagens best practice guide

The MRC will provide a safe environment employ best practice to ensure health, safety and welfare within the workplace. This document sets the expected best practice guidance for the use of potential reproductive hazards, carcinogens and mutagens under its overarching Health and Safety Policy.

Scope

This document deals with those substances known or suspected of presenting a reproductive, carcinogenic, or mutagenic hazard when used in the workplace. It explains what is meant by the terms reproductive hazard, carcinogenic, or mutagenic substance. It details the safety measures that must be in place before work on any of these materials can be initiated. By following the guidance notes in this document the research worker will ensure that this best practice guidance is implemented.

Director’s Summary

This document looks at substances and materials known or suspected of presenting a reproductive, carcinogenic or mutagenic hazard to man\(^1\). The underlying emphasis is to ensure that individuals working with such agents are competent to do so and that the working environment is designed for the task. It also stresses the importance of ensuring that an adequate risk assessment has been completed prior to any work activity actually starting. This theme is central to ensuring the safety of any activity and more so when dealing with any substance or material coming into one or more of the above categories.

Directors should ensure that the following points are in place:

- Risk assessments and procedures for any substance or material coming into one or more of the above categories
- All persons working with any substance or material coming into one or more of the above categories are competent to do so and that where necessary this competence is recorded
- Those deemed to be particularly at risk i.e. pregnant or breastfeeding mothers, young persons or others with particular medical or physical conditions have been identified and that appropriate control measures are in place to adequately address their particular needs\(^2\).
- Management systems are in place to ensure that sensitive issues are dealt with in an appropriate fashion.

This document is intended for line managers and local safety personnel.

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\(^1\) Man in this context is the human race, male and female

\(^2\) Personal risk assessments must be in place prior to work being started
Guidance notes

This document looks at the hazards and risks related to working with chemicals and materials or substances that are known to be or suspected of being carcinogenic, mutagenic or harmful to the reproductive capacity of man. The document is organised in four sections each dealing with a specific subject matter.

Introduction  MRC general principles
Guidance note 1  Reproductive hazards and associated risks
Guidance note 2  Carcinogenic hazards and associated risks
Guidance note 3  Mutagenic hazards and associated risks
Appendix 1  Risk and safety phrases, Toxicity values and Air measurements.
Introduction

Many chemicals and agents that have a detrimental effect on man, including pre-natal development, can act in synergy with other known or suspected harmful agents. When using an agent or chemical known or suspected of being a carcinogen, mutagen or having a detrimental effect on the reproductive capacity of man then possible synergistic effects must be considered in any risk assessment. One example of synergy comes from studies on smoking and exposure to harmful asbestos dust. In combination the incidence of lung cancer is greater than the expected sum of these two particular agents.

Many agents have one or more of the above hazardous properties. For some agents more than one guidance note will apply. In many instances the advice in one guidance note will apply to the measures in the other guidance notes.

Guidance Note 1

Reproductive hazards and associated risks

Background

Introduction

It has become increasingly evident that the human embryo is subject to a variety of environmental influences that can have a deleterious effect upon its development. It is now recognised that birth defects represent a complex interplay of genetics and the environment. Known environmental causes of birth defects in humans can be grouped into chemical agents (other than drugs), drugs, physical agents and biological agents.

What are reproductive hazards?

Reproductive hazards are agents (normally chemical toxins), which affect men and women's ability to have children. They can also affect the development of the foetus or baby, when the mother is exposed during pregnancy to a reproductive hazard or while breastfeeding. Fetotoxins, for example, are substances with the ability to cause harm to a developing foetus thus considered reproductive toxins.

A reproductive hazard is defined in the context of this guidance note as any substance or activity that is known to or has the potential to cause harm to;

- The reproductive capability of man
- New or expectant mothers
- The unborn child
- The newly born child

There are several important factors that determine whether exposure to a chemical, biological or physical agent or other type of work situation will have negative effects on reproductive health.
These factors are:

- Length of exposure
- Exposure dose
- Possible synergistic effects
- Genetic disposition

Workplace reproductive hazards can be:

- **Chemical agents** commonly found in industrial workplaces (for example metals such as lead and cadmium and solvents such as glycol ether, benzene or toluene), in agricultural work (for example pesticides) and in all sorts of laboratory work.

- **Physical agents** such as radiation (for example ionising radiation such as X-rays used in hospitals and industrial processes such as food irradiation).

- **Biological agents** found in laboratories and health and child care workplaces, particularly viruses such as rubella, mumps, hepatitis B or cytomegalovirus.

- **Work practices** which are physically stressful or which are difficult and potentially unsafe for pregnant workers (for example, climbing ladders, standing all day and excessive bending during late pregnancy).

Reproductive hazards in the workplace

**Chemicals**

**Classification**

Chemical reproductive hazards are classified into 3 major categories\(^3\).

**Category 1**

1a

In this category there is sufficient evidence for a direct causal link between exposure to the substance and an impairment of human fertility. These substances are known to impair human fertility.

1b

These are substances known to cause developmental toxicity in man. There is sufficient evidence to establish a causal link between human exposure to the substance and subsequent developmental toxic effects in the progeny.

\(^3\) Users should refer to Appendix 1 for the Hazard Phrases and symbols associated with each category of carcinogens, mutagens and reproductive hazards.
Category 2

2a

These are substances where sufficient evidence has accumulated to provide a strong presumption that exposure will result in the impairment of fertility in man. This information comes mainly from animal studies where fertility impairment comes from a primary effect of the substance and not from secondary non-specific toxic effects.

2b

There is sufficient experimental evidence to strongly suggest that exposure in man leads to detrimental developmental effects. The evidence is primarily from relevant studies in animals where the toxicity observed is not from secondary non-toxic effects of the substance.

Category 3

Substances in this category are strongly suspected of causing an impairment of fertility in man but the evidence is not strong enough to warrant placement into either (a) or (b) of the category 2 class.

The thalidomide incident in the early 1960s is probably the best documented example of the affect a drug can have on the developing foetus. Prior to this incident it was generally thought that the placental barrier actively protected the developing foetus from any drug administered to the mother. Since this time a large number of associations between drugs and birth defects have been reported.

Examples of chemical agents and drugs

- Anaesthetic gases and liquids
- Prescription only medicines (POM) and drugs/controlled substances
- Aniline (dye)
- Organic solvents (benzene, hexane, glycol ether, toluene)
- Butadiene (rubber manufacture)
- Carbon disulfide (synthetic textile manufacture)
- Chloroprene (rubber manufacture)
- Ethylene dibromide (fumigant, antiknock in petrol)
- Ethylene oxide (sterilant used in hospitals and sterile packaging)
- Heavy metals (lead, mercury)
Physical agents

Work in the early 1920s recognised that exposure of pregnant women to therapeutic doses of radiation (for treatment for a pelvic malignancy) resulted in the birth of children with serious defects of both a physical and mental nature.

Examples of physical agents,
- Ionising radiation (X-rays, Gamma-rays)
- Electromagnetic radiation (microwaves, radio frequency radiation)
- Ultrasound

Biological agents

The classical work of Gregg in 1941 demonstrated that maternal rubella infection could cause malformations to the developing embryo. Other biological agents have since been identified with the potential to disrupt normal foetal development. Included are the Hepatitis and HIV viruses, the tuberculosis bacterium, Mycobacterium tuberculosis and Zoonotic organisms such as the ovine strain of Chlamydia psittaci. Pregnant women coming into contact with sheep infected with this organism has resulted in miscarriage.

Examples of biological agents
- Rubella
- Cytomegalovirus (CMV)
- Hepatitis B
- Mumps
- Toxoplasmosis

Who can be affected?

Sexual function in either men or women may be affected even if they are not planning to have children. All staff including visitors may be potentially affected and reproductive hazards should be controlled like any other workplace hazard. That is, hazardous agents should be removed or exposure to them should be controlled so that the workplace is safe for all staff and visitors.

Male Reproductive Capacity

Studies on this subject have focussed on occupational exposures to substances such as lead, styrene and fungicides to establish possible affects on male reproductive health. There is evidence that prolonged exposure to high concentrations of these substances and to certain other chemicals in particular phthalates can impair spermatogenesis in animals. Most of these studies have been carried out in animals and it is highly unlikely that men will be exposed to concentration levels of this nature. It is also true that in many instances it is difficult to extrapolate directly from the results of animal experiments to man. However, it
cannot be discounted that future studies will show that exposure to specific chemicals will have a deleterious effect on male fertility.

At the present time, it is suspected that the main cause of a decline in male fertility is exposure of the unborn male foetus to harmful agents particularly in the first trimester stage of pregnancy. If this evidence is confirmed then it further emphasises the need for care during pregnancy.

The below diagram illustrates the how the developing foetus can be effected by various harmful agents.

**Female Reproductive Capacity**

Reproductive hazards do not affect every woman or every pregnancy. Whether a woman or her baby is harmed depends on how much of the hazard they are exposed to, when they are exposed, how long they are exposed, and how they are exposed.

In women, reproductive hazards may adversely affect sexual activity or fertility through effects on hormones, the nervous system or the ovary. Just as chemicals can affect orgasm and interest in sex in men, so they can affect women by interfering with nerve and/or hormonal function. Ova (eggs), like sperm, are susceptible to injury, particularly mutation.

Women are born with a fixed number of ova, one of which develops each month under the influence of female hormones and is released by the ovary in mid-cycle. If an agent interferes with these hormones, the cells of the ovary or the developing egg, the menstrual cycle may become irregular. If this occurs, infertility is likely because release of the egg may not occur, or even if it does, the womb may not be 'ready' to receive the fertilised egg. If immature ova are damaged, the supply of eggs will be depleted which may cause early menopause.
Women who smoke tend to reach menopause a couple of years before non-smokers, and chemical exposures in the workplace, if high enough, may have similar effects. The possible consequences of exposure to reproductive hazards for women are:

- Impaired sexual activity
- Infertility
- Irregular periods
- An abnormal pregnancy
- Early menopause

**Developing Foetus**

The foetus may be affected at all stages of development, from the moment of conception to birth.

During the first few weeks, the embryo implants itself in the uterus and the placenta (the organ through which nutrients pass from the mother to the foetus) develops.

Agents can affect the development of the placenta. This may affect the growth of the foetus and if severe enough, may cause miscarriage.

During the first 8-9 weeks after conception, the major organs of the foetus develop (heart, brain, limbs, nervous system). Agents which interfere with the formation of the foetal organs cause birth defects or congenital malformations (for example, heart defects, cleft palate, limb defects). These agents are known as *teratogens*. The foetus is particularly susceptible to damage during this period; this is a problem because most women do not realise they are pregnant until about 6-8 weeks.

The foetus is also susceptible later in pregnancy. The brain, for example, continues to develop throughout the whole of the pregnancy and even after birth. So does the body's system for defending itself against infection (the immune system) and for getting rid of toxic substances (the liver and kidney).

The foetus is also particularly susceptible to agents causing DNA mutations. Exposure to mutagens may cause cancer in infancy or childhood and may also impair reproductive function later in life.
Possible effects of a reproductive hazard on the foetus are:

- Foetal death and miscarriage
- Impaired growth
- Birth defects
- Developmental abnormalities (e.g. learning and behavioural difficulties after birth)
- Childhood cancer

The consequences of uncertainty about reproductive effects

Hundreds of new chemicals are introduced onto the market each year, but only a limited number will be investigated as to whether they have adverse effects on reproductive health.

Most studies of human reproductive effects face a fundamental problem: in many workplaces “exposure” is a general term for contact with all the chemical, physical and physiological stress factors in the environment. Reproductive effects are a question of the combined effects of all these conditions and factors.

It is difficult to identify and attribute a specific reproduction problem to a single factor. There is no doubt that the foetus is particularly vulnerable to damage. Both sperm and ova (eggs) are also susceptible to damage and this may be transmitted to the foetus.

Until chemical agents are adequately tested prior to their introduction to the workplace, all chemicals should be assumed to be potentially dangerous and exposure should be controlled as far as is reasonably practicable.
General Principles

The number of substances (chemical, physical or biological in nature) known or suspected of having a deleterious effect on the health and welfare of man continues to rise. In many instances there are long latent periods between the exposure to a substance known to be deleterious to the health of man and the diagnosis of a medical condition.

The Medical Research Council (MRC) has the following code for staff or any visiting worker who work with any material or substance known or suspected of having carcinogenic or mutagenic properties, or properties that can in any way pose a reproductive hazard to man.

The code is set out as four principles.

<table>
<thead>
<tr>
<th>Principle 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substances or materials with or suspected of having any of the above properties should only be used if it is experimentally justified and that no safer substitute can be used.</td>
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</table>

<table>
<thead>
<tr>
<th>Principle 2</th>
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</thead>
<tbody>
<tr>
<td>Such substances or materials should only be used in areas that are both suitable for the task in terms of hazard containment and where staff and visitors and the environment are not placed at risk.</td>
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<table>
<thead>
<tr>
<th>Principle 3</th>
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<tbody>
<tr>
<td>Staff or visitors using such substances or materials must be competent and trained in their use. The training must include emergency action procedures.</td>
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<table>
<thead>
<tr>
<th>Principle 4</th>
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<tbody>
<tr>
<td>All work with such substances and materials must have a full risk assessment that is understood and followed by those working with such materials or substances. The work must follow clear standard operating procedures that include waste and end product disposal. The risk assessment must introduce work practices that reduce exposure to any substance posing a reproductive, carcinogenic or mutagenic hazard to man to a level that is “as low as reasonably practicable”.</td>
</tr>
</tbody>
</table>
The following two flow charts are an aide-mémoir to the four general principles by outlining the process that must be followed when a known or suspected carcinogen, mutagen or substance having a known or suspected detrimental effect on the reproductive capacity of man is being used.

**Flow Chart 1 questions to ask**

1. **Do I have to use this chemical?**
   - **Yes**
   - **No**

2. **Can I use a safer alternative?**
   - **Yes**
   - **No**

3. **Can I use less?**
   - **Yes**
   - **No**

**Carry out the risk assessment and include:**
- Experimental aim
- Experimental procedure and methods
- Engineering control measures
- Personal protective equipment
- Health monitoring requirements
- Environmental risks
- Emergency procedures

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Risk Assessments

The policy of the MRC is that the responsibility for ensuring that an appropriate risk assessment has been completed lies with line managers and group or team leaders. This is clearly explained in the related MRC policy note on “Risk assessment of work with chemical, biological and ionising radiation hazards”. The risk assessment once completed should then be discussed with, and understood by, the staff involved in the work.

The risk assessment procedure is the way to approach any work-based hazard. A properly carried out risk assessment will identify the hazard(s) whether it be physical, biological or chemical in nature and hence identify the risk to individuals. Additional measures to remove
or reduce or control the risk to particular individuals should be part of this process. Current practice applied through risk assessment will normally be sufficient to control exposure to reproductive hazards. In some instances it will be necessary to review a risk assessment in the light of changes in personal circumstances. It may for example be necessary to review the work practices of a woman in early pregnancy when dealing with ionising radiation or working with steroids particularly androgens. The outcome of such a review may well come to the conclusion that work of this nature be carried out by a non-pregnant worker.

**Employer and employee responsibilities**

Having and caring for children is part of normal everyday life and should not be associated with ill health. Many women continue to work throughout their pregnancy. For the vast majority of female Council staff who do continue to work through their pregnancy, the precautions taken to ensure the safety of all staff will enable them to continue with their normal duties.

All the evidence suggests that the first three months of pregnancy is a critical time for the foetus in terms of the effects outside factors may have on development. Early pregnancy can be a difficult and a particularly sensitive time for a woman. In addition, several weeks can pass before the pregnancy is suspected or confirmed and even when confirmed personal circumstances may prevent a woman from discussing this issue with her immediate line manager.

Currently the present legislation places a responsibility for the newly pregnant woman to alert her employer, in writing, to her change of circumstances before the employer is obliged to act. It is also recommended that provision be made within an MRC establishment to ensure that a sensitive situation of this nature can be dealt with effectively.

As a responsible employer the MRC would expect managers to carry out initial risk assessments on the basis that any of its female employees of child bearing age could be or become pregnant. Even when this has been done there will be the need to re-examine the work practices of female employees who are pregnant or are breast feeding a new born infant.

All female employees should be made aware of and understand what is expected from them, specifically, the legal requirement to react responsibly by alerting their employer if they become pregnant.

**Local policy statement**

Establishments are required to testify that they have reviewed all work activities to determine if there are additional risks to women of child bearing age, through an inclusion in the local policy statement. A suggested example for a policy statement can be found in the MRC Health and Safety Management Guide.

**Other work practices**

Women should always be aware of other factors that may present a hazard during pregnancy and in the immediate post-natal period. These will include any manual handling
activity. The ergonomic design of computing and display screen equipment work-stations should always be re-assessed during pregnancy and after child birth.

- Ergonomics stressors (long working hours, excessive manual handling including heavy and frequent lifts)
- Standing for long periods

Guidance on these activities can be found in the best practice guides ‘Manual handling and lifting’ and ‘Work with Display Screen Equipment (DSE)’. Lone working, working from home and work related travel may also feature in this review process.

It is imperative that all appropriate expertise is called upon to conduct the risk assessments. This may include seeking guidance from occupational health, the corporate SSR (Safety, Security and Resilience) team and where ionising radiation is concerned the radiation protection adviser.

Expectant mothers should also have access to facilities where they can lie down and rest. The rest room must be outside laboratory and work areas. Individuals who wish to make use of such a facility should not be left alone for unnecessarily long periods of time.

In addition all expectant mothers must be informed that the Maternity (Compulsory Leave) Regulations 1994 forbid a mother to return to work within two weeks of giving birth.
Guidance Note 2

Carcinogens

Introduction

One definition of cancer is that it is the unregulated growth and proliferation of cells in the body leading to the development of a neoplasm which can be either benign or malignant in its properties. Benign tumours remain localised whereas malignant tumours can give rise to secondary sites of growth in different parts of the body and organs. Malignant tumours and associated secondary growths are primarily responsible for the fatalities from cancers.

The actual causes of cancers are still not well defined although it is known that exposure to certain chemicals and agents directly or indirectly, through the formation of carcinogenic intermediate metabolites, leads to the formation of cancers. In many instances there is a long “latent period” from the initial exposure to the harmful agent to being medically diagnosed as having cancer. This latent period may be in excess of 40 years and because of this aetiology it is important to ensure that stringent safety measures are implemented when working with any agent known or suspected of being a carcinogen.

Categorisation

Chemicals and agents known or suspected of being carcinogenic are placed into 3 categories based upon present knowledge of their carcinogenic properties. In many instances it is difficult to prove a causal link between the suspected carcinogenic agent and cancer in man. One reason being the long latent period discussed above and the other the synergistic affects that appear to be associated with exposure to agents sometimes with dissimilar physical or chemical properties.

Carcinogenic category 1

These are agents known to cause cancer on the basis of human experiences.

Carcinogenic category 2

On the basis of animal experimentation the evidence is considered reliable enough to be able to extrapolate the carcinogenic properties of the agent to man.

Carcinogenic category 3

The evidence from animal data is not considered sufficient to warrant extrapolation to man.

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4 The major pieces of legislation are the “Control of Substances Hazardous to Health (4th edition) (the Control of Substances Hazardous to Health Regulations 2002)”, GHS (Globally Harmonised System), CLP (Classification, Labelling and Packaging of Substances and Preparations Regulations plus the 2004 amendments and “Approved classification and labelling guides (Chemicals (Hazard Information and Packaging for Supply Regulations 2002)). The International Agency for Research on cancer (IARC) also classifies agents according to known or suspected carcinogenic properties.
**Note**

All chemicals come with relevant “hazard” and “safety phrases” (Appendix 1). Care has to be taken when more than one risk or safety phrase applies to any chemical. In this case the first “hazard” or “safety” phrase indicates the major hazard. It is important to remember that a mix of chemicals may well produce a hazard risk greater than the sum of each individual component. Thus any risk assessment must also consider this possibility.

The exception to “hazard” and “safety” phrases would be novel chemicals or intermediates. In this instance the researcher must evaluate these products in terms of hazard to man by assessing the probable properties of the components used in the reaction and the generic properties of the functional groups of intermediates and the products. The inability to make a reasoned judgment automatically puts the products into the highest risk category i.e. category 1.

Many biological materials will not come with either “hazard” or “safety” phrases but may pose a serious health risk to man. For example, many viral and retroviral particles can pose a serious risk of promoting neoplastic events through insertion or recombination events in the human genome.

Some carcinogenic materials are natural products such as silicate mineral dusts and fibres, some hardwood dusts and some metals such as nickel and cadmium.

**Control measures**

No work with known or suspected carcinogenic agents can proceed unless the four principles stated on page 10 have been followed. These principles are based upon a hierarchy of controls. This hierarchy must be adopted with any work using such agents i.e. consider whether substitution or reduction can be applied.

No one should be working with known or suspected carcinogenic agents without being adequately trained. Included in this training must be knowledge of how to deal with the unexpected such as a spill or accident.

Lone working should be avoided as far as is practicable (i.e. work outside of normal hours).

No work with a known or suspected carcinogenic agent can proceed until a risk assessment had been completed, read and completely understood by those directly involved. It should be normal practice for standard operating procedures (SOPs) to be followed when working with these agents.

The SOP will normally contain the following minimal information.

- The chemical, and /or biological and physical properties of the agent. (e.g. routes of entry etc.)
- Quantities to be used, disposal and waste procedures.
- Laboratory to be used
- Engineering control measures required.
- Personal protective measure required.
- Emergency procedures in case of spills.
- Storage of products.
Engineering controls should be used whenever appropriate (i.e. a fume cupboard or safety cabinet). Personal protective equipment should be worn as determined by the risk assessment. Where a “face mask” or other “respiratory equipment” is required then quantitative fit tests must have been done and recorded. Gloves must be suitable for the task and must provide the correct type of protection should contamination occur. Eye protection must be suitable for the task. The wearing of contact lenses avoided.

The flow diagrams in guidance note 1 should help when considering work practices.

Manipulation of agents (e.g. weighing) should be done in a fume cupboard. Any spills should be dealt with promptly by the user.

Contaminated equipment (glassware, test tubes, measuring cylinders etc.) must be cleaned by the user and preferably all such equipment should be dedicated for this purpose.

Waste

All waste should be segregated and bagged separately. It is not good practice to store carcinogenic waste of any kind in the laboratory. Solid and liquid waste materials will normally be disposed of by incineration. Waste bags and containers must be labelled with appropriate hazard warning signs (see appendix 1).

Storage

All category 1 and 2 carcinogenic chemicals must be stored in a secure place. Storage should be in a labelled dedicated container preferably designed to hold such materials.

Only those trained and competent to use these chemicals should have access.

Personal hygiene

Great care should be taken at the completion of work with carcinogenic agents. Gloves should be removed without contaminating hands (you must know how this is done). Laboratory coats and eye and respiratory protection for carcinogenic work (glasses and non-disposable masks) should be stored separately from other similar materials. Care must be taken to avoid unnecessary contamination of equipment or surfaces such as door handles, telephones etc when working with carcinogens. Gloves must always be removed before touching door handles or telephones. Personal hygiene should be of the highest standard.

Records

Concise records should be kept of what category 1 and 2 chemicals are in storage and a comprehensive audit trail of when and how they were used must be in place.

It is also extremely important that well documented records are kept for any MRC staff member or visiting worker who has worked with known or suspected carcinogenic agents.
These records should be stored for at least 40 years after the last known exposure has occurred\(^5\)

**Health Surveillance**

It is appropriate to consider health surveillance for all those working with known agents or agents suspected of having carcinogenic properties. The decision of whether health surveillance should be implemented must be made in conjunction with occupational health. Health surveillance is only appropriate if;

- There is a known causal link between exposure and an ill health condition
- There is a method available to test the health status of the individual exposed

Failure of any control measure during the experimental procedure or exposure due for example, to an emergency situation (e.g. an accident leading to uncontrolled release of the agent) will result in immediate occupational health involvement.

The following flow chart outlines when medical surveillance is required.

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\(^5\) Note that working with a known or suspected carcinogenic agent is regarded as potential exposure to that agent. Quantitative face fit tests must be done for any respiratory protective equipment (RPE) used to ensure protection is afforded to the wearer.
Flow Chart 3 when is medical surveillance required.
Guidance Note 3

**Mutagens**

Mutagens are chemical or physical agents that increase the frequency of cellular mutations. Essentially all mutagens show some specificity for the type of mutations produced. The first report of mutagenic action of a chemical was in 1942 by Charlotte Auerbach who showed that nitrogen mustard (component of poisonous gas used in the first and second world wars) could cause mutations in cells. Since then many more chemicals have been shown to be mutagenic. Mutagens cause changes in nucleic acids in DNA leading in most instances to detrimental affects. Mutagens may also possess carcinogenic and reproductive properties.

The following table indicates the type of mutations typically produced by some laboratory used mutagens.

<table>
<thead>
<tr>
<th>Mutagen</th>
<th>Mechanism</th>
<th>Types of mutations produced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>DNA replication and repair errors, spontaneous modification of nucleotides</td>
<td>All types of mutations produced</td>
</tr>
<tr>
<td>UV irradiation</td>
<td>Pyrimidine dimers induce error prone repair (SOS)</td>
<td>Mainly G-C to A-T transitions, but all other types of mutations including deletions, frameshifts, and rearrangements at somewhat lower frequency</td>
</tr>
<tr>
<td>2-aminopurine (2AP)</td>
<td>Base analogue</td>
<td>A-T to G-C and G-C to A-T transitions</td>
</tr>
<tr>
<td>Bromouracil</td>
<td>Base analogue</td>
<td>G-C to A-T and A-T to G-C transitions</td>
</tr>
<tr>
<td>Hydroxylamine (NH$_2$OH)</td>
<td>Alkylating agent, generates N$_4$-hydroxycytosine</td>
<td>G-C to A-T transitions when used in vitro</td>
</tr>
<tr>
<td>N-methyl-N$'$-nitro-N-nitrosoguanidine (MNNG)</td>
<td>Alkylating agent, generates O$^\circ$-methylguanine</td>
<td>G-C to A-T transitions, multiple, closely spaced mutations common</td>
</tr>
<tr>
<td>Ethylmethane sulfonate (EMS) (EMS)</td>
<td>Alkylating agent, generates O$^\circ$-methylguanine</td>
<td>G-C to A-T transitions</td>
</tr>
<tr>
<td>Ethylethane sulfonate (DES)</td>
<td>Alkylating agent, induces SOS response</td>
<td>G-C to T-A transversions, other base substitution mutations</td>
</tr>
<tr>
<td>Nitrous acid</td>
<td>Oxidative deamination</td>
<td>G-C to A-T and A-T to G-C transitions</td>
</tr>
<tr>
<td>ICR-191</td>
<td>Intercalating agent, alkylacridine derivative that stabilizes looped out bases by stacking between them</td>
<td>Frameshifts, mainly additions or deletions in runs of G or C</td>
</tr>
</tbody>
</table>
Ionizing radiation

X- and gamma rays are energetic enough that they produce reactive ions (charged atoms or molecules) when they react with biological molecules at the molecular level. Thus both types of energy can induce damage to nucleic acids although they do so in a non-specific way. UV radiation is non-ionizing but can react more specifically with the formation of thymine dimers in the deoxyribonucleic acid (DNA).

Classification of mutagens

Mutagens are classified into 3 categories.

Category 1

A substance known to be a mutagen to man. In this category there is sufficient evidence to establish a causal relationship between exposure to the substance and heritable damage to man.

Category 2

There is sufficient evidence (normally based on long-term animal studies and possibly in vitro cell culture work) to provide a strong assumption that uncontrolled exposure to man will lead to heritable genetic damage.

Category 3

Experimental evidence (usually from animal studies) is not sufficient to make an accurate assessment that heritable genetic damage in man will occur.

Control measures

The controls outlined in Guidance Note 2 for carcinogenic substances apply equally to mutagenic substances in categories 1 and 2. Mutagens may not necessarily exhibit carcinogenic or mutagenic properties in vivo. However, even in situations where in vivo data is either lacking or unequivocal current advice would be to adopt control measures that prevent exposure to as low as is reasonably practicable. The use of ionising radiation will in addition require the Radiation Protection Adviser (RPA) to be consulted prior to use. The risk assessment will also consider the need for additional measures to be employed such as the provision of occupational health surveillance, emergency procedures etc. Like carcinogens many mutagens have no known safe level of use. All control measures must therefore be in place prior to any work commencing.
Appendix 1

Risk and Safety Phrases

Hazard (H) and safety (S) phrases are provided as guides to users about the hazard of a particular material or chemical. Certain chemicals in particular, will have more than one hazard or safety phrase supported by aetiological studies on man, animals or by in vitro experiments.

The classification is concerned with both acute and long-term effects of agents known or suspected of being deleterious to man. Acute is normally associated with a single or prolonged exposure to a harmful agent whereas long-term usually is considering accumulative or additive exposures to one or more substances.

In addition to “H” or “S” phrases materials or substances may carry additional health warning symbols such as “toxic” (“T”) harmful (“X”) followed by the relevant “H” phrase.

Acute toxic effects (“T+”) will normally have the LD₅₀ (dose where 50% or less survival is expected) values.

Hazard phrases

The list below for “H” phrases is not exhaustive.

- H351 Suspected of causing cancer.
- H340 May cause genetic defects.
- H350i May cause cancer by inhalation.
- H360F May damage fertility.
- H360D May damage the unborn child.
- H361f Suspected of damaging fertility.
- H361d Suspected of damaging the unborn child.
- H362 May cause harm to breast-fed children.
- H341 Suspected of causing genetic defects.

Formally known as Risk (R) phrases.
Classification

Category 1

Where there is firm evidence (normally epidemiological) that the substance is toxic for man, that substance will be placed in category 1 and be afforded the risk phrases H315, H350i, H340, H360f, H360d and H362 as appropriate. They will also be assigned the 'T' (toxic) symbol and carry the toxic pictogram (below).

Category 2

These are substances that should be regarded as toxic to man but where the majority of evidence has been acquired from long-term animal studies. The risk phrases and symbols used are as for Category 1 substances.

Category 3

Substances carry the risk phrases H341, and H351 and H361f to H362 as appropriate. Inclusion in this category would be made on the basis of a strong suspicion that the substance might be harmful to man by extrapolation of the results of in vivo animal studies. These substances are assigned the Xn (harmful) symbol and carry the harmful pictogram

Note that some materials may carry more than one risk phrase. In this instance the first “R” term usually denotes the highest concern for danger.
Safety phrases (“S”)

Safety phrases give advice on the precautions that should be adopted when using a dangerous chemical or dangerous substance.

Examples are:
- S7 - Keep container tightly closed
- S8 - Keep container dry
- S15 - Keep away from heat
- S16 - Keep away from combustible material

Occupational Exposure Air Measurements

Work Exposure Levels (WELs)

WELs are occupational exposure limits established to protect the health of workers. WELs are concentrations of hazardous substances in the air, averaged over a specified period of time, referred to as a time-weighted average (TWA).

Two time periods are used:
- Long-term (8 hours)
- Short-term (15 minutes)

Short term exposure limit (STELs)

Define the maximum concentration of a chemical to which workers may be exposed continuously for up to 15 minutes without danger to health.
Toxicity Values

Toxicity assessment is a major component of the risk assessment procedure. A toxicity assessment is a tool to investigate the potential for a substance to cause harm and how much causes what kind of harm.

All substances are toxic in quantity. Many therapeutic medications are acutely toxic, but beneficial when used at the appropriate level. Vitamin D, table salt, oxygen, and water are toxic in quantity. Thus, the mere presence of a substance does not automatically imply harm.

There is no one measure of toxicity. Effects may occur in the short term (acute effects) or after repeated exposures over a long time (chronic effects). They may affect only one part of the body or many, and they may vary greatly in severity.

The term toxicity refers to the inherent potential of a substance to cause systemic damage to living organisms. The term hazardous is very different. It refers to the potential of a substance to (1) cause any of several kinds of harm, through toxicity, flammability, explosiveness, corrosiveness etc., and (2) the ease with which people can come in contact with it. Hazardous is not a synonym for toxic.

Toxic Effects

Toxic effects are classified as two types; acute or chronic.

- Acute effects happen very rapidly after a single exposure has occurred (food poisoning, breathing fumes from a chlorine spill). Sweating, nausea, paralysis, and death are examples of acute effects.

- Chronic effects happen only after repeated long-term exposure (cigarette smoking, eating foods with low levels of contaminants, breathing polluted air). Cancer, organ damage, reproductive difficulties, and nervous system impairment are examples of chronic effects.

These chronic effects fall into two categories:

  - carcinogenic effects and non-carcinogenic effects.

Examples of non-carcinogenic chronic effects:

- **Organ damage:** cirrhosis of the liver from long-term alcohol consumption; emphysema from long-term tobacco smoking.

- **Reproductive difficulty:** decreased fertility from the pesticide DBCP (dibromochloropropane).

- **Nervous system impairment:** mental retardation in people exposed to high levels of lead during early childhood.
Assessing Toxicity

All quantitative toxicity assessments are based on the dose-response concept: as you increase the dose (exposure), the response (toxicity) also increases. Studies are carried out to determine exactly how high a dose causes what kind of a response, or effect. The smaller the dose needed to cause an effect, the more potent (toxic) the substance is.

For all compounds other than cancer-causing agents (carcinogens), it is assumed that there is a dose below which no effect occurs (a threshold). This is similar to a drug where too small a dose has no beneficial effect. This is termed the ”No observable threshold limit” (NOTL). All of the air-borne related hazards (WELs) are based upon the NOTL factor.

For carcinogens, it is often assumed that even the smallest dose can cause an effect thus for many if not all known carcinogenic substances there is no practicable NOTL. All risk assessments should therefore ensure that they are written with this in mind.

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