

Health surveillance for work with carcinogens and mutagens in research laboratories

Additional Guidance

To be read in conjunction with the main HEOPs health surveillance guidance

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Introduction

The COSHH Regulations require, wherever possible, avoidance of work with carcinogenic or mutagenic substances. Where work with such substances cannot be avoided Regulation 7(5) of COSHH specifies specific engineering & procedural controls to minimise, as far as is reasonably practicable, opportunity for exposure. Additionally, where harmful exposure may still occur, health surveillance of those at risk of exposure may be required.

The need for health surveillance as a control measure for work with a carcinogen or mutagen is specified in Regulation 11. The same criteria apply as for other hazardous materials: (1) an identifiable disease or adverse health effect linked to exposure, (2) a likelihood of hazardous exposure occurring and (3) a valid technique is available to detect early signs of exposure.

As there is a long latency period— typically measured in decades— between exposure to a carcinogen and the development of detectable cancer, for most carcinogens there are no screening tests that are useful at the time of exposure. However, where hazardous exposure may occur, a health record should be maintained in lieu of active monitoring for the effects of exposure¹.

For most carcinogenic and mutagenic substances there is little evidence available on what constitutes a safe level of exposure. Most carcinogens do not appear to have a 'no-effect' threshold. However, the risk of cancer induction is linked to intensity and duration of exposure to a carcinogen. In a research laboratory environment quantities in use are often very small— grams or millilitres— and often handled for only short periods of time. With appropriate safety controls in place the likelihood of exposure occurring sufficient to cause harm will be very low. Health surveillance will therefore not always be required.

Monitoring to assess exposure against Workplace Exposure Limits (WELs), where these exist, is not always feasible where only small quantities of material are handled. Additionally, WELs are devised on the assumption that exposure occurs for much of the working day and so are of limited applicability to the research laboratory environment. Accordingly, this guidance proposes a pragmatic, staged assessment process based on simple, easily measured criteria which determine the credibility of hazardous exposures occurring within a laboratory environment.

It utilises the precautionary principle so that health surveillance will be required for any work that does not fall within the specified criteria, unless a more detailed risk assessment considering a wider range of factors concludes hazardous levels of exposure are unlikely to occur.

It assumes that all work is carried out in accordance with the principles of good laboratory practice, including the use of basic personal protective equipment such as laboratory gloves and protective clothing and no eating or drinking etc.

It does not remove the fundamental requirement under COSHH to avoid work with carcinogens or mutagens or, where this is not possible, to control exposure to any carcinogenic or mutagenic substance to the lowest level reasonably achievable

¹ The Control of Substances Hazardous to Health Regulations 2002 (as amended) Approved Code of Practice and guidance para 239.

Definitions

Carcinogen: any substance classifiable as a carcinogen (category 1 or 2) under the Classification, Labelling and Packaging of Substances and Mixtures Regulation (CLP Regulation) or novel substances considered to be potentially carcinogenic on the basis of their chemical or physical similarity to a known carcinogen.

Commercially supplied carcinogenic substances will be labelled as R45 or H350— *may cause cancer* or R 49 or H350— *may cause cancer by inhalation*

Mutagen: any substance classifiable as a mutagen under the Classification, Labelling and Packaging of Substances and Mixtures Regulation (CLP Regulation), or novel substances considered to be potentially mutagenic in humans on the basis of their chemical or physical similarity to a known human mutagen.

Commercially supplied mutagenic substances will be labelled as R46 or H340— *may cause heritable genetic damage*

Exposure: contact with a substance in any physical form which results in absorption of the substance into the body

Hazardous exposure: exposure sufficient to cause some likelihood of cancer induction or lasting genetic damage. In most instances, the total (cumulative) exposure occurring over the expected duration of the work should be considered when evaluating whether or not exposure may be harmful

Low risk work

For some work in a research laboratory with carcinogens & mutagens, typical conditions of work are such that exposure sufficient to cause harm will be extremely unlikely. The amount of hazardous material in use is small. The substance is used for only a short period of time. Most manipulations are low energy processes and so unlikely to generate dust or generate aerosols. All handling is carried out inside safety cabinets. Implements are used to transfer material between containers so that no direct handling is necessary. PPE— lab coat and chemically resistant gloves— should guard against inadvertent skin contact.

Where all these conditions are met and the carcinogen or mutagen is in a physical form that will not easily generate dust or vaporise it can be concluded that, in normal use, exposure sufficient to cause harm is exceedingly unlikely and no form health surveillance will be required, unless an accident or spillage resulting in unplanned exposure occurs. (Figure 1)

Figure 1 Work with a carcinogen or mutagen where COSHH Health Surveillance will not be required.

1. The hazardous substance is a non-volatile liquid (see p. 8) or a granular or mass solid.
2. The total quantity of substance used over the course of the work does not exceed 1kg or 1 litre
3. The maximum duration of the work is 4 weeks
4. The handling time per day is less 1 hour
5. There is no intentional direct handling of the substance i.e. it is manipulated using implements and containers
6. Manipulations undertaken outside of enclosure are limited to
 - weighing out
 - pipetting,
 - dissolving
 - transfers between vessels
7. Protective clothing:— laboratory coat, chemically resistant gloves and, if a liquid, safety glasses or face shield— is worn.

Where the above conditions are **not** met, a more detailed risk assessment will be required to determine whether exposure sufficient to cause harm may occur and health surveillance required.

The threshold for harm

The likelihood of exposure to a carcinogen being harmful i.e. capable of causing cancer will be determined by the cumulative dose: the quantity absorbed per use and the number of times the substance is used.

This guidance seeks to define in terms of the quantity of carcinogen or mutagen used in the work the circumstances in which health surveillance should not be necessary. It utilises a pragmatic exposure threshold of 10 µg/day (see Appendix 1). We consider that for periods of work of up to three months, the cumulative exposure will be insufficient to significantly increase the risk of cancer induction or, for mutagens, lasting genetic damage

Where the calculated daily exposure is less than 10 µg/ day health surveillance will be unnecessary for work of less than 3 months duration. Where daily exposure is higher than 10µg or the duration of work exceeds 3 months, health surveillance should be instituted.

Assessing exposure

The most important factors determining the level of exposure in a research laboratory setting are:

1. The quantity of material in use.
2. The duration of exposure
3. The physical form of the substance.
4. The type of process
5. The type of ventilation containment used as a control.

Quantity of material in use

The chance of a hazardous exposure occurring will increase in line with the quantity of material in use. This guidance considers only the quantity of material being handled or actively used in experimental processes. In a research laboratory environment, no significant exposure to stock quantities is likely, except in the circumstances of a recognised accident e.g. spillage or breaking of a storage container.

Duration of exposure

Experimental work in research laboratories typically involves only relatively brief periods of time handling materials, or directly observing a process.

This guidance assumes that the potential daily exposure time i.e. the time spent directly handling the material, or processing the material outside of an enclosed vessel or apparatus does not exceed one hour per day and that the total duration of use of the material will be less than 3 months.

If the daily exposure time will exceed 1 hour, or the duration of use will be longer than 3 months, then the threshold amounts given in this guidance for determining whether COSHH health surveillance should be instituted should be reduced accordingly.

Physical form

In a research laboratory environment, the main route by which hazardous exposure could occur is through inhalation of dust or aerosol, fume or gas generated during handling or processing of the material.

Given the typically small quantities of materials used, significant dermal exposure is unlikely to occur: use of implements, flasks and other containers obviate the need to directly handle hazardous substances. Use of laboratory coats and gloves will provide good protection against inadvertent skin

contamination in normal use. PPE will also safeguard against gross contamination of personal clothing when only small volumes of hazardous material are being worked with. Accidental ingestion is not a likely circumstance in a laboratory setting.

For solids, the likelihood of hazardous exposure will be determined by the capacity of the material to become airborne during handling. This is largely a function of particle size: the finer the size, the greater the proportion of material than may become airborne.

For liquids the quantity becoming airborne will be chiefly determined by the vapour pressure of the material at the operating temperature of the process(es) in which it is used.

Type of process

Processes that impart kinetic energy to a particulate or liquid can generate aerosols and so create opportunity for exposure through inhalation. The risk will be higher for higher energy processes e.g. sieving, grinding or sonication than for lower energy processes such as weighing out, pouring or stirring.

Heating will increase the rate of vaporisation of volatile liquids.

Research suggests that for powdered solids, between 0.01% and 0.9% will become airborne during low energy processes depending on particle size².

Ventilation control

Ventilation controls limit inhalational exposure to airborne particulates and gases.

This guidance considers three levels of control, with different levels of effectiveness:

1. Open bench working
2. A performance-regulated safety cabinet
i.e. either a chemical safety hood conforming to BS EN14175 and achieving NERC Class 1 performance³
or a Class I/II biological safety cabinet constructed and maintained in accordance to BS EN 12469:2000 which is externally exhausted or specially designed for the containment of chemicals.
NB Other forms of LEV not conforming to these BS standards e.g. positionable exhausts or re-circulating cabinets are not appropriate for work with carcinogens or mutagens which require ventilation control for safe working
3. Isolation i.e. totally contained system, isolator or Class III biological safety cabinet)

Open bench provides no control of airborne exposure so is considered to have a protection factor of 1. Open bench work with carcinogens or mutagens will only ever be appropriate where the substance is not capable of becoming airborne in appreciable amounts i.e. a liquid with a boiling point higher than 150°C, or a pelleted solid.

A regulated chemical or biological safety cabinet if properly installed, maintained and used will reliably achieve greater than 99% containment (theoretically you can get higher than this but operator factors can reduce the effectiveness of containment). Dispersal within the laboratory through air movement and the dilution achieved through room ventilation will mean that operators will be exposed to only a fraction of any material escaping the cabinet.

² D Brouwer et al (2006) Size selective dustiness and exposure; simulated workplace comparisons Ann. Occup. Hyg; 50: 442-452

³ The safe use, maintenance and testing of laboratory fume cupboards Natural Environment Research Council, 2007 http://www.nerc.ac.uk/about/policy/safety/procedures/guidance_fume_cupboards.pdf

We therefore allocate a nominal protection factor of 1000 to work with powders or liquids undertaken in a safety cabinet.

Isolation or total containment should prevent any exposure occurring during use, although some exposure is credible when the equipment is opened for charging or removing materials. We therefore limit the protection factor for this form of containment to 10000.

Thresholds for surveillance

The following guidance is based on typical manipulations that are carried out within a research laboratory. If the quantities handled per day are below the threshold specified for the containment used then exposure can be regarded as well enough controlled for health surveillance not to be necessary. If the quantities are greater than those specified, health surveillance may be necessary. Additional controls to further limit exposure should also be considered.

Powders

Based on Brouwer's research⁴ we assume that the maximal amount of a powder that could become airborne during standard lab procedures such as weighing out, transfer between containers using a spatula or similar, or from manual stirring to be 1%.

Therefore a total of 1mg (1000µg) of hazardous substance could, in theory, be handled on the open bench without exceeding 10 µg of absorption.

Larger quantities can be handled without significant risk of harmful exposure if ventilation controls are in place. The thresholds above which health surveillance will be required for work with powders according to the form of ventilation containment in use are given in Table 1 .

Table 1: Threshold for requiring health surveillance for work with powders

Ventilation control	Protection factor	Quantity threshold	Comment
Open bench	1	1mg	Theoretical: containment will always be required
Regulated safety cabinet	1000	1g	
Total enclosure	10000	10g	

Volatile liquids

Volatile liquids classed as carcinogens or mutagens should always be handled in regulated safety cabinets or enclosed systems, irrespective of the quantity in use.

A volatile liquid is defined as one with a boiling point of less than 150°C or less than 5 times the temperature of the process plus 50°.

Where an exposure limit exists and it is feasible to monitor concentration, health surveillance should be instituted unless the ventilation control can reduce the concentration in the breathing zone of a worker to less than 10% of the WEL, or STEL as appropriate.

Where no exposure limit is set, health surveillance should be instituted for work if the concentration of the hazardous substance in the worker's breathing zone exceeds 0.1 ppm.

⁴ *ibid.*

Where it is not practical to measure exposure levels the threshold for health surveillance will be as per Table 2 below. This is based on the lowest level reasonable practicable and the exposure limits of known carcinogens.

The protection factor, calculated on the same basis as for powders, for vapours/gases will be 1000 for a regulated safety cabinet and 10000 for an isolator.

Table 2: Threshold for requiring health surveillance for work with volatile liquids

Ventilation control	Protection factor	Quantity threshold	Comment
Open bench	1	0.1 ml	Theoretical
Regulated safety cabinet	1000	10 mls	
Total enclosure	10000	1 litre	

If the quantities handled are within these limits then exposure can be regarded as adequately controlled and neither monitoring nor health surveillance is required.

Larger solids

Pelleted or larger solids will not become airborne unless crushed or fractured in use. Consistent use of protective clothing and gloves will prevent significant dermal exposure. Adherence to good laboratory practice will prevent exposure through ingestion.

The likelihood of hazardous exposure is so low that health surveillance should not be necessary unless quantities in excess of 1kg are in use.

Non-volatile liquids

Liquids with a boiling point above 150°C or, if heated, with a boiling point greater than 5 times process temperature plus 50°C, should pose no significant risk of hazardous inhalational exposure, unless large volumes are in use.

Health surveillance will be necessary only for work where the volume required by the process is greater than 1 litre

Solutions

Where a carcinogen/mutagen is used in solution, the exposure risk should be assessed on the basis of the volatility of the solvent at process temperature.

Water can be considered as a liquid of low volatility at ambient temperatures.

Accidental exposure

Accidental or other incidents which may have resulted in an uncontrolled exposure to a carcinogen/mutagen should be recorded in the COSHH Health Record.

Where no surveillance was instituted for the work, a health record should be set up for the person(s) involved in the exposure incident. The risk assessment for the work should be reviewed and the decision on the need for routine health surveillance for all involved in the work reconsidered.

Form of surveillance

For most work where surveillance is judged necessary, the appropriate form of surveillance will be a COSHH health record. Given the very low levels of exposure likely in a controlled laboratory environment, it is unlikely that there will be any level or burden or biological effect that can be measured.

Although not specifically required under the COSHH Regulations, the record should include information or links to information on the specific nature of the work, the risk assessment for the work and records of any accidental exposures to enable an exposure assessment for an individual to be made years after work should cancer develop

Appendix 1 Justification for threshold levels used

There are very few official exposure limits set for the types of carcinogen likely to be encountered in powder form in laboratories. Of those which have a UK WEL the lowest is Beryllium with a limit of 0.002 mg/m² as an 8h TWA. On the assumption that 1 m³ of air is inhaled in an hour and all material inhaled is absorbed this gives a daily absorption of 16 µg. All other listed carcinogens with WEL's are significantly above this figure.

A better guide perhaps are the in-house exposure limits set by suppliers of cytotoxic anti-cancer drugs which are often mutagenic or carcinogenic. Examples include methotrexate 2 µg/m³, doxorubicin 0.5 µg /m³, paclitaxel 0.8 µg/m³ and cisplatin 2 µg/m³. These are all in a similar range to the daily absorption of 10 µg which we have chosen.

With regard to volatile liquids most carcinogens with a WEL are in the range 0.05 to 5 ppm. BCME is an outlier with a WEL of 0.001. However we feel that this would be too stringent a level for the vast majority of carcinogens encountered. As described in the document all materials with a WEL must be handled within that limit.

Prohibited substances

The following substances are prohibited under COSHH and require an exemption certificate

- 2-naphthylamine
- Benzidine
- 4-aminodiphenyl
- 4-nitrodiphenyl

The prohibition extends to their salts and any mixture in which they are present at greater than 0.1% by mass.

Handling must always be in total containment and person exposed must always be under health surveillance.

Appendix 2 Worked Examples for Specific Materials

The carcinogens reported as being most commonly used in laboratories fall into the following groups.

Materials in biosciences

Trypan Blue

Trypan blue is used in cell cultures to enable the counting of viable cells. It is classified in the EU as Carcinogen 1B (*Presumed to have carcinogenic potential for humans, classification is largely based on animal evidence*). It has no official exposure limit.

We therefore apply our standard criteria and consider that there is no reasonable likelihood of it being hazardous to health if handled in quantities less than 1 mg on the open bench or 1g in a standard fume hood.

Trypan blue should, whenever feasible, be obtained in solution, to avoid unnecessary handling in powder form to make up solution for use in the laboratory.

Acrylamide

Acrylamide is used in the production of gel for acrylamide gel electrophoresis. It has a workplace exposure limit of 0.3 mg/m³ (8h TWA). Using the absorption factors and the levels of control as discussed above. If we assume that the maximum volume of air inhaled in a day is 10 m³ and that all the material inhaled is absorbed we have a worse case of this equating to an absorption of 3 mg or 3000 µg. Under our proposals a health record should not be necessary if exposure is controlled to one tenth of this – that is an absorption of 300 µg.

As above we assume that the maximal amount of a powder that could become airborne during standard lab procedures such as weighing out, transfer between containers using a spatula or similar, manual stirring to be 1%. So this absorption will not be exceeded if the quantity handled is less than 30 mg.

The quantity limits are:

Ventilation control	Protection factor	Quantity threshold	Comment
Open bench	1	30 mg	
Regulated safety cabinet	1000	30g	
Total enclosure	10000	300g	

Acrylamide should, whenever feasible, be obtained in gel form to avoid the need to work with powder.

Nickel salts

Nickel salts have a workplace exposure limit of 0.1 mg/m³ (8h TWA). Using the absorption factors and the levels of control as discussed above. If we assume that the maximum volume of air inhaled in a day is 10 m³ and that all the material inhaled is absorbed we have a worse case of this equating to an absorption of 1 mg or 1000 µg. Under our proposals a health record should not be necessary if exposure is controlled to one tenth of this – that is an absorption of 100 µg.

As above we assume that the maximal amount of a powder that could become airborne during standard lab procedures such as weighing out, transfer between containers using a spatula or similar, manual stirring to be 1%. So this absorption will not be exceeded if the quantity handled is less than 10 mg.

The quantity limits are:

Ventilation control	Protection factor	Quantity threshold	Comment
Open bench	1	10 mg	
Regulated safety cabinet	1000	10 g	
Total enclosure	10000	100 g	

Materials in medical research

Cytotoxic antineoplastic agents

Cytotoxic anti-cancer drugs pose a varied range of severe toxic effects. Many are also classed as carcinogens. They do not have official Workplace Exposure Limits, but may have exposure limits provided by the manufacturer or by other bodies such as the ACGIH.

If we take doxyrubicin as an example. It is classed by the supplier as a carcinogen and the MSDS quotes an internal manufacturer's exposure limit of 0.5 µg/m³. Using the absorption factors and the levels of control as discussed above. If we assume that the maximum volume of air inhaled in a day is 10 m³ and that all the material inhaled is absorbed we have a worse case of this equating to an absorption of 5 µg. Under our proposals a health record should not be necessary if exposure is controlled to one tenth of this – that is an absorption of 0.5 µg.

As above we assume that the maximal amount of a powder that could become airborne during standard lab procedures such as weighing out, transfer between containers using a spatula or similar, manual stirring to be 1%. So this absorption will not be exceeded if the quantity handled is less than 50 µg.

The quantity limits are:

Ventilation control	Protection factor	Quantity threshold	Comment
Open bench	1	50 µg	
Regulated safety cabinet	1000	50 mg	
Total enclosure	10000	500 mg	

Chemical laboratories

Carcinogenic alkylating agents are often handled in chemical laboratories for chemical synthesis:

- Alkyl halides
- Nitrogen mustards
- Alkyl sulphates

Dimethyl sulphate

These materials are often liquids. As an example we will take dimethyl sulphate. Its volatility is low but it is often used warmed to improve handling so volatility can be an issue.

Its workplace exposure limit is 0.05 ppm and health surveillance will not be necessary if exposure is controlled to one tenth of this – 0.005ppm

In terms of volumes that can be handled, the table above is based on an exposure limit of 0.1 ppm so the figures must be halved.

This is based on a protection factor, calculated on the same basis as for powders, for vapours/gases of 1000 for a regulated safety cabinet and 10 000 for an isolator.

Ventilation control	Protection factor	Quantity threshold	Comment
Open bench	1	0.05 ml	Theoretical
Regulated safety cabinet	1000	50mls	
Total enclosure	10000	500 ml	