Topic 12: Assessing Carcinogenic Hazards

This *Topic* (dated 2016) is an updated version of *Topic 12*, which appeared in the 3rd edition of *Topics in Safety* (ASE, 2001). While the hazards of carcinogenic chemicals has not changed, the changes affecting labelling, as well as ongoing research in this area is sufficient to make this revision timely.

This *Topic* is written for anyone who uses chemicals, not just chemists. It eschews extensive tables of chemicals and their hazards, concentrating instead on the principles, as other publications are available with more extensive information, e.g. CLEAPSS *Hazcards*[1] and SSERC *Hazardous Chemicals Database*[2].

Introduction

Many chemicals are known to be carcinogenic, including some that are found in schools. Recent estimates have shown that about 8 000 cancer deaths and around 13 500 cancer registrations per year in Great Britain could be attributed to past occupational exposure. These represented 5.3% of all cancer deaths and 4.0% of all newly diagnosed cancers[3]. Many carcinogens are encountered in everyday life, examples being components of paints, epoxy resins, cigarette smoke, some foodstuffs and traffic fumes, all of which are used or encountered in a relatively uncontrolled way. On the other hand, in the school laboratory, substances of lower carcinogenic potency will be handled with care and on a much smaller scale.

There is a danger that the emotive nature of cancer will cause the relatively remote risk of a chemical's low carcinogenic potential to be exaggerated, compared to more immediate hazards such as flammability and toxicity. The purpose of this article is to present the known facts about those chemicals with carcinogenic potential which are likely to be found in schools and to suggest precautions in their use. Section 1 covers definitions and classification. In Section 2 carcinogenic agents are discussed under a number of groupings. Section 3 contains recommendations for particular applications in schools.

12.1 Carcinogenicity

12.1.1 Toxicity[4] and carcinogenicity

Acute toxic effects are manifested immediately and are thus readily understood. On the other hand, dangerous carcinogenic effects are usually only seen many years after the exposure and some carcinogens may be effective at levels that do not produce obvious toxic effects. The same, of course, applies to other chemicals which exert chronic toxic effects which may at first go unnoticed. It is important to realise that some carcinogenic chemicals may be treated with insufficient care because they are not unduly toxic in the short term.

Those substances which may cause cancer in lengthy and high levels of exposure in industry are most unlikely to cause a threat to a careful laboratory worker using sensible laboratory techniques to avoid risk from toxic, as well as from any possible carcinogenic, effects. In schools, many chemicals are used only a few times in a year and usually in low concentrations and quantities. Even so, potent carcinogens are rightly excluded from school use.

Some substances lead to cancer only if taken into the body by a particular route and it is often simple to ensure that such an entry route is blocked. For example, potassium bromate(V) is a

[1] CLEAPSS Hazcards (http://www.cleapss.org.uk/secondary/secondary-science/hazcards)
[2] SSERC Hazardous chemicals database (http://www.sserc.org.uk/index.php/chemistry-health-a-safety138/hazardous-chemicals276)
[3] HSE Occupational Cancer in Great Britain (http://www.hse.gov.uk/statistics/causdis/cancer/cancer.pdf)
[4] The word 'toxicity'(or toxic) here is used to refer to substances which if inhaled, ingested or absorbed by the skin may lead to serious acute or chronic health effects or even death.

carcinogen by ingestion but it is hard to see how titration with a standard bromated(V) solution can lead to an exposure. Pipette fillers are used but in any case the bromate(V) solution is in the burette. Other examples where knowledge of the route of entry plays a part are given in sections on particular chemicals.

12.1.2 Recognising carcinogens

Teachers and others in schools, wishing to find out information on carcinogens can consult a wide range of publications. Aside from this Topic and its website appendix, the sources of help most readily available to schools are suppliers' catalogues and the SSERC Hazardous Chemicals Database or CLEAPSS Hazcards. The classification of substances legally defined in the UK as carcinogens is now carried out on a Europe wide basis by the European Chemicals Agency (ECHA). Information about the legal status of carcinogens in the UK (and much other information) can be found in COSHH Approved Code of Practice (ACoP). However, many other substances which are considered by some sources to be carcinogens are missing from these lists and some of these are discussed here. It is also valuable to have a feel for the type of chemical structure or groupings likely to confer carcinogenicity on a molecule (see Figure 1).

a) Consulting the classifications under the Classification, Labelling and Packaging Regulations[5] (CLP), the European Union instrument that implements the Globally Harmonised System (GHS), we find that carcinogens are classified, according to the ECHA Database[6], as follows

Category 1A and 1B carcinogens should have the relevant hazard statement on their labels - H350 (may cause cancer) as well the 'health hazard' pictogram (GH508) and the signal word 'Danger'. If the substance is only carcinogenic by a particular route, that information should be appended to the Hazard Statement.

> **Category 1A carcinogens** are those known to be carcinogenic to humans, usually on the basis of lengthy industrial exposure. Examples which might be used in schools are zinc chromate(VI), chromium(VI) oxide and sulfides and most nickel compounds.
>
> **Category 1B carcinogens** are those presumed, on good evidence from animal studies to be carcinogenic to humans. Examples used in schools might include chromium(VI) compounds in general, cobalt salts or epichlorohydrine (hardener for epoxy resins).
>
> **Category 2 carcinogens** carry the Harmful pictogram (GH507) (unless they are also toxic in other ways) and the Hazard statement H351 (suspected of causing cancer). The placing of a substance in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B. Examples are phenylamine, ethanal or dichloromethane.

(b) Consulting Schedule 1 of COSHH Regulations (in particular Appendix 1 of the ACoP)[7]

Those referred to which might be relevant to schools are aflatoxins, arsenic (and presumably its compounds) hardwood dusts, used engine oils, coal tar, pitch and coal tar fumes. Several processes are also listed, e. g. the manufacture of magenta and auramine dyes and the fume or dust from rubber manufacturing

(c) Consulting a suppliers catalogue or Safety Data Sheet (SDS)

[5] http://echa.europa.eu/regulations/clp/legislation
[6] http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database
[7] The Control of Substances Hazardous to Health Regulations 2002 (as amended) Approved Code of Practice and Guidance (http://www.hse.gov.uk/pubns/priced/l5.pdf)

Be wary of safety data sheets. Make sure that you are consulting one from a company based in the EU as some US-based companies, seem to be more motivated by possible litigation than that of providing sensible and helpful advice.

Companies such as Sigma-Aldrich and Fisher have extensive libraries of Safety Data Sheets which are free to download.

(d) Making predictions by examining the structure

A glance at the type of functional groups can provide a useful pointer to the likelihood of a substance being a carcinogen. Figure 1 shows the main groups which may confer carcinogenicity on a molecule. In a few instances closely related isomers show quite different carcinogenicities.

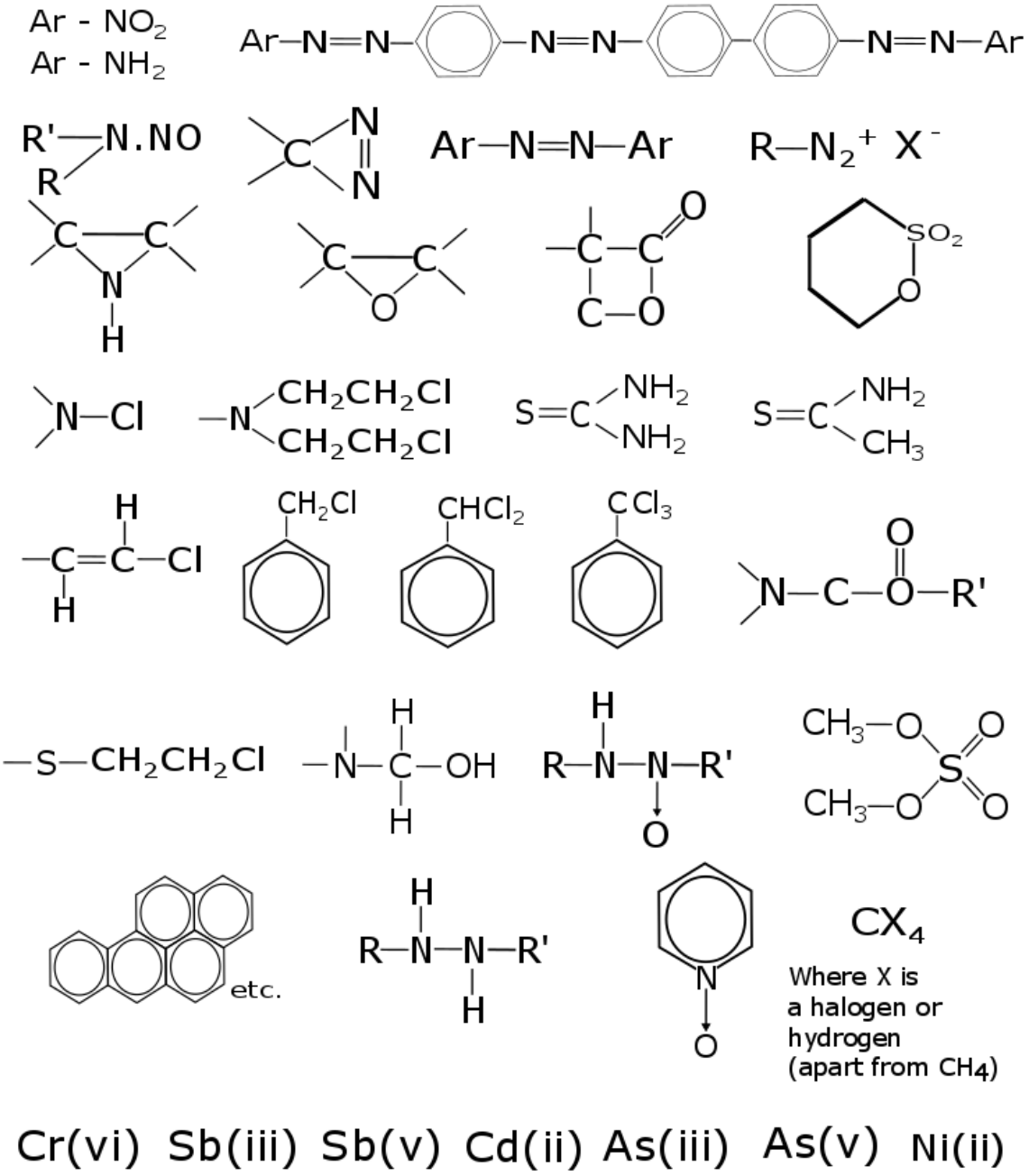

Figure 1 Main groupings which may confer carcinogenicity on a molecule (Ar = Aryl = aromatic ring).

12.1.3 Potency

The three GHS/CLP categories do not represent a rank order of potency. Most substances currently identified as Category 1A (known human carcinogens) were those used in industry in the nineteenth and first half of the twentieth century when industrial hygiene was poor. This resulted in people receiving high exposure for long periods of time. Category 1B contains more of the relatively modern chemicals for which there has been little or no human exposure thanks to improved industrial practices. This category will almost certainly contain carcinogens which prove more potent to humans than those in Category 1A. Category 2 is likely to contain substances whose carcinogenic effect is lower than category 1 but this cannot be taken for granted. There is a variety of reasons why evidence for a higher classification may be lacking, and absence of evidence does not equal evidence of absence.

Ideally, for the purposes of setting up regulatory standards, and for making risk assessments, quantitative information on the carcinogenic potency of a range of chemicals on humans would be highly desirable. Unfortunately such a list does not exist and the information that does exist is patchy. There is an extremely wide difference in the magnitude of the exposure to or of the dose of different chemicals needed to give rise to tumours. This can range from a short exposure lasting minutes to repeated contact or quite high doses over a period of many years.

There is, however, a wealth of information on the carcinogenic potency of many chemicals in animals. One of the main parameters used is the TD_{50}. This is the dose rate, expressed as the mass (g, mg, µg or ng) per kg bodyweight per day required to produce well-defined tumours in 50% of a population of test animals compared with the control. A small selection of values from a database is shown in Figure 2[8]. The potencies are seen to range over 6 or 7 orders of magnitude from 1 µg for aflotoxin to just under 1 g for 2,4,6-trichlorophenol and there seems to be no clear boundary between a weak carcinogen and a `non-carcinogen'. The majority of carcinogens of most interest fall in the middle range.

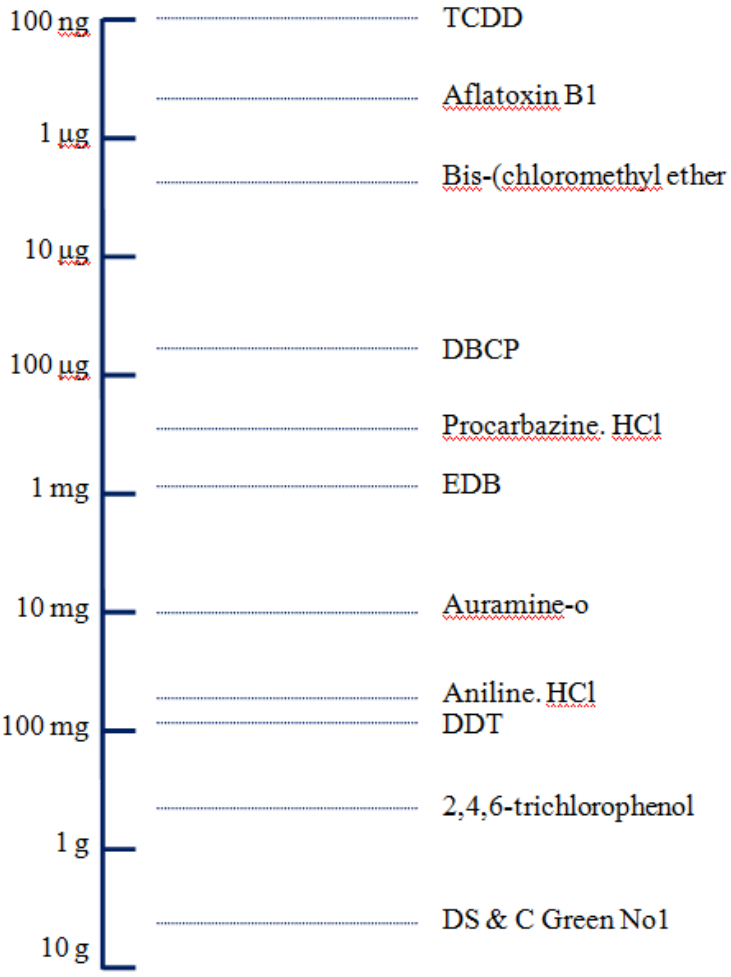

Figure 2 TD50: Daily dose (unit/kg body weight/day) to give 50% of animals tumours in a standard lifetime (adjusted for background incidence).

[8] Adapted from Gold, L. et al (1984) A carcinogenic potency database of the standardized results of animal bioassays. Environmental Health Perspectives, 58, pp 9 – 319. Now taken on and extended in the Carcinogenic Potency Database (http://toxnet.nlm.nih.gov/cpdb/index.html)

Extrapolating from these data to make predictions for humans is beset with several difficulties. As well as the TD_{50}, other factors such as the variations in response by different species of animals (including humans) have to be considered, namely differences in metabolic pathways and detoxification mechanisms, normal life spans, etc. This having been pointed out, it can nevertheless be seen that the order on the table reflects fairly well most of the generally held opinions on the magnitudes of potency to humans. Where available such a potency grading has been marked against certain chemicals in the website Appendix.

There are two main types of carcinogens:

Genotoxic carcinogens - Certain types of carcinogen react directly with some of the nucleotide bases in DNA. These genotoxic carcinogens are generally electrophiles, or are metabolised to electrophiles, which then form adducts on the nucleotide bases. The resulting corrupted coding in the DNA may be propagated when further cell division occurs.

Epigenetic carcinogens -Epigenetic, or non-genotoxic, carcinogens do not react directly with DNA. They may act as promoters or co-carcinogens, which means that, although they may not themselves initiate tumours by attacking DNA, they can accelerate the carcinogeneses which had been initiated by other agents. Other epigenetic carcinogens act by suppressing the immune system or by inducing peroxisome formation leading to the production of free radicals.

The existence of these two types of carcinogens has implications for human health. Because of the mode of action of a genotoxic carcinogen, a single molecule of it could in theory lead to cancer and hence it is generally believed that there is no safe threshold for such a chemical. In practice this is unlikely to be the case as the chemical will have to reach the target organ. For this to happen the chemical has to pass many barriers, namely being absorbed and the many digestive and detoxifying processes. For an agent or its active metabolite to be present at the site of its target organ it would need to be reaching the site faster than it is being removed by the other processes. This might happen only after a sustained exposure. With powerful carcinogens, zero exposure must be the goal. On the other hand, some epigenetic carcinogens lead to tumours often only after lengthy and repeated high levels of exposure cause physiological abnormalities and prolonged tissue damage. Thus ‘safe’ thresholds almost certainly exist for many

12.1.4 Legal Requirements

Regulation 4 of the COSHH Regulations prohibits in the UK the manufacture or use of 2-naphthylamine, benzidine, 4-aminobiphenyl, 4-nitrobiphenyl and their salts (these latter at a concentration of over 0.1% by mass).

The COSHH (amendment) regulations 1991 prohibited benzene and preparations containing more than 0.1% of benzene apart from applications in research and development and in Industry. The 6th edition of these regulations has removed that specific prohibition. The fact remains, however, that petrol still contains benzene and benzene is still a potent airborne carcinogen and we find it difficult to envisage a procedure where using benzene or a substance containing benzene would be acceptable. (If in doubt, contact SSERC or CLEAPSS).

Prevention of exposure to carcinogens is the main objective of the Carcinogens ACoP asssociated with the COSHH Regulations. There are various ways to prevent such exposure:

> **Substitution**.The most certain way of eliminating the risk of cancer is by substituting the carcinogen with a non-carcinogen, whilst ensuring that the replacement is not highly hazardous in terms of toxicity, flammability or instability, etc. If a sufficiently large educational benefit does not accrue then the use of a carcinogenic substance cannot be justified.

Control measures. Where substitution is not possible, the risk must be reduced to very low levels by using control measures which are appropriate to the nature of the risk.

a. using a fume cupboard for substances which are volatile and

b. using glassware and apparatus which will contain substances well. A flask and reflux condenser provides better containment than an open beaker.

c. Solids should preferably be used in crystalline form rather than as fine powders.

d. Where a substance, or its carrier solvent if it is in solution, is known to enter the body easily by the dermal route, then gloves made of suitable materials should be worn.

12.2 Carcinogenic agents

The following section contains a list of various different types of carcinogenic substances and how they should, or should not, be used in schools.

12.2.1 Aromatic amines and nitro compounds

Certain aromatic amines are the only chemicals widely believed to have caused cancer in laboratory workers, but these chemicals are all banned for use in schools, either by the COSHH Regulations or by individual employers' health and safety policies.

Generally, single-ring aromatic amines have low carcinogenic potential. Phenylamine (aniline), over which suspicion had hung for a long time, has recently been assigned the status of a Category 2 carcinogen. In animal experiments high doses of this substance fed over a long period of time resulted in a low yield of tumours. Any carcinogenic risks from this substance are greatly overshadowed by its high toxicity and capacity for being rapidly absorbed by the skin. Tests on the N-acetylated derivative N-phenylethanamide have failed to show evidence of tumours. Other derivatives such as the 2-methylphenylamine (o-toluidine) are carcinogenic but the methyl or ethyl esters of 4-aminobenzoic acid have not been shown to be carcinogenic.

Carcinogenic compounds identified so far in this group almost all have an amino group at a position on an aromatic ring equivalent to the 2 position in naphthalene (Figure 3a) or para to a biphenyl link (Figure 3b). The biphenyl link may also be extended by inclusion of other structures (Figure 3c). Compounds corresponding to these structural types should not be prepared in schools.

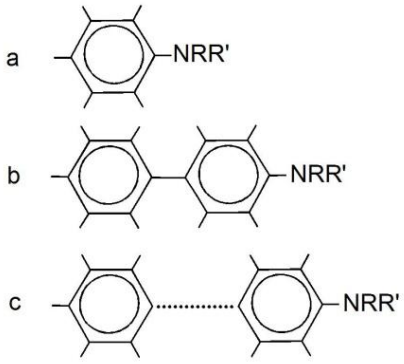

Figure 3: Some carcinogenic structural types

Substituting certain electron-donating substituents, such as methyl, methoxy or halogeno in a 2- or ortho position to the amino group in any of the amines mentioned above greatly increases the potency.

2-methoxyphenylamine (o-anisidine) is a potent bladder carcinogen in animals and though the results for the 4-isomer were less clear, there was concern that it might be capable of inducing tumours in humans. One might therefore expect the corollary to be true, that the substitution of

electron-withdrawing groups would reduce the potency. In this case, a carboxyl group will give anthranilic acid, not classed as a carcinogen. (See Figure 4)

While this seems to be true in general, it should not be assumed that a substance with an electron-withdrawing group is safe because of this.

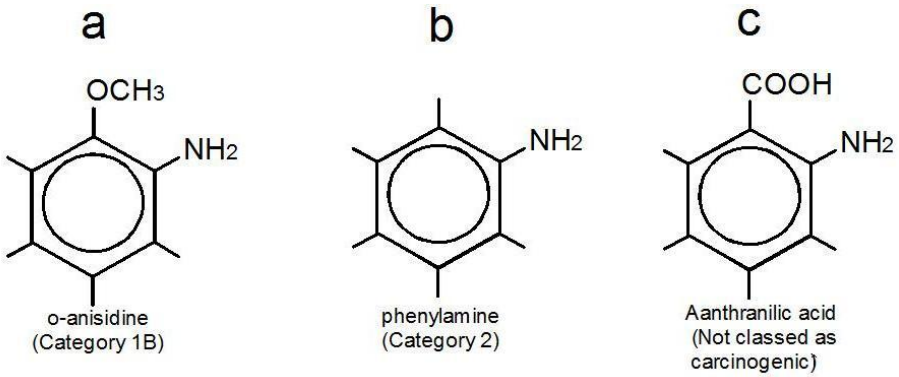

Figure 4: The effect of side-groups

The presence of one or more solubilising sulfonate groups in the nucleus of an aromatic amine ensures that the amine is rapidly excreted, thereby reducing the carcinogenic potential, usually to negligible proportion. A good example of this effect is the fact that 2-naphthylamine sulfonic acids fail to produce tumours in mice, even after very heavy doses.

Nitro compounds corresponding to carcinogenic aromatic amines should be assumed also to be carcinogenic. In general nitroarenes are biologically transformed in the body to the corresponding aryl amines. Nitro derivatives of unsaturated hydrocarbons formed in the combustion of diesel oil are potent carcinogenic.

12.2.2 Dyes. Benzidines and azo compounds

Some azo dyes are carcinogenic but the generalisation that all of them are is unfounded. The human gut flora breaks down azo compounds by reductively cleaving the azo bond to form two aromatic amines. Hence, if either product is a carcinogenic amine then the parent azo dye will also be carcinogenic.

Substitution with a sulfonic acid group often renders an azo dye non-carcinogenic. This generalisation is true for azo dyes, especially where both moieties astride the azo link contain a sulfonic acid, e.g. Sunset Yellow. The molecule as a whole is water soluble, but so are the two amines formed when the azo link splits (Figure 5).

However this generalisation is not true for diphenylazo dyes or benzidine dyes, e. g. Direct Blue 6. Here, although the parent dye molecule is soluble, the biotransformation in the gut will yield the recognised human bladder carcinogen, benzidine, in addition to the two sulfonated amines (see Figure 6).

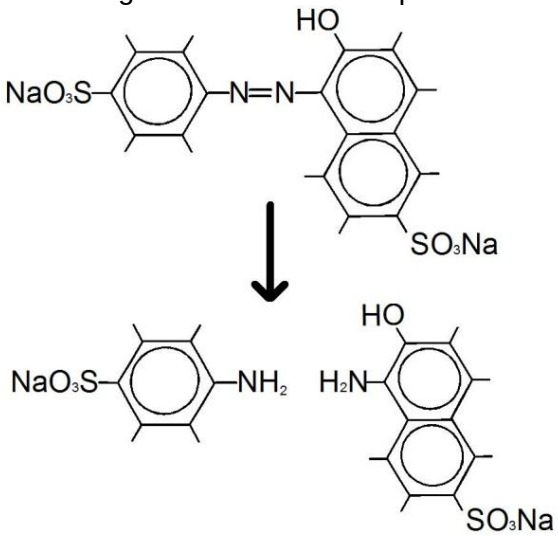

Figure 5: Sunset yellow forming two water-soluble, sulfonated amines

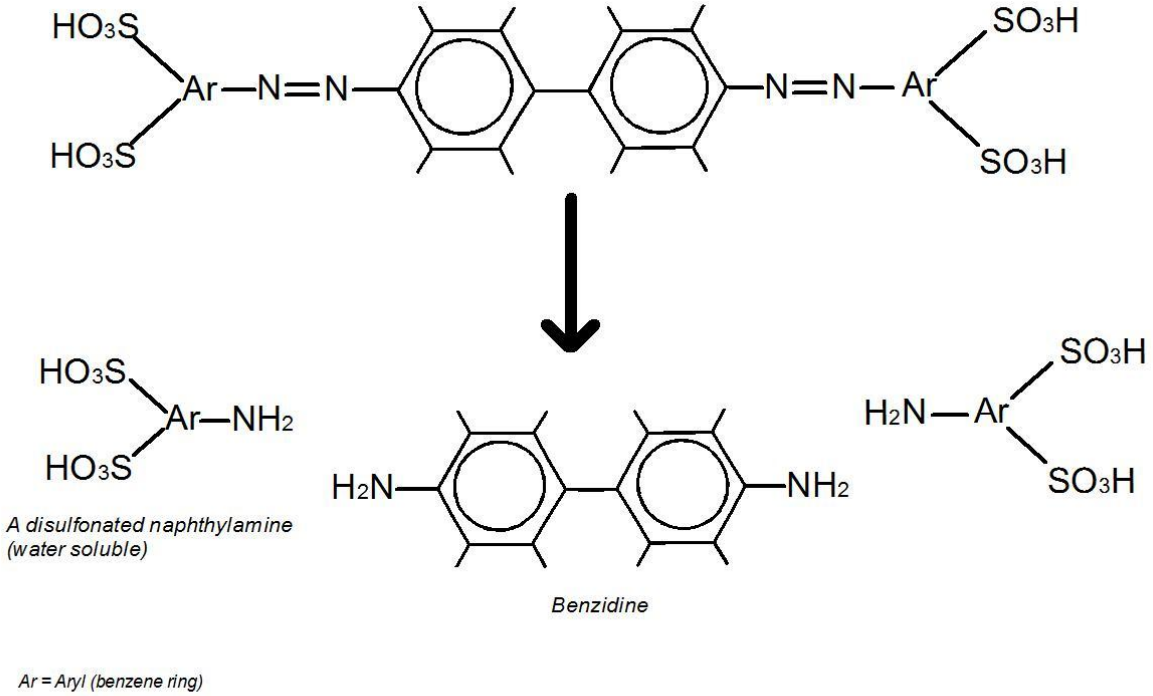

Figure 6: Direct Blue 6, a diphenylazo or benzidine based dye

Direct Black 38, Direct Brown 95, Trypan Blue, Direct Red 6, Congo Red and other 4,4'-diarylazobiphenyl dyes have a similar skeletal structure and will almost certainly be carcinogenic regardless of the substituents of the outer aryl or naphthyl group. As for amines, the presence of methyl and other electron donating groups in a position to ortho to the azo nitrogen and hence in the 2-position to the amino group will increase the potency of the parent dye.

It is suggested that year 12 (England, Wales & Northern Ireland) and sixth year (Scotland) preparations of azo dyes be restricted by:

- avoiding the preparation of dyes which conform to the structural types given for carcinogenic aromatic amines or contain such components:
- purchasing commercial dyes in as pure a state as possible because of the risk that commercial samples of many dyes may contain carcinogenic intermediates or by-products as impurities. Many dyes are now manufactured overseas and quality control during manufacture may be poor.
- preparing water-soluble azo dyes where possible. E.g. methyl orange. A better choice is to diazotise sulfanilic acid ($NH_2C_4H_4$ SO_3H) and couple it to a heavily sulfonated naphthol.

- avoiding the possibility of a diazonium salt coupling with an undiazotised amine to form azoaminoarenes. This can be achieves by ensuring that diazotisation is complete before proceeding to the next stage. Use excess of nitric(III) acid (nitrous acid) and check for its presence with starch/iodide paper (Figure 7)

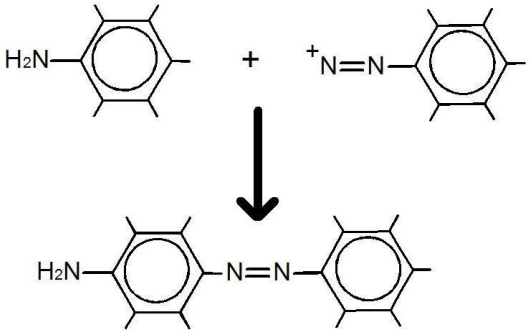

Figure 7: Ensuring diazotisation is complete

In the recent past some school courses have used various dyes including Disperse Yellow 3, Direct Red 23 and Acid Blue 40.

Sudan I, II, III and IV are probably weak carcinogens.with the evidence against Sudan IV seeming to be more reliable.

There is no evidence of either Magneson I or Magneson II being carcinogenic, although, as is the case with the Sudan dyes, the structures hint that the possibility exists.

The metallochromic indicators used in complexometric titrations e.g. of metals with EDTA, are mostly naphyhyl azo dyes, all of which are water soluble. Solochrome black T (also called eriochrome black T), solochrome black 6B, Patton and Reeder's indicator, calcon and calmagite all have one sulfonic acid grouping. Ponceau 3R is a suspected carcinogen.

There is no evidence that, in general, the reactive dyes used in schools are carcinogenic. The great care that must be taken on account of their sensitising potential means the risk of any possible tumour formation should be virtually non existent

Some anthraquinone and triphenylmethane dyes may be carcinogenic depending on the presence of particular substituents. It is relevant to emphasize here that all dyes should be handled with care as some may contain carcinogenic impurities. Dyes that are known to carry this risk, although thought to be safe themselves, and that are used in schools, are Magenta (basic fuchsin or rosaniline) and Disperse Yellow 3. The quoted purity for the latter is often as low as 30%. However Disperse Yellow is widely used in textile dyeing without discernable adverse effects and it is unlikely that it could be hazardous in small scale experiments in school science.

12.2.3 Nitroso compounds

Many of these compounds are potent carcinogens and they should not be used in schools.

N-Nitroso compounds could accidentally be made if nitric(III) acid (nitrous acid) was generated in the presence of secondary or tertiary amines. Even nitrogen dioxide gas in the laboratory atmosphere can react with amines in this way, though the toxicity of nitrogen dioxide means this circumstance is unlikely to arise.

1-nitroso 2-naphthol, a commonly used reagent for several metals, is only weakly carcinogenic. There is some evidence that Cupferrin (N-nitroso-N-phenylhydroxyamine, ammonium salt), a reagent for several metals, is moderately carcinogenic.

12.2.4 Hydrazines

Large doses of hydrazine itself have produced a low incidence of tumours in mice. Both 1,1- and 1,2-dimethylhydrazine are quite potent. Hydrazine has been used for making small fuel cells, but its use should be discontinued. Phenylhydrazine seems to be of a low potency, but the commonly used 2,4-dinitrophenylhydrazine is not thought to be carcinogenic.

12.2.5 Aromatic hydrocarbons

The only pure chemicals of this group likely to be found in schools are methyl- and some other substituted benzenes, naphthalene and possibly anthracene. Benzene, which was widely used as a chemical to study aromatic properties and as a solvent, is now effectively banned in educational establishments. This also means that unleaded petrol and crude oil, which often contain l% or more of benzene, should not be held or used in schools other than as a fuel in vehicles, lawnmowers, etc. (see 12.1.4 Legal Requirements on p5)

For showing aromatic substitution reactions, methyl benzoate or methylbenzene are alternatives for benzene. For solvent purposes a variety of other alternatives can be used, e.g. cyclohexane with a short term workplace exposure limit (WEL) of 300 ppm, methyl and dimethyl benzenes (with short term WEL values of 150 ppm). Because of their volatility and flammability, an efficient fume cupboard should normally be used together with all the usual precautions taken to prevent fire.

There is evidence that naphthalene is weakly carcinogenic and it is absorbed by inhalation and via the skin. There is no such evidence, however, for anthracene. There is also no evidence that simple derivatives of any of these hydrocarbons (including those of benzene), with the exception of amino, nitro and azo compounds, are carcinogenic but they may be toxic.

Carcinogenic polycyclic aromatic hydrocarbons are present in most samples of genuine crude oil and in the tarry messes left after some distillations of organic materials or compounds, including wood or coal. Tars are readily absorbed through the skin and hence the main danger of significant exposure arises when apparatus is being washed up. The wearing of suitable gloves for this operation is strongly recommended. In practice, real crude oil is now difficult to obtain and in any case should not be used on account of its benzene content which is well above concentrations of 0.1%. Using artificially made crude oil[9], whether DIY or obtained from a supplier, does not completely solve the problem. Although made from ingredients of low hazard, the resulting tarry pyrolysis products are almost certainly potent carcinogens. Tars collected in demonstration smoking machines should also be disposed of carefully.

12.2.6 Halogeno compounds

As a result of the damage they cause to the ozone layer, many halogenated hydrocarbons that were commonly used are no longer available, tetrachloromethane and 1,1,1-trichloroethane for example.

Many of these compounds are severely toxic to the liver and, in addition, some are carcinogenic. The simple halogenated compounds vary greatly in their physiological activities. While l,2-dibromoethane, trichloroethene and1,2-dichloroethane do appear to have significant carcinogenic activity (Category 1B) others such as 1,1,1-trichloromethane (chloroform), bromoethane and triiodomethane (iodoform) are of lower activity (Category 2).

The use of these substances as solvents should be restricted to those instances (rare in schools) where no satisfactory substitute is known. Unfortunately there is no universal substitute: it is a case of horses for courses and each application which formerly used the chlorinated hydrocarbon solvent may use a different solvent. Given that it too is a Category 1B carcinogen, trichloroethene is not a

[9] Recipes for this can be found on the CLEAPSS and SSERC websites.

favoured substitute solvent. Generally these compounds should be the last choice for use as solvents.

As a solvent for extraction purposes, dichloromethane has long been used on account of the combination of its solvent properties and high volatility. It is a weak carcinogen and is assigned Category 2 status. It can be used with care for extraction purposes eg of caffeine.

Many of the recognised analytical methods in the Standard texts (such as Vogel[10]) for determining several metal ions often recommend tetrachloromethane or trichloromethane for extracting the organometallic complexes from aqueous solutions and for spectrophotometric methods. It is usually possible to find alternatives, e.g. in the case of the lead dithizone complex, butyl ethanoate is found to be a good alternative of much lower toxicity, though flammable.

The HSE recommended that no exposure or contact, by any route: respiratory, skin or oral as, detected by the most sensitive methods, shall be permitted to 1,2-dibromoethane. This compound should neither be used nor prepared in schools. However the use of bromine water (not bromine in other solvents) as a test for ethene is safe as only a trace of dibromoethane is formed, the main product being hydroxybromoethane, In this application, the quantities of the products are minute and the contents of the tube can be disposed of immediately without isolating the products.

12.2.7 Direct alkylating agents

Again, these compounds, some of which are very potent carcinogens, should not be used in schools. However, one potent carcinogen of this type may be met in schools as a product of a chance reaction. Methanal (formaldehyde) and hydrochloric acid vapours react to give trace amounts of chloromethoxy-chloromethane (bis-chloromethyl ether or BCME) which is highly carcinogenic. (Concentrations of greater than one part per thousand million are forbidden in industry).

It has been stated that, depending on the humidity and temperature, as little as 10 ppm each of methanal and hydrogen chloride could give rise to this order of concentration of BCME. Other investigations have failed to confirm this. Because of the uncertainty it is best that methanal vapour should not be allowed to interact with hydrogen chloride from hydrochloric acid or from volatile, easily hydrolysed chlorides.

Dimethiyl and diethyl sulfate are reasonably potent carcinogens, both readily absorbed by the skin

12.2.8 Miscellaneous organic compounds

Various other organic compounds have been reported to be carcinogenic and are discussed below.

Thio compounds

There is some evidence that thiourea has produced thyroid cancer in rats, though none of cancer in humans; it is classed by IARC as a Group 3[11] (not classifiable as to its carcinogenlcity) but under GHS/CLP as Category 2, i.e. it is possibly carcinogenic to humans.

The Department of Cancer Studies at Birmingham University carried out a literature search on phenylthiourea (PTU, phenylthiocarbamide, PTC) and concluded that it should be acceptable for limited taste-testing experiments with necessary precautions to limit possible intake. Use only one paper strip containing no more than 0.1 mg of PTC per student. In reality, the extreme acute toxicity of PTC is far more of a hazard.

Purine and pyrimidine analogues, e.g.thiouracil, should be handled extremely carefully, if at all

[10] Vogel's Quantitative Chemical Analysis (6th Edition – 2000) ISBN-13: 978-0582226289

[11] http://monographs.iarc.fr/ENG/Monographs/vol79/mono79-24.pdf

8-hydroxyquinoline

This substance is of low carcinogenic potency. Where necessary it may be handled with care.

Ninhydrin

There have been rumours that this substance is carcinogenic, but there is no reliable evidence that this is so. Nevertheless it is a biologically active compound and the spraying of chromatograms should only be carried out in a small disposable spray booth` in a fume cupboard not least because of the hazards associated with the solvent, usually butan-1-ol..

Cotton Blue stain

This contains phenylamine and will therefore be a weak carcinogen.

Janus Green

There seems to be no evidence against Janus Green. It is available in a highly pure form.

1,4-dioxane

This substance, sometimes used as a solvent, is weakly carcinogenic. In addition it is highly flammable and like ether readily forms peroxides which can be explosive.

Methanal (formaldehyde)

This is a toxic chemical with a WEL of 2 ppm. It is relatively easy to comply with this limit in schools if sensible precautions are taken in handling preserved specimens etc. (Such as rinsing before examination). Epidemiological tests do not show any cancer risk to humans.

Monomers and polymers

In general monomers are by definition reactive species and several of them are carcinogenic; there are even reports of ethene being carcinogenic. Usually the polymers are safe, but there is probably no guarantee that polymerisation is complete. Burning or destructively heating polymers may release monomers.

In the past some schools made their own polyacrylamide gels for electrophoresis by purchasing and carrying out the polymerisation. Apart from its medium carcinogenicity, acrylamide is a powerful neurotoxin and great care is needed in preparing a solution of the monomer (which is a light powder). Fortunately, the alternative of agarose gel works satisfactorily. If acrylamide gel is necessary, it can be purchased as a pre-polymerised sheet.

Inorganic compounds and minerals

Chromium, cobalt and nickel compounds are now commonly reported to be carcinogenic. Much of the evidence of carcinogenicity for these compounds comes from industry, particularly mining, where workers are exposed to high levels of dust or fumes for lengthy periods. In pottery, many of these may be used as fine powders.

Chromium compounds

Chromium compounds in mining operations have been reliably associated with nasal and lung cancers; and the use of chromate baths in the plating industry has given rise to non-malignant skin ulcers. Most experimental evidence points to the Cr(VI) oxidation state alone being carcinogenic; and then the highest potency is the less soluble compounds such as the chromates(VI) of zinc or calcium, but not barium.

Hexavalent chromium compounds can cause ulcers on the skin but are carcinogenic by inhalation of dust or aerosol. Inhalation of dust is highly unlikely if the usual crystalline salts are used to prepare solutions. Avoid electrolysis of the solutions or any process where a gas is released in solution, or carry out such procedures in a fume cupboard. The only slight possibility of raising

some dust of a dichromate(VI) would appear to arise from the 'volcano' experiment. This should be done preferable using a containment method or in a fume cupboard. (Consult SSERC or CLEAPSS for advice on carrying this demonstration out safely). It is found, of course, outside the laboratory in the form of fireworks.

Nickel compounds

Over recent years, the carcinogenicity of nickel compounds has been investigated and found to be higher than previously thought. Industrial exposure to insoluble, dusty nickel compounds such as nickel(II) oxide and the sulfides has long been shown to be a source of industrial cancer. All the nickel compounds likely to be encountered in school are category 1A carcinogens, in the main, though, by inhalation only.

The chloride, nitrate and sulfate, generally used in hydrated form, are crystalline and would not form a dusty aerosol. However the oxide, hydroxide and carbonate are usually in the form of powders and could form a dust if not handled carefully.

If solutions of the salts are electrolysed, this should be done in a fume cupboard. In nickel plating, no gases should be evolved when a nickel anode is used and the current density kept to the recommended value. The process should be carried out in a fume cupboard. Nickel salts are appreciably toxic if ingested and are well known skin and respiratory sensitisers. Following the good laboratory practice needed to avoid possible sensitisation or toxicity should ensure the carcinogenic risk is minimal.

Cobalt metal and compounds

As with nickel, over recent years, the carcinogenicity of cobalt compounds has also been found to be higher than previously thought. These are now classified as Category 1B by inhalation. (No reliable epidemiological evidence is available for humans as those industrially exposed to cobalt and its compounds were simultaneously exposed to chromium and arsenic, though it seems likely that they may well be carcinogenic to humans). Crystalline solids can be handled safely. Care is needed with the powdery forms.

Minerals

Many ores are a mixture of minerals and should be handled carefully. Depending on the mineral, e.g. sulfides which may be mixed with arsenides, it may be prudent to take extra precautions if these are to be roasted/digested, etc, prior to analysis. Other minerals may be radioactive. Careful choice of sites for collection of minerals or ore samples should be made.

12.2.10 Carcinogens of biological origin

Aflatoxins and other mycotoxins, metabolites of fungi such as Aspergillus and Fusarium spp and other fungi are usually absorbed through the gut and the mould is easily dispersed. The spores of bracken fern are quite potent and field trips should avoid walking through bracken-covered areas during late summer when the fronds are bearing spores.

12.2.11 Physical agents

Ionising radiations

Work with ionising radiations and the sources producing them is controlled by The Environmental Permitting (Amendment) Regulations 2011 (and in Scotland, The Radioactive Substances Exemption (Scotland) Order 2011). The sealed radioactive sources, when used in accordance with the appropriate guidance (See Topic 19 and advice from SSERC and CLEAPSS) on the use of ionising radiations in schools, do not present a significant risk of producing even a skin cancer. Open sources are a greater risk. Fine powders which are very easily spread and inhaled present greater risk than crystalline, non-dusty, salts.

Another significant source of radiation, which in some areas of the country is rather high, comes from radon gas seeping from the ground underneath the building. Ensuring minimisation of this risk is rightly the responsibility of the employer.

Fibres

The main hazard is via the inhalation route. Asbestiform minerals have long been banned from schools, though they can occasionally still be found in odd places. Where the asbestos is broken and fibrous, e.g. oven door seals, it should be replaced, but hard unbroken cement panels are often best sealed and left. Care is needed in collecting and handling certain minerals on field trips. Of the machine-made mineral fibres (MMMF), the wools (rocksil, slag wool, and glass wool) are of low potency, and the glass wools made of drawn filaments rather than by spinning are of very low potency. Glass wools are unpleasant to use but are less potent than ceramic fibres. Mineral wools are classified as Category 2 carcinogens (H351), while Refractory Ceramic Fibres (RCF) are Category 1B (H350).

Superwool 607 is an alternative which, certainly as yet, is not classified as a carcinogen. Its manufacturers claim a very low biopersistence which negates any long term effects.

After prolonged heating the ceramic fibres change to cristobalite or mullite which are even more toxic than the original ceramic fibre. Dust from Kevlar (l.4-aramid) fibres is carcinogenic, but that from Nomex, the 1,3-isomer, is not. There is weak evidence linking graphite fibres with tumour formation.

For the Arculus ‘wet asbestos’ method the mineral wool can be replaced by glass fibre or Superwool, though scrunched-up filter paper serves as a liquid reservoir superior to that made of any of the wools. Vermiculite is another alternative.

Platinised ceramic wool can still be used, but should be reduced to a minimum. Place it in the catalytic chamber’ (usually a combustion tube or side-arm test tube) in a fume cupboard with a small loose pad of glass wool at the ends to help retain it. After use, stopper the ends and store for next time.

Ultraviolet radiation (UVR)

In the laboratory, UVR is used for locating purposes in chromatography or for demonstrating fluorescence and the photoelectric effect. In general, avoid lamps emitting radiation with wavelengths under 300 nm. However, lamps designed for viewing specimens or chromatograms commonly use 265 nm, but are safe in that they are arranged to shine on artefacts or chromatograms without being viewed. More likely to cause skin cancer is the UVR received from sunlight. (See Topic 18)

3 Summary of guidelines

12.3.1 Strategy for limiting exposure

The main approach is that of carrying out a risk assessment and setting up adequate control measures as for any hazardous substance, but with carcinogens the emphasis on using an alternative is greater than is the case for other chemicals. Situations which can lead to releases and significant exposures are as follows.

- Handling volatile carcinogens or using processes which might result in a release of vapour eg distillation. Ensure stores are well ventilated
- Weighing out powders to make up solutions (often once this stage is complete the chance of an exposure is minimal).

- During solvent extraction, especially if using a separating funnel.
- Absorption through the skin. Many chemicals, including solvents, are rapidly absorbed through the skin and through gloves of materials unsuited for that chemical. Discussion and guidance on choice of glove types can be found on the SSERC [12]and CLEAPSS[13] websites.
- Some compounds, particularly aromatic amines and several dyestuffs, although themselves relatively safe may contain carcinogenic impurities. An example is diphenylamine which is not thought to be carcinogenic but some commercial samples of it contain the potent carcinogen 4-biphenylamine. In general, any compound that is likely to contain as an impurity any of the substances listed in Section 3.2 should be avoided or at least obtained in as pure a form as possible and handled carefully.

12.3.2 Compounds that should definitely not be kept or used in schools

- Benzene, petrol and crude oil
- Naphthalene-1-amine or naphthalene-2-amine (α or β naphthylamine)
- Biphenyl Substituted by:

  i) at least one nitro or primary amine group or by least one nitro and primary amino group;

  ii) further substitution by halogeno, methyl or methoxy groups, but not by other groups in addition to substitution as in (i) above. 3,3'-dimethyl-biphenyl-4,4'-diamine (o-tolidine) and 3,3'-dimethoxybiphenyl-4,4'-diamine (o-dianisidine) were used as reagents for detecting sugars or determining chlorine. These uses should be discontinued. The active end of a Clinistix strip contains o-tolidine and should not be touched. Diabur test strips are a safer alternative.
- Naphthylbiphenylazo dyes in general. Some may be safe.
- Nitrosamines. (N-nitroso compounds should not be prepared. Avoid accidental preparation (Cupferron reagent contains a similar structure: where possible use an alternative, but normal good laboratory practice should ensure nil risk.)
- Nitrosophenols. (4-nitrosophenol is thought not to be carcinogenic and may be used in schools.)
- Nitronaphthalenes.
- Chloroethene (vinyl chloride monomer).
- Nitronaphthalenes.
- Chloroethene (vinyl chloride monomer).
- 1,2-dibromoethane, l,2-dichloroethane.

12.3.3 Highly toxic compounds which may also be carcinogenic

Hydrazine, iodomethane (methyl iodide), methanal (formaldehyde, formalin), phenylamine, tetrachloromethane (carbon tetrachloride), trichloroethene (trichloroethylene)

Use substitutes wherever possible. If the chemicals are used avoid breathing their vapours or splashing them on the skin. Wear suitable gloves and eye protection. 1,1,1-trichloroethane, which had been used as a safer substitute for tetrachloromethane and trichloromethane in some solvent applications, is no longer manufactured. Possible alternatives are cyclohexane, butyl ethanoate,

[12] http://www.sserc.org.uk/index.php/chemistry-health-a-safety138/background-info208/protective-equipment/1745-personal-protective-equipment-gloves
[13] PS 50 - http://www.cleapss.org.uk/attachments/article/0/PS50.pdf?Secondary/Science/Guidance%20Leaflets

Lutoxane or Volasils. In the case of the nylon rope trick, it is better to use a solution of the dioyl chloride in cyclohexane which will form the upper layer over the aqueous amine in water. To show the typical reactions of phenylamine, substitute esters of 4-aminobenzoic acid.

3.4 Less toxic compounds of carcinogenic potential

Bromoethane, dioxane, ethanal, ethanamide, 8-hydroxyquinoline, naphthalene, thiocarbamide (thiourea), thioethanamide (thioacetamide), α-mono-, α,α,di and α,α,α-trichloromethylbenzenes.

Ethanal is very volatile (boiling point 2l°C) and to show the properties of alkanals it is preferable to use the less volatile propanal, which has not been demonstrated to be a carcinogen. Naphthalene is quite volatile and readily absorbed by inhalation or through the skin; for cooling curves to show liquid/solid transition naphthalene should be substituted by octadecanoic acid or by the alkanols, hexadecanol or octadecanol. Side-chain chlorinated methylbenzenes should be used with care. They are in any case extremely irritating. As with other toxic substances, wear gloves and eye protection when handling these compounds and take care to avoid contact with the skin.

12.3.5 Azo dyes

Use water-soluble indicators where possible. Avoid staining the skin with indicator solutions. In preparation of azo dyes check that dlazotisation is complete in the first stage by testing for excess nitric(III) acid (nitrous acid). (Starch/iodide paper goes blue)

Prepare water-soluble azo dyes in which both ‘halves’ contain many sulfonic acid groupings by diazotising sulfanilic acid and coupling it to a disulfonated naphthol. 2-naphthol-3-6-disulfonic acid, 1-naphthol-3-6-disulfonic acid and 4,5-dihydroxy-2,7-disulfonic acid (chromotropic acid, sodium salt) arc available and work well. Methyl Orange is another suitable example.

Avoid using diphenylazo or benzidine based dyes. Where a microscope stain is of this type and no alternative is available; take precautions to avoid skin contact.

12.3.6 Methanal (formaldehyde) together with hydrochloric acid.

To avoid possible formation of BCME, store methanal separately from concentrated hydrochloric acid or volatile, easily hydrolysed chlorides such as phosphorus(III) chloride, aluminium chloride and ethanoyl chloride. Where concentrated hydrochloric acid is specified in a chemical reaction also involving methanal eg preparations of condensation polymers involving methanal, use 50% sulphuric acid instead. Glassware that has contained methanal (or formalin) should not be cleaned with hydrochloric acid.

12.3.7 Thorium and uranium compounds

Check the condition of the plastic tubing and bottle of radon generators regularly in case they become cracked or split. (In Scotland, the only permitted radon generators are the thoriated gas mantles used in a bottle with the Cooknell ionisation chamber kit) Take care to avoid spillages and keep a paper-lined tray underneath when handling. Store and use protactinium generators in a small beaker.

12.3.8 Chromates,

Chromate, Category 1B and H350i (by inhalation only) should always be handled wearing gloves and eye protection. The generation of dust or spray (as in electrolysis) should be avoided. The preparation of a solution is unlikely to lead to an aerosol as the crystalline salts are used. Although dichromate(VI) is a primary volumetric standard, it can be substituted with potassium manganate(VII) for titration of iron(II). Tests for reducing agents, e.g. sulfur dioxide, and tests on alkanals, alkanones and alkanols can be carried out on a small-drop scale using 0.1M or less. The ionic migration experiment can be demonstrated but copper sulphate and potassium manganate(VII) can be used instead.

Organic Preparative oxidations, eg of alkanols, should be carried out on a small scale using enclosed techniques. The 'volcano' demonstration can be carried out on a small scale using enclosed techniques[14]. Anyway, the use of chromium(VI) compounds will, on environmental grounds, have to be limited.

12.3.9 Nickel and cobalt and their compounds

Use alternatives wherever possible. Handle the powdery forms of the metals or their compounds with care to avoid raising dust and avoid generating aerosols. When nickel catalysts are used for hydrogenating oils, they should not be recovered as a metal but left embedded in a block of the solidified fat. Finely divided nickel catalysts are pyrophoric. The demonstration of water loss through the skin has often been done by holding cobalt chloride paper against the skin. As cobalt salts are carcinogenic only by the inhalation route, there should be virtually no risk of inducing cancer. However, cobalt salts are also skin sensitisers and it is therefore essential to wash hands after handling cobalt chloride paper.

The website appendix

The website appendix extends the range of chemicals listed under the same headings used in Section 2. It includes:

- The category of carcinogens and the hazard statements of substances as classified by the European Chemicals Agency (ECHA).
- Those which are banned
- Estimates of the relative potencies of the carcinogens where the information is available

[14] Consult CLEAPSS or SSERC for suitable methods.