Review article

Formaldehyde in pathology departments

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SUMMARY Toxic effects of formaldehyde in humans are discussed in relation to occupational exposure and tolerance to this agent. Carcinogenic and mutagenic properties of formaldehyde have been reported in animals and this has led to concern about a possible role in human cancer. The current state of affairs is reviewed in the light of a lack of direct evidence linking formaldehyde with cancer in man and in relation to recommended exposure levels. It is important to employ effective means of containment and practical methods for reducing exposure to formaldehyde in pathology departments and post-mortem rooms are described.

Post-mortem changes in cells and tissues can be retarded or even prevented by the use of chemical fixatives. Histological technique is built upon the use of these agents in order that fixed tissue should resemble as accurately as possible the form that it held in life. Early histologists made extensive use of ethyl alcohol but around 100 years ago formaldehyde was established as the "classical" fixative and could now be described as the stock-in-trade of all hospital pathology laboratories.

Formaldehyde (HCHO) is the gas produced by the oxidation of methyl alcohol. It is colourless and flammable with a strong pungent odour and may form an explosive mixture with air and oxygen and is most commonly produced by reacting methanol vapour and air over a catalyst. Produced in this way, it contains trace amounts of methanol and formic acid. Formaldehyde is extremely soluble in water and the aqueous solution containing some 37% formaldehyde is called formalin. Commercially available formalin is generally a solution containing 37% formaldehyde together with some 10–15% methanol to inhibit polymerisation. Without this inhibition the aqueous phase can slowly polymerise to paraformaldehyde, a form in which it is also available.

Besides being widely used in pathology laboratories formaldehyde is a basic chemical used in many industrial processes including the manufacture of adhesives, deodorants, dyes, explosives, tex-

tiles, laminates, pharmaceuticals, etc. In the building industry, urea formaldehyde is widely used in the manufacture of chipboard and hardboard and in cavity wall insulation.

It is difficult to be accurate about the quantity of formaldehyde produced and used in the UK and estimates vary between 60 000 and 145 000 tonnes per year!¹

OCCUPATIONAL EXPOSURE TO FORMALDEHYDE During the last few years there has been concern about both short and long term exposure with conflicting opinions as to the possibility that formaldehyde is carcinogenic. Many groups of people are in some way or other exposed to formaldehyde and the US Department of Health and Human Services lists some 225 occupations where it might be encountered.² In this list are included such unlikely occupations as accountants, health administrators, sailors and deck hands and even writers, artists and entertainers.

It has been estimated that iron foundry workers might be exposed to formaldehyde concentrations between 0.02–18.3 ppm whilst dye stuff operatives and people working in plywood industries would be exposed to between 0.1–5.9 and 1.0–2.5 ppm respectively. By comparison, it was thought that hospital necropsy rooms produced concentrations between 2.2–7.9 ppm. The present UK threshold limit value for formaldehyde is 2 ppm³ whereas, for example, it is 1 ppm in Germany whilst the USA has a short-term exposure limit of 1 ppm for 30 min.

Toxicity to humans

ABSORPTION AND METABOLISM

The high solubility of formaldehyde in water means that it is readily absorbed in the upper part of the respiratory tract with relatively small amounts of any inhaled gas penetrating to the lungs. Once absorbed, formaldehyde is metabolised to formic acid both in the liver and blood by the enzyme formaldehyde dehydrogenase. Direct oxidation by red blood cells has also been reported and further oxidation may take place in tissues other than liver or blood. Carbon dioxide and water is finally produced by further oxidation of the formic acid.

INGESTION

There have been reports of death from the ingestion of around about 100 ml of formalin in adults (much less in the case of children).⁴⁻⁶ The symptoms are similar to those produced by a strong acid with severe irritation of all mucosal surfaces of the gastrointestinal tract resulting in ulceration, inflammation and tissue necrosis.

EFFECTS ON EYES AND RESPIRATORY TRACT

The first signs or symptoms associated with exposure to formaldehyde occur in the eyes at concentrations of 0.1–5 ppm with a burning sensation and the production of tears. It is suggested that the threshold for the eyes to respond to formaldehyde is as low as 0.01 ppm. Accidental splashes of aqueous solution of formaldehyde cause severe irritation to the eyes and have, on occasions, resulted in permanent damage even when the eyes were immediately washed with water.⁷⁻⁹ 4% formaldehyde solution splashed in the eye has been reported to produce a strong irritant effect with visual disturbance persisting for one day after which time the eye returned to normal.

At concentrations around 0.5 ppm mild throat irritation and a tingling sensation occurs. It is generally regarded that formaldehyde in a concentration of some 5 ppm is intolerable in a room and at concentrations approaching 10 ppm (a danger level) a choking sensation occurs. Exposure to 50 ppm (even of short duration) can be expected to cause serious injury.^{10,11}

EFFECTS ON SKIN

Dilute aqueous solutions of formaldehyde and the vapour itself are irritant to the skin. Many cases of dermatitis have been reported amongst persons exposed to formaldehyde in the course of their work. In normal human volunteers it has been shown that solutions containing less than 2% formaldehyde are unlikely to produce irritant effects. In addition to the reports of allergic contact der-

matitis, skin sensitisation has also been noted from experimental studies with volunteers.¹²

There are reports of asthma-like symptoms in workers exposed to formaldehyde.¹³ In particular, respiratory symptoms have been reported in nurses in haemodialysis units where formalin was used to sterilise the dialysis equipment. In 1982 a follow-up study of two nurses who were shown to develop occupational formaldehyde asthma in 1977 showed that one nurse, who had ceased to be exposed after 1976, had lost all symptoms. She had also lost her asthmatic sensitivity to formaldehyde and lung function studies were almost normal. The second nurse in this study however had continued to be exposed to formaldehyde (although at a reduced level) and persistent asthmatic responsiveness could be demonstrated in 1981. In this case there was no evidence of any progressive chronic airway obstruction.

In spite of the widespread use of formaldehyde there have only been a few reported cases of respiratory illness due to allergic sensitisation.

TOLERANCE TO FORMALDEHYDE

There is some evidence of acclimatisation or tolerance to the irritant effects particularly in the action of tear production. This evidence comes from experiments with healthy volunteers exposed to 13.8 ppm for 30 min.¹⁴ There was initially considerable irritation to the eyes and nose but the effects rapidly wore off with no signs of eye irritation being observed after 10 min.

Formaldehyde and cancer

A known carcinogen, bis-chloromethylether (BCME) is produced when formaldehyde reacts with hydrogen chloride.¹⁵⁻¹⁸ The reaction of hydrochloric acid with formaldehyde in situations where the two agents are stored together permits the possibility of forming this potential carcinogen. However, the concentrations of both agents would need to be considerably in excess of their respective threshold limit values and in such an atmosphere work would become impossible. The separate storage of these substances and the maintenance of their levels below the threshold limit values is regarded as providing adequate safeguards against carcinogenic risk due to the formation of BCME.¹⁹

Mutagenicity, or the ability of an agent to cause a change in the genetic material within a cell, is associated with most chemicals known to cause cancer. Tests for mutagenicity can therefore help in determining carcinogenic potential. In this regard formaldehyde has been known to be mutagenic for some time from laboratory experiments with fruit flies (*Drosophila*) grasshoppers, flowering plants,

Formaldehyde in pathology departments

fungi and bacteria.²⁰⁻²²

There is a recent report that formaldehyde at a level of 4 ppm was found to be mutagenic in diploid human lymphoblasts in culture.²³ In another study no chromosome abnormalities were found in a group of 15 workers exposed to formaldehyde over a long period (average 28 yr)²⁴

In March 1979, workers at the University of Birmingham published a report on the possible carcinogenic hazards of formaldehyde.²⁵ In reviewing human data they concluded that the Registrar General's occupational mortality tables for 1961-1970 did not show any increased incidence of cancer in two groups of workers, namely chemists and physical and biological scientists. In the study of the causes of death of 131 pathologists, death from some cancers (especially respiratory cancers) were less than expected but there were significantly more deaths from lymphoid tumours (8 were found when 3.3 were expected). These authors concluded that the possibility that this was associated with exposure to formalin should perhaps not be excluded.

They also concluded that "it seems to us that carcinogenicity tests carried out so far would probably have shown if formaldehyde itself had a high degree of carcinogenic activity. It is, however, possible that more thorough tests now being carried out may show up a relatively weak carcinogenic action."

In October 1979, preliminary results from studies in animals showed that when rats were exposed to 15 ppm for 6 h/day for 5 days/wk for 16 months three developed squamous cell carcinoma originating in the epithelium of the nasal turbinates.²⁶ Further results from this study in 1980 showed that after 24 months of exposure to 15 ppm of formaldehyde some 93 rats developed squamous cell carcinomas of the nasal turbinates. Two developed respiratory epithelial carcinomas and two rats exposed to 6 ppm and two mice exposed to 15 ppm had also developed squamous cell carcinomas of the nasal turbinates.²⁷

In April 1981, the US National Institute of Occupational Health and Safety, in consideration of these carcinogenic features of formaldehyde, recommended that formaldehyde be handled in the workplace as a potential occupational carcinogen.² Since that time, there have been a number of investigations seeking to clarify any relation between occupational exposure to formaldehyde and the incidence of cancer in humans. Concurrently, there have been calls to limit the general exposure of workers to this agent and to seek ways of producing containment whereby environmental contamination by formaldehyde is kept at a very low level.

At the time that US National Institute for Occupational Safety and Health (NIOSH) issued its

recommendations concerning the potential carcinogenicity of formaldehyde there had been no hard evidence of specific cases of human cancer due to the agent. The prime reason for the recommendation seems embodied in the statement that "although humans and animals may differ in their susceptibility to specific chemical compounds, any substance that produces cancer in experimental animals should be considered a cancer risk to humans." In 1981, the Health & Safety Executive in the UK issued a *Toxicity review* about formaldehyde and stated "there is at present no evidence that exposure to formaldehyde has produced cancer in humans". A number of epidemiological studies are in progress to investigate this aspect.

One of the immediate results of the US recommendation was that the American Consumer Products Safety Commission decided to ban the use of urea formaldehyde foam used for insulation in the building industry. This was because of "unreasonable risks to consumers from the irritation, sensitisation and possible carcinogenic effects of formaldehyde emitted by this substance" the Commission concluded that at that time no standards, voluntary or mandatory, to reduce the risk were feasible.

In a recent publication, the British Plastics Federation, sought to defend the use of urea formaldehyde foam and to criticise the American Consumer Product Safety Commission for recommending a ban on the substance.²⁸ In regard to the release of formaldehyde in dwellings it asserts "there remains no evidence to suggest that formaldehyde can cause anything more than short-term irritation to humans at the levels liable to be experienced in properly insulated dwellings." Further concern for the industrial use of formaldehyde is expressed in a publication from the Chemical Industries Association which says "the acute (short-term) effects of excessive exposure to formaldehyde are mainly transitory and reversible".²⁹ The long-term effects are summarised as chronic skin disorders and chronic respiratory tract conditions but with very few examples cited in the scientific literature.

Recently, Sir George Young, Under Secretary of State for the Environment, in a written answer in Parliament concerning the carcinogenicity of chemicals in food, consumer products and the environment, said that an Advisory Committee was looking at research on the effects of formaldehyde and that "in its view there is no evidence that formaldehyde gas causes cancer in man."

From the available literature there would, therefore, appear to be no evidence to suggest that the concentrations of formaldehyde encountered in the practical working environments of hospital pathology laboratories and post-mortem rooms would

produce a carcinogenic hazard. Personal exposure to this agent is effectively self-limiting because of the extremely unpleasant effects at relatively low concentrations with the consequent behavioural response of avoidance.

Nevertheless, there do exist problems of formaldehyde toxicity related to asthma, dermatitis, sensitisation and irritation where guidelines for exposure reduction are appropriate.

By 1982 it was thought that there might be some pressure from the Health and Safety Executive to impose restrictions on the use of formaldehyde but there was some disagreement between this agency and the Health and Safety Commission (the governing body of the HSE) who were less satisfied that such constraints were justified. A number of agencies and organisations were already preparing guidelines and policies in anticipation of new regulations which might result but which in the event did not materialise.

Practical containment measures

In 1980 the Medical Research Council had indicated that work with formaldehyde should be carried out with the following reasonable precautions:

- 1 Solutions should be made up in a fume cupboard.
- 2 Vessels should be covered as much as possible.
- 3 Work should only be done in well ventilated rooms.
- 4 Time of exposure should be kept to a minimum. The reduction of operator exposure to splashes and gross contamination by formaldehyde is a matter of laboratory technique together with the use of gloves and eye protection where appropriate. However, the formaldehyde vapour concentration in the air may need to be controlled and this can be achieved in a number of ways.

ROOM VENTILATION

The laboratory may be ventilated in order that any formaldehyde gas released into the atmosphere is purged and the concentration maintained below the threshold limit value. Care must be taken not to produce excessive air change rates; for example, in laboratories some 7 m × 5 m the maximum air removal rate for comfort conditions would be of the order of 0.2 m³/s. Greater extract would also increase revenue costs as far as heating of input air is concerned.

FUME CUPBOARDS

To complement the effects of overall ventilation systems more local extraction of formaldehyde vapour is often appropriate and here there are a number of

alternatives. The most obvious is to make use of the laboratory fume cupboard, particularly when handling large volumes of formaldehyde.

In correctly designed cupboards the vapour will be carried away and diluted before discharge to the atmosphere at high level. In older buildings where multiple fume cupboards may be on one air system, the fume cupboard and its duct work should be proved to be effective and should on no account allow leakage of formaldehyde gas back into other laboratories.

Recently, there has been considerable interest in the use of relatively inexpensive portable fume cupboards which do not require major installation work. These devices incorporate absorption filters to remove gases and vapours from the air before returning it to the laboratory.

Such cupboards initially appear very attractive in terms of capital cost, installation and operating expenses. There are, however, a number of significant problems which should be reviewed in the light of a potential use as far as formaldehyde absorption in the pathology laboratory is concerned.

If a recirculating fume cupboard is to be safe and effective at removing formaldehyde and maintaining the concentration below the correct threshold limit value it must:

- 1 Achieve adequate containment of fume at the front by an inflow air velocity of at least 0.5 m/s (and not greater than 1.0 m/s).
- 2 In order that the harmful agent is effectively removed by the filter the contact time with the filter medium must be sufficient for adequate absorption to take place. In addition, because these filters have a finite absorption capacity there must be some reliable indication of filter saturation. In the case of formaldehyde it has been suggested that the sense of smell by those within the laboratory would be adequate to determine the end-point of filter life!

The charcoal filters have a wide range of absorption characteristics for different chemical agents. Their effectiveness for a particular compound is generally expressed as the proportion of the clean filter weight that can be absorbed. The absorption can be as high as 15–20% for some agents but in the case of formaldehyde it is very much lower at only around 1–2%. One consequence of this is that for a filter to be effective over a reasonable period of time it must be fairly large and one manufacturer suggests that filter weight for a practically useful life is some 36 kg.

The use of recirculating fume cupboards is generally regarded as unsatisfactory and only in exceptional and rather specific circumstances where the fume has a nuisance value rather than being toxic

Fig. 1 A novel ventilated necropsy table with air exhausted from over the surface of the body by means of adjustable exhaust ports which may be positioned at a height and length appropriate to the work area concerned. Courtesy of Howorth Air Engineering Ltd.

Fig. 2 Postmortem room layout incorporating a clean air zone over the table and local exhaust at the cutting up bench. Courtesy of Medical Air Technology Ltd.

could the use of these cupboards be considered.³⁰

POSTMORTEM ROOM

Airborne contaminants can pose problems in the post-mortem room. The minimisation of the release of potentially pathogenic droplets or tissue aerosols together with the reduction of exposure to formaldehyde at the cut-up bench require special measures. There is some debate as to the extent of the problem and whether effective precautions can be devised whereby the overall "air quality" in these areas can be guaranteed, and if so do the chances of acquiring infection, particularly tuberculosis, become smaller.

New designs of ventilated necropsy tables in conjunction with overhead canopies producing downflowing air curtains can contain aerosols liberated during the post-mortem procedures. Exhaust air from these systems is filtered in order to remove particulates before the air is discharged to outside. Such systems can also purge the post-mortem room of noxious vapours including formaldehyde. As gases will not be arrested by filtration the exhaust should be treated in much the same way as for a fume cupboard. Fig. 1 shows a novel ventilated necropsy table using exhaust ports which are adjustable in height and length appropriate to the work area.

CUT-UP BENCHES

Cut-up benches adjacent to the necropsy table require local air extraction of formaldehyde and Fig. 2 shows such a system incorporated into a post-mortem room where there is also a ventilated necropsy table and overhead air curtain.

Besides being suitable for post-mortem rooms, the ventilated cut-up bench is also important in preventing a build-up of formaldehyde in the pathology laboratory. Care should be taken that the design is effective for gathering formaldehyde from a reasonably large working volume on the bench and partial enclosures to entrain the contaminated air are generally required as shown in Fig. 3.

FUMIGATION

The widespread use of microbiological safety cabinets and the requirement for routine servicing means that the laboratory staff are frequently called upon to effectively decontaminate these cabinets before maintenance engineers start work. Many contractors now require certification of decontamination procedures and the Health and Safety at Work Act requires that appropriate safety measures are carried out.

The normal method of decontaminating safety cabinets and their filters is by fumigation with for-

Fig. 3 An example of a local fume extraction unit suitable for bench extraction of formaldehyde in the postmortem room or pathology laboratory. Courtesy of Howorth Air Engineering Ltd.

maldehyde gas. It is now also fairly common for complete laboratories to require fumigation, from time to time. This requirement may be extended to post-mortem rooms, necropsy tables and air-handling systems that are being proposed for new installations.

There are several methods of fumigating safety cabinets and rooms with formaldehyde. In the case of a safety cabinet the front closure should be in place and the exhaust duct blocked off. 25 ml of formalin can be vaporised by being placed in a dish on an electric heater. Alternatively, 25 ml of formalin can be placed in a 500 ml beaker and 10g of potassium permanganate added. The mixture will react vigorously producing formaldehyde gas. If too much potassium permanganate is used there is the risk of explosion. Once the formaldehyde is produced in the cabinet it should be introduced into the filter by running the cabinet fan for a few seconds. After this it should be left overnight. At the end of

the fumigation period the cabinet should be run normally to purge the formaldehyde gas. It should be noted that fumigation is only fully effective as long as adequate water vapour is present. Liberation of formaldehyde gas, for example by subjecting paraformaldehyde to dry hot air is not satisfactory.

When cabinets are not ducted to the outside fumigation produces considerable problems if formaldehyde is not to be released into the laboratory. These may be overcome by for example, incorporating a damper into the safety cabinet exhaust and using a flexible tube attached to the exhaust duct to take the formaldehyde to a window or fume cupboard at the end of the fumigation period. Most of these decontamination procedures involve larger volumes of formaldehyde than are encountered in general laboratory work and staff should therefore be fully instructed in the appropriate techniques and safety precautions.

When installing new safety cabinets the provision

of external ducting should be reviewed in the light of decontamination procedures which may be required at reasonably frequent intervals and should produce minimum exposure of staff to formaldehyde.

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