F O R M A L D E H Y D E

I N T H E

I N D U S T R I A L E N V I R O N M E N T

by

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A B S T R A C T

Consideration has been given to the toxicity of formaldehyde in the industrial environment. The available literature has been reviewed critically against a background of technological awareness of the usefulness of the material and the factors which influence the assessment of absorption by the body fluids following exposure are examined. Data from experimental work carried out in a number of factory locations has been analysed in an attempt to establish the relationships between somatic absorption and levels of formaldehyde found in ambient air. Specific topics include (i) The effects of repeated exposure, (ii) The sensitivity of the skin, and (iii) The adaptive tolerance found in man. The results indicate that following repeated exposure an accumulation of formaldehyde occurs in the saliva with a time proportional characteristic. The peak levels that are achieved appear to be independent of the ambient levels encountered in the work place. The protective effect of silicones for the skin when incorporated into high yielding formaldehyde resin systems has been quantified and specific types have been adopted for commercial use. In terms of human adaption, possible correlations have been considered for those levels found in the urine and saliva which reflect the physiological consequences of absorption and dissipation. The contribution of formaldehyde as a potential toxic hazard in industry has been assessed and appropriate recommendations have been made.

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FORMALDEHYDE

IN THE

INDUSTRIAL

ENVIRONMENT

PART

I

PREFACE

L. Goldberg, when introducing his Milroy lectures on the "Amelioration of Food", advocated that the central issue for man had become environmental pollution, and more particularly its avoidance. He put his philosophy into perspective in the following way.

> 'Life and its environment, primarily the chemical environment of air, water, and food, are an indissoluble continuum. The normal healthy organism is poised in a state of dynamic, and perhaps uneasy, equilibrium between exogenous chemicals and nutrients and the body's endogenous metabolites. Changes in the world around us have presented all organisms with an increasing host of new compounds with which they have to contend. The extent of the chemical environment is so wide that the all-pervading exposure has to be borne in mind when considering any element within the environment, or the interactions between elements, in relation to man. The world's increasing population attests to a successful biological adaptation to our environment, including the chemicals in it, at any rate for the time being. While presenting the complexities of chemical exposure, therefore, equal stress must be laid on man's protective mechanisms and powers of adaption; intra- and extra-cellular adjustments coupled with hormonal regulation can bring about dramatic changes in man's capacity to deal with foreign compounds.'

At the time of its presentation in 1968 the inference in these remarks summed up not only the attitude of mind, but the underlaying resolve of the authorative bodies of the day to procure for society a clean pollution free environment.

In the event unfortunately little real progress has been made as a result of these endeavours in spite of continuous efforts which span more than a decade.

Objectively speaking, environmental pollution may be regarded as the addition of any offensive or harmful substance to the environment, which produces a significant change in the natural composition; and subjectively as any impairment of the quality of that environment.

But the single most important issue to be reckoned with is the total cumulative effect of such pollutants, their interactions and amplification and ultimately their damage.

By enhancing and favouring certain natural ecological elements, whilst depressing and retarding others we are knowingly displacing ecological equalibria. Our power to transform the natural environment would seem, by far to exceed our ability to control or understand it. There is an urgent need for knowledge of the impact of industrial technologies. Even now there are innumerable contaminants to which the body plays host, perhaps underlining man's powers of adaption. But is the limit of this adaptive ability on the horizon, and if so will the new technologies provide the ecological systems to replace the present ones?

Certainly theoretical models exist, and they suggest some answers but in fact the problems are complex for both biologists and governments. Awareness, rather than contentment, would seem to be the best investment in environmental safety, in the hope that man's ultimate understanding of his own requirements will be the key to preserving the continuum.

CHAPTER I

INTRODUCTION

i) The nature of environment

ii) Purposes and objectives

INTRODUCTION

The Nature of Environment

The environment pertaining to a 'living thing' may most easily be defined as the region of space containing the matter, forces and energy which interact with an organism at any level of organisation. Thus the concept of an environment embraces a group of elements which may be thought of as variables, conditions and stressors, which comprise the surroundings, and which influence the function and development of the living thing. Such an environment may be closed, semi-closed or an open system, its component matter variable in distribution, its energy in type, potential, and capacity, and its intrinsic force benign or hostile.

An environmental system can equally potentate physical form, the parameters being constant and describable in terms of properties and characteristics. Each element in the system can be classified in terms of its biological relevance and hence analysis and quantification become possible. The extent of variability, rate of change and average values can be measured and described. Often it is necessary to record the combined action of stressors or constraints, some variables being continuous in a mathematical form as with the thermodynamic aspects of artificially closed systems.

The single physiological effect of a stressor on an environmental system is perhaps describable. The action of two, simultaneously applied, however, is highly complex and current knowledge of such processes remain fragmentary. Some environmental elements on the other hand, such as ambient temperature, pressure and humidity are common to all the individuals of an exposed group. Each organism of the group becoming part of the others environment the so called "environment-individual" interface, being unique for each concerned.

An environment must have qualitative as well as quantitative aspects, each may remain constant or vary independently with respect to the other. The qualitative aspects require understanding in terms of sensory, psychological, and physiological reactions of a given organism.

Thus an organism samples or perceives certain elements of its environment by means of special sensory organs. Individuals within a species (including humans) differing greatly in their respective abilities in this regard. Following detection sensory information is processed and interpreted and it is within this sequence of events that the unique response of an individual to a particular environment is established.

It becomes clear that the quantitative aspects of environment characterise the environment itself. The qualitative aspects on the other hand are dependent on the response of the organism. Although the idea of 'environmental quality' may be somewhat abstract in origin its importance in life cannot be overlooked.

The extent of displacement of the physiological processes following exposure in a particular environment, and the nature and intensity of the reactions caused by polluting substances depend on many factors. Among the more important it must be recognized are the physico-chemical properties of the material, its concentration, and the availability of receptor sites in the body.

The climatic environment of temperature and humidity influence the impact of a polluting substance as indeed will species differences, individual tolerances, and often the access and route of entry into the body.

It is clear that an environmental pollutant will interact with the body systems resulting in a displacement, however minor, of the steady state equalibrium of biochemical and physiological processes, at levels ranging from the molecular to the whole organ. These displacements triggering in turn, biochemical processes which are under somatic and CNS control and which form the basis of the homeostatic response. Anatomically it has been observed that pathological changes in an organ depend on the nature and distribution of the toxic material, and equally on the tissue structure that has been affected.

No general model exists which serves to describe the mechanism involved in cell reaction to injury, and low continuous exposures to gaseous toxic agents.

It is known, however, that continuous exposure to airborne pollutants stimulates proliferation of alveolar epithelial cells, thickening the alveolar membrane and increasing the connective tissue component in the lung.

Apart from those toxic materials of industrial origin the natural environment supports innumerable substances which may constitute an actual or potential allergen. Allergic sensitisation of the respiratory tract, and of the skin, accounts for almost 40% of common predisposing symptoms to more serious illness. Paroxysmal tachycardia, migraine, angioedema of the skin, and scotomata, are clinical manifestations often found in industry, which are known to be triggered by ingestion of allergens in a sensitive individual. It is seldom that anyone is exposed to a single pollutant or allergen. Significantly exposure to combinations of pollutants may produce different effects from those that would result from exposure to each pollutant separately.

The combined effects may be purely additive, synergistic, or antagonistic. Simultaneous exposure to two or more pollutants does not mean that the combined effect will be greater than the effect of exposure to either alone. In some instances the interaction between two or more toxic, simultaneously present substances, such as in the case of a toxic material and a drug, reduces the toxicity of the pollutant or enhances the metabolism of the drug. It is not unreasonable to assume that a foreign substance in the body is likely to interact with an enzyme which can itself then liberate a toxic product.

The ultimate effect may well be the disorganisation of cell architecture. The toxigenesis of formaldehyde and methanol solutions in the body are well-known in this regard.

Pollutants may counteract one another by purely physical means, as with the use of an oil mist to diminish the toxic effects of oxidant pollutant gases such as ozone and nitrogen dioxide. The important fact is that a toxic material may not be harmful when acting alone, but could be life-threatening in ostensibly innocent combinations. The subject of exposure to noxious and toxic substances may, therefore, be thought of as consisting of three separate elements:

i Occupational exposure

ii Exposure to environmental pollution (ecological)

iii Exposure to natural allergenic material

The potential for overlap is clear, and each is an integral part of the fabric of life, but repeated chronic occupational exposure is likely to have the more critical consequences.

The irritant effects of exposure to gaseous pollutants are most usually accepted by industrial workers as a necessary part of the particular environment in which they are invited to work. Indeed in the majority of instances no attempt is made to camouflage the fact of an inherent hazard, albeit slight, the danger simply being considered as coincidental to the job.

Formaldehyde as a component of breathed air in working areas may well fall into this category.

This was one of the factors which prompted our examination of the effect of formaldehyde on humans in relation to air quality, effects on the skin, and to metabolism. Our objectives in the investigation are set out below.

Purposes and Objectives

Researchers have examined environmental air for formaldehyde for a variety of reasons, but predominantly with a view to relating single, or multiple low level exposures, to specific symptoms in the human being.

In the present work whilst being mindful of the importance of observing and recording human responses the study has sought to monitor a variety of working conditions over many months.

For this reason it was considered relevant to monitor five factory areas and augment this data with up to six separate studies in related (external) companies. The factory areas were precisely zoned to facilitate later comparisons. It was also hoped to monitor improvements in air quality, and therefore designated areas were examined repeatedly on different shifts, and at preselected times.

In the past considerable difficulty has been experienced in pinpointing the precise level of formaldehyde in a given working area. Thus it was pertinent to assume that the level of formaldehyde established is for that area alone and for that moment in time. The only realistic regional vector that can be assigned is that associated with the collection and withdrawal of air in the very limited area of the sampling pump. Usually formaldehyde is omni-present throughout a factory, and sometimes harmful levels are so transient that they may pass undetected, or are ignored by staff. Only on few occasions do the testing procedures detect excesses, though high concentration pockets are known to exist. It was hoped to discover how these might occur and if it were possible to simulate such phenomena.

One of the most important objects of monitoring air is to be able to compare data from different periods of active factory work,particularly to view any improvements or deteriorations in environmental conditions by these means.

It is considered equally relevant to be able to distinguish between variations due solely to changes in ambient conditions and those brought about deliberately by engineering control.

Gross changes in the ambient conditions of factory air following accidental leakage are best monitored in exhaust and filter areas. Under such circumstances comparitor tubes are usually employed to assess the level of formaldehyde repetitively over a short period of time. Knowledge of the reliability of these procedures would be of value, as would an indication of the severity of personnel exposure in such situations. The mechanism of the body's adaptiveness being of particular interest, man seeks a comfort zone in any form of environment, particularly if it is contaminated.

Acclimatisation may, perhaps, be regarded as a suppression of such instincts, but, in fact, probably represents one of the more important of the body's defences against an enforced exposure. It would be of most value to determine the nature of such acclimatisation at low levels of formaldehde and whether or not it was progressive phenomena and if there were any limiting features.

It is conceivable that the degree of acclimatisation is an index of biological tolerance, which may be destroyed either on the basis of time, or increase in concentration of formaldehyde or by a combination of both these factors.

It is perhaps within this phase of an individual's perception of imminent danger, that the genetic and environmental components of a contaminant become most meaningful, signalling the need for evacuation from the area.

These aspects require consideration, and from an industrial point of view their solutions may vary with the type of industry and processes involved.

In general terms, however, a number of important factors emerge:

i Technological in terms of engineering methods (air control)

ii Metabolic in terms of de-toxification

iii Personal health monitoring

iv Company based central monitoring of personnel

Each of these has been examined in relation to an individual's tolerance of the factory working conditions commonly encountered in resin manufacturing and processing. The central issue has been the quality, and control of the air movement in those areas in which an employee is expected to spend some eight hours of his working day.

The metabolism of formaldehyde and the related routes of de-toxification are intriguing, and it should be possible to characterise formaldehyde as a free material in the body fluids, then, perhaps, potential accumulations could be demonstrated.

On this basis it was hoped that a group of simple tests might be developed which may reflect the presence of formaldehyde at a specific level in relation to metabolism, and thereby identify the presence of formaldehyde metabolites or derivatives in the plasma.

Principal among the objectives relating to human metabolism is the route of de-toxification. Free clearance in the body is thought to be via formic acid but this is also known to be very variable. The most favoured route is by oxidation to formate followed by further oxidation to carbon dioxide and water. The process occurs principally in the erythrocytes and in the liver, the bio-transformation being seemingly folic acid dependent.

How rapidly de-toxification takes place may well be a function of the site of entry into the body, the extent of any accumulations that might occur, and the degree of physical exertion being experienced by an individual during exposure. A combination of these factors are likely to influence the progress of recovery following removal from the contaminated environment. In prolonged low level exposure (particularly in atmospheres that are warm and/or contaminated with dust) possible cumulative effects may be damaging, resulting in poor clearance, and in hyper-sensitive individual's potential deterioration of health.

The homeostatic responses of the body are known to inter-relate with the mechanisms of de-toxification. The ionic balances of the blood and urine, and the protective processes of the plasma and the kidney function are likely to be influenced by dissolved pollutant gases in the blood.

Formaldehyde is thought to produce microcrystalline 'ice cover' at membranes or the surface of proteins and could, perhaps, bio-physically induce a degree of physiological narcosis, or other form of inhibited activity.

Temperature factors in relation to environment can often contribute to a reduction of total work capacity. The ability of an individual to handle normal consequential loss of this kind may be further inhibited by the presence of formaldehyde in the breathed air. Normal increases in metabolic rate following physical exertion may well be enhanced when the work load is applied in contaminated atmospheres.

Knowledge of the human physiological response in these situations would be of great value in establishing acceptable working tolerances and emphasize any need for control of ambient conditions. It is known from previous work that a definite relationship exists between behavioural and symptomatic factors for the human being in certain controlled environments. Particular among these, and for which data is established, is the metabolic control of ionic equalibria and the temperature systems in the body.

An attempt has been made to correlate the factors which it is thought may strongly influence behavioural responses following continuous low-level exposure to formaldehyde. The metabolic aspects of formaldehyde dissipation are also considered together with those effects which may be said to be homeostatic in origin.

The third aspect considered was that of the sensitivity of the skin. Dermal sensitisation with erruptive manifestations appear to follow closely the establishment of continued contact of formaldehyde with the skin. Some of the better known examples are those associated with textiles and cosmetics. Inhalation exposure from transient contact with

chemicals or resinous materials will elicit a similar response. In some instances an effect may be observed with medicaments and in rare cases from foodstuffs containing very small amounts of free formalehyde.

It would be of interest to learn if it were possible to impede formaldehyde affinity for the skin and mucus membranes, and if a means could be found, its physiological effectiveness.

Preventative procedures in the context of dermal sensitivity are most important and currently international legislation is helping this situation.

It must be recognized, however, that market demand for formaldehyde treated products tend to undermine precautionary measures, and limit government control. Careful and unbiased manufacturing vigilance is, therefore, essential. We have attempted to assess the degree of an individual's sensitivity and related symptomology. A mechanism has been sought, and a hypothesis suggested as to the interaction between the dermis and formaldehyde at the cellular level. The effects of introducing an inert chemical system which can be polymerised in combination with high yielding formaldehyde resins for textile usage have been evaluated.

CHAPTER II

FORMALDEHYDE TECHNOLOGY

i) Chemical technology

ii) Chemical metabolism

Chemical Technology

Historically the preparation of the major aldehydes took place in the mid-19th century, but it was some years later in 1859 that Butlerov first prepared formaldehyde while attempting the synthesis of methylene glycol. Butlerov is also credited with having been the first to prepare polyoxymethylene by reaction of methylene iodide with silver oxide. The reactions of the polymeric product with ammonia yielding the well-known hexamethylenetetramine complex. It was not until 1867, however, when Hofmann brought about the direct synthesis of formaldehyde by passing a mixture of methanol and air over a heated platinum spiral. It was this method which was the forerunner of the modern day techniques of high volume production.

The chemistry of formaldehyde is characterised by several phases of reaction: Thus in the vapour phase formaldehyde exists as a monomer while in aqueous solution a number of polymeric forms are known.

Walker, 1966, together with other authors in the patent literature, discusses reactions of formaldehyde monomer with itself, the primary factors being temperature and concentration. The presence of small amounts of water, metals, or other impurities significantly accelerating the reactions. Formaldehyde as an anhydrous gas (formaldehyde monomer) is thought to be stable in the temperature range 75^{o} - 105^{o}, but when cooled will undergo polymerisation.

Formaldehyde in solutions of water or water and alcohol will slowly polymerise forming paraformaldehyde, and some amorphous higher polymers or polyoxymethylene. An industrial high quality paraformaldehyde can be distilled and evaporated, and very often forms the basis for the manufacture of urea-formaldehyde resins.

Polyoxymethylenes of several hundred residues can also be derived from formaldehyde monomer and are classified as alpha-polyoxymethylenes. They can commercially be formed by the addition of sulphuric acid to paraformaldehyde, together with a group of compounds known as (PO Beta) polyoxymethylenes which arise when the sulphuric acid addition is made between 0^{o} - 5^{o}. The products are highly ordered clear crystalline

materials.

Estification of PO alpha compounds yields a relatively stable amorphous product which undergoes rearrangement on heating and forms polymeric ethers and esters. With continued reaction higher molecular weight insoluble polyoxymethylenes are formed. Repeated distillation of the cyclic trimer, trioxane, yields a polyoxymethylene residue known as PO epsilon.

On dissolving in water, or by destructive distillation PO alpha will yield formaldehyde monomer. Other PO derivatives are more resistant to degradation and are not generally regarded as sources of formaldehyde monomer.

Aqueous solubility of the higher polymers decreases with increasing molecular weight, resulting in precipitation of the high polymers from solution. The table below summarises the formaldehyde content of common polymers.

Material Polymer	General Formula	Range of Poly'ation	Formaldehyde content Wt%
Lower polyoxy-methylene glycols	$HO(CH_2O)nH$	2-8	80-95
Paraformaldehyde	$HO(CH_2O)nH$	8-100	90-99.5
Alpha-polyoxy-methylene	$HO(CH_2O)nH$	100-300	99-99.5
Beta-polyoxy-methylene + H_2SO_4	$HO(CH_2O)nH$	100-300	98-99
Epsilon poly-oxymethylene + higher Mol Wt products.	$HO(CH_2O)nH$	500-5,000	99.9-100

Freshly prepared aqueous solutions of formaldehyde exist as a monhydrate from methylene glycol and dependent on the age of the solution and its concentration, a series of paraformaldehyde and low molecular weight polyoxymethylene glycols may be present. These compounds have the general formula: $HO.(CH_2O)nH$.

Lower concentration of formaldehyde favour formation of methylene glycol as the principal molecular species while higher concentrations and ageing of the solutions favour formation of polymeric forms of formaldehyde. Aqueous solubility of the higher polymers decreases with increased molecular weight, resulting in precipitation of the higher polymers from solution.

From the industrial point of view this instability represents a nuisance and to prevent continuous polymerisation methanol or other alcohols are added to formulations as stabilisers. Aqueous solutions of formaldehyde generally contain less than 0.1% of formaldehyde monomer, however, following distillation of such solutions the vapour consists of primarily unhydrated formaldehyde monomer, in equilibrium with low concentrations of methylene glycol. Although it has been proven that formaldehyde monomer is not found in significant amounts in solid or liquid products it is likely that such materials may contain significant amounts of formaldehyde monomer gas. Formaldehyde monomer is often recovered industrially by the distillation of alkaline solutions containing polymeric aldehydes derived from formaldehyde.

The chemical and resinous products manufactured from formaldehyde are considerable in number and serve the requirements of a large breadth of chemical industry. They include, urea and melamine formaldehyde resins, polyacetals, hexamethylenetetramine, fertilizers and acetylene derivatives.

Some of these materials it is quite certain contain unreacted formaldehyde residues or yield formaldehyde on decomposition.

The formaldehyde solutions of commerce in many instances possess an uncommonly high proportion of free material and are often specifically designed for this purpose.

The commercial production of formaldehyde is accomplished in a variety of ways among the more popular techniques in Europe are the controlled oxidation of low molecular weight hydrocarbons, and oxidation of methanol with a metal catalyst. In the United Kingdom methanol oxidations are the preferred methods, operation of the process in the fuel-rich mode allowing substantial variations in the product quality to be tolerated. There is a danger in running plants in such a way as it is possible to spoil catalyst efficiency. Unless the methanol purity is above 99% and gas recirculation closely controlled catalysts can be completely poisoned within an hour. It is for this reason that formaldehyde manufacture is invariably a vertical process in the sense of having in-house availability of all raw materials.

The pure dry product of formaldehyde gas has a characteristic odour and remains stable in the temperature range 80^{o}-100^{o}. At normal room temperature, however, a process of slow polymerisation occurs which produces a white film of polyoxymethylene on the walls of the container. The stability of the monomer depends on purity, very minute traces of polar compounds accelerates polymerisation, and, therefore, specially stabilised grades are prepared for commercial use.

Aqueous solutions, which are extensively used consist of 0-15% alcohol (usually methyl, propyl, n- or iso-butyl) in water containing 30-55% of dissolved formaldehyde by weight. The formaldehyde is introduced as a gas consisting of formaldehyde monomer. Hexamethylenetetramine, formed by reaction with ammonia, reacts as formaldehyde in many instances and is used extensively in industry as a convenient formaldehyde precursor.

Chemical metabolism

As the simple organic molecule, formaldehyde can be used readily by chemists as a starting point in the synthesis of many complex materials and polymers. Biologists, on the other hand, take the view that formaldehyde functions most often as an intermediate in the formation of amino acids and pyrimidines. This concept being supported by incorporation of formaldehyde in primative-earth simulation experiments, and on the grounds of the molecules potentially simple abiotic formation.

Interestingly in recent years radio-frequency spectroscopy has revealed water, ammonia and molecular formaldehyde in intersteller dust clouds. The conclusions tend to sight formaldehyde as being of fundamental biological importance, with, perhaps, exobiological significance.

From the biochemical stand point as can be appreciated from the reactivity profile of formaldehyde bio-transformation processes are the most usual reactions. This is clearly dependent upon the amount of free and/or partially oxidised material present in a system. Thus formaldehyde in excess readily combines with the free-unprotinated amino group of amino acids to give methylol derivatives. This reaction causing an isoelectric amino acid to lose a proton from the $—NH_3^+$ group, as follows:

$$H_3\overset{+}{N}\ CHRCOO^- \rightleftharpoons H_2\ NCHRCOO^- + \overset{+}{H}$$

Zwitterion

$$H_2NCHRCOO^- + 2HCHO \rightleftharpoons (HOCH_2)_2\ NCHRCOO^-$$

Dimethyl amino acid

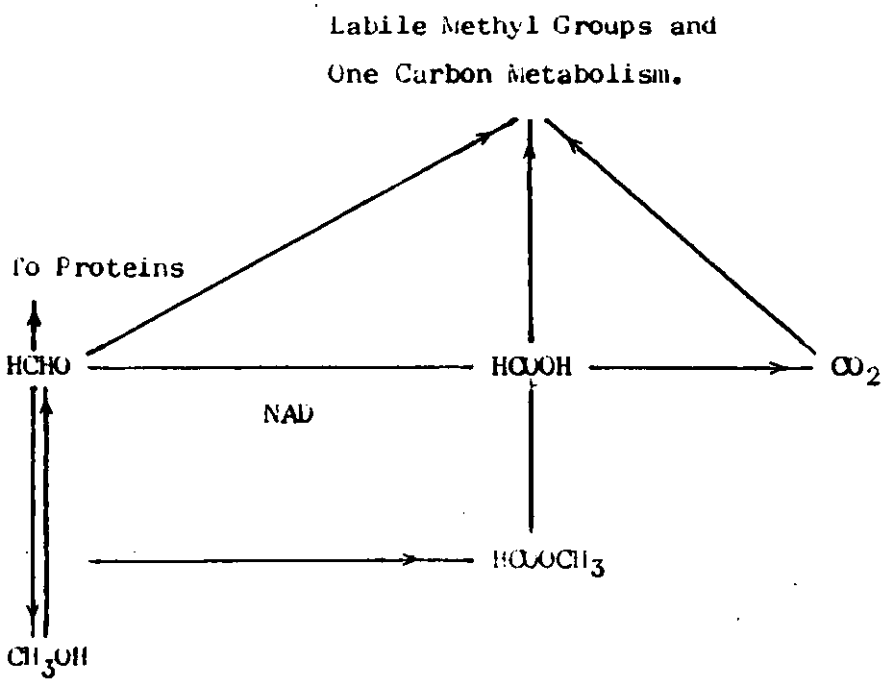
The proton $\overset{+}{H}$ so liberated can actually be titrated with NaOH and indeed forms a useful analytical method for following the formation of free amino acids during hydrolysis of proteins by proteolytic enzymes.

The metabolism of foreign compounds in the body occurs predominantly in the liver although mucosa in other organs including the kidneys, lungs and skin have some metabolising capacity. Generally it is considered that the products of metabolism are biologically inactive, although a few remain as potent (and in some cases more so)than their parent compound.

In man the metabolism of an invading molecule such as formaldehyde can be conveniently divided into two phases. Phase I that of oxidation, reduction or hydrolysis, exposes functionally active groups or adds them to the molecule. Phase II may involve in general terms interconversions e.g. to sugars by glucuronidation, or perhaps methylation or acetylation. The conjugation of the invading molecule at the site of a reactive group produced during phase I being the important aspect.

Water soluble matabolites after phase I would usually be eliminated by renal excretion. On the other hand, each phase tends to produce metabolites which increase water solubility and decrease lipid solubility. As with renal excretion reduced rates of metabolism may give rise to accumulation and increase the probability of adverse somatic reaction. Equally other routes are subject to wide individual differences because of genetic and environmental influences. In 1959, Williams suggested that one route of bio-transfer for formaldehyde could be oxidation to formic acid, which would fall into phase I of present day metabolic schematics. Williams also characterised formaldehyde as a compound which reacts with amino groups of proteins and amino acids. A general representation is shown below.

Metabolic Schematic for Formaldehyde
After Williams: 1959

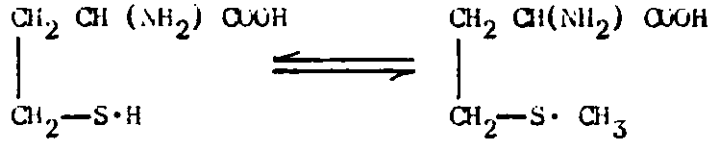


In the scheme phase II reactions in relation to the pathways represented would be the formation of the protein-aldehyde conjugate, while the reduction to methanol may involve subsidiary reactions, the extent of which is still largely unknown.

The scheme was a useful model but did not take account of any environmental factors, an influence which may give rise to the formation of free metabolic pool of formaldehyde in the body. In these circumstances subsidiary pathways may account for a much higher proportion of the metabolism than was proposed by Williams. Free clearance of the formaldehyde from the body perhaps being concentration dependent or conceivably related to one-carbon metabolism. It is not known with certainty if, for example, airborne formaldehyde as an adjunct to breathed air contributes to formate metabolism. It has been shown, however, using isotopes that the tissues can synthesize substances containing labile methyl groups such as choline.

$$(CH_3)_3 \overset{+}{N} CH_2\ CH_2OH \rightleftharpoons (CH_3)$$

The process occurring on a large scale provided that the normal dietary amounts of vitamin B_{12} and folic acid are present in the system. In this event it seems likely that methionine is first formed from homocysteine.



Homocysteine Methionine

The methionine then acts as a transmethylating agent to bring about the formation of e.g. noradrenaline or guanidoacetic acid, in the synthesis of creatine.

The precursor of synthetic methyl groups is the one-carbon unit known as formate, it is carried as a formyl $H{\cdot}CO^-$ or hydroxymethyl group on the N atoms of folic acid derivatives. Formaldehyde will participate in the normal metabolic pathway for one-carbon fragments, providing labile methyl groups which are utilized in the biosynthesis of choline and amino acids. Metabolic acidosis is thought to be limited in man because of the relatively rapid metabolism of the formate anion, the excess of bicarbonate being excreted as alkaline urine.

The fraction of formic acid arising from the primary oxidation route will clearly be very rapidly absorbed from the stomach, following oral ingestion in undissociated form. Tissue absorption, particularly via the lungs, and ultimate transport by the plasma is controlled by a different set of parameters, and is not completely understood. It is hoped in the present work to suggest a means by which clearance occurs and perhaps a time-cycle for complete metabolism in vivo.

CHAPTER

III

HUMAN EXPOSURES

TO

FORMALDEHYDE

i) Historical literature

ii) Effects on the skin

iii) Effects on the respiratory tract

iv) Effects on the gastrointestinal tract

v) Human perception of formaldehyde

Historical Literature

As early as 1893 Blum was able to demonstrate that formaldehyde combined with proteins. Later investigation was to show that the aldehyde was capable of combining with specific amino acids, in the work of Benedicenti, 1897, Sollmann 1902 and Zipf & Bartscher in 1933.

Stewart showed that red blood cells treated with formaldehyde at 0.2% in solution lost the ability to take up oxygen but retained normal permeability to ammonium chloride and normal impermeability to sodium chloride. A more concentrated solution of formaldehyde 4.0%, destroyed the selective permeability of the red cells presumably produced by cross-linking of protein chains and opening pores in the envelopes of the red blood cells.

In 1925, Kline described twelve fatal case histories listing clinical treatments and pathological changes that resulted from the ingestion of formaldehyde. Common pathological findings revealed damage that was severe in the lower oesophagus and even more extensive in the stomach. Damage produced in these organs varied from hardening of the tissue to extreme corrosion. Congestion, oedema, tissue erosion, and hemorrhage were frequently observed in the lower oesophagus. The author noted that in the cases where the victim died, ten hours or more after ingestion degenerative changes and necrosis were observed.

In 1935 a report by Krans drew attention to chronic exposure to fumes and vapours in a hot moulding operation involving formaldehyde based resins. The subject observed at this time was again encountered some six years later when slight coughing by the operative was noticed. Observation over the next six month period demonstrated a progressive development and worsening of the cough. The worker ten months later was suddenly taken ill with what was diagnosed as pneumonia. The author drew special attention to the shortness of the time scale and concluded that the condition was actually due to secondary broncho-pneumonia. The cause was thought to be the continued irritant damage resulting from prolonged mixed exposure to vapour and dust containing formaldehyde at high concentrations. Nothing was mentioned in the report about dermatitis, or skin sensitisation.

The bulk of the literature describing the effects of short and long term exposure to formaldehyde was published in Europe. Considerable emphasis being placed on individual differences in susceptibility to the material, and to resulting vesicles, fissures, and ulcerations, to the dermis. Work in recent years has largely substantiated earlier findings, and has underlined the hazards associated with any form of formaldehyde contamination of the skin.

Effects on Skin

A review suggests a number of causative agents for the sensitivity suffered by many workers when in contact with the material. Direct gaseous exposure being thought to be responsible for most primary irritation. Allergic dermatitis arising from solutions of resins, and from, for example, formaldehyde treated textile materials. Very often complaints are received from factory operatives that dust in the work rooms or fibre particles from the fabrics are the most irritant, more so, than that of the formaldehyde itself.

Horsfall, 1934, has presented detailed studies on hyper-sensitive individuals in an attempt to establish a meaningful threshold of sensitivity. He investigated cutaneous hyper-sensitivity, specificity of sensitivity to formaldehyde and cutaneous hyper-sensitivity following inhalation. Intradermal injections of 0.02 ml were given in the back of the hand, it was found that subjects responded to solutions as dilute as 1:8,000,000. While the skin of the forearms reacted only to solutions of 1:4,000,000. or less dilution. Horsfall observed a latent period of 15-40 h between injections and response, which in general, it was concluded related directly to the amount of formaldehyde injected, but had a long plateau between dilutions of 1:640,000 and 1:20,000. Tests using similar procedures for evaluation of sensitivity to acetaldehyde, propionaldehyde, and paraldehyde produced no positive reactions. In addition immersion of the fingers in solutions of formic acid, hexamethylenetetramine, and methanol failed to elicit any positive response.

Rostenberg, 1952, reported exzematous sensitivity to formalin in five nurses handling thermometers kept in 10% formalin solution. The papules and vesicles that formed on the fingers were described. Patch tests of

the individuals showed positive sensitivity to 0.2-5.0% concentrations of formaldehyde. Further sensitivity was noted when injections of formalinated protein was tried. In the later case the reactions were less pronounced than to formaldehyde solutions believed to contain aldehyde at a concentration equal to that in solutions of formulinated human serum albumin.

Cases of mixed inhalation and direct application of formaldehyde solutions to the skin producing dermal eruptions would seem to follow a reasonably predictable pattern. Difficulties arise, however, when attempting to isolate one or the other as the primary causative agent. Regarding direct application, individuals sensitive to formaldehyde have been shown to develop allergic contact dermatitis from textiles which have been treated with formaldehyde containing resins. The studies of Peck & Palitz (1952) and of Fisher (1962) did not confirm this. In their studies twenty volunteers did not show any positive skin reaction when patch tested with textiles and paper containing free formaldehyde. Although all the subjects were reportedly sensitive to the material.

Berrens in 1964 set out to establish if there was any clinical value in patch testing subjects' clothing which had been proven to contain formaldehyde. In the study 600 samples of clothing were taken from subjects with non-occupational formaldehyde contact dermatitis who gave positive patch tests with 3.0% solutions. Very sensitive subjects gave positive patch tests reactions to 0.3% formaldehyde and in some instances to 0.03%. Fabric samples were used to estimate the formaldehyde content of the clothing from each subject. Nearly 57% of the samples contained less than 0.05% formaldehyde and patch tests with these samples were negative. Withdrawal of the clothing was almost always accompanied by a disappearance of the dermatitis.

In spite of the breadth of the trial the authors were only partly able to correlate the results, and could not positively affirm the usefulness of patch tests as a clinical indicator.

In the same year, Frenk reported on the simultaneous appearance of 26 cases out of 120 employees of red macules mostly wheal and flare in a foundry area. He was able to correlate the outbreaks with lack of

ventilation in the work place, but identified formaldehyde as the causative agent.

In 1971, Kamchatnov and Gayazova examined the effect of formaldehyde vapour on 99 women in a sheep-skin dyeing factory. Apart from general physiological observations they were interested in thermal asymmetry following exposure. It was found that exposed women had three times the incidence of pre-shift asymmetry when compared with a control group. The exposure during the shift had a greater proportional effect in shift workers symmetric to asymmetric state, and produced the greatest absolute shift. Kamchatnov and Gayazova attributed these differences to CNS effects. The complaints of persistent headache, vertigo, and a tendency to depression were also thought to relate to CNS disturbance. No evaluation of the possible contribution from other chemicals in the atmosphere was made, a factor which, perhaps, highlights the difficulties in assembling a symptomological profile for formaldehyde exposure.

Out of numerous other studies few implicated free formaldehyde as the primary causative agent in producing dermatitis of the skin. Most concluded that either the parent solution, or materials giving rise to the formation of free formaldehyde, or the vapour, was the precipitating agent. Thus within the contex of dermatology it was considered unlikely that formaldehyde, or its oxidation products could contribute to the manifestation of lesions.

Effects on the Respiratory Tract

Of seemingly greater concern than eruptive manifestations was the irritations frequently observed in subjects following ingestion or inhalation of the gaseous material.

Localised effect were quickly evident particularly in the nose, the throat, and the tracheo-bronchial tree. Ettinger and Jeremias (1955) noted these irritations in sewers and other employees handling nylon fabrics coated with urea-formaldehyde resins. These symptoms were attributed primarily to formaldehyde gas present in the work room in concentrations of 1-11 ppm and also to the contaminations of employees' hands with fragments of resin during handling. Subsequent rubbing of

the eyes with the hands caused irritation and conjunctivitis. They also noted that gaseous formaldehyde was released from the fabrics during curing and storage, but airborne concentrations of formaldehyde were not reported.

The authors concluded that the ideal method for elimination of the health hazard was improvement of the curing system to achieve complete polymerisation in as short a time, and at as low a temperature as possible. They felt that the amount of unreacted urea and formaldehyde components could conceivably be as high as 25%. Subsequent exposure to the atmosphere of the work-room would almost certainly give rise to the level of gas suggested.

Zannini and Russo in 1957, as part of a study of irritant gases, examined a man who had undergone a single acute inhalation of formaldehyde. The patient complained of dyspnea, asthma attacks, asthenia, weight loss, and nervousness. An initial chest radiograph showed accentuated bilateral bronchiovascular markings. Clinical examination revealed pulmonary oedema with diffuse harsh respiration. A 40% decrease in vital capacity was noted and a maximum loss of pulmonary ventilation of 45%, and enlarged left atrium, an accentuated second pulmonary sound, and hyperthyroidism. A second radiograph made five months later revealed that the left atrium and the right ventricle were enlarged. Diaphragmatic hypomobility was also noted. An electrocardiogram showed slight signs of atrial overloading and an intraventicular conduction effect.

The initial clinical findings were particularly severe making the relatively short time of recovery the more remarkable. The work, however, serves to illustrate the possible extent of physiological damage, of a single exposure, and may indicate the level following less acute but repeated exposure.

A further example of a single case reported in detail was that of Porter (1975) who experienced acute respiratory distress after working with formalin solution. As a neurology resident, he spent two hours preparing specimens and inhaled high concentrations of formaldehyde gas. The previous week he had been exposed under similar conditions for a

period in total of an estimated fifteen hours. Following his more recent exposure he developed dyspnea and tightness of the chest which became progressively worse during the next twenty-four hours. Immediately before onset of respiratory distress, there were unpleasant effects on the conjunctivas and nasal mucosa. A radiograph of his chest was interpreted to indicate an inflammatory reaction in his lungs with early oedema. Isolated occasional rhonchi were noted and soft diffuse rales were heard over both lung fields. Porter was known to be atopic to a wide range of allergens, and the respiratory distress could have been due to a hyper-sensitivity, but more likely was an acute chemical pneumonitis provoked by formaldehyde. The author suggested that inhalation of formaldehyde gas may entail serious danger to susceptable individuals, and advocated provocation tests for medical staff similarly employed.

Bourne and Seferian, 1959, reported complaints of burning and stinging eyes, headaches, and nose and throat irritation of customers and employees in a number of dress-wear shops. The odour was described as suffocating.

Complaints were most numerous when the ambient temperature was the highest. Air samples in the dress shops was found to contain 0.13-0.45 ppm formaldehyde. Samples of apparel from these shops contained 5-8 mg of formaldehyde for each 10 g of rayon textile and 3.4 mg/10 g of cotton, while a wool dress was found to be formaldehyde free. The authors recommended an improvement in ventilation rate to a level of fifteen air changes an hour for the shops, the measure greatly helping the situation particularly among the staff.

Glass in 1961 and Morrill in the same year both publisned the results of studies which implicated formaldehyde (at concentrations between 0.9 and 1.6 ppm) as the precursor of respiratory irritation, with dermatitis and oedema of the face. Hovding's work on four operatives employed in a plastics thermal-cutting unit, concurred, but the transient effects of those agents thought to be 'carriers' were also highlighted. Particular among these were acrolein, but dust and fibres were considered the most important.

It was in 1966 that the Department of Public Health in the United States carried out studies with precisely documented analytical techniques. The investigators endeavoured, as far as possible, to isolate exposure to formaldehyde alone. A large clothing store on the West coast was chosen with these criteria in mind. The general level of formaldehyde recorded was between 0.9 and 3.3 ppm using the MBTH method. Similar comparative work was carried out in a textile garment manufacturing plant, the Sodium Bisulphite method being used in this case. In the factory, the concentrations of formaldehyde were in the range 0.9–2.7 ppm. The greatest discomfort, running eyes, and irritation of the nasal passages were reported in storage areas, concentrations up to 2.7 ppm having been recorded. The irritant effects were greatest at the beginning part of the day and after lunch breaks. Irritation lasted for about fifteen minutes during these two periods after which the formaldehyde tended to become tolerable. The study was reinforced by the observations of Shipkovitz (1968) and later by Kerfoot & Mooney (1975) that an 'acclimatisation' effect seemed to occur. The effect lasted no more than a few hours and was found to return after interruption of exposure.

Shipkovitz in 1968 extended his studies when observing eight textile plants following reports of formaldehyde release from fabrics treated with resins. Sodium Bisulphite was the analytical technique chosen by Shipkovitz 0–2.7 ppm of formaldehyde being reported.

based on details obtained from plant records, and interviews with employees, the prevalance of respiratory illness was established at over 15% for four of the plants and between 5 and 15% for the remaining four.

Two Russian studies reported in 1968 and 1970 by Yefremov and Zaeva et al confirmed these findings.

In the Russian work 278 employees underwent medical examinations. The results showed that 78% of the work force had signs of upper respiratory tract irritation, including hypertrophic inflammatory or atrophic rhinitis. Formaldehyde concentrations ranged from 2.1–8.9 ppm with a maximum recorded of 31.2 ppm. These conditions producing illness in 40–60% of those that were exposed and observed. Airborne formaldehyde

concentrations of 0.4–4.1 ppm with a maximum of 7.1 ppm was said to produce an illness rate of 15–37%. A control group of 200 individuals of corresponding ages had an incidence of respiratory catarrh of 8.9%.

Yefremov noted that signs of chronic respiratory tract irritation were most common and pronounced in persons between the ages of 30–59 years, and also in those that had worked for less than five years. He further noted that pronounced morbid states developed from inflammatory phenomena in the mucosa of the upper respiratory tract consequent to inhalation of formaldehyde vapour. He postulated initial signs indicating onset of inflammatory pneumonia might be as follows:

i Increased time of carbon particles to travel from nares to nasopharynx

ii More rapid absorbtion of noratropine from tampon inserted in nasal cavity

iii Decreased olfactory activity for such substances as thymol, camphor, and tar

Zaeva, co-author of Yefremov, was particularly concerned with the sensitivity of individuals at low concentrations of formaldehyde, drawing attention to mucus membrane irritations at 0.8 ppm. He also highlighted the changes in the function of the autonomic nervous system and enhancement of the alpha-rhythm of the EEG. Both authors were very firmly committed to the idea of formaldehyde exposure predisposing to acute chest diseases particularly bronchitis in a high proportion of employees.

In 1971, however, the work of Kratochvil tended to disprove this concept. In an evaluation of the health status of an unspecified number of employees in a textile processing company Kratochvil examined formaldehyde concentrations which did not exceed 4.2 ppm. He found the employees were complaining of irritation of the conjunctivas, nasopharynx, and skin. In his conclusions it was stated that catarrhal conjunctivitis was discovered in 72% of the employees, inflammatory rhinitis in 28%, slight reddened dry facial skin in 11% and chronic bronchitis in 22% of the work force.

The author believed that the frequency of occurrence of bronchitis did not differ significantly from that found in the general population. Nonetheless the fact of an association between formaldehyde exposure and respiratory illness had become defined. The extent of the disablement was potentially alarming. In this respect Kerfoot & Mooney in their study on behalf of the American Association of Hygineists in 1975 were careful to select conditions of environment which were known and reproducible. They surveyed six mortuaries which used formaldehyde and paraformaldehyde in the embalming procedures. The chromotropic acid absorbtion technique which was followed by spectrophotometric analysis was the method of choice for estimating formaldehyde concentrations.

The average concentration recorded in the air was between 0.24 and 1.39 ppm in the embalming rooms. The total range for the study was reported as 0.09–5.26 ppm. The investigators suggested that the embalmers became 'inured to the vapour' as concentrations gradually increased with time, and that such chronic exposure undoubtedly contributed to lung disease. Gamble et al in 1976 working on behalf of the same Association conducted a similar enquiry for workers in a rubber factory. In their conclusions to the Association both authors implicated formaldehyde as the causative agent in respect of the respiratory symptoms that had been observed. In many instances a specific reduction in respiratory volume percent could be demonstrated. The Association ultimately reporting their findings and consensus of opinion in the matter to the Federal Health Authority.

In the United Kingdom, the British Journal of Industrial Medicine, publish the findings of Hendrick & Lane in this subject in 1977. In their paper a detailed account of the experiences of hospital staff in a haemodialysis unit was discussed in relation to formalin hyper-sensitivity. Inhalation provocation tests suggested formaldehyde vapour may be the cause of attacks of wheeze and a productive cough. The symptoms become apparent only a short time after joining the unit in the case of most staff, all described the symptoms as bronchitic in character. The reactions persisted after the respective shifts were finished. The onset of wheeze was usually between two and three hours after exposure, peak expiratory flow rates falling by a maximum of 50%. In all cases the symptoms remained for between ten hours and ten days depending on

the exposure. The most predominant feature was the productive cough. The sputum produced being described as mucopurulent, but culture produced only a very minute growth of Haemophilus influenzae, together with upper respiratory tract commensals. The cellular content being non-homogenous. Examination of the peripheral blood showed variable responses of neutrophil and eosinophil leucocytes. The authors were unable to isolate material quantities of the bacterium Haemophilus influenzae in their search for secondary infection in the respiratory tract in the subjects and saw no noteworthy changes in leucocyte characteristics. Their general feeling, however, towards the use of formalin was such as to recommend cessation of its use in all units. The observed effects were reported to have disappeared following this measure a week or two later.

In the latter part of 1978 a number of authors focused their attention, particularly in the USSR, on the general environmental effects of exposure: Ishchenko & Pushkina examined the effects of processing phenol-formaldehyde containing resins on plant operatives, reinforcing earlier work of a similar nature. Nerjureva & Rakhmanin on the metabolic mechanisms involved in embrionic toxticity. Ionescu et al examined the broncopulmonary changes induced in rabbits following repeated exposure to formaldehyde believing the material to be associated with hyper-plasia of the lung. Nagornny reviewed current literature in respect of the harmful activity of formaldehyde at low concentrations, the conclusions in the report supporting the findings of the American Association of Hygineists in respect of sensory and respiratory irritations.

Major environmental studies considered the potential danger involved in the use of formaldehyde containing foam materials employed in home insulation. In West Germany the threshold value being set at 1.0 ppm formaldehyde for an installation whose occupants stay no longer than eight hours in the building. For permanent exposure a level no greater than 0.02 ppm was defined. Current thoughts, are that a house or apartment insulated with formaldehyde containing foam resins would lead to exposure levels much higher than this. Perhaps in the order 5.0-20.0 ppm in the initial stages. The levels would clearly decrease, but the dissipation process could take many months.

In the United Kingdom the best and most closely controlled installation techniques have been found to leave a residual formaldehyde level of between 0.04 and 1.4 ppm for greater than six months. These amid many complaints of respiratory distress, tearing, headaches, and persistant nasal irritations. There are no official figures for permitted levels for this type of installation in the U.K. A relatively unsatisfactory situation still exists particularly as foam manufacturers are unwilling to disclose their formulations. Although the two main ingredients of foams - urea and formaldehyde are considered non-carcinogenic (United States Dept. of Public Health: Publication No. 149) it seems likely in accordance with the findings of Morin & Kubinski (1978) that there is an isolated observation that exposure to formaldehyde leads to tumour induction. This cautionary claim is supported by the earlier work of Horton et al (1963) who suggested the effects of gaseous formaldehyde on rodents' respiratory tracts demonstrated morphological changes in the exposed tissue similar to that seen in chronic cigarette smokers. In their conclusions to the U.S. Public Health Dept. Morin & Kubinski sited formaldehyde as a potential precursor to respiratory tract tumour induction and was in their opinion a much wider hazard to humans than was first thought. The work attracted international interest and stimulated a number of metabolic and toxicity studies on formaldehyde which are discussed in detail in the next chapter. The food industry in Europe also became alerted to the potential dangers of the material.

Effects on the Gastrointestinal Tract

In their own researches the industry had been able to confirm the low oral toxicity of formaldehyde, and obtain authorative endorsement for the use of the material as a food preservative. This acceptance was based almost exclusively on very low concentrations being adequate to maintain the preserving characteristics, work from sources outside the industry suggested otherwise however.

Pathologically, in cases of accidental ingestion of formaldehyde solution the extent of tissue corrosion and necrosis is very considerable indeed. Aspects of policy were influenced by this and early findings of Kathery in 1940 and Yonkman in 1941. Yonkman described trials involving two male volunteers who received daily 22 mg of formaldehyde during a period

of 14 days. Dosage being increased during the 13th week of administration to a level of 200 mg. Blood samples revealed no change in concentration of haemoglobin in the red and white cell counts, or any change in the appearance of the cells. The level of complaints varied from mild gastric pain to considerable congestion of gastric mucus with regurgitation and difficulty in swallowing. Concentrations of 0.029% were considered tolerable. It was not until the early seventies that further concern developed in relation to reactions of formaldehyde in vivo.

In 1973 in a letter to the editor of Chemistry in Britain Keene referred to the spontaneous reaction of formaldehyde and hydrochloric acid to form chloromethyl methyl ether and bis-chloromethyl ether (bis-CME). In a review article in the New Scientist in 1977, Willard et al suggested a connection between the deaths of a number of Rohm & Haas plant workers in the United States (they reportedly died of lung cancer) and the formation of bis-CME in the plant environment. The article was intended as an exposure of an apparent cover-up and highlighted the work of Nelson (of the New York Institute of Environmental Medicine) who established that bis-CME was one of the most powerful carcinogens known. His published work was contrary to the wishes of Rohm & Haas. Further work resulted in the TLV for the material being lowered to one part per billion. From the technological point of view bis-CME is a common chloromethylating agent and is used extensively in the dyestuff, textile, ion exchange resin and polymer industries. The fact of its carcinogenic nature for man at the level of potency indicated by research in the U.S.A. and Japan strongly implicates formaldehyde as the precursor. The six classical routes to its manufacture involve quite severe chemical and physical conditions, but the major hazard was thought to come from accidental or inadvertent formation. Among these were those in the vapour phase, and particularly the liquid phase, in the stomach. From the literature it would seem to be unlikely that the conditions would be suitable for such a combination, unless the formation was catalysed by a mechanism as yet unknown. Kinetic studies suggest that because of the rapid hydrolysis of the compound it is unlikely to exist in solutions below 9 ppb. It is however this general aspect which concerns the food industry, and others, in that for example the breakdown of hexamethylenetetramine in the stomach could conceivably yield bis-CME or one of its derivatives. Metabolic studies are currently

in progress which are attempting to elucidate this problem. For the moment hexamethylenetetramine is permitted by the E.E.C. as a preservative at the level of 25 mg/kg in certain foodstuffs but the regulations are generally viewed with caution.

Human Perception of Formaldehyde

Relatively few studies of a specific nature, referring to the effect of formaldehyde on the eyes appears in the literature, although passing reference within a group of symptoms has been made. Oedema and conjunctivitis are the most usual of manifestations following contact with peripheral parts of the eye, tearing is often perfuse.

Schuck, in 1966, interestingly refers to differences of concentration response curves for mixtures of ethylene oxidation products and formaldehyde, emphasizing the potential synergistic effect of gaseous pollutant mixtures in which formaldehyde takes an active role. Russian investigators have noted altered visual sensitivity and changes in cerebral electrical activity in selected groups that have suffered exposure. Further Russian studies have revealed optical chronaxie changes after inhalation of formaldehyde from concentrations of 0.07-1.3 ppm for ten minutes. The participants having been selected for their ability to detect formaldehyde odour at levels of 0.06 ppm. Detection by these means (altered chronaxie of the optic nerve) may, it is thought, have application in the control of industrial exposure, nothing specific has been suggested, however. It has been shown by many authors that an individual's perception of formaldehyde odour becomes less sensitive with time as one adapts to the presence of the material. The threshold of response has puzzled researchers for some time, and there remains some disagreement as to the best way of assessing this parameter.

Leonardo, in 1969, defined the detectable threshold as 1.0 ppm using an odour panel. His figure representing the lowest concentration to which four trained panelists could positively respond. A mean of five tests were taken, and several different concentrations were used throughout the test sequence. Earlier work by Melekhina, in 1964, attempted to relate odour threshold and the effect of formaldehyde on the central nervous system.

Melekhina used twelve subjects whose ages ranged from twelve to sixty years. The formaldehyde gas for the experiment was generated form a glass aspirator containing 5 ml of formalin through which air was blown. The formaldehyde concentrations were measured by means of the chromotropic acid technique. Optical chronaxie determinations were made by using a chronaximeter every three minutes during a fifteen minute period of breathing formaldehyde containing air. The concentrations were between 0.06 and 1.29 ppm for each of a large series of tests. Formaldehyde at 0.07 ppm decreased the chronaxie in two subjects and increased it in one. Maximum changes for the subjects occurred after breathing formaldehyde containing air for nine minutes. The most pronounced changes were noted at concentrations of 0.16 and 1.29 ppm. An odour panel established that 0.09 ppm was the threshold concentration for all the subjects tested.

There was, however, no change of subject acclimatisation in the Melekhina study as no excessively high level exposures were possible even for a short time. Comparison of the studies does not reinforce the idea of a threshold value being index related to the time allowed for acclimatisation. In an other experiment the same twelve individuals as in the Melekhina experiments all adapted to a dark, noise-free, and odour-free environment during a five day training period. Initial curves of response in receptors in the upper respiratory passages were established for the inhalation of fresh air. They were then exposed to 0.06, 0.07, 0.098, 0.2, 0.3, and 1.7 ppm formaldehyde gas for four-five minutes. Under these conditions, as was expected, the threshold of perception of formaldehyde was lower than in the previous work, viz at 0.07 ppm for all subjects. The sensitivity of the eyes to light was increased in two subjects, in the presence of formaldehyde at 0.1 ppm, and was decreased in all subjects tested by formaldehyde levels of 0.25-1.7 ppm. The authors did not comment further on the apparent ocular sensitivity accept to suggest a possible industrial application. The tentative agreement in respect of threshold response was of value and was later verified by Fel'dman & Bonashevskaya. These authors reported the biological effects of low airborne concentrations of formaldehyde on both rats and humans in 1970. Methods of generation and measurement of formaldehyde concentration were the same as those used by Melekhina. The effects on humans were evaluated by determining olfactory thresholds

and changes in cerebral biopotentials. Fifteen healthy human subjects were exposed to formaldehyde at four concentrations between 0.06 and 0.098 ppm. After numerous observations, seven subjects were found to be unable to detect 0.06 ppm of formaldehyde but were able to detect a level of 0.08 ppm. Four other subjects were unable to detect 0.06 but were able to detect 0.09 ppm. The five most sensitive subjects as determined by the olfactory threshold tests were monitored by an EEG during further exposures. A concentration of 0.06 ppm produced statistically reliable changes in cerebral electrical activity in all subjects whereas 0.048 ppm produced no effects in any of the subjects. Again the odour threshold measurements of these authors agreed reasonably well with those of Melekhina, but EEG appears to be a more sensitive indicator of an effect than either optical chronaxie or the sensitivity to light of the dark-adapted eye used by Melekhina.

CHAPTER IV

FORMALDEHYDE TOXICITY

i) Metabolic studies

ii) Carcinogenic activity, mutagenicity, teratogenicity

The Metabolism of Formaldehyde

The uncertainty that surrounded the industrial use of formaldehyde is perhaps reflected in the very large number of metabolic and toxicity studies that have appeared. As far back as 1893 Pohl studied the effects of administering formaldehyde subcutaneously to dogs in an attempt to evaluate formate metabolism. Between 1938 and 1952 Lutwak-Mann & Kendal, and Ramanathan investigated the dismutation of formaldehyde to methanol and formic acid, Malorny examined formic acid and formates in dogs, and it was shown that formaldehyde oxidises to formic acid after its absorption by human erythrocytes. There was speculation that formaldehyde may be retained in some proportion following exposure (particularly at high concentrations) and possibly cumulatively by the lungs and other organs. It was these questions which prompted industry to look carefully at formaldehyde and its acute and chronic effects in animals.

Studies using rats exposed for eighteen hours at a level of 35 ppm showed pathological changes in comparison to a control group. The exposed rats had dyspnea, both eye and nasal irritation and significantly higher liver alkaline phosphate activities than the controls. At this stage of the research it was generally believed that inhalation toxicity may be influenced by the presence of other physical or chemical agents in breathed air. Among the studies that set out to verify this was the work of Salem & Cullumbine in 1960. They reported inhalation toxicity of a number of groups of fifty mice, twenty guinea-pigs and five rabbits. Exposure times were up to ten hours in a specially prepared cabinet. One group was exposed at 16.0 ppm of formaldehyde with the use of an aerosol of formalin and another group at 15.2 ppm using formaldehyde gas. The mean particle size of the aerosol was quoted as 0.7 mM. Both aerosol and gas concentrations were analysed quantitatively following exposure in the chamber.

The result can be summarised as follows;

Animal Deaths	Number/Type	Comments
48	50 Mice	Aerosol Exp.
17	50 Mice	Gas Exp.
1	20 G. Pigs	Aerosol Exp.
8	20 G. Pigs	Gas Exp.
1	5 Rabbits	Aerosol Exp.
3	5 Rabbits	Gas Exp.

Following pathological examination of the animals it was found all had experienced, oedematous, and herorrhagic lungs. Considerable distension of the alveoli was also noted. The differences in animal deaths appeared to depend to some extent on the method by which the atmosphere of formaldehyde had been created, (at the time of the experiments unexplained). The fact that they may reflect those conditions found in certain sections of industry alerted other workers in the field and the interest of the trade press.

Amdur's work which was carried out at about the same time was based on a similar premiss to those of Salem & Cullumbine. Amdur exposed guinea-pigs for periods of one hour to formaldehyde at various concentrations, together with other irritants, with and without simultaneous exposure to an aerosol containing sodium chloride. Intra-pleural pressures were monitored by a technique developed by Amdur & Mead. An in-out flow dynamic exposure chamber was used in the experiments. The concentrations of formaldehyde in air were analysed by both the Schiff's reagent and the chromotropic acid method. The concentrations of sodium chloride were determined conductometrically. In cases where the aerosol was used in combination with formaldehyde a filter procedure prior to the formaldehyde generator was used. Conductometric measurements being made on the filter deposition of the salt.

Amdur suggested that an increase in the product of resistance and compliance indicated that bronchial constriction was the main response to formaldehyde. When three guinea-pigs were exposed to 50 ppm formaldehyde for four hours the resistance increase produced by formaldehyde reached its maximum by the end of the first hour of exposure. During the second hour, the resistance decreased slightly, and then remained

constant during the remaining two hours. Two hours after the end of the exposure, the resistance had decreased markedly but had not returned to the control value. Exposure to formaldehyde had increased the amount of work required to over-come the increased elastic resistivity, and elastic plus resistivity components of ventilatory recoil. In further experimental work normal and tracheotomised guinea-pigs were exposed to formaldehyde and to formaldehyde in the presence of NaCl aerosol. The effect of the bypass of the upper-respiratory tract being of interest. A much greater response was obtained for formaldehyde gas alone, at a particular atmospheric concentration when the protective effect of the upper airway was eliminated. Untracheotomised animals exposed to formaldehyde and NaCl aerosols had additive effects of exposure. In respect of the effects of exposure to formaldehyde in combination with NaCl aerosols, the greatest changes were observed in tracheotomised animals receiving both formaldehyde and NaCl aerosol. All responses within an exposure group were proportional to the concentration of formaldehyde employed.

In further studies reported by Amdur normal guinea-pigs were exposed to formaldehyde alone, and to formaldehyde with the addition of NaCl. Concentrations of 0.9-50.0 ppm formaldehyde being used. The results indicated increased resistance and decreased compliance after exposures. Tidal air volumes were found to be unchanged by the exposures in all groups except those receiving formaldehyde at 5.2, 20.0, and 50.0 ppm, and those receiving formaldehyde at 3.6 ppm in the presence of NaCl aerosol. The elastic work was increased significantly only in the group exposed to formaldehyde at 50.0 ppm. The conclusions made in Amdur's previous report remained unchanged. Dose response curves seemed to indicate that resistance was increased in accordance with the concentration of formaldehyde and that the addition of aerosol injected NaCl may have increased the effectiveness of formaldehyde in heightening resistance. Those untracheotomised guinea-pigs receiving formaldehyde plus the aerosol were more severely affected than tracheotomised animals receiving formaldehyde alone. The increased resistance to air flow was later to be proven in a number of animal species and the presence of another molecule, such as NaCl, to specifically enhance tidal volume.

Murphy & Ulrich, in 1964, in their work on guinea-pigs concurred

with the general findings of Amdur. In their sequential measurements of respiratory rate, tidal volume, and resistance during expiration, it was found that the presence of formaldehyde at concentrations of 3.9 and 12.5 ppm increased resistance to airflow in 61% and 81% respectively of the animals examined. Increased tidal volume was noted in 29% and 36% of cases and decreased respiratory rate in instances of 27% and 37%. Results which aligned interestingly with the findings of Amdur, excepting the enhancement of tidal volume.

Chronic exposure to formaldehyde was also examined by Coon, and by Feldman & Bonashevskaya in 1970. Coon studied the effects of continuously exposed animals to a number of industrial gases among them formaldehyde. The animals were exposed for a period of ninety days and in the case of formaldehyde exposure the level was reported as 3.7 ppm. One out of the fifteen rats used in the experiments died during the continuous exposure to formaldehyde, none of the other animals showed any clinical signs of illness or toxicity. On microscopic examination of the lungs of all the exposed animals varying degrees of interstitial inflammation was observed. The hearts and kidneys of both the guinea-pigs and the rats in the experiments had focal chronic inflammation changes. The investigators were uncertain as to whether these changes resulted form the inhalation of formaldehyde, however. In the same year Feldman & Bonashevskaya reported the effects of low airborne concentrations of formaldehyde on rats. Microscopic studies of the lungs of the animals exposed to 0.81-2.43 ppm formaldehyde revealed proliferation of lymphohistiocytic elements in the inter-alveolar walls and in the peribronchial and perivascular spaces, against a background of moderate hyperemia. The liver was said to have exhibited nuclear polymorphism, and a profusion of binuclear cells around the triads, focal hyperplasia and activation of the elements of the reticuloendothelial system. At the same time, the liver cells exhibited a moderate decrease in glycogen content and enlargement and rarefraction of RNA granules. The kidneys of rats in the group exposed at both 0.81 and the 2.43 levels exhibited somewhat dilated vessels in the juxtamedullary zone of the cortex. The parietal area of the cerebral cortex exhibited focal proliferation of the glial elements, with many satellites of oligodendrocytes and astrocytes.

No structural histologic changes were noted in the groups exposed at the lowest concentrations. The authors did not mention any details of formaldehyde generation techniques, or methods of analysis.

In 1972 Egle attempted to discriminate between retention of formaldehyde in the upper and lower respiratory tract of mongrel dogs. He found that total tract retention was 100% regardless of the ventilatory rate, formaldehyde concentrations of the tidal volumes having been measured. Retention of the membranes and tissues, at low concentrations was also examined by the Russian author Merjureva in 1978 in relation to embryotoxicity. Similar levels of absorption to those found by Egle were confirmed.

The microscopic studies of Coon, and Feldman & Bonashevskaya had done much to emphasize the highly necrotic effect of formaldehyde, in its molecular form, on certain of the tissues. Researchers were confident that sufficient knowledge had been gained to assess the toxicity profile for formaldehyde and if necessary limit its use in certain circumstances. In the event this has not taken place in the United Kingdom although legislation would have it so. The hesitancy centres around the suspected, but unconfirmed, carcinogenic potential of the material.

Formaldehyde Carcinogentic Activity

In this regard Horton in 1963 published the results of a study in which mice with lower than usual incidence of pulmonary adenomas were exposed by inhalation to formaldehyde and coal tar at various concentrations. The objectives in the study were to discover if formaldehyde would; (i) Induce bronchogenic carcinoma. (ii) Predispose mice to cancer if they were exposed sufficiently to produce metaplasia of aquamous epithelial cells. (iii) Render exposed animals more susceptible to cancer of the lungs than the control animals.

In the preliminary range finding experiments Horton found that exposure of mice to 731 ppm formaldehyde for two hours caused death from pulmonary hemorrhage and oedema. Further tests at 32 ppm for two hours per day for four days failed to kill any of the test animals and produced no substantial distress, or any weight loss. Subsequently test groups

were exposed at 41 ppm for one hour per day for thirty-five weeks. The animals were then killed and microscopic examinations of the lungs carried out. Other groups were exposed at formaldehyde levels in the range 81-162 ppm. They were then examined in a similar way. The author found structural changes in respiratory tissue, but no tumours were found.

Godmekler in 1966 carried out inhalation experiments in pregnant rats who had been exposed continuously in formaldehyde for upto fifteen days. Pre-conditioned groups were then caged with male rats for six days. Two exposure groups were chosen at 0.01 ppm and 0.8 ppm together with controls. There were 135 fetuses in the control group, 235 at exposure level 0.01 ppm and 208 at level 0.8 ppm

Total body weight and the weight of the adrenal glands for the offspring of the dams exposed to formaldehyde at both concentrations were greater than those of the offspring of the control dams. The weight of the kidneys and the thymus of the offsprings from the females exposed at 0.8 ppm were also greater than those of the offspring of the control dams. In contrast the lung and liver weights of the offspring of both exposure groups were less than those of offspring of the control group. There was no evidence that would suggest any carcinogenic activity in the results, although further special studies were instituted by the joint FAO/WHO Expert Committee on Food Additives. They too, in later reports, were to find little incriminating evidence relating to the carcinogenic activity of formaldehyde.

On the other hand, there was some evidence that formaldehyde could act as a mutagen. Auerbach in 1951 demonstrated such activity in Drosphila, although conceded in his conclusions that he believed formic acid to be the causative agent.. Stumm-Tegethoff in 1964 verified the essence of Auerbach thoughts, while Rosenkranz in 1972 reported weak mutagenic activity in E. Coli. with Sutton & Harrison in the same year describing formaldehyde as a mutagen for Neurospra. The general consensus of opinion would seem to suggest that the action of formaldehyde on bacterial DNA is actually exerted by the reaction products of formaldehyde, rather than the compound itself.

The possibility of teratogenicity was investigated by Watanabe et al in 1952-55 in three separate papers in which the phenomena of malformation, in relation to formaldehyde exposure was examined in the rat. The results of the study were supported by Della Porta (1970), and his colleagues who were attempting to establish a toxicological profile for formaldehyde in vivo in the mouse. Essentially it was concluded from the pathological findings from both research groups that there was no difference between test animals and controls. Although both in agreement, there were some anomalies mentioned in the Watanabe studies. On the whole, however, formaldehyde could not justifiable be incriminated as contributing to carcinogenic or teratogenic activity in animal species and there was no reason to suggest that is should be so in the case of man.

CHAPTER V

LITERATURE REVIEW

i) Correlations

ii) Environmental standards

iii) Industrial implications

Correlations

The metabolism of formaldehyde in the animal body would seem to be characterised by several phases of reaction. Among the more important from a toxicological point of view are the following:

i The major fraction would seem to be oxidised via formic acid

ii Formaldehyde participates in the normal metabolic pathways for one-carbon fragments (furnishing labile groups) being utilised in biosynthesis e.g. choline

iii Formaldehyde is a potential allergen producing immunological sensitisation with eczematous reactions. Its pathogenisis is associated with protein-aldehyde conjugates, probably arising from the interaction of formaldehyde with the amino group of proteins.

iv In the presence of liver aldehyde dehydrogenase preparations, formaldehyde is reduced to methanol. Liver preparations also catalyse the conversion of formaldehyde into methyl formate. These reactions are thought to contribute little to the metabolism of formaldehyde in vivo.

The metabolism of formaldehyde via formic acid in mammalian species is species-dependent. Thus both formaldehyde and formic acid are excreted in the urine of cats and dogs who are given unpreserved fish. Humans in similar circumstances show an increase in the excretion of both formaldehyde and formic acid as compared with controls.

In vivo human blood oxidises 30% formaldehyde to formic acid within four hours. The rate of formaldehyde oxidation being comparable in several animal species (rats, dogs, guinea-pigs, rabbits, and cats.), with a half-life of only one minute. By comparison, the half-life of

formic acid is species-dependent. Rapid oxidation of formaldehyde into formate followed by further oxidation to CO_2 takes place principally in the erythrocytes and in the liver. Biotransformation of formic acid in mammals is folic acid dependent, and pretreatment of cats with this vitamin reduces the half-life for formic acid. Treatment of dogs with the folic acid inhibitor methotrexate prolongs the half-life significantly.

In dogs formaldehyde administered orally is absorbed and rapidly converted to formate. No molecular formaldehyde can be detected in the plasma and only traces occur in the erythrocytes. In cats the production of formic acid and influx of lactic acid into the blood causes a temporary acidosis. When formaldehyde is added to human blood in vitro it is rapidly absorbed on to the erythrocytes and then oxidised to formate. Both NAD and NADP-independent formaldehyde dehydrogenases and catalase appear to be involved in the oxidation, so that both erythrocytes and the liver play an important role in any rapid de-toxification of orally and parentally-administered formaldehyde.

Radioactivity distribution studies in the cat have revealed a complete body distribution after five minutes following intragastric administration of ^{14}C, after twelve hours approximately 40% is expired as $^{14}CO_2$, 10% excreted in the urine and 1% in the faeces. The homogenised whole animal contained 20% of the radioactivity after twenty-four hours and 10% after ninety-six hours. Further studies have verified the completeness of the tissue distribution and the formation of methionine, serine and an aldehyde-cystein adduct in the urine.

The principal hazards which have been associated with human exposure to airborne formaldehyde are irritation of the respiratory tract, the eyes, and of the skin. The effects on the skin may be particularly offensive in individuals who have become sensitised to formaldehyde by prior exposure or by other means. In addition the odour of formaldehyde is very perceptable and may be disturbing to individuals that are unaccustomed to it at concentrations which will vary from one individual to another. These concentrations are generally at or below 1 ppm. Reports of allergic reactions to free formaldehyde in textiles finishes are very common. Estimates of the free material have been made and reported to

be between 0.027 and 0.75%. Allergic reactions from the repeated use of facial tissues treated with formaldehyde have caused concern. The Eurotox symposium on cosmetics, in 1961, specified a maximum allowable concentration of 0.05%. This was also regarded as the level in clothing below which dermatitis was unlikely to be produced. Positive patch test reactions have, however, been obtained with 0.03% solutions of formaldehyde in sensitive subjects and it is difficult to specify a level which will not produce dermatitis in a hyper-sensitive individual. A series of cases have been reported of subjects having contact with urea-formaldehyde and melamine-formaldehyde resins, developing dermatitis. The skin reactions being generally apparent after one week. The concentrations were as low as 0.01 to 0.03% the subjects reacting positively to patch tests with freshly prepared material supporting the diagnosis of contact dermatitis.

Acute irritation of the human respiratory tract from inhalation of formaldehyde has caused pulmonary oedema pneumontitis and death. Damage to the lungs in animals has been found following low level exposure.

In humans irritation of the upper respiratory tract has been reported in working areas with formaldehyde concentrations between 0.09 and 11 ppm. Other studies support the possibility that aldehyde concentrations of 1-2 ppm may be irritating to some individuals. Some investigators have noted that irritation is independent of any acclimatisation effect suggesting that initial irritation subsided to some extent after an hour only to return again following periods of absence from the working area.

Russian investigators have noted altered visual sensitivity and changes in cerebral electrical activity in preselected groups exposed to formaldehyde at 0.08 ppm. Further Russian investigations reveal optical chronaxie changes after inhalation of formaldehyde for ten minutes at concentrations below the TLV. EEG measurements following exposure appears to be the more sensitive method, however.

Once skin sensitisation to formaldehyde has occurred exposure to as little as 5.0 ppm for ten minutes has caused well defined skin reactions. Reddening of the skin surface in the presence of formaldehyde is very

common in airborne concentrations of half the TLV level. In this regard it is believed by Jordan et al, 1979, that formaldehyde has very strong haptenic potential for both delayed and immediate skin reactions. In a sixteen strong study of specially selected sensitive individuals all were subject to a continuous (repeated-use) patch test. The levels of formaldehyde ranged from 0-100 ppm and were obtained from pH sensitive release agents. Threshold levels of sensitivity from various sources including cosmetics, clothing and tissues were confirmed at 30 ppm, or below a lower limit not having been specified.

In general, considering differences in body weights and respiration rates, animal data appear to support the observations made in man. This is particularly applicable to the effects of airborne exposures to formaldehyde. The indications are that adverse reactions in animals from exposure to low airborne concentrations are, in fact, generally lower than those that affect humans similarly. Formaldehyde at a concentration of up to 49 ppm for one hour, caused airway resistance changes in guinea-pigs which persisted for more than one hour after cessation of exposure, whereas exposure to formaldehyde at 11 ppm for one hour produces transient changes in resistance to the flow of air into and out of the lungs which disappeared within a half hour of cessation of exposure. Monkeys, rabbits, guinea-pigs, rats and dogs exposed to concentrations of 3.7 ppm for twenty-four hours/day for ninety days developed interstitial inflammation of the lungs. Slight changes in the structure of the lungs have been found after exposure of cats to as little as 0.8 ppm. Amdur found airway resistance changes after exposing guinea-pigs to 0.31 ppm formaldehyde for one hour. Such changes being more dramatic when aerosol saline solutions were included in the formaldehyde atmospheres.

Following continuous twenty-four hour/day exposure of pregnant rats to formaldehyde concentrations of 0.01 ppm a change in gestation time and both increases and decreases in the organ weights were reported. There was also an increase in litter size in comparison with the controls.

While it has been shown that formaldehyde is mutagenic to certain bacterial species, the relevance of these observations to man is arguable. At the present time there is no evidence to incriminate formaldehyde as

constituting either a carcinogenic, or teratogenic hazard to man.

Tissue destruction by ingestion of formaldehyde has been demonstrated in accidents, in human experimental feedings studies, and many other circumstances. The ingestion of as little as 50 mg has been known to be fatal in a small child, while 330 mg has caused the death of an adult. An experimental dose-controlled daily intake of 100-200 mg in milk has produced very severe headaches, stomach pain, and burning sensations in the throat, and a rash, in four out of eleven subjects treated in this way. Gastric and pharyngeal discomforts were also reported from daily ingestions of 22-200 mg of formaldehyde by another group.

Twelve human volunteers have received orally 1.48-2.96 g of sodium formate. They excreted an average 13 mg formic acid per twenty-four h from the control diet and only 23% per twenty-four h of the additional formic acid. Most of the additional load was excreted within six hours and all had been eliminated after twelve hours. No cumulation was noted in the observations. Thus the excretion of formate is accompanied by an alkaline urinary pH and mild diuresis. The biological half-life of orally administered sodium formate was found to be forty-six minutes as determination by plasma levels in three volunteers. It was found that 4-7% of the administered dose was excreted in twenty-four hours. Metabolic acidosis is limited in man because of the apparent rapid metabolism of the formate anion, excess of bicarbonate being excreted in the urine.

As the toxicological effects of hexamethylenetetramine appear to be due to the liberation of formaldehyde and also to formic acid, studies on each of these compounds have been used to develop a toxicological profile of formaldehyde. The FAO/WHO Expert Committee on Food Additives, estimated an acceptable daily intake of 0-0.15 mg/kg body weight. On the basis of complete hydrolysis to formaldehyde the acceptable daily intake of hexamethylenetetramine would be equivalent to an approximate 12 mg formaldehyde per day for a 60 kg man. It must be borne in mind, however, that such a figure does not include additional direct intake, from certain foods, such as fresh fruit and honey, and a work place environment which could conceivably increase this level by many fold.

Environmental Standards

The contribution to the human intake of formaldehyde form the airborne source is not generally quantifiable, except in so far as standards have been agreed to attempt to limit high risk exposures. In the United States the National Institute, in 1967, specified the following as a minimum safety standard to try and restrict such potentially hazardous conditions:

i The acceptable maximum for peaks (unidentified) above the ceiling concentration for continuous exposure:- 10 ppm for a total of no greater than thirty minutes for a complete eight hour shift.

ii Acceptable ceiling concentration for limitation of somatic discomfort:- 5 ppm for an eight hour shift/working week.

iii Acceptable eight hour TWA within limits of (i) and (ii):- 3 ppm. (N.B. Sensitised personnel may react unfavourably to concentrations below 3 ppm.)

iv Minimum level for sensory detection (qualified as to tolerance) should be 1 ppm odour detectable:- 2-3 ppm slight discomfort.

The essence of this particular standard was based on the observations of Fassett and the work of Sim & Pattle.

The American Conference of Governmental Industrial Hygienists, however, were more critical and recommended an eight hour ceiling limit of 2 ppm. This level being adherred to particularly if continuous exposure over many months was envisaged. Such a limit was adopted by the Federal Authorities in 1973. The documentation for the TLV for substances in work-room air had a chequered history, however.

Henderson & Haggard, 1957, noted employee susceptibility on repeated exposure to formaldehyde and cited data that a threshold limit of 5 ppm might be appropriate. Elkins, 1959, refused this, reporting to the ACGIH on persons with severe irritation difficulties at levels below 3.5 ppm. He suggested that the maximum acceptable concentrations should be based on signs of cutaneous rather than pulmonary effects. He conceded that a level for the TLV of 5 ppm should be low enough to prevent subjective evidence of irritation. Further work revealed identical symptoms at concentrations of 1-2 ppm in some workers. Industry finally, (though in many cases reluctantly), accepted the new standard as an enforceable adjunct in 1976 when a short term exposure limit (STEL) was tentatively introduced.

Although the reports of Bourne and Sefarian, and Shipkovitz were the primary references cited for the new TLV the former authors actually studied lower concentrations, in the order 0.13-0.45 ppm, which produced similar complaints from workers. The work of Shipkovitz was probably the more representative in terms of the levels actually encountered in industrial processing, and certainly so for those found in Europe. Other countries have set their own standards for formaldehyde but these are variable and on occasion their enforcement is suspect. In Czehoslovakia the maximum allowable concentration (MAC) should lie below the limit of irritation, and the peak below the limit of damage or severe irritation. This was assessed by industrial committees at 0.8 ppm. From the health and safety stand point this was excellent but in practice could not be adherred to, though manufacturers in the USSR claim to operate plants within this tolerance. German law sets the threshold value for formaldehyde at 1.0 ppm in the working area, 'indicating' a residence time of eight hours in this concentration is not dangerous. They further state that for permanent exposure the MAC should be no greater than 0.02 ppm. Which is a very important rider to the legislation but in practice is an extremely difficult parameter to work to. It essentially means that plants either do not use formaldehyde, or do so, and operate outside the law.

In the United Kingdom the current recommended standards for work place environments are designed to protect all but the sensitised worker from the adverse effects associated with exposure to formaldehyde. It remains

an unfortunate fact, however, that during an eight hour shift an employee is very likely to have been exposed to levels far in excess of that recommended by the standard.

Interestingly it can be demonstrated that the overall average level of formaldehyde in a plant is consistently below the TLV, indeed this can be shown over the period of a week, or many months. Nonetheless the transient peak levels can vary between 1.5 and 13.5 ppm and be as great as 30 ppm. Based on observation in the present work it would seem reasonable to predict that the cumulative level of formaldehyde in the body can very quickly exceed those that are recommended as tolerable.

Differentiation between that which may be metabolised by a particular route over a period of twenty-four hours, and that which may remain to form the basis of further accumulations is discussed in chapter 8, part II.

Industrial Implications

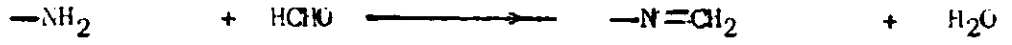
The technological limitations of assessing the threshold limit value for formaldehyde, and the use of the concept for the evaluation of safe working conditions has been examined, and has proven to be of value. The fact that an accumulation of formaldehyde can be characterised in the body fluids following exposure would seem to emphasize the need for caution in monitoring atmospheric levels against an arbitarily fixed standard. The better alternative, and much safer practice would be to monitor personnel physiologically on a bi-monthly basis. The potential seriousness of the effects of long term, low level exposure to formaldehyde can only be appreciated when the progressive nature of the symptoms of formalin asthma are witnessed over a long period of time. Formalin asthma is a respiratory condition which is progressive and is characterised in the early stages of onset by a cough and slight reduction in vital capacity. The asthma tends to disappear but returns at frequent intervals, coinciding with exposure at shift changes and rest periods. It is for this reason that the coughing episodes have become known as 'Monday fever' by many staff in plant areas. Over a period of several years in such environments the one day effect can be seen to carry over for several days during the week the spasms becoming progressively more

acute. This general effect is quite different in character from the intense asphyxiation felt by an individual who suddenly breathes fresh air following exposure at high concentrations. Although primary metabolism is taking place in these circumstances together with related peripheral processes in the lungs and tissues, a measurable level of accumulated free material may be present. This being so there is an ever present risk of synergy in the plant areas.

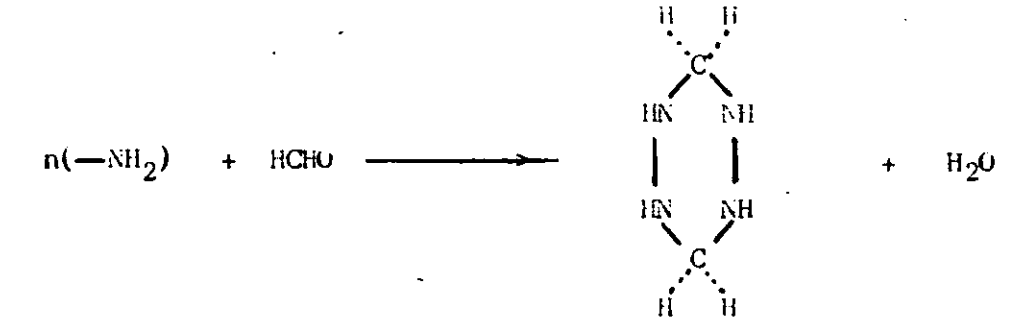
Thus in the case of an individual's encounter with HCl fumes, the likely product would be the formation of bis-CME, the potential tissue accumulation of formaldehyde being the precursor. In order that a physiological interpretation can be suggested for the observed symptomology, it is necessary to consider the effects of the presence of formaldehyde on phospholipids and the other chemical agencies essential to lung function.

Lamellar lecithin systems have been studied by Chapman & Fluck, 1966, Salsbury & Chapman, 1969, Kornberg & McConnell, 1971, and Sackmann & Trauble, 1972. It is apparent that phospholipids and corresponding lecithin show a greater intolerance of water than do the ethanolamine based cephalins. The most straight forward explanation for this is that the bulkier trimethlammonium group and the associated water structure of lecithin prevent the lipid chains from packing as effectively as can, for example, occur with phosphatidylethanolamine. These factors are also consistent with the findings from a number of studies based on the thermotropic behaviour of monolayers of such compounds. Endothermic transition is accompanied by a decrease in the thickness of the lipid bi-layer volume, and changes in permeability, as demonstrated by Overton and other workers. The changes in permeability are of particular importance in systems which involve the diffusion of small organic molecules. both their direction of movement, and leakage into and out of the cellular membranes are strongly influenced by such parameters. At the molecular level formaldehyde cannot be visualised as being dissolved in the bound water of phospholipids or existing as a sub-phase. It is far more likely that a reaction will take place in the region of the terminal NH_2^+, or $N(CH_3)_3^+$, groups. This being the case a number of reaction sequences are possible as shown below.

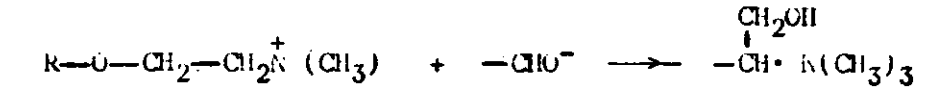
1) 

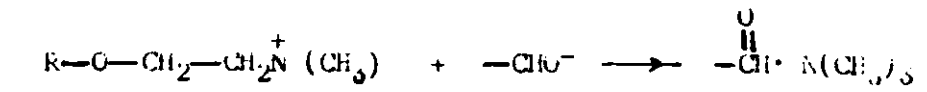
2) 

3) 

4) 

At the choline residue of the lecithin complex, attack at the ionic site is favoured as opposed to a reaction at the esteric, as in reaction 5) and 6).

5) 

6) 

The aggregation and consequent phase shift to form a gel with water in such as system as 5) would result in the production of liposomes. The predominance of the formation of the Schiff base when formaldehyde reacts with amino groups has been demonstrated by Trillant, Blum, and Treves & Salomone. Bangham et al, 1958, and Bangham & Standish, 1965, have further established the involvement of the Schiff base in controlling the permeability of artificial membranes of phosphotidylethanolamine. At neutral pH the free amino group of the phosphotidylethanolamine molecule may be expected to compensate for the negatively charged phosphate group in the form of a Zwitterion. Formation of the Schiff base blocks the amino group which would make the phosphotidylethanolamine membrane more negative. This has also been confirmed by Bangham et al, 1968, in studies relating to the electrophorectic mobilities of membranes prepared from retinene and retinol. Increase in the negative charge of membranes with cation leakage was also observed by Bangham & Berg, particularly for the leakage of Na^+ and K^+ when, for example, erythrocytes are treated with the reagent 1-fluro-2, 4-dinitrobenzene.

In biological systems it can be shown readily that membranes can become negatively charged with a considerable increase in cation leakage. The Schiff base formation, however, is essential to the phenomenon. Thus at the cellular level cations from the environment can cause aggregation of inter-membranous particles (IMP) and there is much evidence to support this idea, such changes in aggregation leading to alterations in membrane permeability. Inter-membranous particles carry strong negative charges which give rise to electrostatic repulsion. Changes in the net charge of the cellular environment also brings about aggregation, and may be the physical basis for permeability increase.

Overton and a study by Naccache & Shaaf, 1973, demonstrated the importance of molecular volume in relation to permeability and the relevance of lipid solubility of small organic molecules. Boldin, 1973, suggested that biological membranes contained 'islands' of protein and glycoprotein and that lipids are able to diffuse freely within such a system. The general influence of formaldehyde in, for example, the bronchial tree would be to freely permeate the tissues, giving rise to aggregation of IMP protein and glycoprotein, and the formation of a Schiff base with selected phospholipids. Air contaminated with formaldehyde

in the work place when breathed will be transported to the terminal bronchioles and alveoli, finally to come into contact with the blood of the pulmonary capillaries. In terms of lung function, within the confines of the alveolar sac, the lamella bodies provide mixed phospholipids and in the presence of an active organic molecule such as formaldehyde a chemical reaction will take place. In practical terms the initial ease of breathing noticed when entering an atmosphere contaminated with formaldehyde is thought to arise from changes in membrane permeability. The overall reaction of formaldehyde on the phospholipids and membrane of the lung take place in essentially two phases. In the initial phase there is a leaching out process with removal of lung surfactant and the formation of liposomes. In the second, a large increase in cation leakage from the alveoli membrane. The resulting permeability changes in the alveoli wall will be sufficient to substantially alter gas transfer with a decrease in oxygen tension in the pulmonary capillaries. The extent of hypoxaemia can be difficult to judge, but it is likely to be directly related to the length of exposure. Physiologically also to any thickening of the alveoli wall following previous membrane damage. The ventilation-perfusion ratio will reflect these changes giving rise to an extension of the alveolar dead space, with the appearance of a shunt-like situation.

The tendency of the alveoli to closure and congestion reduces compliance, although this to some extent is offset by an increase in the rate and depth of breathing. These compensatory changes also increase the proportion of the tidal air volume that is expended in ventilating the physiological dead space. In these circumstances the alveolar ventilation is reduced and the tension of O_2 in the arterial blood is increased. The resulting acidemia raises the pressure in the pulmonary circulation directly by causing vasoconstriction, and indirectly due to an increase in the central blood volume. At the same time, the wide range of ventilation-perfusion ratios, and the associated hypo-ventilation gives rise to hypoxaemia.

The importance of ventilation-perfusion ratios in pulmonary desease being well known particularly in conditions of asthma and congestive atelectasis. Formalin asthma presents with clinical features of increased smooth muscle tone in the bronchial tree, increased secretion

of mucosal glands, with a productive cough and attacks of wheez. Onset may be somewhat unusual in that several hours of fresh air breathing is often necessary before the symptoms are observed or become troublesome. Exposure to those levels of formaldehyde normally accepted in the work place as safe has produced respiratory distress of this kind and of widely varying severity. Among those symptoms which have been observed to 'carry-over' are a lack of co-ordination, an apparent inability to concentrate, headache, and disturbed sleep patterns. In conditions of daily exposure between 0.3 and 1.5 ppm an altered functional state of the cerebral cortex can be demonstrated together with shifts in the equilibrium of sensation and distortions of the alpha rhythms. Rebuck et al in his studies of neurological sensitivity to oxygen lack showed that a very small degree of hypoxaemia (such as could be produced by O_2 pressures of 9 kpa = 67 torr) gave rise to very similar symptoms in healthy subjects. Clearly, even the slightest tendency of environmental conditions, producing hypoxaemia in an individual, will inevitably lead to bad psychomotor performances, and irregularities in EEG traces, particularly if the exposure is long term.

FORMALDEHYDE IN THE INDUSTRIAL ENVIRONMENT

PART II

CHAPTER

VI

ANALYTICAL TECHNIQUES

i) Historical and development

ii) Sampling formaldehyde in air

iii) Formaldehyde in textiles

iv) Special tests

v) Correlations

Historical Development

The desirability of possessing the necessary analytical skills for estimating formaldehyde quantitatively in air has been recognised for over half a century. It is the industrial sector however that has been responsible for the development of the majority of the innovations and newer methods.

In general, air purity investigations are satisfied by what is termed 'total aldehyde' procedures, but which do not quantify the amount of formaldehyde present. The reagents concerned react with formaldehyde but also with its analogues, and in this sense are regarded as non-specific. In order to monitor the atmosphere completely in a working environment it is necessary to perform qualitative analyses initially to identify the range of aldehydes present, followed by the application of selective methods as appropriate. Methods for total aldehydes were described by Goldman and Yagods 1943 who were the first to propose the use of a non-volatile formaldehyde bi-sulphite complex for the estimation. The main advantages claimed were the high collection efficiency (98%), and the production of a stable salt in good yield. The procedure was adopted as a standard in the United States in 1958. Though not the preferred method today the technique is still satisfactory when formaldehyde is known to be the only aldehyde present in the atmosphere to be studied. Work by Kersey et al 1940 and Barnes and Speicher 1942, with solid phenylhydrazine complexes prompted Fedotov to suggest the impregnation of silica gel with phenylhydrazine for the purposes of constructing indicator tubes. Being concentration graded these were convenient in industry as estimates of the level of formaldehyde could be obtained without the use of laboratory facilities. In 1969 the Public Health Service in the United States was among the first authorities to adopt the (MBTH) method, a technique which also relies upon the formation of a solid reaction product 3-methyl-2-benzothiazolone hydrazone.

The procedure was adopted by the Intersociety Committee; (an alliance of 10 professional societies for standards) in 1970 following modifications by Elfers and Hochheiser 1969 to incorporate the use of a

visual colour comparator. Many other successful field applications were made in the early seventies. The very wide range of applications for formaldehyde eventually led to the development of a technique which had little or no interference from other aldehydes present in an atmosphere to be sampled. The reagents were chosen specifically for their response to formaldehyde alone, or their selectivity in responding very weakly to other analogues. The most widely used colour-forming reagents were the Schiff reagent, pararosaniline sulphite, and chromotropic acid. Others that were known included 2-hydrazinobenzothiozole, J-acid (6-amino-1-napthol-3-sulphonic acid) and phenyl J-acid (6-anilino-1-napthol-3-sulphonic acid). Interestingly, one of the earliest applications of Schiff's reagent has been for the characterisation of formaldehyde in 1866. It was not until 1936 however that the technique was used in air analysis being described by Zhitkova. Numerous modifications to the method were published but all used reagent mixtures of fuchsin or pararozaniline which, together with sulphite and formaldehyde yield the well known rose-violet colouration. The Chief Sanitary Inspectorate in the USSR adopted the method in essentially the same form, while a slightly modified technique by Yunghans and Monroe was used to determine atmospheric formaldehyde by an automated analytical system. Other modifications of note which were based on the Schiff's reagent included those of Brewer, Knight and Tennant 1973. The currently favoured analytical system relies on the production of a purple colour by reaction between formaldehyde and 1,8-dihydroxynaphthalene-3, 6-disulphonic acid (chromotropic acid) in sulphuric acid. Actually, this reagent was first proposed as specific for formaldehyde in 1937 and various investigators have reported on its use. McDonald was the first to apply it for the analysis of formaldehyde in air in 1954, and developed the method in essentially the form in which it is employed today.

Altshuller et al 1963 were responsible for the modifications which resulted in improved sensitivity, stability and current freedom from interference. The use of concentrated sulphuric acid as the collection medium is clearly impractical for personal air sampling in the industrial environment, but in most other situations the technique has become accepted. Cares 1968 noted that oxides of nitrogen interferred with the colour development and recommended that samples be collected in bisulphite

solutions to avoid this interference. Other attempts to minimize interference have included the use of porous polymer absorbents, and a chromatographic separation technique for styrene and cresols. Levaggi and Feldstein 1970 in their report to the Intersociety Committee suggested that formaldehyde be collected in a 1% sodium bisulphite solution and then the chromotropic acid technique applied, by these means they claimed an improvement in accuracy. Saeicki et al compared the chromotropic acid method with the J-acid and phenyl J-acid methods and pointed out the potential interference from some formaldehyde-releasing compounds which would not normally be present in an industrial setting. They established that J-acid and phenyl J-acid are extremely sensitive selective reagents, and in some ways, are superior to chromotropic acid. J-acids have however not found the same favour among analysts that the chromotropic acid technique enjoys. Perhaps the singular exception is the acetyl acetone method which forms a coloured compound with formaldehyde by means of the Hantzsch reaction (Nash 1953). Some lesser used reagents for formaldehyde include 2-hydroxycarbozole, paraphenylenediamine, an equilibrium mixture of potassium tetracyanonickelate and dimethylglyoxime and a reagent used together with the acetyl acetone procedure, 5,5-dimethyl 1,3-cyclohexanedione (Dimedone, Methone).

In general, gas-liquid chromatographic techniques have not been so successful for analysing formaldehyde, compared to the higher aldehydes. A possible explanation is that various problems of interference and sensitivity have been experienced with the chromatographic conditions.

In 1975 a report by Wood and Anderson stated that attempts to develop gas-liquid chromatographic analyses were unsuccessful. Levaggi and Feldstein 1970 in their research described successful determinations of C_2 - C_5 aldehydes but could not make recommendations for using this technique for analysis of low concentrations of formaldehyde in air. Wood and Anderson did however publish evidence that formaldehyde could be collected satisfactorily on solid absorbents such as alumina. Subsequent analysis was by means of the chromotropic acid technique but elution of formaldehyde from alumina must be performed immediately to prevent loss. It is for this reason that the method is rarely used in

field applications. The modified chromotropic acid method remains the technique of choice in industrial practice although monitoring schemes are still to be found which are based on the use of Drager tubes. The specialised applications of chromotropic acid to the analysis of textiles substrates and to biological fluids require selective modifications and are discussed in detail later. The question of monitoring individual personnel on a continuous basis is open to argument. When concentrated sulphuric acid needs to be used there exists an obvious element of risk, which some people avoid by using less sensitive methods for sampling in air.

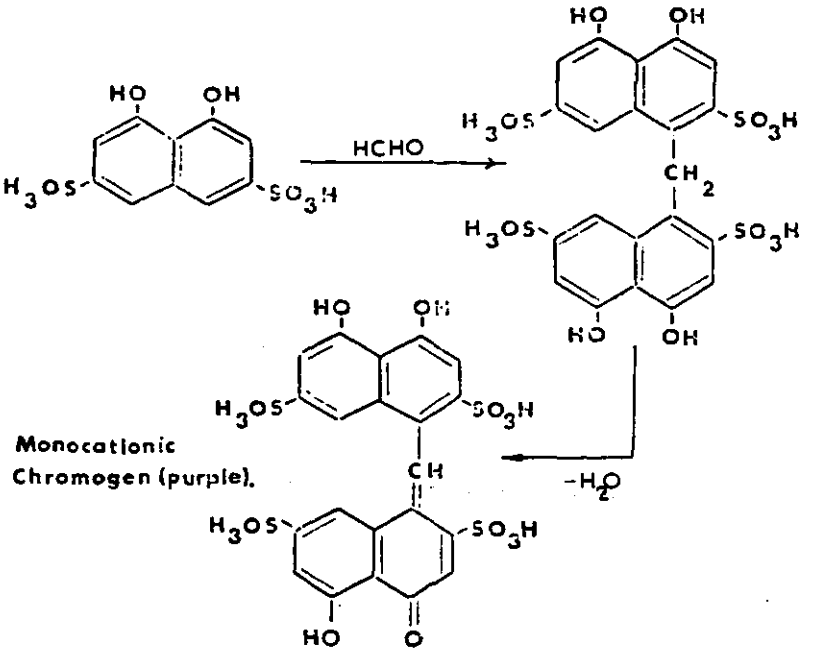
Sampling Formaldehyde in Air

A number of methods are available the most popular being the use of two glass midget impingers in series through which air is drawn by means of a pump. Each impinger contains distilled water, (if other aldehydes are present 1% sodium bisulphite solution). The sampling unit and pump are operated in the appropriate breathing zone, the positions and frequency of sampling conforming to a specific pattern.

The flow rate with on-line impingers is difficult to control on occasions and is checked regularly as a minimum precaution with their use. With two impingers a collection efficiency of 95% is normal. If relatively high concentrations are being examined it is convenient to analyse the contents of each impinger separately.

The accuracy of the analysis depends on the volume of air which is measured, the accurate calibration of the sampling device is equally important. The frequency of calibration in turn depends on the use and handling to which the pump is subjected, frequent checks being necessary for damage. In industrial practice a sampling time of ten minutes is used with an air flow equal to 100 ml with a total air volume of 1000 ml. Care is exercised in the assembly of the apparatus in respect of the quality of the seals and joints and the length of the rubber tubing used for connections. The choice of calibration instrument will depend largely on the nature of the calibration to be performed. For laboratory testing a 1-litre burette or wet test meter is used although standard calibratine instruments are also employed.

The principle of the method is based on the fact that formaldehyde reacts with chromotropic acid/sulphuric acid solution to form a purple monocationic chromogen. The absorbence is read in a spectrophotometer and is proportional to the amount of formaldehyde in the solution. The chemistry of this colour reaction is uncertain. However Fiegel proposed that the chromogen is formed as follows.



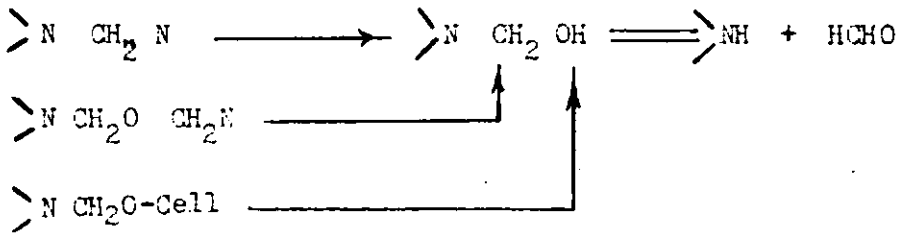
The sensitivity of the methods is considered to be such that a concentration of 0.16 ppm can be determined in an original 25 litre air sample. This in turn is based on an aliquot of 4 ml from 20 ml of absorbing solution and a difference of 0.05 absorbence units from the blank. During constant use over a number of years it has been found that the procedure has very few interferences from other aldehydes. Saturated aldehydes giving less than 0.1% of positive interference, and the unsaturated aldehyde acrolein for example, gives a 1-2% plus value. Ethanol and other higher molecular weight alcohols and olefins in mixtures with formaldehyde produce negative interferences.

Ethylene and propylene in a 10:1 excess over formaldehyde result in a 5-10% reduction in value and 2-methyl-1, 3-butadiene in a 15:1 excess

will give rise to a 15% reduction. Aromatic hydrocarbons may produce a negative interference as it has been found that cyclohexane causes a bleaching of the final colour of the chromogen for which appropriate filters have to be used. The overall accuracy and reproducibility of the technique has been established by comparing the analyses of standard solutions of formaldehyde on different instruments. A reproducible straight line calibration graph is obtained. The application of the technique to textiles has special interest and is discussed below.

Formaldehyde Free Textiles

In order to prevent any health hazards thought to exist with garments finished with agents containing formaldehyde, the Ministry of International Trade and Industry in Japan initiated and enforce specific standards. The regulations cover all infants' clothing specifying a level of not greater than 75 parts per million (Law No 112 1973 Ordinance No 34). To cope with these regulations special finishes needed to be developed, as hitherto levels exceeding 1000 ppm were common place. In the Western World the textile trade demands a high standard of performance from the resin systems used in finishing. In particular good appearance and easy care properties need to be imparted to the fabrics that are treated, coupled with a low cost of application. In the event through co-operation between the chemical manufacturers, and the market outlets, a range of low formaldehyde and formaldehyde-free finishes were developed. These were collectively known as reactant systems but were found in practice to be expensive to apply as compared with the cheaper, urea-formaldehyde containing materials. Technologically the conditions under which a resin system is applied can influence very strongly the level of free-formaldehyde likely to be present in the finished material. Conditions of cure, catalyst, and any backwashing processes pertaining to the particular substrate need close attention, as indeed do special additives to the system such as so called 'formaldehyde scavengers'. These materials, which are designed as preferential co-solvents for formaldehyde, are used to advantage in many finishes. Some of the intrinsic reactions which can lead to the formation of free-formaldehyde at the resin-substrate interface are summarised below.



In addition there are other environmental factors which influence these reactions and which may be summarised thus:

Humidity Moisture Content	- Chemical	-Change with time lapse
Temperature		
Remaining Unreacted resin and catalyst		
Desorption and absorption	Physical	

Control of ambient conditions in storage having proven to be an invaluable asset in reducing in-situ development of formaldehyde, and undesirable amines.

The analytically determination of the levels of free-formaldehyde in textiles though commonly quoted, are not determined in line with specific international standards. The Japanese Government approved the use of the acetylacetone test for this purpose in 1974. Since that time it has become mandatory that any textile material used or imported into Japan carries both a general licence and batch certificate of compliance to the approved standard. The principle of the technique is the development of a coloured solution by reaction of formaldehyde with acetylacetone (Nash Reagent) with subsequent estimation of the concentration of the original formaldehyde.

The analysis is carried out by accurately weighing a specimen of textile, which is extracted in distilled water. The extract is filtered and an aliquot is treated with acetylacetone reagent. A blank, using standard formaldehyde solutions, is also prepared. The absorbence of the test and standard solutions are measured at 412 nm against a reference solution in a spectrophotometer.

In 1975 it was suggested by the Shirley Institute (a textile research organisation representing a large body of textile processors in the U.K.) that free-formaldehyde levels in textiles are best estimated by means of an adapted chromotropic acid in sulphuric acid test procedure. The method employed a mild aqueous extraction to remove un-reacted N-methylol crosslinking agents from the surface of the fabric. These, when hydrolysed by strong acid in a subsequent part of the analysis, gave rise to

formaldehyde which is in fact included in the final colourimeteric assessment using chromotropic acid. The Shirley Institute believe that inadequate curing of a resin system can lead to residual water-soluble formaldehyde derivatives being left in the fabric and which are considered potentially dermatitic. They further suggest that the chromotropic acid method (with the initial modification they suggest) gives a better assessment of the severity of proported risks of this kind. In their experience free formaldehyde levels which exceed values of 700 ppm using the technique are generally undesirable and are likely to give rise to skin irritation during garment manufacture and subsequent wear. In certain quarters these ideas are very strongly challenged particularly in respect of any remaining water soluble formaldehyde derivatives in fabrics following finishing. In principle the analysis is carried out by weighing a specimen of treated material followed by extraction for 20 min in a known volume of distilled water containing a wetting agent. This solution is filtered and an aliquot treated with chromotropic acid and concentrated sulphuric acid and heated in a water bath for 20 min. A deep red violet colour is produced. The solution is then cooled and diluted to a fixed volume and the absorbence measured at 570 nm using a spectrophotometer. The amount of formaldehyde corresponding to the determined absorbence is obtained by reference to a calibration curve, prepared under similar conditions. The free formaldehyde (F) content of the fabric is expressed as parts per million on air dry fabric, the weight of which is given by the following formula.

$$F = \frac{f.V}{v.W}$$

Where
- f = formaldehyde (μg) in the test aliquot of the aqueous extract (as obtained from the calibration curve)
- V = Total volume of 0.1% Lissapol N solution (20ml)
- W = Weight of air-dry fabric specimen (g)
- v = Volume of aqueous extract taken for analysis (usually 0.5 ml).

The test has met with only marginal success, the acetylacetone technique being considered to more closely align with resin substansiveness, and the conditions in wear and storage to which a fabric may be subjected.

The many tests reported as specific for formaldehyde probably reflect the importance of an accurate determination particularly in certain industrial applications but equally in research and for specialist use. In the latter case several moifications are of interest.

Special Tests

In, for example, the selective determination of free urinary formaldehyde, Chen Tsun-ming et al (Warner-Lambert Inst 1972) found that in the urine following oral administration of methenamine mandelate the level of free formaldehyde was not decreased 24 h after voiding if the urine was diluted ten fold with distilled water and stored at 4 C. The reaction of formaldehyde with urea to form monomethylolurea having been inhibited. Further that precipitation of methenamine with $HgCl_2$ prevented its continued hydrolysis to formaldehyde. The latter being determined colourimetrically as the 3,5-diacetyl-1, 4-dihydro-2, 6-lutidine, which was formed by the Hantzsch reaction with acetylacetone and ammonia. In the course of the present work it has been found practical to adapt some of the techniques described by Chen Tsun-ming et al, in the determination of the free urinary formaldehyde levels following exposure to formaldehyde containing environments.

The United States pharmacopoeia advocate a sensitive test for the presence of formaldehyde in cosmetics. Test identification (USP XVIII) relies on the reduction of silver nitrate to metalic silver. Ammoniacle silver nitrate solution in the presence of formaldehyde giving rise to the familiar grey finely divided ppt of silver or bright metallic mirror. Fisher 1978 made use of the test in studies of dermatitis due to formaldehyde-releasing agents in cosmetics and medicaments. The release agents were linear and cyclic reversible polymers of formaldehyde which are capable of producing the monomer at biological temperatures and pH.

The test proved to be very sensitive in practice and can actually be employed in the plant situation as a convenient spot test for formaldehyde in air.

An equally useful and semi-quantitative test is the application of Drager

tubes. In essence these consist of a glass tube with fused tips containing a reagent ampule (which houses solid paraffin and xylene vapour), a pre-marked break point, a shrunk-on tube embodying formaldehyde sensitive reagents and a pre-test and indicator layers. A colour comparison zone to facilitate estimation of the results is also provided. The indication is based on the reaction of formaldehyde with xylene in the presence of sulphuric acid. Viz a colour change from white to pink. The reagents are also sensitive to acetaldehyde, acroiein, furfuryl alcohol and styrene in the presence of which the indicator layer on the tube will show a yellow to brown colouration. A sensitivity of 0.5 to 10.0 ppm is claimed or a higher range dependent on the tube design. Ambient conditions are said not to influence the accuracy of measurement provided the range of 0 - 40 C is not exceeded and the humidity level of 3-15 mg water per litre is maintained. The convenience of the technique in practice is undeniable.

Correlations

Of all the techniques employed in both industry and research the chromotropic acid method has been demonstratably consistent in application over many years. Proposed in 1937 as a specific reagent for formaldehyde its use was examined by Bricker and Johnson in 1945, further developed in 1954 by McDonald and adopted by the Intersociety in 1970. It has appeared as a recommended procedure to government bodies concerned with environmental control of air pollution including Czechoslavkia, West Cermany and the U.S.S.R. The method has few interferences, the major exception is the presence of aromatic hydrocarbons, where it is known for example that cyclohexane reduces the colour intensity of the chromogen complex.

The procedure for the sampling of air as part of a plant monitoring scheme, or as a government environmental control measure, can be time-consuming and often very costly. It is for this reason that shortened methods have been sought which are simple to apply in the field, but do not greatly sacrifice accuracy. One such method is the Lovibond Comparitor which in principle relies on the comparison between calibrated tints and the colouration developed by a given concentration of formaldehyde in chromotropic acid reagent. Reasonably good agreement with conventional analysis can be obtained with an experienced observer. The use

of Drager tubes falls into a similar category, the technique is simple, as described previously, and it is possible to use the tubes and pump when in difficult plant conditions. Reproducibility of results, however, can present serious problems. Comparisons using the tubes, and chromotropic acid procedures has demonstrated this on a number of occasions in our work. Nonetheless, there are situations where the tubes are most useful, such as in the open air, and when sampling vents and exhaust stacks.

One of the better spot check field instruments currently available is produced by the Perstorp Regeno Company of Sweden. The instrument is claimed to be sensitive to a level of 0.05 yg formaldehyde being developed for the Swedish National Social Welfare Board.

The system of analysis depends upon the development of a colour with acetylacetone reagent followed by measurement with a calibrated photometer. Trials in Europe have been very encouraging, particularly when the Nash reagent is used although it is claimed by the company that other absorbents are suitable.

The acetylacetone technique is internationally popular particularly among biological workers, but it is not commonly used for the monitoring of factory air. The only exception being the Swedish Welfare Board, who adopted it in 1979. The technique is considered to have advantages when applied to textiles also, and was adopted for this purpose by the Japanese Government in 1974.

Both the chromotropic acid and the acetylacetone techniques are not without their critics, but these have been confined to minor anomalies of procedure rather than serious technological defects. An interesting observation was made by Fisher in 1978 when he was studying the free formaldehyde levels in cosmetics. He believed that when using chromotropic acid for the detection of formaldehyde the effect of heating with concentrated sulphuric acid may be to generate formaldehyde in-situ. Also in the colour reaction using acetylacetone heat is often used to shorten the time of colour development, formaldehyde could be generated where none would have existed under ordinary conditions. No other comments were given in the paper. In deciding which tests to employ in the present work an attempt was made to evaluate these ideas, particularly for the Hantzsch reaction.

Of the traditional qualitative and spot tests for aldehydes perhaps one of the best known is the formation of the formaldehyde-bisulphite complex, a stable compound, and one which by back titration permits an indirect quantitative estimation of formalhyde.

The Schiff reagent in its many forms and modifications has been successfully applied since 1866 both as a qualitative and quantitative procedure. The Russian Sanitary Inspectorate incorporated some selected forms of this test into their procedures for their worker protection programme in 1965.

The silver nitrate test, has been found to be a very sensitive and adaptable procedure, capable of detecting formaldehyde at levels of 0.01 ppm in samples of absorbed air, and biological fluids. The reliability and ease of practical application of the test suggests that it should be worth developing for use in personnel monitoring.

CHAPTER

VII

METHODOLOGY

i) Estimation of Formaldehyde in Air

ii) Formaldehyde in Textile Substrates

iii) Formaldehyde as a Salivary Constituent

iv) Formaldehyde as a Urinary Constituent

Estimation of Formaldehyde in Air

In the industrial site used for these studies the analytical method was based on the reaction of formaldehyde with chromotropic acid in sulphuric acid. Plant sampling locations are important and were precisely specified. All samples were spot checks and not time-weighted averages. Sampling time and air flow were standardised. Known areas of accumulations were carefully surveyed particularly in resin mixing areas, stenter rooms and the immediate vicinity of curing ovens and presses.

Reagents:

Chromotropic acid reagent: (5% aqueous solution) 2.5 g of chromotropic acid is dissolved in 50 ml of freshly distilled water in a volumetric flask.

Sulphuric acid solution 75% (AR Sulphuric acid concentrated S.G. 1.84) to 50 ml of distilled water is added 150 ml of concentrated sulphuric acid and the solution cooled and stored.

Chromotropic acid-sulphuric acid mixture: 10 ml of the 5% chromotropic acid is pipetted into a 200 ml of 75% sulphuric acid solution and the mixture retained in a stoppered bottle.

Standard formaldehyde solutions are prepared and their absorbency against concentration of formaldehyde (ppm is then plotted).

Sampling in Air:

A clean absorber is charged with 10 ml chromotropic-sulphuric acid reagent from a pipette, and the unit then connected to an aspirator, or pump and the air to be sampled drawn through. One litre of air has been found to be a satisfactory volume. The contents of the absorber are then incubated at 70 C for 30 min. The mixture is then cooled, and the absorbence of the sample measured in a 10 ml cell against distilled water in a reference cell. The concentration of formaldehyde (ppm) in the sample solution may then be calculated. The results are expressed as the formaldehyde concentration per ppm (V/V) in air.

Application:
The results of air monitoring analysis are recorded for specific factory areas and times. Overall air movement in the plant environment is very variable and the levels of formaldehyde found often reflect this. Known 'still' areas can give rise to excessive accumulations and these values, though always included in summaries of results are specifically identified. The number of samples taken in selected areas are greater than would normally be required for plant monitoring and it is hoped by doing so to highlight any unusual levels.

The effectiveness of attempts to improve the environmental conditions may also be evaluated by these means. The general criteria against which such improvements are measured is the Threshold Limit Value (TLV), the level in the case of formaldehyde is 2.0 ppm.

The potential dangers of exceeding this limit in areas such as resin mixing and stenter rooms, is considered important. The possible 'blunting' of the sensory and neurological responses of the human subject working in such areas has been examined. A survey of plant workers own assessments of their personal tolerance of similar conditions augments the results of the biological testing.

Formaldehyde in Textile Substrates
The sampling and estimation of free formaldehyde in textile substrates can be based on either the chromotropic acid, or the acetylacetone technique of colour development followed by spectrophotometric measurement. It is sometimes of value to apply both tests depending on the type of information that is being sought. When the effect of resin formulation changes are being examined it is appropriate to apply both, in the case of salivary specimens it is necessary only to use the acetylacetone method.

Reagents:
Chromotropic acid procedure: The standard chromotropic acid-sulphuric acid reagent is made up as outlined in Methodology section (i).

Sampling Fabrics:

An accurately weighed specimen (2.0 g air dried) of the textile material is extracted for 20 min in a measured volume of distilled water containing 20 ml of 0.1% wetting agent. Following filtration to remove loose fibre an aliquot of 0.5 ml of the filtrate is treated with 10 ml of chromotropic acid-sulphuric acid reagent. The sample together with blanks, in stoppered glass tubes are then incubated on a water bath at the boil for 20 min in order to develop a deep violet colouration. The mixture is then cooled and diluted to a volume of 50 ml with distilled water. The optical density of a sample of this solution is then measured against a reference in a spectrophotometer. A calibration curve is prepared using standard formaldehyde solutions. The free formaldehyde (F) is expressed in parts per million (ppm), on the weight of the air dried fabric.

Reagents:

Acetylacetone procedure: The acetylacetone (Nash reagent) is prepared by dissolving 15 g of ammonium acetate in a small quantity of distilled water to which is added 0.3 ml of glacial acetic acid and 0.2 ml of acetylacetone (1,3-pentanedione). The whole is then made up to 100 ml with distilled water.

Standard formaldehyde solutions: For the purposes of preparing a calibration curve solutions of formaldehyde of known concentration are assayed by measuring optical density and plotting the relationship between absorbence and formaldehyde concentration.

Sampling the Fabric:

An accurately weighed specimen of textile (1.0 g) is extracted for 1 h at 40 C. The extract is filtered and a 4.0 ml aliquot is treated with 5.0 ml of acetylacetone reagent. A blank is also prepared using a standard formaldehyde solution of 4.0 yg HCHO. Both samples are incubated at 40 C for 30 min. The absorbence of the test and standard solutions are measured against a reference solution prepared using 5 ml of water and 5 ml of acetylacetone solution.

The free formaldehyde may then be calculated and is expressed as the quantity yg of soluble formaldehyde per one gram of sample.

Application:

The skin-formaldehyde interface can be established in the presence of a textile material or garment that has been treated with a formaldehyde containing resin. Items of toiletry, cosmetic creams, or medicaments can also establish such a membrane due to the presence of formaldehyde release agents, many of which are sensitive to the pH of the skin. It is desirable therefore, to monitor the pattern of free-formaldehyde generation in textile fabrics or other substrates containing the material. Urea-formaldehyde resins probably have the highest incidence of free-formaldehyde generation, and the greatest chance of producing dermatitis on contact with the skin.

It is possible to stabilise such a system but the reology of resin formulation is of lesser significance than the functionality of e.g. silicones in establishing stable polymer architecture. It was of technical importance to discover if the addition of silicones contributes to the chemical isolation of formaldehyde by co-polymerisation, or simply impedes formaldehyde contact with the skin in some way. It is undeniable that the presence of very small amounts of such materials has a marked effect on polymer performance. The easiest means of assessing the propensity to dermatitis of a particular finish is by patch testing, and some selected textile substrates have been examined in this way.

The convenient length of time for such tests is 48 h although longer durations were employed. The patch area used was one square inch, and the nature of the papules were assessed with a piece glass. The appearance of the test sites, were compared with the effects produced by known concentrations of formaldehyde placed on the subject in tandem. Care was taken in selecting participants, particularly as individuals occupationally in contact with low air-borne concentrations of formaldehyde appear to develop some immunity. In general hyper-sensitivity was found to be rare, but in those individuals in which it could be demonstrated, correlations of effect were considered against fabrics traditionally finished and samples treated in special ways.

Formaldehyde as a Salivary Constituent

Following from work on textile substrates it was found feasible to analytically detect and quantify formaldehyde as a salivary constituent on cotton dental swabs. By similar means it is possible to characterise and monitor the fluctuations of other chemical agencies, together with those parameters such as pH which may vary over the period of a shift in the working environment.

Reagents:

The acetylacetone, Nash reagent, and standard formaldehyde solutions (used for calibration) are prepared as described in Methodology (ii).

Sampling and Procedure:

Two pre-weighed cotton dental swabs are inserted into the mouth of the subject under test. A position of comfort is selected for the swabs (usually beneath the tongue) with the object of absorbing the major secretions for a maximum of 45 s. The swabs are then carefully removed, avoiding any contaminations, and are placed into a stoppered flask containing 50 ml of distilled water. The flasks are then incubated at 40 C for one hour. A 4.0 ml aliquot of this solution is pipetted into 5 ml of the acetylacetone reagent. A blank is also prepared using a standard formaldehyde solution. Both samples may then be incubated at 40 C for 30 min. The absorbence of the test and standard solutions are measured against a reference solution prepared using 5 ml distilled water and 5 ml acetylacetone solution. The formaldehyde in the original swab may then be calculated. The results can either be expressed as the quantity yg of soluble formaldehyde per gram of sample or as ppm of free formaldehyde in the saliva by reference to the calibration curve.

Development of the Procedure:

We have found that although the 'cotton bud' type of swab was of considerable practical convenience, largely because of the wooden or plastic stem, the weight of cotton that is present is too small for our purposes. Initial experiments showed that the 'bud' could be used in much the same way as a clinical thermometer, and indeed the positioning and timing of forty five seconds were similar to the technique of temperature measurement. In the early work formaldehyde was shown to be present in the buds

following the test procedure as described. Reproducibility of the results of successive tests however, turned out to be a problem. This was thought to be on account of the over-saturation with fluid of the relatively small amount of sterile cotton present, which later work confirmed. It became necessary to use a weight of material equal to approximately 1 g in each test. The dental swab, though slightly more cumbersome in use, was found to be ideal for this purpose, each swab weighing 0.6 g and being manufactured to remarkably constant weight and quality of materials. We believe that when correctly positioned, two swabs give a representative absorption of the salivary constituents present in the mouth at the time of the examination. In our experience, based on the comments of a number of subjects, a more exaggerated salivary flow is brought about when the swab is positioned in a semi-circular configuration at the root of the tongue. A downward pressure from the base of the tongue in this situation serves to reduce the natural urge of the subject to swallow, also diminishes the slight feelings of nausea experienced by one or two individuals, during the test sequence. We have found that if the swab is in position for between 30–45 s the subject's mouth is generally dry, and major secretions have ceased. Equally over this time-course very few complaints of discomfort have been mentioned by participants, and the swabs are dry enough to remove quickly without being over saturated with saliva.

Formaldehyde as a Urinary Constituent

Antibacterial formaldehyde has been used in the treatment of urinary infections and may be released at the site of action by means of hydrolysis of e.g. methenamine mandelate following oral dosage. Studies by Tsun-ming Chen and L. Chafetz 1972 have successfully demonstrated the possibility of following the course of such hydrolysis with varying dosage of the methenamine preparation. In principle their work was based upon a selective determination of free urinary formaldehyde by means of the Hantzsch reaction with acetylacetone and ammonia. Some of the analytical criteria are those associated with the pH of the urine, its concentration and the ambient temperature of storage after voiding. The presence of proteins under certain conditions will change the formaldehyde concentration, as do reactions involving urea to form monomethylolurea, and other derivatives of this type.

Reagents:

Details of the preparation of the Nash reagent and standard formaldehyde solutions (used for calibration) are discussed in Methodology (ii).

Sampling and Procedure:

The volume, pH and temperature of the urine is recorded on voiding. One half of the sample is immediately diluted to a ratio of 1:10 parts of distilled water. The remaining half is stored intact at ambient temperature for separate assay. A convenient volume (approx 200 ml) of the diluted sample is incubated at 0 C for eight hours or over-night. Into three 25 ml stoppered flasks is pipetted 10 ml of the chilled sample, 10 ml of undiluted urine and 10 ml of standard formaldehyde solution. In a separate assay the possibility of interference from the presence of protein in the urine is assessed. If this is found positive each of the three flasks can be treated with 2.0 g of solid mercuric chloride and mechanically shaken for 10 min.

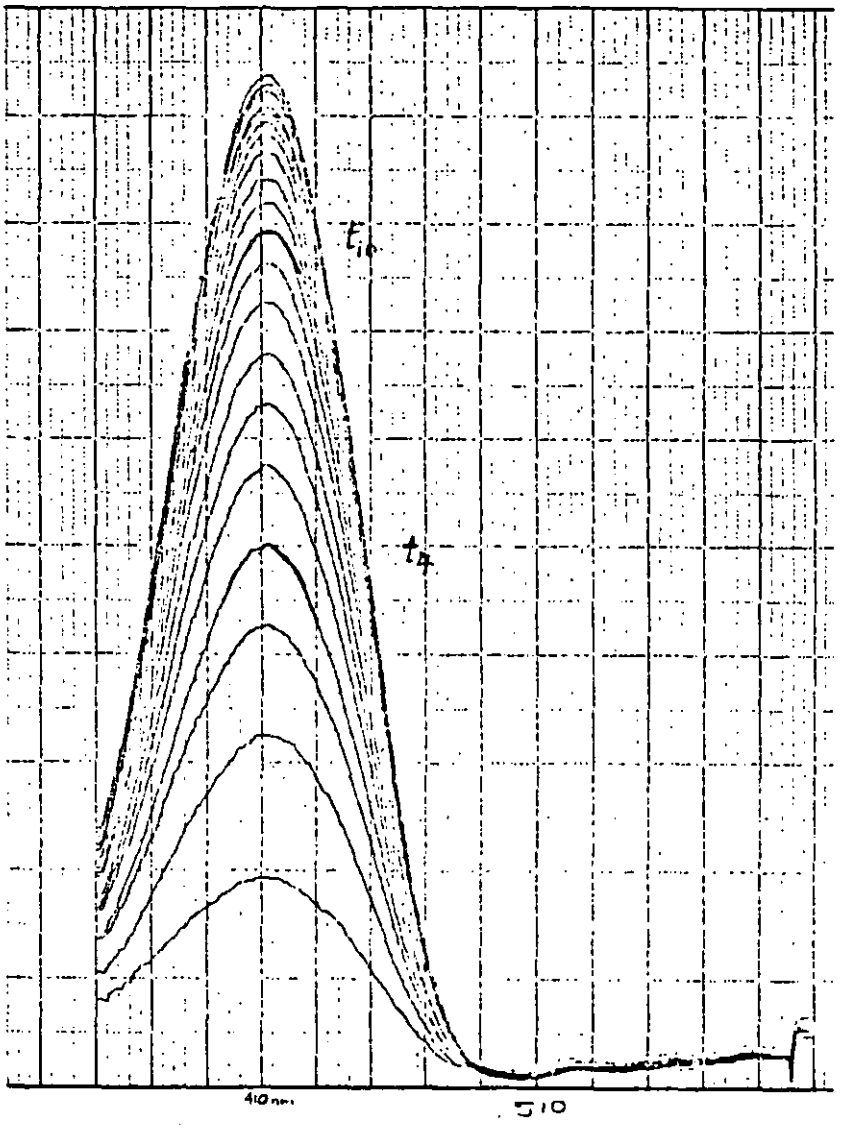
The mixture is then filtered and 1.0 ml of each of the filtrates is transferred to an analytical flask to which is added 5.0 ml of Nash reagent. Incubation at 40 C is carried out followed by cooling to room temperature. The absorbence of the two samples together with the standard formaldehyde solution and reagent blank are determined in a spectrophotometer. The level of formaldehyde may then be calculated and is expressed as µg or ppm by reference to a pre-prepared calibration curve.

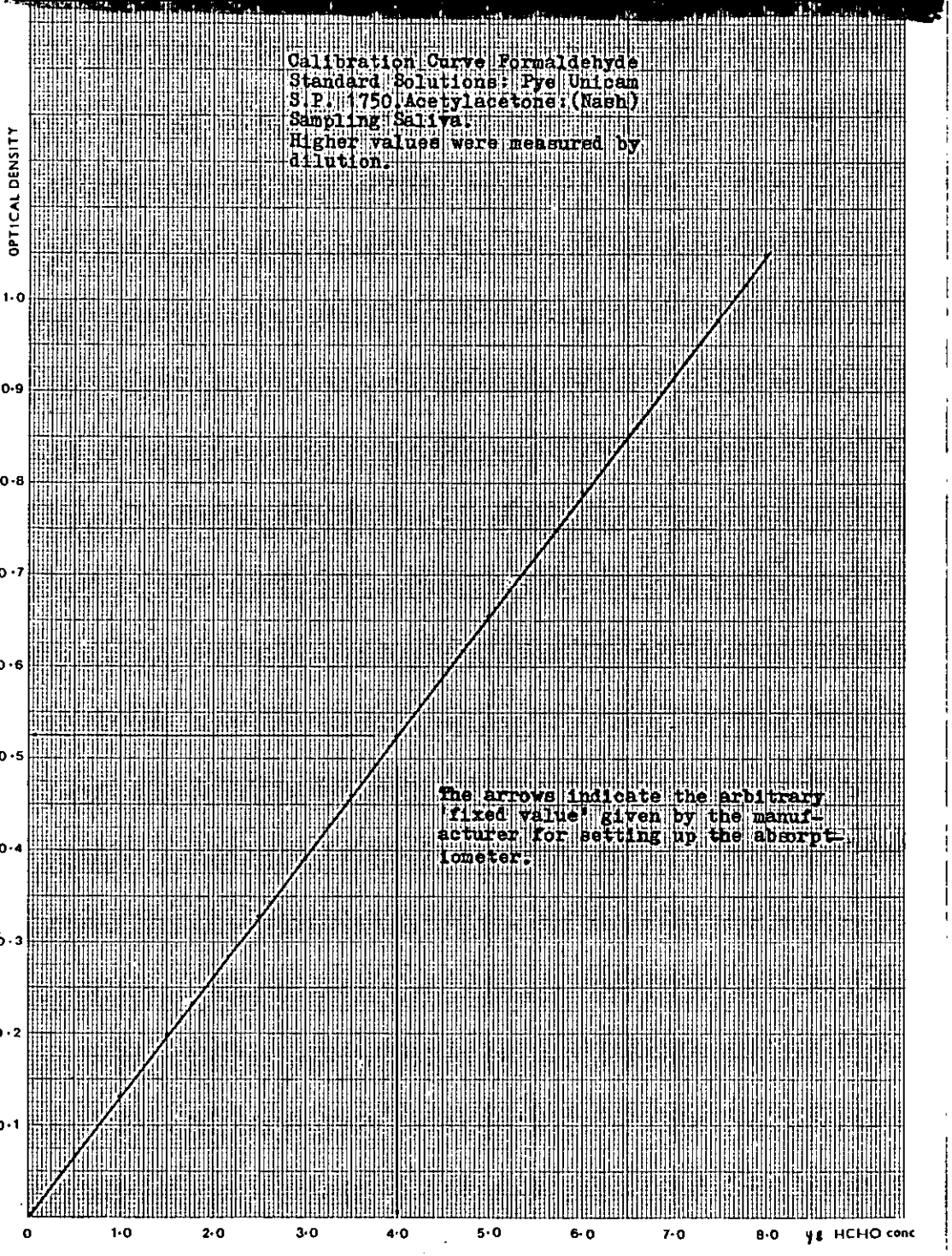
Application:

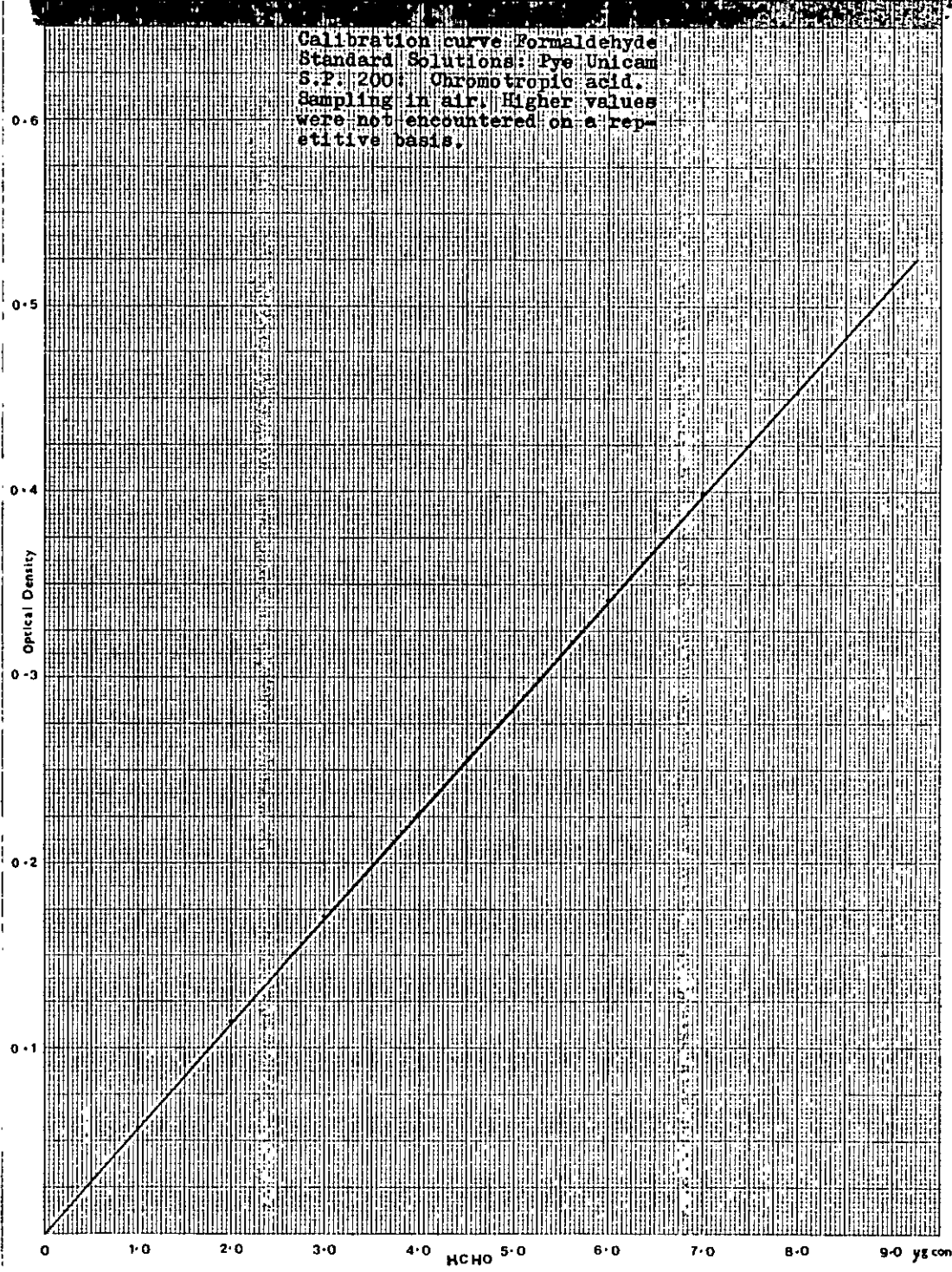
The work of Jackson and Stamey 1971 and of Greenfield 1969 have indicated the need for immediate analysis on freshly voided urine. Research by Miller and Phillips 1970 stressed the time and temperature dependence on formaldehyde degradation rate, and Grebe 1967 has described the effect of interference from other chemical agencies. From whatever source formaldehyde as a free material can be characterised in the urine. Much of the research hitherto has been concerned with the therapeutic advantages of products designed to release formaldehyde following partial hydrolysis in the urinary tract. The extent of hydrolysis most usually being a function of the acidity of the urine. Formaldehyde measurements have been hampered by the fact that methenamine itself interferes with the determination. Clearly in the case of a healthy subject being examined following

environmental exposure, no such drugs would be present. There is, however, some physiological interferences from proteins as described by Crebe. Although this is not universally so it is wise to assess any potential interference of this kind by appropriate separate assay. Should it be necessary, interference from proteins can be masked quantitatively by reaction of the urine sample with mercuric chloride. The importance of immediate dilution to the analysis becomes apparent when noting the difference in absorbence readings between the dilute and concentrated samples as assayed. The major solid component of urine being urea, the formaldehyde loss would be expected to be directly compatible with the urea concentration. This being accounted for by Crowe and Lynch 1949 in their studies of the formation of urea and methyol derivatives. A practical technique has been developed which will reliably assay formaldehyde levels in the urine and which can be easily adapted to automatic methods of analysis.

The figure below is a general illustration of the colour development in a formaldehyde/acetylacetone solution. The traces have been superimposed at five minute intervals to demonstrate the stability of the measurement over a time course of one hundred minutes.




Calibration Curve Formaldehyde
Standard Solutions: Pye Unicam
S.P. 1750 Acetylacetone (Nash)
Sampling Saliva.
Higher values were measured by dilution.
The arrows indicate the arbitrary 'fixed value' given by the manufacturer for setting up the absorptiometer.
OPTICAL DENSITY
1·0
0·9
0·8
0·7
0·6
0·5
0·4
0·3
0·2
0·1
0
1·0
2·0
3·0
4·0
5·0
6·0
7·0
8·0
µg HCHO conc


Calibration curve Formaldehyde
Standard Solutions: Pye Unicam
S.P. 200: Chromotropic acid.
Sampling in air. Higher values were not encountered on a repetitive basis.
Optical Density
0·6
0·5
0·4
0·3
0·2
0·1
0
1·0
2·0
3·0
4·0
HCHO 5·0
6·0
7·0
8·0
9·0 µg conc

CHAPTER

VIII

DISCUSSION

OF

RESULTS

i) Adaptive Tolerance in Man

ii) Aspects of hyper-sensitivity and dermatitis

iii) Effects of repeated exposure

iv) De-sensitisation mechanisms

FORMALDEHYDE LEVELS IN THE SALIVA AND CORRESPONDING LEVELS IN URINE

Staff Ident/Sample		Times of Exposure (Hours) 1·5	2·25	3·0	3·75	
A	(S)	0·026				
B	(S)	0·019				
C	(S)	0·029				
A	(U)		0·009			
B	(U)		0·007			
C	(U)		0·011			
A	(S)			0·034		
B	(S)			0·023		
C	(S)			0·027		
A	(U)				0·016	
B	(U)				0·011	
C	(U)				0·008	O.D.

Adaptive Tolerance in Man

In assessing man's adaptive tolerance to the type of environments commonly found in industry it is worth considering the homeostatic responses in such circumstances. Research on man creates special problems as the standard measures of e.g. adaptive limit cannot be assessed except by very lengthy epidemological study. In terms of body function however two courses are possible. One, metabolic in the sense of producing an unusual population of metabolites, the other homeostatic in inducing a temporary and in most cases a reversible acclimatisation. It was thought a further understanding of formaldehyde metabolism might be possible if an index or time scale could be established for the later event.

Sequential tests were arranged on the basis of selected salivary sampling throughout the course of a shift followed at appropriate time intervals by urinary testing. Some of the results obtained are shown in the table opposite, in which it will be seen that from the start of the shift a period of ninety minutes was allowed to elapse before the salivary samples were taken, and a further forty five minutes before the urinary samples were collected.

The actual volume of urine collected varied from between 44 ml and 100 ml at a pH of 5.5.

The samples obtained were immediately diluted with distilled water in preparation for analysis according to the procedures discussed in Methodology section (iv).

Aspects of Hypersensitivity and Dermatitis

The skin in its role as a protective organ relies mainly on the intact epidermis to provide an effective barrier against invading organisms. Cutaneous absorption being thought of as requiring specialised cell transport, as well as simple diffusion through the stratum corneum. The tactile sensory organs may also have a role in the selection and setting up of protective or interferring membranes, and are influential in reflecting sensitivity. In reviewing the literature it is clear that inhalation of formaldehyde will cause allergic dermatitis in hypersensitive subjects at 10 ppm (or below), following very brief exposure. Additionally when the skin is allowed to come into contact with formaldehy directly a similar response is observed. A subject's wet hands in contact with air containing 10 ppm can give rise to skin surface concentration of the order 0.16 ppm. In general, levels of 2% and below, following repeated skin contact, will bring about a sensitisation reaction in most individuals.

A factor which led to the discontinued use of formaldehyde solutions as topical antiseptics. In textile materials the reports of allergic reactions to common finishing chemicals are numerous. Estimates of the free formaldehyde levels which bring about such a response are between 0.027 and 0.75% Beerens, Young and Jansen 1964.

The repeated use of facial tissues have been reported to give rise to dermal sensitivity, Peck and Palitz 1956, particularly of the face and neck. Such sensitivity was also reported by the Eurotox symposium on cosmetics in 1961, the maximum levels of formaldehyde in cosmetics being set at 0.05%. This was also regarded by Beerens et al as the level of

formaldehyde in the clothing below which dermatitis was unlikely to be produced. Positive patch tests have however been obtained with 0.03% solutions and much lower concentrations, and indeed it is difficult to specify a level which will not produce dermatitis in a hypersensitive individual. Allergic contact dermatitis has been reported in patients receiving orthopaedic treatment using plaster casts incorporating Melamine-formaldehyde resins, Wharton and Levinskas 1976. The skin reactions being generally apparent within one week, and being found attributable to a free formaldehyde content in the plaster of 0.01-0.03%. The patients in the survey reacted positively to patch tests with formaldehyde solutions and to ten day old resin strengthened plaster, but not to freshly prepared plaster; supporting the diagnosis of contact dermatitis. It is in this latter area of formaldehyde contact particularly in respect of items of apparel that our observations were made. The question of the need to use formaldehyde containing resins in textile finishes, and the current legislation was discussed in a previous chapter. The two key factors are, product performance and resin formulation. The hoped for minimum international standard being placed at a level of 75 ppm, though the European standards are less rigorous than those of America and Japan.

Experimentally the amount of formaldehyde contained in a fabric finish is the sum of the formaldehyde present in the resins themselves, together with that which can be formed by selective reactivity and decomposition during and after processing.

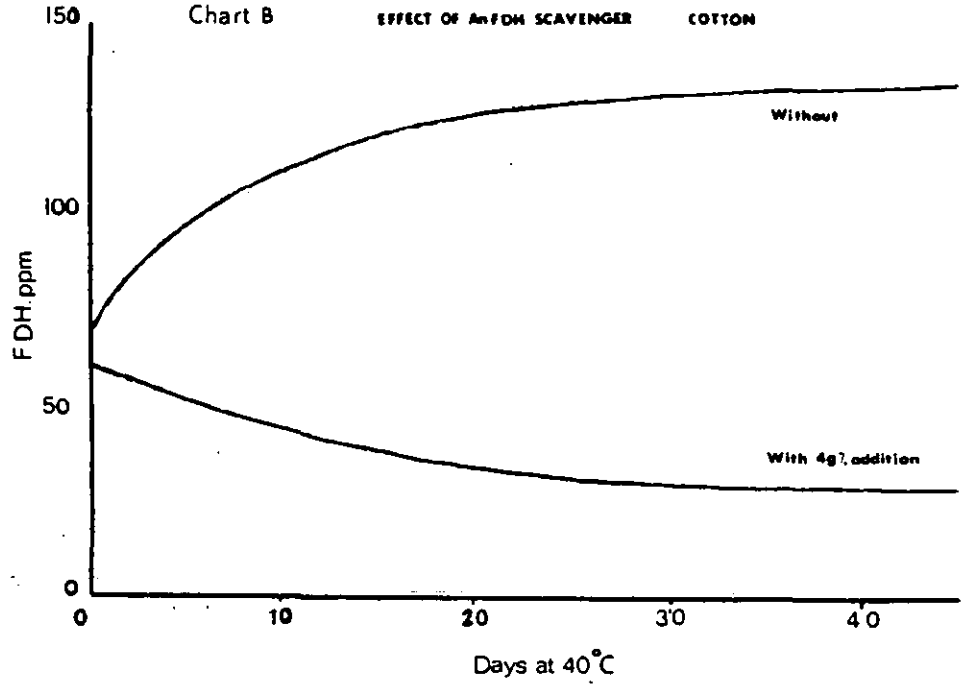
In order to accomplish a low free formaldehyde finish strict attention must be paid to the methods of application, catalyst and curing conditions. In commercial practice many techniques have proven satisfactory, but on examining the level of free formaldehyde in the fabrics, excessively high residual values are found. Thus at the skin-formaldehyde interface there is likely to be present residues of methylolamine, dicyandiamide, and free formaldehyde. In these circumstances, as shown by Overton and others, the presence of a polar substance will encourage membrane permeability changes. In the case of human red cell membranes, it has also been shown that the degree of chain branching of the lower molecular weight polar

substances influence penetration Naccache and Shaafi 1973. The difference, which is known to be large between various tissues is probably a consequence of lipid packing. In terms of the membranes of the skin, the total disruptive effect could be sufficient to destroy the protective characteristics of the epidermis.

Barrier creams are commonly used in many industrial processes to good effect. Any system which allows the functional integrity of the cutaneous membranes to be maintained is of value. Unfortunately in the case of formaldehyde there is unequivocal evidence to suggest that contact sensitivity can give rise to systemic rashes, which in turn can be induced by inhalation exposure. The table adjacent shows a typical range of resins and the corresponding free-formaldehyde levels detected in the respective finishes. For reference purposes high volume products have been identified with an asterisk. In the sample reference key the formula identification is also given together with the company who markets the major proportion of the product. As wider range as possible of cloth constructions were examined particularly those fabrics which were to be made-up into bed sheetings.

It is clear that the general level falls short of the target value of 75 ppm. Nonetheless these finishes and fabric types are in common use Patch tests on a number of the formulations employed did cause irritations on sensitive subjects. The patch test procedure is described in methodology section (ii). During the tests two particular subjects were found to be hyper-sensitive and it was possible to illicit a response from these individuals in less than the period of a shift. The effects for the most part may be described as a reddening with irritation, but giving rise to considerable personal discomfort. Further experimental work was directed towards reducing free formaldehyde by formulation adjustment and control of finishing temperatures. The greatest improvement was obtained by using a cure temperature of 160 C. This can be seen by reference to chart (A) following.

The effect of the use of a formaldehyde scavenger as in chart (B) emphasises the stability of the resin system following storage. Unfortunately acid conditions will bring about re-formation of formaldehyde in very high yield.



Experimentally, the best results and most durable effect from an additive, in terms of reducing free-formaldehyde was obtained using silicone polycarbynols as shown below.

FREE FORMALDEHYDE WITH THE ADDITION OF SILICONE DC111

Sample Ref	Silicone %	Free Formaldehyde
DC/1/UF	2.5	153.0 ppm
DC/2/UF	2.0	122.8 "
DC/3/UF	1.5	126.8 "
DC/4/UF	1.0	71.5 "
DC/5/UF	0.5	61.8 "

FREE FORMALDEHYDE LEVELS IN TEXTILES SOME COMMON FINISHING - FORMULATIONS

Sample Ref and Source	Resin Type and Composition %		Free Formaldehyde
A/BIP/FF01* Pendle Velvet	U/Form	40	1098.6 ppm
	Melamine	60	
B/BIP/FF02	U/Form	100	1229.5 "
C/BIP/FF03	Reactant	60	
	U/Form	40	1214.2 "
A/CRS/AA01 Crossfields Polyester	Reactant	85	
	Filler	15	402.9 "
B/CRS/AA02	Reactant	85	
	U/Form	15	514.7 "
A/CV/01 Dorma Ser II* and Ser IV	Reactant	70	
	Melamine	30	702.2 "
B/CV/02	Reactant	70	
	U/Form	30	1005.8 "
V1/COU/04 Courtalds * (M & S)Cotton	Urea-Form aldehyde	80	545.8 "
	Melamine	20	
V2/COU/05	Reactant	80	
	U/Form	20	415.0 "
V3/COU/06 *	Reactant	90	
	U/Form	10	443.0 "
PV/BIP/COU/6 Development	Mod/Ret	70	
	Melamine	30	363.0 "
PV/BIP/COU/8	Mod/Ret	100	262.0 "
514. Fast.BIP	Mod/RFC	100	80.0 "

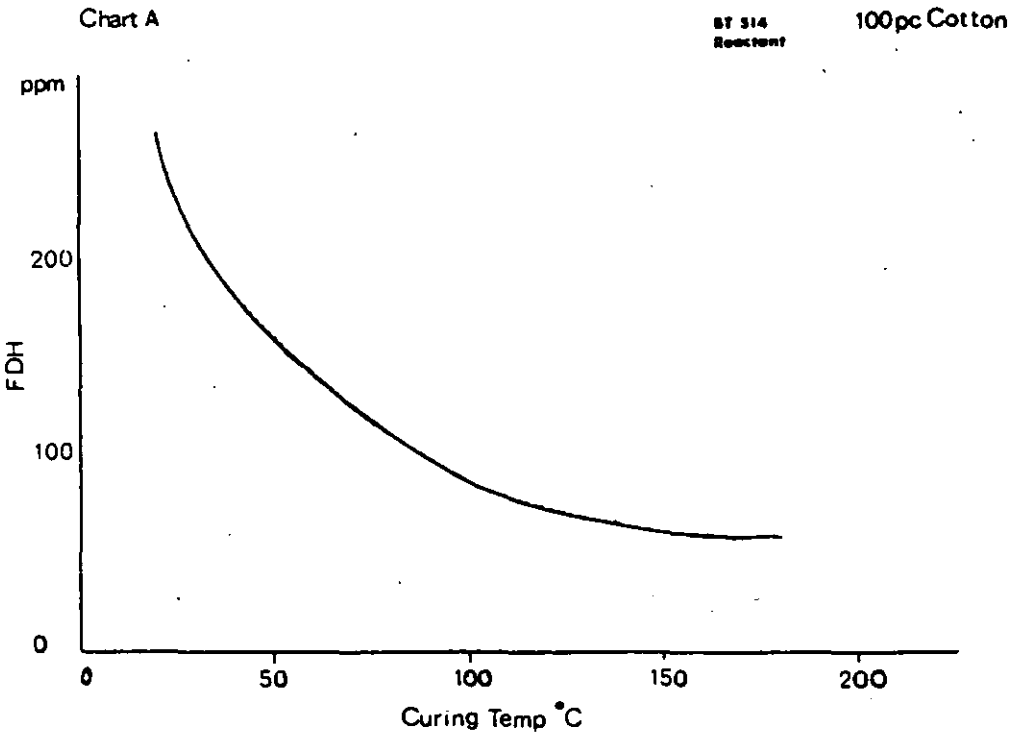


Chart A
ST 514
Reactant
100pc Cotton
ppm
200
100
0
FDH
0
50
100
150
200
Curing Temp °C

A variety of silicone types were examined but a distinct advantage was noted with a Dow Corning product (Ref: D.C. 111). It was found unnecessary to separately catalise the silicone system with this material thereby considerably reducing the complexity of the finishing procedure in the works. Subsequent plant trials (on a production scale) indicated that a worthwhile reduction in free formaldehyde could be obtained with 0.25% additions, the best optimum level however was found to be 0.6% on 100% cotton fabrics. Heavy-weight fabrics such as velvets required up to 1.8% additions before patch tests failed to illicite a skin reaction from those subjects designated as hyper-sensitive in previous experiments. In order to determine the possible threshold of effectiveness of silicone additions, the total % addition was progressively reduced using similar fabrics to those used in pilot production runs. The results are shown below.

FREE FORMALDEHYDE WITH THE ADDITION OF SILICONE DC111 PROGRESSIVE REDUCTION

Sample Ref	Silicone %	Free Formaldehyde
DC/7/UF	0.50	39.7 ppm
DC/8/UF	0.25	72.4 "
DC/9/UF	0.20	58.3 "
DC/10/UF	0.15	94.1 "
FC/OA/UF	Zero	553.5 "
FC/OA/RT	Zero	345.1 "

It was evident that by suitable additions to the resin formulations an effective means could be found to maintain a free formaldehyde level below the suggested maximum of 75 ppm. More importantly perhaps from the commercial point of view, the substansiveness of the finishes proved to be excellent.

Further work on the control of chemical properties of resin systems was not conclusive. It was not known if the silicone was contributing to stable polymer architecture, or simply acting as an absorbing media for formaldehyde. Subsequent molecular weight determinations by Dow Corning on the cured materials suggested that the silicone may be acting as an initiator-promoter during the cross-linking stage of the systems

polymerisation. The chemical composition of the resulting matrix being characteristic of a coating resin, but with the added properties of flexibility and substansiveness, both vital for commercial success.

Technically the applications of silicones can be expensive although it is easily shown that an effective reduction in free-formaldehyde can result. Cost, in this context can only be off-set by high volume markets for the products, examples of which are bed sheetings and lingerie. The most important aspect is protection of the would-be hypersensitive individual from the effects of chemical irritants. The fact is, that although technology is available whereby all the necessary aesthetic properties can be imparted to fabrics, only those which are valuable at point of sale are considered essential. Fortunately legislation is beginning to force manufacturers to take account of community health, with encouraging results. Currently the more expensive ranges of bed linens are finished with silicone additives, a move which has effectively reduced complaints of irritations and offensive odours, and has greatly improved wash-wear performance.

Our experiments with bed sheetings using hypersensitive volunteers showed no irritations at a residual level of free formaldehyde of 150 ppm. A transient reddening effect was on some occasions recorded however. Four other subjects within this group suffered no discomfort or ill-effects following prolonged periods of contact with the fabrics. Some of the sheetings used as blanks in the experiments contained residual formaldehyde levels of over 1,200 ppm, very little discomfort being reported during their use. The major exceptions were complaints of odour and slight reddening of the chin, face and neck, the latter disappearing rapidly when contact with the fabrics ceased. The fact that silicone additives, at a quantifiable level appeared to impede the effects of formaldehyde on the skin was interesting. Particularly as the reology of the resin formulations were virtually un-altered. Several mechanisms were possible which might explain the phenomenon the simplest of which was the concept of a barrier layer. In this case it is conceivable that a protective surface is set up at the inter-face of skin and fabric and with an electrical neutrality which helps to maintain the functional integrity of the dermis. The system is complicated by the fact that

following pre-cutaneous absorption of aldehydes and their simple derivatives very deep penetration into the tissues can occur. This is characterised by the formation of labile complexes with proteins which are often stored in the stratum corneum which acts as a reservoir for several days. The often seen 'delayed response' in some workers who are exposed to high concentrations of formaldehyde may well fit this pattern although cross-sensitivity with other chemical irritants cannot be discounted. The problems associated with hypersensitivity are obviously apparent, and we are convinced of the connection between this effect and the ionic inversion of the eccrine secretions in certain individuals. In terms of general sensitivity the chance of developing allergic contact dermatitis varies with the site of contact and of application. It is important to appreciate however that once a subject's skin has been sensitised to formalin solutions by contact, then systemic absorption, for example from the tidal air, will provoke a skin eruption. The latter may be seen to resemble the original contact dermatitis but is usually far more wide spread, a sequence of events commonly witnessed in the course of our own observations.

The Effects of Repeated Exposure in Man

Information on the effects produced by prolonged repeated exposure to low airborne concentrations of formaldehyde have been evaluated.

The current United Kingdom Threshold Limit Value (TLV) of 2.0 ppm in the working area is reviewed in the light of data obtained from different occupational groups. The clinical findings from results of bio-chemical tests on samples taken from each group are also examined.

The odour of formaldehyde is easily perceptible, particularly to previously unexposed individuals at concentrations varying from one individual to another but generally at or below 1.0 ppm. The lowest concentration at which formaldehyde has been perceived by odour is known to be 0.06 ppm. Although perceptible at this level it does not necessarily signify a health hazard, studies defining the odour threshold serve as an indication of environmental concentrations which are below the threshold of irritation. An annoyance may occur at any concentration, at or above the odour threshold, and in most cases below the TLV.

When inhaled at massive concentrations formaldehyde has caused pulmonary oedema and death, while at concentrations of between 0.5 and 11.0 ppm it has produced sensory irritations of varying severity. In the guinea pig it has been demonstrated that transient alterations of airway resistance occur following exposure for 1 h at 11.0 ppm, but which disappear after removal from the atmosphere, but which persist if the concentration is above 49.0 ppm. Immediately reversible airway resistance changes were noted following the exposure of guinea pigs to 0.31 ppm of formaldehyde for 1 h. In the presence of a sodium chloride aerosol which acted as a carrier the same effect could be noted with concentrations as low as 0.11 ppm. Bearing in mind the susceptibility of the guinea pig to bronchio constriction the data appear to be in line with reported upper respiratory tract irritations in humans. Many investigators have indicated a diminishing ability to perceive the odour of formaldehyde following two-three hours exposure, but an increased awareness after return from a lunch break or overnight. Based on this type of data the TLV was reduced from 5.0 ppm to 2.0 ppm in 1976 by the Department of Labour OSHA in the United States. The United Kingdom and other countries following this example some two years later. As reviewed earlier the work of Morrill and of Bourne, provided evidence of sensory irritation in humans at concentrations of between 1.0 and 2.0 ppm. While documentation by international research organisations and health associations confirmed similar effects between 0.69 and 1.6 ppm. The work of Kerfoot and Mooney showed very convincingly that concentrations from 0.25 to 1.39 ppm provoked complaints from embalmers of intense irritation of the eyes and upper respiratory tract on prolonged exposure during a shift. At higher levels the volunteers of Schuck and Renzetti suffered severe and lasting effects following only a few minutes' exposure to concentrations of 4.0 ppm, and particularly so if often repeated. It is not unreasonable therefore to speculate that the present TLV of 2.0 ppm is based on the reactions of persons that have become de-sensitised to the presence of formaldehyde. This process of de-sensitisation and diminishing perception for the material could in our view be related to a biological pattern, or special sequence of acclimatisation by the body. If such an event were to be

quantifiable, then a definitive time-concentration relationship to exposure could possibly be established.

The goal of the TLV should be to define conditions under which it is believed that almost all workers may be comfortable, and repeatedly exposed without fear of adverse effects. If indeed an acclimatisation process is at work then a steady state of bio-tolerance will exist, in which case the presence of a hazard will become imperceptible to an individual. The present procedures by means of which the TLV is advocated for formaldehyde is undoubtedly designed to protect workers from any possibility of such happenings.

Equally, and quite correctly, it is assumed that if an area is monitored for formaldehyde by quantitative means, and the work-place is found to be below the TLV then that area is considered safe. Unfortunately this is only true in terms of the definition of the TLV as it currently stands.

Our experience dictates that the monitoring of air quality even during very short term exposure is subject to some variability, and must be viewed with caution. The reason for this appears to be intrinsic in the plant operations rather than in unreliable analytical techniques. The following tabulation illustrates in summary the range of values obtained when five different plants were studied between July and December 1978. Reference is made to sampling area, to frequency and technique, in Methodology dealing with estimation of formaldehyde in air.

THE WORK PLACE FORMALDEHYDE LEVELS IN AIR (JULY - DEC 1978)

Area Surveyed	Number Taken	Average Value	Percent Below TLV	Range of Values
Moulding Powders	99	1.5	72	0.2-6.9
Moulding Granulated	79	1.1	92	0.1-9.8
Resin Plant Coating	58	1.2	88	0.2-5.4
Resin Plant Aqueous	40	1.1	88	0.1-5.6
Spray Plant Dried	27	1.4	81	0.3-4.9

Site selection was done very carefully, particular attention being paid to those areas where personnel remained for long periods. Ventilation was by means of engineering control, the haphazard opening of door and windows being avoided where possible. It can be seen readily that in four out of five plants surveyed, over 80% of the values recorded are below the TLV. It is significant that the Moulding Powder plant has the highest values which is accounted for on the basis that large volumes of formaldehyde are handled and solvent evaporation occurs in this area. In common with the remaining plants the average value does not exceed 1.5 ppm however, and for the most part a level of below 1.2 ppm is maintained. It was found possible to identify high spots, but although predictable to some extent isolation proved very difficult. The occurrences were related to the loading and discharging of processing equipment, high level 'pockets' being detectable at between 4.8 and 13.5 ppm, the latter value being a singular exception however.

The survey examined specific areas of plant which were considered potential trouble spots. Additionally it was hoped to gain an impression as to the kind of work pattern that best fitted with the complaints that had been received from operative staff in previous months. The conditions in the plant areas were considered on the whole to be good, by reference to the TLV, but it was thought worthwhile to try to reduce the incidence of high level exposure. To achieve this a number of operative work patterns were altered, e.g. when the stills were charged, drying plant unloaded and during moulding trials. Also an attempt was made to control the movements of staff that had consistently complained of respiratory distress in designated areas. A further six months' systematic observation was then carried out between January and June 1979. The results are summarized in the table below. An increase in the number of samples taken will be noted, which was necessary in order to try to relate factory activity with the particular levels found. No correlations were discovered, which was thought to be due to the factory operations being programmed on a twenty-four hour basis. A minor exception was the loading bay which is much less active on the night shift. By comparison with the previous six months a clear improvement had been brought about in the general level.

THE WORK PLACE FORMALDEHYDE
LEVELS IN AIR
(JAN - JUNE 1979)

Area Surveyed	Number Taken	Average Value	Percent Below TLV	Range of Values
Moulding Powders	179	0.9	97	0.2-7.8
Moulding Granulated	186	0.9	98	0.2-4.4
Resin Plant Coating	100	1.4	84	0.2-7.8
Resin Plant Aqueous	78	0.8	99	0.2-2.3
Spray Plant Dried	63	1.0	92	0.3-4.1

This was particularly encouraging as the increased sampling was in the hope that any high spots and spurious levels would be detected. It is believed that one of the major factors which contributed to the improvement in air quality was the change in handling procedures for the drums of formalin and para-form. Also the number and methods used by personnel involved in the charging of stills and reaction vessels. Despite the fact that the overall average value of formaldehyde detected was 1.0 ppm or below, the incidence of complaints remained disproportionately high. It was accordingly decided that further efforts were needed to improve air quality. At the same time, as already referred to, a scheme of salivary testing was underway on a selective basis.

The further control of plant operations was brought about by introduction of the following measures.

i) Ducted air at the mouth of stills and reaction vessels.
ii) Air filtration in areas where dust might contaminate the breathed air.
iii) All formalin solutions were to be piped directly from the point of production into the processing receivers.

It was hoped by these means to considerably reduce handling and contact with formaldehyde solutions and bring down the detectable level to 0.5 ppm.

Plant operations were again studied for a period of six months between July and December 1979, together with salivary testing.

The table below shows the levels of formaldehyde recorded in air. The general improvement achieved was self-evident, frustratingly however the incidence of complaints from operative staff showed no significant fall. A further difficulty was that complaints of discomfort, particularly those of tearing* and respiratory spasm could not be associated with any trends in the data. Nor could specific episodes of high level pollution following leakage in the factory, be tied into a meaningful pattern of symptoms in an individual or group.

THE WORK PLACE FORMALDEHYDE
LEVELS IN AIR
(JULY - DEC 1979)

Area Surveyed	Number Taken	Average Value	Percent Below TLV	Range of Values
Moulding Powders	241	0.7	98	0.1-3.9
Moulding Granulated	190	0.7	99	0.1-2.3
Resin Plant Coating	109	0.7	93	0.2-4.5
Resin Plant Aqueous	83	0.5	95	0.2-8.3
Spray Plant Dried	41	0.7	100	0.2-1.1

It must be acknowledged that formaldehyde is omni-present throughout the factory and at a level well below that of the TLV. On the basis of the present work it would seem reasonable to suggest that this background level is between 0.5 and 1.1 ppm. Accepting that the level could rise by at least a factor of seven, the theoretical probability of exposure over the TLV is approximately 42%, averaged over all areas

* Crying or Tear-forming

surveyed. Such a situation leads inescapably to a reinforcement of the concept of individual acclimatisation. If this were not the case then the background level suggested would be sufficient to produce an alarming array of symptoms, and intolerable discomfort. It was considered important to examine the biological factors which apparently allowed this mechanism to operate, and particularly at the low intrinsic levels of formaldehyde that were known to exist. In the six months' period January to July 1980 this aspect was examined in greater depth as part of the overall monitoring of the same five factory areas. The table below shows the results.

THE WORK PLACE FORMALDEHYDE LEVELS IN AIR (JAN - JULY 1980)

Area Surveyed	Number Taken	Average Value	Percent Below TLV	Range of Values
Moulding Powders	170	1.1	85	0.2-5.4
Moulding Granulated	135	0.9	96	0.1-6.1
Resin Plant Coating	84	1.0	91	0.1-5.0
Resin Plant Aqueous	62	0.9	92	0.1-6.9
Spray Plant Dried	34	1.1	91	0.1-3.0

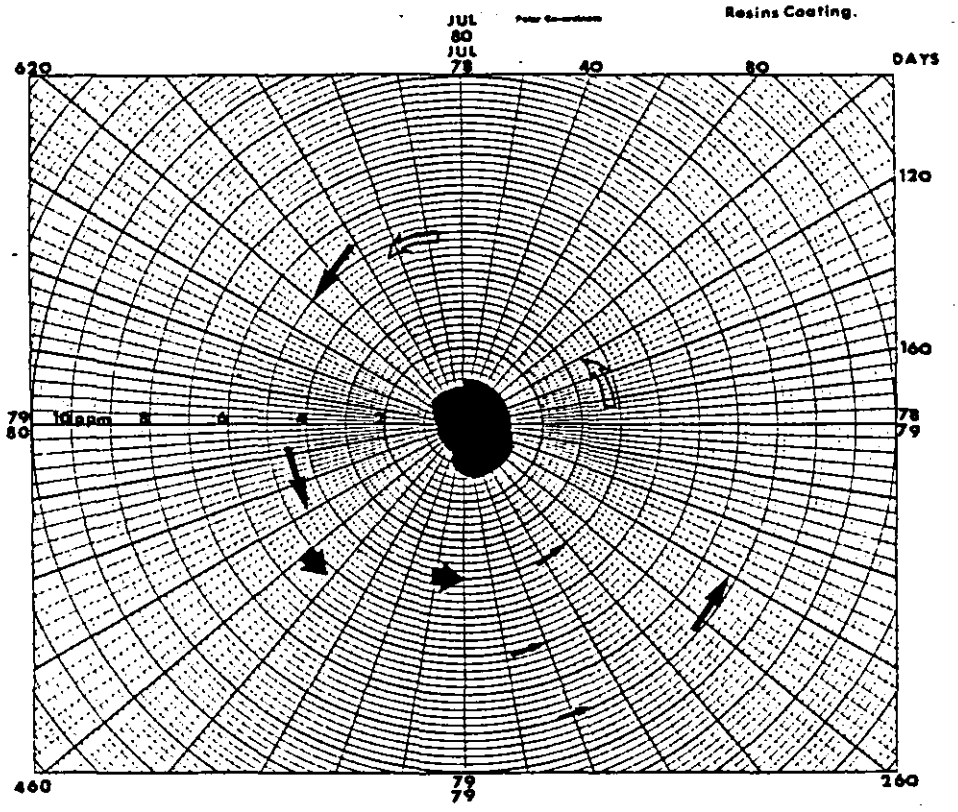
General supervision in the plant in relation to health and safety monitoring was made less obvious during this series of trials with a view to realistically apprising the effectiveness of the earlier measures. Clearly the overall levels are good but the trend is slightly in excess of 1.0 ppm. The effectiveness of the engineering control features that were introduced are very obvious however and their importance cannot be over-emphasised. Complaints from personnel were nominally at the same level during this period, and local atmosphere tests in the works environs showed no excesses. Of vital importance is the personal awareness of staff and operatives of the risks involved in handling formaldehyde without the proper protection. Some degree of habitual carelessness has been observed which probably stems from the lack of perception of the material, and hence an unawareness of the hazard. Unfortunately such incidents are a very major contributor to the pollution of the working areas. Nonetheless definitive

improvements can be made following the application of engineering and supervisory controls. In the adjacent chart and those that follow the complete series of observations are illustrated.

Each six month period is represented by one quadrant, overall levels of formaldehyde by the dark shaded area and the TLV by a broken line. Excessively high concentrations, following leakages, are shown with an arrow. It was found that in normal circumstances high concentrations built up slowly but relatively infrequently. Clearly, accumulations are a consequence of ineffective plant ventilation and it has been our experience that concentration pockets can easily be dispersed by improving air-circulation with portable equipment. To some extent it is possible to create cumulative effects by reducing overall air movement in the factory the eventual site of accumulation being reasonably predictable. At customers' installations the problems are more acute however, accumulations occurring at certain shift times and positions in relation to processing equipment.

Plant design and the performance of such equipment has a very great bearing on the prevailing environment. Unfortunately it is simply not possible to ventilate all areas adequately while simultaneously maintaining personal comfort. This is the main reason why continuous monitoring of customer premises is strongly advocated by manufacturers of formaldehyde containing materials. Drager tubes and other simple colour-comparative methods being used in the absence of the more sophisticated spectrophotometric procedures. The most basic objective of any scheme being to identify those regions of highest potential risk. We have found the Drager tube most useful for spot checking, but would advocate their use to detect sudden changes in air quality rather than to indicate a safe working environment. In general our experiences suggest a better and more reproducible performance at levels above 5.0 ppm rather than those at or below the TLV level.

In attempting to encompass the value of air monitoring in manufacturing industry it is essential to view the technique and results in proper perspective. Air monitoring should be regarded as a tool by means of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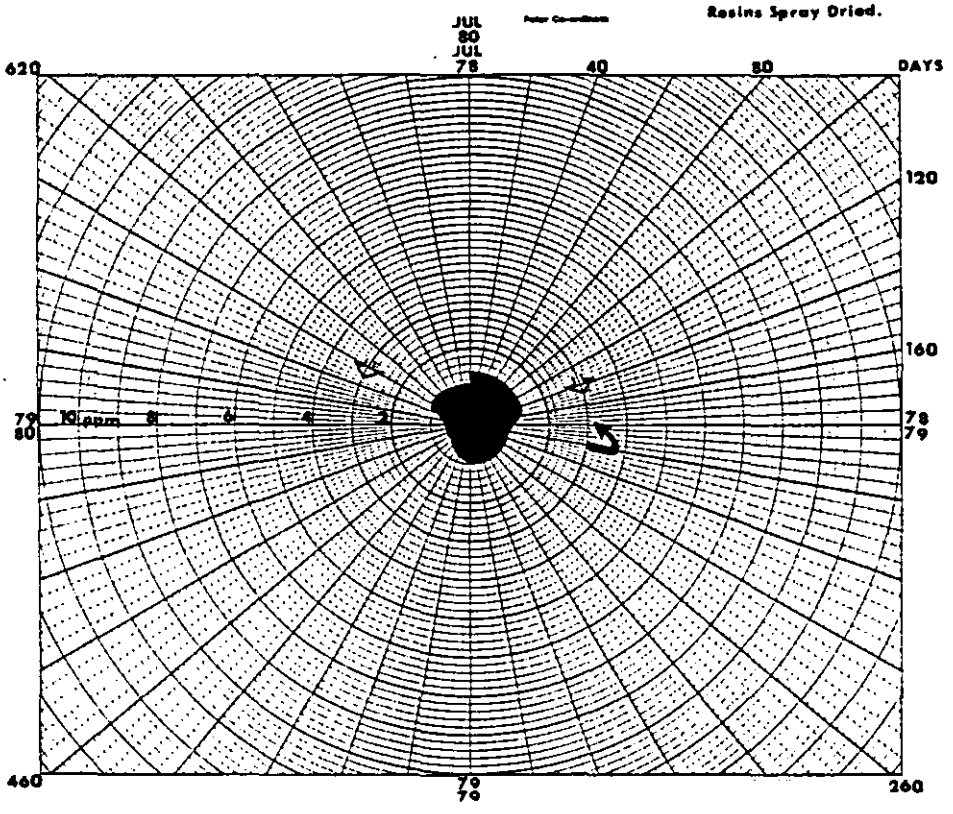
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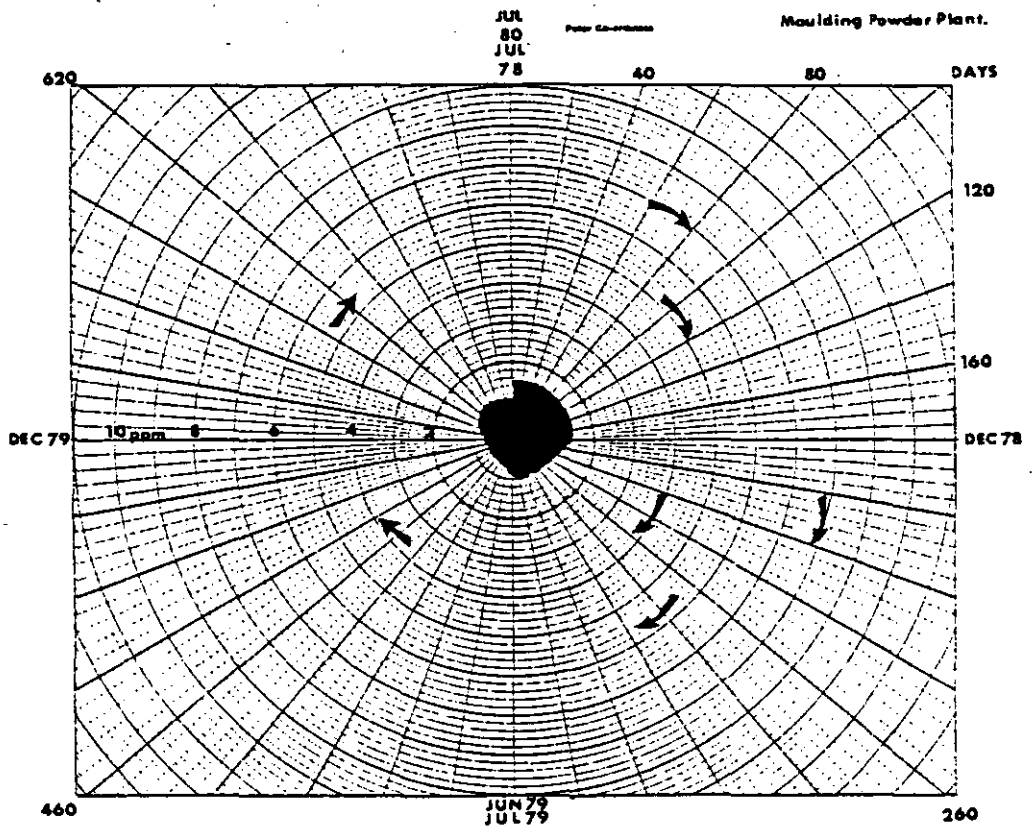
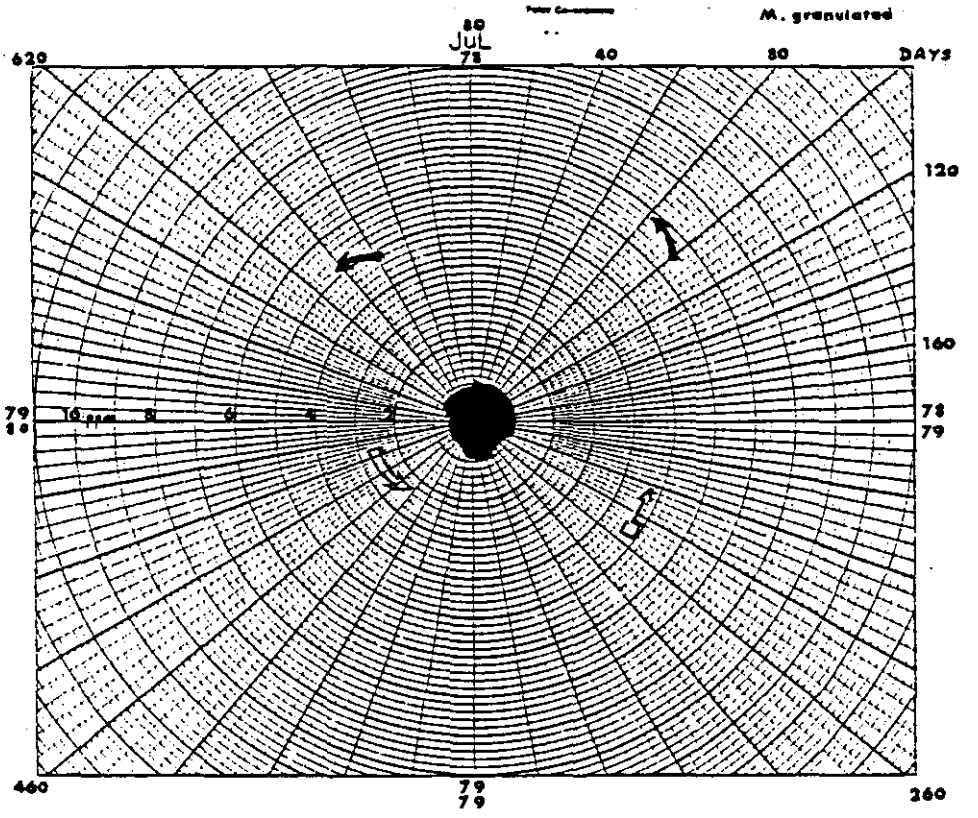
THE WORK PLACE FORMALDEHYDE LEVELS IN AIR SUMMARY CHARTS

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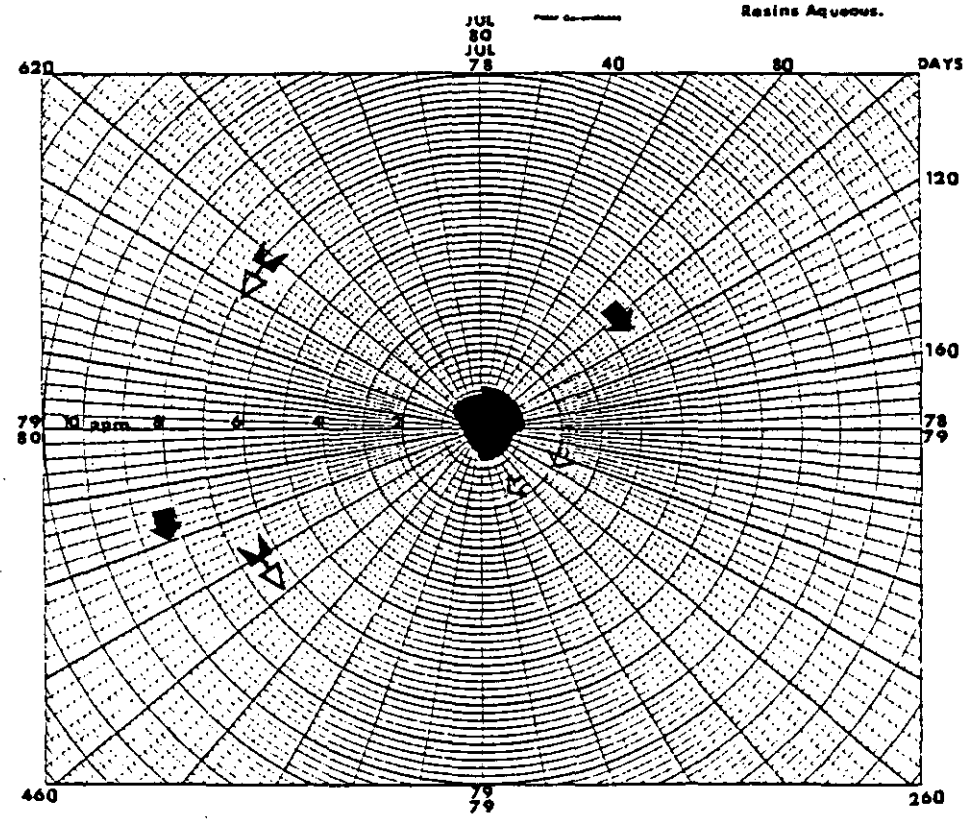
Resins Aqueous.
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which the effectiveness of engineering control of plant conditions can be judged. Evaluation and critical measurement of these factors represents the best investment in safety, rather than assessing a level of pollutant against an arbitary standard. The ultimate goal must be clean air, and not air that is polluted to the permissible level.

We are convinced of the improvements possible by paying the proper attention to air movement in the factory and to the value of monitoring schemes. Personal commitment of all operative and supervisory staff to safe-handling of materials is essential. Our belief is that the TLV remains inappropriately high and is seemingly advocated for a level of adaptive tolerance rather than for the protection and comfort of the exposed worker. We are led to the conclusion that adaptive tolerance must be a form of consequential acclimatisation and that a mechanism exists which protects all but the hyper-sensitive. Our evaluation of salivary and urinary specimens in exposed workers lends support to this view.

De-sensitisation Mechanisms in Man

From our work there is evidence of a pattern of diminishing sensitivity to somatic discomforts and to odour perception in environments containing formaldehyde at levels of 0.8 - 2.0 ppm suggesting a process of adaption. The mechanism leading to what has become known as an acclimatisation in man is likely to be a finely tuned sequence of biological events which are triggered immediately by exposure. This type of acclimatisation is not a lasting phenomenon as it can be demonstrated that on leaving a contaminated area followed by a return some time later, involves a new period of re-adjustment to the conditions. The magnitude of the eventual acclimatisation or tolerance may appear to be greater than it was previously, and in many cases to be arrived at more quickly. The route of entry into the body of any toxic material governs the level of absorption. Thus via the oral-nasal route a soluble gaseous contaminant such as formaldehyde, transported in the tidal air could reach the blood-brain barrier in twenty to thirty seconds. By other pathways, such as gastrointestinal absorption in twenty to thirty minutes, and by cutaneous absorption in four to five hours. If acclimatisation to formaldehyde is viewed as a progressive accumulation of the free material in

the body fluids then a quantitative mechanism for the phenomenon should exist.

In studying the human responses to low level formaldehyde exposure in manufacturing areas a number of personnel were selected for tests on saliva. Initially a group of six volunteers were chosen, three men and three women, each of whom only rarely came into direct contact with formaldehyde. None of this group being involved in plant operations of any kind. It was proposed to identify the threshold level detectable in salivary specimens and if possible establish a definitive zero point in analytical terms for quantitative measurement.

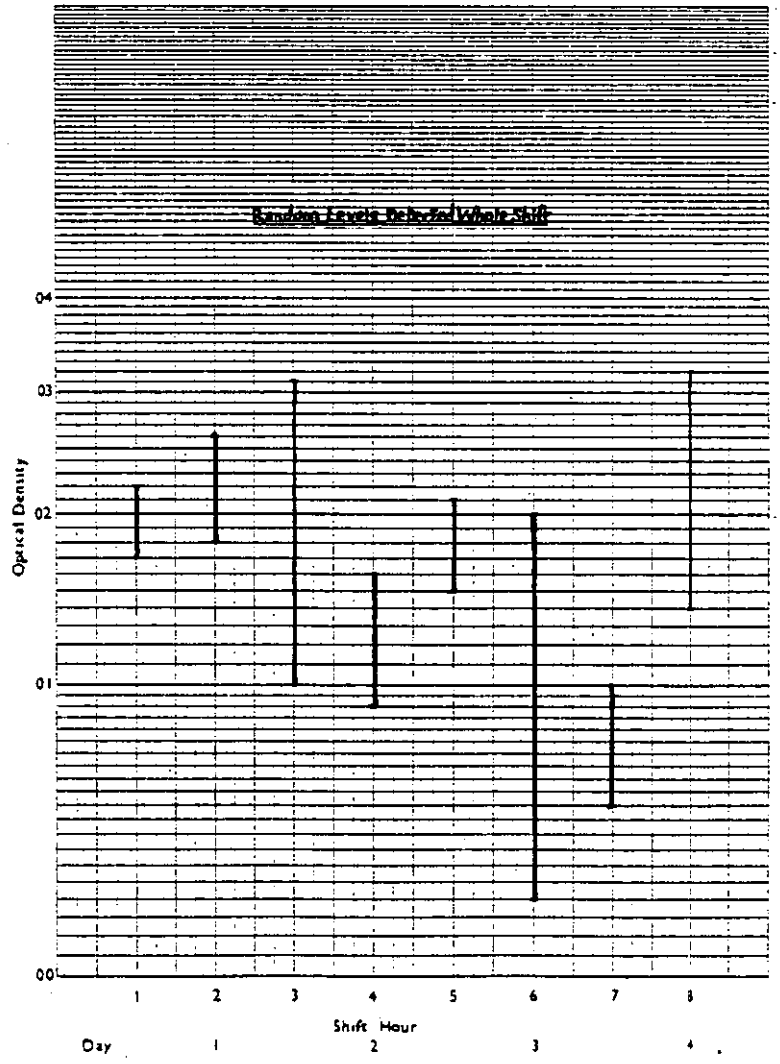
The procedure adopted for the collection of samples of saliva are those discussed in Methodology dealing with salivary sampling and analysis.

It was found that general office workers and technical staff on site showed no detectable formaldehyde presence in salivary samples, which was also confirmed when sedentary workers away from the plant installations were examined. It was established that formaldehyde solutions gave a constant assay over a period of several days using distilled water as the dilutant. Samples of saliva were diluted and stored for various periods of time with and without reagents. All salivary specimens gave a constant assay value up to six days and the transfer from cotton swab to dilutant did not interfere with the analytical results, or instrument sensitivity.

It was decided that five staff members, three normally involved in operative supervision in the plants and two from the control laboratories should be sampled. The specimens were to be taken initially on different days but sequentially in respect of the eight hour shift. The tests had the object of discovering if the ambient level of formaldehyde in the plant was the precursor of the presence of formaldehyde in the saliva, and if those taking an active part in processing were affected similarly or differently from periferal staff. The table and graph overleaf show the results. The figures are recorded optical

LEVELS OF FORMALDEHYDE DETECTED IN THE SALIVA

Staff	Shift Hours								
Ident	1st	2nd	3rd	4th	5th	6th	7th	8th	
A	0.022	0.018	0.010	0.016	0.018	0.011	0.005	0.032	
B	0.017	0.022	0.020	0.015	0.021	0.012	0.008	0.031	
C	0.024	0.013	0.010	0.013	0.015	0.002	0.010	0.015	
TAC	0.021	0.025	0.029	0.009	0.017	0.020	0.004	0.017	
ARB	0.018	0.026	0.031	0.012	0.018	0.019	0.007	0.014	O.D.
Ambient HCHO ppm	0.2-1.8		0.1-2.3		0.6-6.2		0.9-4.2		



density and are the mean of duplicates. The first two shift hours were sampled as shown on the first day, followed by the 3rd and 4th hours on the second day, and so on through the eight hour shift over a period of four days. The three processing personnel and laboratory staff are identified. The ambient levels of formaldehyde in air, maximum and minimum for the appropriate days are also shown.

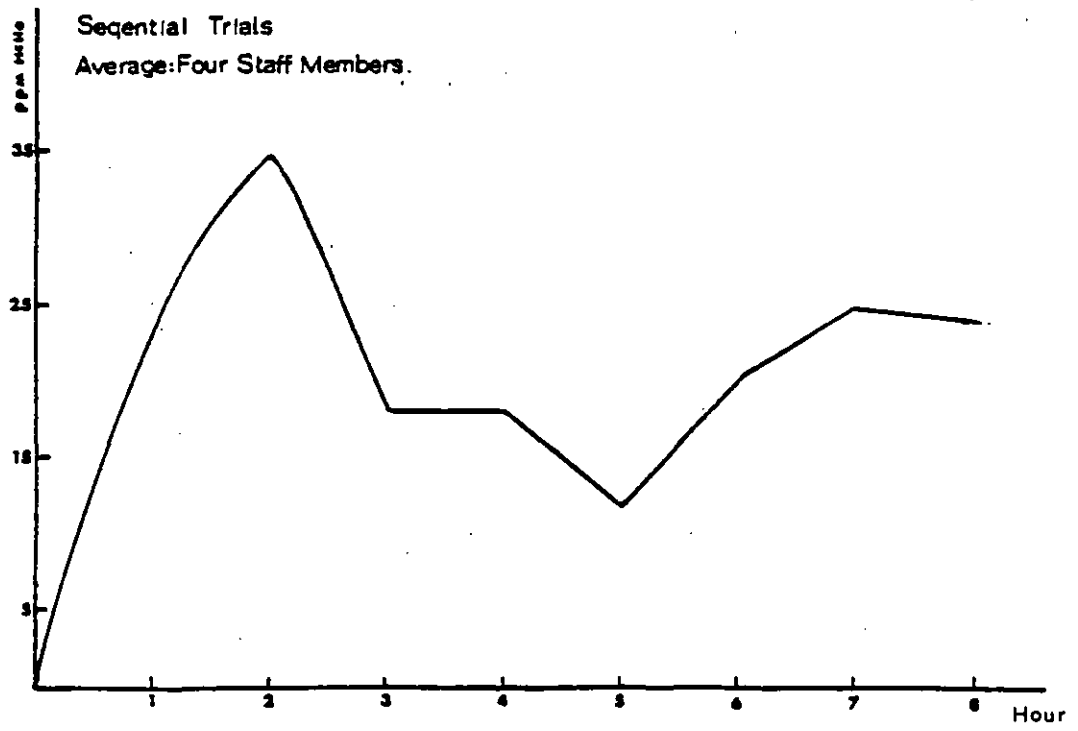
Staff movements in the processing areas tend to be constant in designated areas. Thus, during the first two hours, the loading and weighing of chemicals takes place followed by the charging of stills and reaction vessels.

While later in the shift polymerisation and blending is carried out. Technical and laboratory staff have a roving brief and therefore may be looked upon as less likely to receive high level exposure. In spite of carefully recording staff movements however and comparing their positions in the plant with estimated periods of dwell time, no significant correlations could be found in the results. The level of formaldehyde did not appear to bear any relationship to ambient as compared with intrinsic levels nor did there seem to be an association with the reported periods of physiological discomforts among staff. One important factor did emerge however, which was that the levels of formaldehyde found in the saliva were very much higher than was anticipated.

In order to differentiate between the level at which an individual is exposed and that which appears to accumulate in the body, a series of sequential tests was proposed. A group of four staff members was selected, all of whom normally operated in the plant areas and each was examined hourly, and progressively throughout the duration of the shift. A test on two staff who were not associated with plant operations was also carried out for the purpose of comparison. Where possible the level of formaldehyde in the plant at the time of taking the salivary samples was assessed by the usual method. The results are shown in the chart and table overleaf. All figures are quoted in ppm. It is quite evident from the results that an accumulation of formaldehyde was taking place in the saliva and could be demonstrated. The effect being seemingly independent of the ambient levels encountered in the factory.

LEVELS OF FORMALDEHYDE DETECTED IN THE SALIVA

Staff	Shift Hours								
Ident	1st	2nd	3rd	4th	5th	6th	7th	8th	
A	25.2	32.4	14.9	15.6	10.4	19.8	24.9	22.6	
B	24.8	36.8	19.2	17.8	12.0	20.2	26.4	23.9	
C	26.0	40.1	20.4	19.8	12.0	18.9	22.8	24.0	
D	21.4	29.8	15.6	14.9	11.8	21.4	23.9	23.4	
Average Saliva	24.4	34.8	17.5	17.0	11.6	20.1	24.5	23.5	ppm
Average Air	0.6	0.8	1.4	1.2	3.0	2.1	0.6	0.9	ppm



The staff members used as blanks in the trials gave a zero reading having been tested in a similar way.

The results posed several questions, among them were the following:

i) Was there a time interval between the starting point of exposure and a peak salivary level of formaldehyde, which could be established for an individual?

ii) Is it possible to reach a level of ambience in relation to free accumulated formaldehyde, if so, is this a stable zone in respect of the time of exposure?

iii) Is the recovery profile a simple function or complex, perhaps involving preconditioning as well as environmental levels?

iv) What was the lowest possible level of free salivary formaldehyde that could be characterised and correspondingly the lowest ambient level which following exposure could be pick-up and recorded in the saliva?

v) What was the nature of the dispersal mechanism if any, and was such a process time dependent or related to fresh air exposure?

vi) Is the maximum possible salivary accumulation always at the same level for an individual or interdependent with the nature of the work that is being performed?

These questions clearly reflect the importance of understanding exactly what is involved in the accumulation of free formaldehyde in the body fluids. Particularly so as a study of the literature has revealed a very wide spectrum of symptoms and physiological effects which seemingly can only be accounted for by presuming a cumulative phenomenon.

It was considered important in designing further experimental work to take account of the effects of exposure on behavioural responses. Also observe those elements which might correspond to specific physiological mediation as for example in the attack of mucus membranes and the occurrence of formalin asthma.

To attempt an answer to some of the questions it was necessary to study the ambient conditions in various plant areas and at customers processing mills. The object being to establish those areas which were solely contaminated with formaldehyde, as it was not known for certain what additive effects might be encountered if for example fine dust particles were present in the atmosphere. It has subsequently been demonstrated that exposure in such conditions gives rise to a predictably quicker onset of physiological discomfort, and at a more acute level than in environments containing formaldehyde alone. The required conditions were found in a number of areas of the manufacturing plants and some customer mills. Particularly useful were those factories which were resinating textile materials and several were studied, one used no other volatile chemicals apart from a formaldehyde based resin. Two sequential series of tests were carried out at this plant. The normal routines of the participants were observed as indeed were meal and tea breaks for the shifts concerned. Discomforts during the processing were noted and the appropriate levels of formaldehyde in air assessed. Two staff members not associated with processing were included in the tests as blanks. The sequence was intended to be representative of actual working conditions in a textile resination plant.

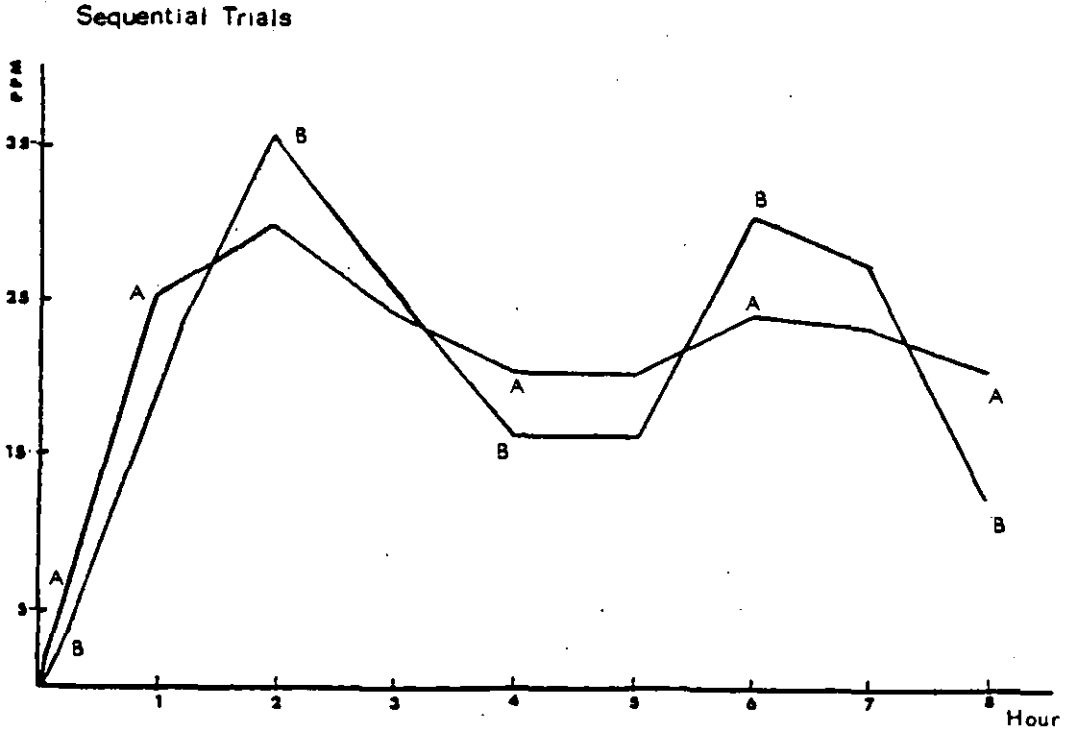
It can be seen by reference to the following table and chart that a time constant for an apparent salivary peak was beginning to emerge at approximately two hours following general exposure. It was still not clear however if there were any additional unknown elements present which might vector the relationship.

It was therefore decided to expose volunteers in selected areas of plant where the conditions were known to vary. Each staff member would be exposed for a known period of time and the results compared. It was convenient to use forty five minutes as the optimum exposure time, the optical density measurements are shown below.

The study demonstrated that although the potential levels of formaldehyde available in air in each of the different locations varied between 0.5 and 11.0 ppm, during the course of a forty five minute exposure the peak level in the saliva suggested a degree of constancy.

LEVELS OF FORMALDEHYDE DETECTED IN THE SALIVA

Staff	Shift Hours							
Ident	1st	2nd	3rd	4th	5th	6th	7th	8th
A_1	0.016	0.024	0.015	0.013	0.012	0.016	0.027	0.024
B_1	0.020	0.027	0.014	0.011	0.016	0.025	0.024	0.011 od
A_2	0.024	0.022	0.022	0.018	0.019	0.022	0.008	0.007
B_2	0.013	0.028	0.026	0.014	0.009	0.024	0.019	0.010 od
HCHO in Air	0.05–0.25	1.45–2.80	1.90–5.60	6.00–2.20	0.80–2.20	3.05–1.66	0.90–2.40	0.90–1.80 ppm



LEVELS OF FORMALDEHYDE IN THE SALIVA AFTER AN EXPOSURE OF 45 MINUTES

Staff — Exposure General Position

Ident	Outside	Resin Store	Mangle Room	Stills Live	Stills Vacuum	Moulding Powders	
A	0.000	0.012	0.011	0.022	0.012	0.014	
B	0.000	0.019	0.016	0.010	0.011	0.011	
C	0.000	0.010	0.013	0.009	0.014	0.008	
D	0.000	0.012	0.017	0.014	0.012	0.009	O.D.
Av.	0.000	0.013	0.014	0.014	0.013	0.011	

Sufficient accumulation taking place, apparently independent of the ambient level, to initiate a sensory response, which to a first approximation was probably coincident with the onset of a desensitisation. It seemed logical that such a biological mechanism should have as its presursor a measurable glandular accumulation.

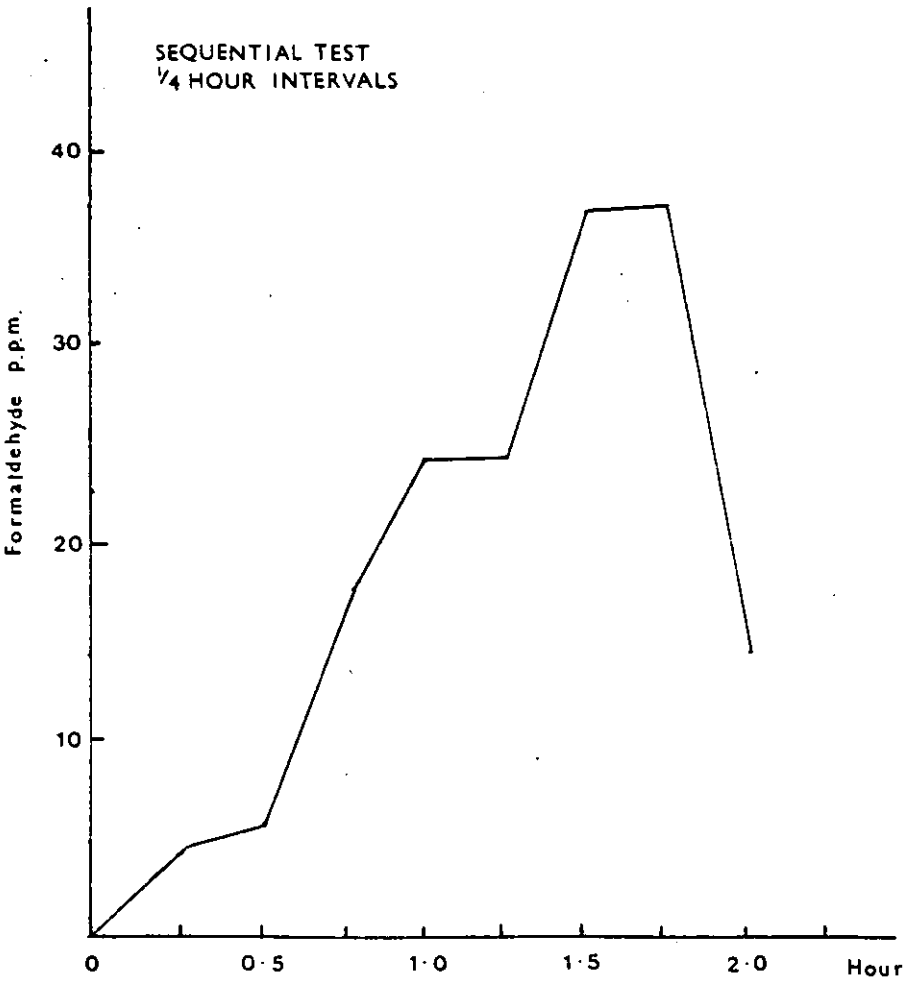
This aspect was examined more closely by testing at fifteen minute intervals during the first two hours of a shift. Although the tests were required to be performed under factory conditions as steady an ambient level of formaldehyde was desirable. Suitable conditions were found in the blending plant where the levels are known and vary by only a small amount.

In the table and charts following the results are shown for four volunteers. During the testing the ambient level of formaldehyde in air was 1.6 ± 0.04 ppm. The steady accumulation of free formaldehyde in the saliva is evident, and the levels would suggest a peak following a ninety minute period of exposure. An initial plateau appears at approximately thirty minutes with a secondary peneplane after one hour Calculations as to the rate of accumulation lead to the postulate that absorption is at the level of 0.44 ppm/min of exposure climbing to a potential salivary maximum of approximately forty parts per million in ninety minutes. A final level of some twenty times the threshold limit value.

LEVELS OF FORMALDEHYDE IN THE SALIVA: FIFTEEN MINUTE INTERVALS

Staff — Shift Time Hours

Ident	¼	½	¾	1	1¼	1½	1¾	2	
A	0.004	0.009	0.015	0.016	0.019	0.029	0.027	0.014	
B	0.004	0.006	0.014	0.018	0.018	0.031	0.028	0.010	
C	0.002	0.002	0.012	0.017	0.011	0.030	0.031	0.011	
D	0.002	0.004	0.014	0.015	0.019	0.026	0.031	0.009	O.D.



CHAPTER IX

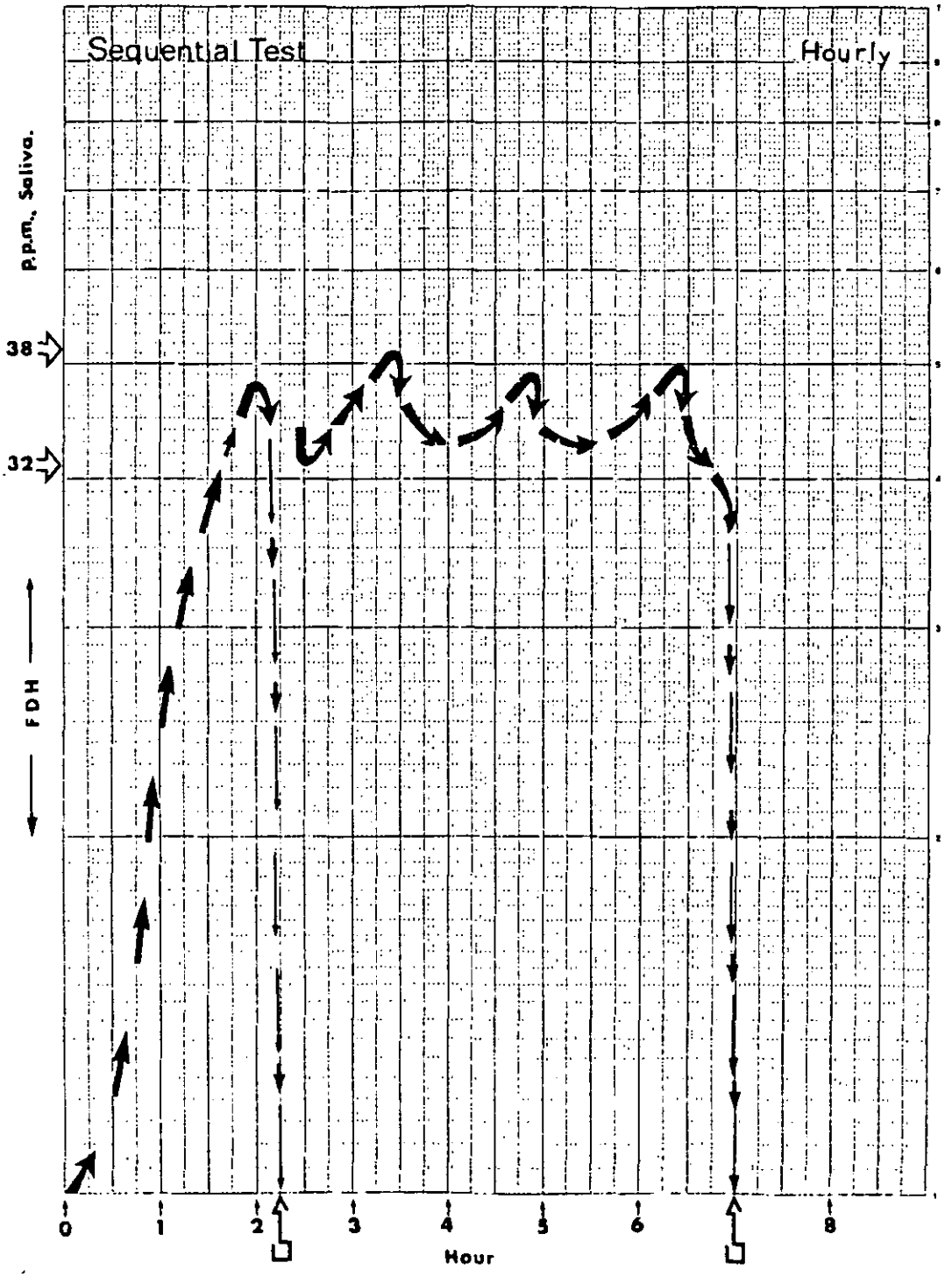
CONCLUSIONS AND RECOMMENDATIONS

i) Recovery from exposure

ii) The mechanism of accumulation

iii) Conclusions

LEVELS OF FORMALDEHYDE
DETECTED IN THE SALIVA
FULL SHIFT TEST HOURLY



Lunch and general breaks were taken in the plant areas.

Recovery from Exposure

Acceptable evidence is available to suggest that residence time in a working environment containing formaldehyde will influence the level of the free material accumulated in certain of the body fluids.

The profiles of the curves for time-accumulation show a considerable reduction in detectable levels immediately following a lunch break, and certainly overnight. In order to try to evaluate this, it was decided to run sequential tests in each of three plants in which break-times and lunches were taken within the immediate plant areas. It was quite evident from the results that the profile of the curve had changed. In the initial regions, i.e. for the first ninety minutes, the primary salivary maxima were achieved in the expected way but the drop associated with the lunch break had disappeared. This effect can be seen by reference to the chart opposite. It will be noted that the peak salivary levels tend to hover in the region of 32-38 ppm. In terms of recovery from the cumulative effect it seemed reasonable to suppose that exposure to fresh air (not re-circulated factory air) was in some way making an important contribution. The curve structure could be modified and hence the question arose, could it be manipulated in the sense of producing a sudden 'cut-off' effect by breathing clean air. The following table shows the results of an experiment in which three participants were exposed for ninety minutes in the plant followed by fifteen minutes of fresh air exposure.

LEVELS OF FORMALDEHYDE DETECTED IN THE SALIVA WITH FRESH AIR EXPOSURE

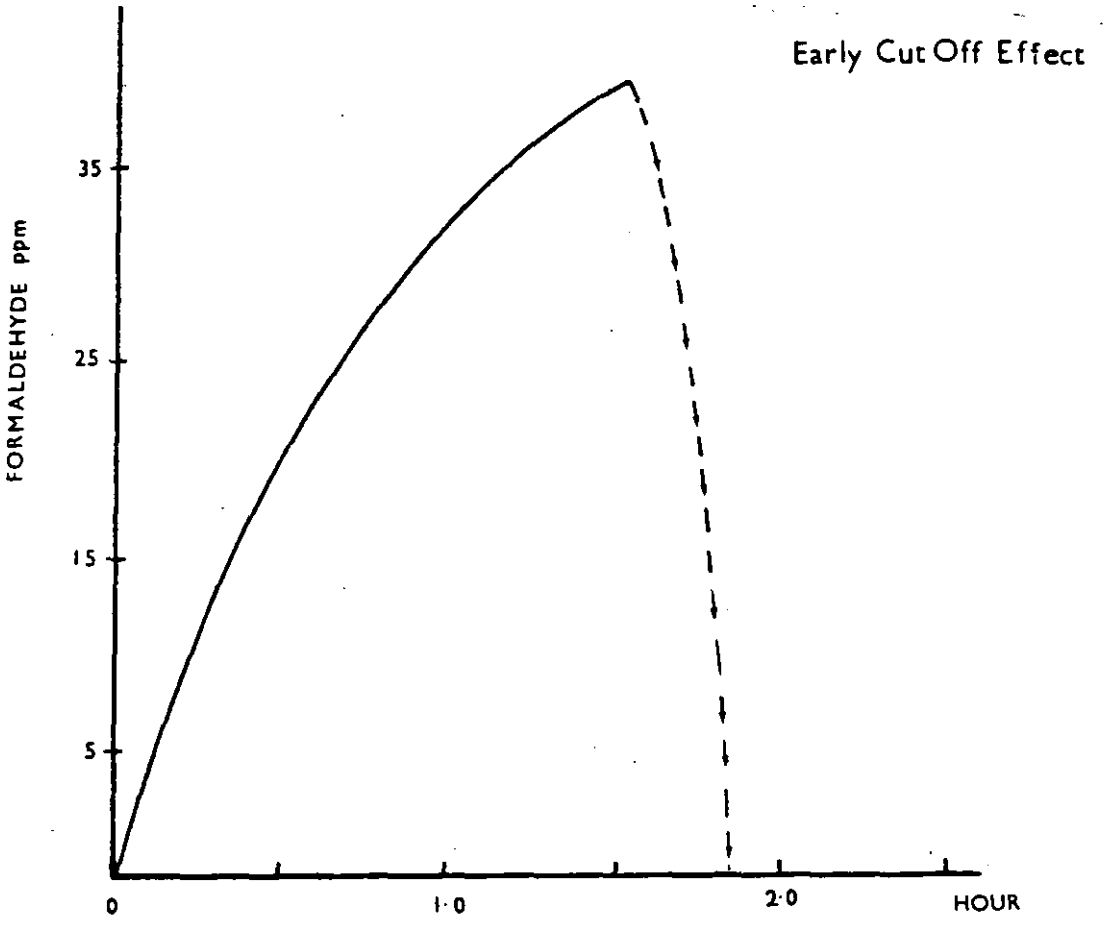
Staff Exposure Times Minutes

Ident	Plant (90)	Fresh Air	15 x 2	
A	0.032	0.020	0.008	
B	0.028	0.019	0.006	
C	0.031	0.017	0.007	O.D.

The abruptness of the reduction in general level after only fifteen minutes in the fresh air contrasts very sharply with the slow progressive character of the build-up to peak level. Subsequent work on a number of individuals in customer's mills has verified the 'cut-off' time to be between twenty and thirty minutes, but this depends to a great extent on the individuals concerned. The important principal feature remained, that the salivary level of free formaldehyde tends to drop to zero very rapidly when a subject moves from a contaminated area into the fresh air. The mechanism may perhaps be explained by reference to the following charts.

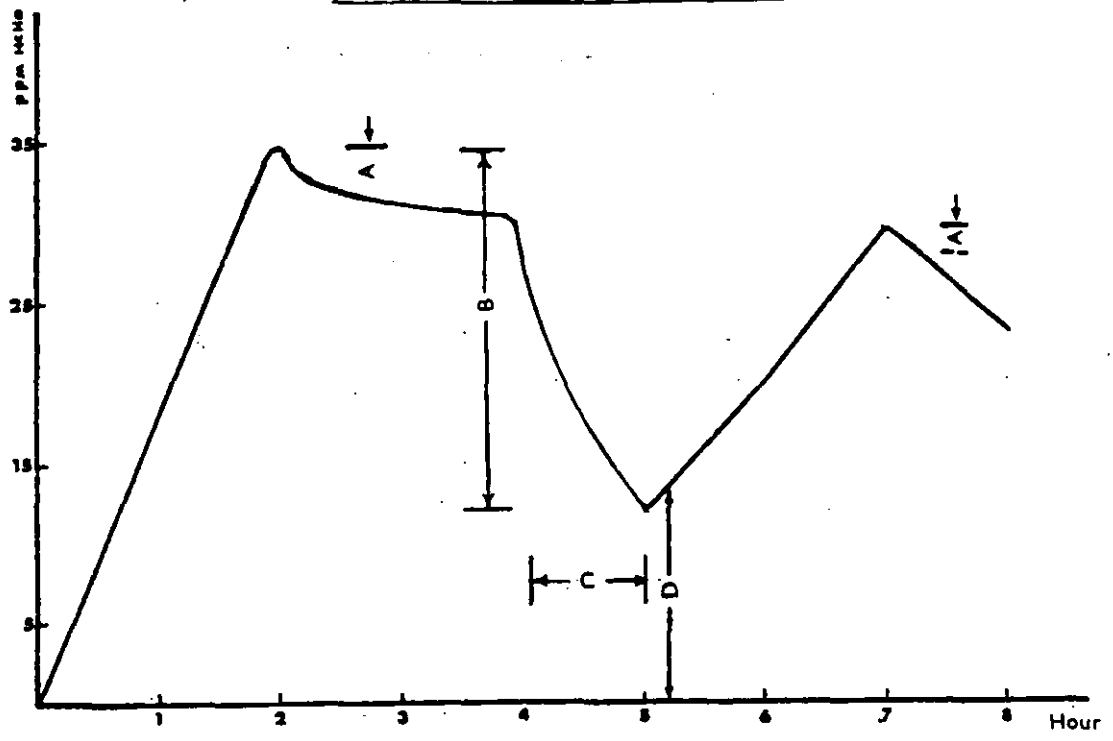
Mechanism of accumulation

The early 'cut-off' effect is illustrated below in which it can be seen that a dramatic reduction in level can be achieved within the space of a little over a quarter of an hour.



In the curve for the general profile of accumulation during the full period of a shift (chart below) it is suggested that the drop in level as indicated by 'A' represents temporary contact with fresh air. For a period not exceeding five minutes. This will have the effect of reducing the formaldehyde load by only a marginal amount so that the accumulated acclimatised effect appears to be maintained. The much greater fall indicated as 'B' occurring during the course of the lunch break 'C' in another room, can be sufficient to reduce the load by 50% or more. Following re-entry into the zone contaminated with formaldehyde a subject will be found to be acutely sensitive to the atmosphere the temporary acclimatisation 'D' having been lost. These factors imply that the acclimatisation may simply be a process of chemical concentration which is carried out in tissues and is detectable in certain of the body fluids.

THE FORMALDEHYDE ACCUMULATION
DURING A SHIFT OF EIGHT HOURS



Thus short term excursions into the fresh air, though tending to reduce the overall load, will have an imperceptible sensory effect. Longer term exposure to fresh air would seem to trigger a metabolic sequence of events which brings about molecular and apparently more permanent dissipation. Nonetheless it is possible to superimpose effects in the sense of an early return to a contaminated atmosphere bringing about physiological discomforts of an acute nature. These are followed equally suddenly by a

complete inability to detect the material. These factors collectively suggest that there is a biological limit of tissue absorption which can be maintained as a metabolic pool of free formaldehyde in the body. Environmental conditions which tend to bring about a significant increase in this level will, in turn, trigger dissipation by a simple oxidative route. The experimental evidence leads to the conclusion that tissue retention is approximately one-third that of dissipation. We believe it is this aspect that has the more serious long-term implications, particularly in relation to lung disease as discussed in Part I.

Conclusions

The results of the investigations have revealed some interesting possibilities in regard to understanding salivary accumulation of formaldehyde and free clearance of the material in the urine.

It is clear that random sampling of atmospheric air in the works on selected subjects shows no correlation between the level present in the breathed air and that fonnd in the saliva. This is equally true for comparisons between subjects and the same individuals on different shifts.

A surprising feature of the early work was the very high levels of free formaldehyde that could be detected. Examination of volunteers' saliva on a sequential basis following exposure, has demonstrated a steady accumulation over the period of a shift with an apparent time proportional characteristic.

The time interval between a zero reading of formaldehyde in the saliva and the peak of the accumulated material is about ninety minutes of exposure. Such a level being achieved seemingly independent of the particular ambient levels that were measured in the plant areas visited.

The general accumulation rate from a fresh air threshold is suggested as 26 ppm in the hour up to a recorded maximum of 40.5 ppm in the saliva. At much higher ambient levels such as 3.0 ppm with a ceiling of 7.5 ppm the rate of accumulation is very slightly increased, however, the maximum level that is built up in the saliva is virtually the same.

The recovery time from this peak is subjective but corresponds with any movements away from the area of pollution. The time cycle from zero to peak absorption remains reasonably constant and would appear to be independent of the subjects chosen.

In terms of both recovery, and the maximum absorption for different individuals, it must be recognised that fresh air (as opposed to re-cycled air) is normally excluded from most plant areas. Logically food and drink would be thought to interfere in some way with these measurements but this was not the case. Although following a lunch break away from the plant, the values detected on return could be reduced, the effect subsequently was shown to be directly attributable to the effects of fresh air alone.

The stability of the free material in the body fluids is noteworthy and lends weight to the concept of a metabolic pool of formaldehyde in the tissues. The completeness of absorption and distribution is a very striking feature.

The metabolic pathways leading to dissipation as was discussed previously, can be inter-active. Thus in the case of the protein-aldehyde conjugate, active transport across cellular membranes gives rise to methionine, which has been characterised in the urine. Free clearance of formaldehyde from the urine taking place at the rate of a 2:1 reduction in relation to salivary accumulation, the kidneys handling a dissipation rate of between 12-16 ppm per hour.

Metabolism by the mucosa of the lungs with increase in phospholipid synthesis and hormonal stimulation is seen as a precursor of broncho-pulmonary disease, particularly formalin asthma. However in isolation these events may be considered to be homeostatic and contributing to the pre-conditioning of lung function to environmental stress. To some extent this is perhaps an open question and the existence of the fresh air cut-off effect supports the latter concept, but a wealth of clinical evidence points to lung deterioration.

It would be a simple matter to suggest that the TLV in the plant areas should be reduced to 0.5 ppm. Indeed in our investigations improvements in engineering and handling have brought about a 75% reduction in level as compared to the TLV, but it is un-realistic to expect this to be maintained in any sizeable commercial operation. To guarantee such a level would require an enormous financial investment, and the fact is that in the long term 0.5 ppm will contribute as much to health deterioration, as twice or even four times this value.

If the optimum figure of 0.8 - 1.1 ppm (the nominal operating level) is accepted in manufacturing and external processing operations then high risk zones must be eliminated. Drager tubes are excellent for identification of such areas, and dispersion can be effected by means of portable equipment.

Plant environment improvement schemes on their own, however, are of little real value and require to be supported by personnel monitoring on a regular basis. The maintenance of bi-monthly checks on salivary and urinary constituents would be a most important adjunct for those employees who are customarily exposed to formaldehyde containing atmospheres.

The possibility of assessment of respiratory deterioration, and any connection between such events and the general levels of accumulations of free-formaldehyde in the body, could be the subject of further work

One is tempted to an obvious conclusion that it might not be unreasonable to adopt a philosophical attitude when monitoring a factory and to ask the most sensitive employee to walk through the works each lunch time. If they return without a rash one could pronounce the area safe!

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CHAPTER X

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