Def Sci J. Vol 37, No 2, April 1987, pp 205-219.

Inhalation Toxicology

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ABSTRACT

A chemical substance can enter the biological system through three major routes like oral, cutaneous and inhalation and induce toxic effects. Toxicity studies of substances through oral and cutaneous routes are considerably simple, easy and methods are well established, while inhalation toxicology is more complicated because it involves several factors. Basically four aspects are important in studying inhalation toxicology viz., generation of respirable particles, design of exposure chamber, determination of concentration and particle size, and the impact of the chemical on the biosystem. This review is primarily intended to describe and discuss various techniques involved in inhalation toxicity studies with special reference to aerosol generation, particle sizing and animal exposure methods.

1. INTRODUCTION

The lungs have a unique proximity to the airborne intoxicants. The inhaled toxic particles, noxious gases, micro-organisms, allergens and carcinogens are separated from the systemic circulation by a thin air-blood barrier. Damage to lungs not only impairs life sustaining process of gaseous exchange viz., oxygen and carbon dioxide but also the defence of the organism against bacterial infection. In addition the lung is now recognized as a major site associated with many metabolic activities, the so called non-respiratory functions of the lungs.

Assessment of the hazards associated with the inhalation of toxic particles is dependent on a number of factors. The toxic effects are effectively minimized by maintaining the concentration of the contaminant below some level which has been deemed unlikely to cause detectable biological damage in people exposed over a long period. Besides, there are other factors that are not directly related to the chemical

Received 5 February 1987

properties that make a substance toxic, nevertheless they play an important role in determining the likely extent of damage. Deposition of particles in the respiratory tract by the process of impaction, sedimentation and diffusion induced by the abrupt directional changes of stream of air and the velocity of inspired and expired air are decisive criteria of assessment of biological damage. Cell population of the respiratory tract, lymphatic, circulatory and airway clearance are other factors that markedly influence the interaction of toxic particles (including gases) with the lung tissue.

Moreover, the blood-air barrier may function as an effective screen between the toxic airborne materials that are swept into the respiratory tract during inspiration. Pulmonary irritants like phosgene and methyl isocyanate damage this barrier and thus open it up for dusts and micro-organisms to enter the blood stream. It is therefore to be appreciated that the toxic effect can be exerted directly on the pulmonary tissue or to other remotely situated organs when the intoxicant enters the general circulation through the leaky blood-air barrier. The pulmonary tissue can also be damaged by a substance or its reactive metabolite which finds its access to lungs through the pulmonary circulation following systemic administration. Paraquat is a classical example of this class of compounds.

The inhalation toxicologists have therefore to advice experimental techniques which would circumvent the built in anatomical barriers of the respiratory passage. Generation of respirable dusts, aerosols, smokes, gases, vapours, design and operation of animal exposure chamber, monitoring of the chamber environment and evaluation of the hazards to biological system are some of the important aspects that need careful consideration in experimental inhalation toxicity studies.

2. METHODOLOGY

Administering a toxic chemical through the respiratory route or inhalation route is the most difficult. For conducting inhalation toxicity studies three basic facilities are required : (i) generation of respirable atmosphere (ii) animal exposure chambers and (iii) analysis of the inhalation chamber atmosphere.

2.1 Generation of respirable atmosphere

The generation techniques for the respirable atmosphere can be broadly divided into (i) gases, (ii) liquids, (iii) dusts and (iv) smokes.

(i) Generation of gaseous atmosphere

The generation of an atmosphere of a gas or a low boiling liquid is simpler than non-vapourisable liquids and solids. The material should be available under pressure in a cylinder. Using a needle valve and gas flow meter a known quantity of the gas can be tapped. This then is diluted with fresh air to get the required concentration. Toxic atmospheres of phosgene, hydrogen cyanide, methyl isocyanate[1] etc. can be generated by this method.

(ii) Generation of liquid toxicant atmosphere

A number of methods are available for the generation of liquid toxicant atmosphere.

If the liquid is highly volatile, filtered dry air at a known flow rate can be bubbled through the liquid kept in a container. The outcoming air saturated with the toxicant can be diluted with fresh air to get the required concentration. Using this method test concentrations of methyl isocyanate were developed by Fergusson et al.[2]

If a liquid can be vapourised at a higher temperature without decomposition, then the liquid can be pumped at a constant rate using a syringe pump into an evaporator which is thermally controlled. Metered air can be passed through the evaporator which will carry the vapours of the liquid into the exposure chamber. Toxicity of petroleum distillates is studied by this technique.

Liquids which have low vapour pressure and which are soluble in water can be delivered as an aerosol. An aerosol is a suspension of a liquid (also solid) as fine droplets in air. Liquid aerosols are generated by three principal methods (a) air blast nebulization (b) ultrasonic nebulization and (c) spinning disc atomization.[3]

A simple commercially available air blast nebulizer is shown in Fig. 1. This utilises compressed air to aspirate liquid from a reservoir. The aspirated liquid is forced onto

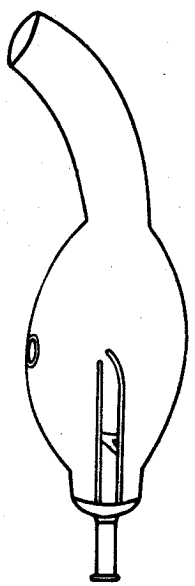

Figure 1. Airblast nebuliser.

an impaction surface breaking it into fine droplets. The finer droplets are carried along with the air stream. Aerosols of dichlorvos (DDVP), a pesticide was generated using this principle.[4]

An ultrasonic nebulizer will be more suitable when high concentrations of aerosols are required. In this apparatus, the energy required to produce the liquid droplets is

supplied by a piezo electric disc, driven by a high frequency oscillator. Aerosol is produced because of high intensity capillary waves formed at the air liquid interface.[5]

While the air blast and ultrasonic nebulizers give polydisperse aerosols, the spinning disc atomizer generates monodisperse aerosols.

Organic solids which can be melted without decomposition can also be nebulized in a modified air blast nebulizer with provision for heating the nebulizer. The nebulized liquid aerosol is carried by the carrier gas (compressed room air) as a fine dust after cooling. This method has been successfully developed by Defence Research & Development Establishment, Gwalior and has been found suitable for generating aerosols of CR, a tear gas for animal studies.[6]

(iii) Generation of dusts

If a solid is insoluble in water, it can then be dispersed in the form of a dry powder. A commercially available device for the generation of dust is the Wright dust feeder.[7] The powder from which a dust atmosphere is to be generated is packed in the dust tube of the device. It is scraped by an electrically driven scraper and the generated particles are driven as a dust by the compressed carrier gas.

The Timbrell dust generator is specially meant for the generation of asbestos dusts in the respirable range.[8]

(iv) Generation of smoke

Due to ever increasing use of synthetic polymers for insulating purposes, there has been a growing concern of the toxicity of thermal decomposition products of these compounds.[9] Barrow et al.[10] have designed a dynamic exposure system for the study of toxicity of thermal decomposition products from synthetic and natural polymers, decomposing them by increasing the heat from room temperature at a rate of 20°C per minute, upto a maximum of 800°C. This method has been found to yield valid concentration response relationship for evaluating acute and lethal effects of a variety of polymers. In subsequent studies[11,12] the heating procedure was modified, so that the animals were first exposed to thermal decomposition products produced during pyrolysis at low temperature (200°C) and then to products occuring during flaming conditions, if ignition occurs. During exposure carbon monoxide, carbon dioxide and oxygen are monitored continuously. Formaldehyde, hydrogen cyanide and hydrogen chloride were also measured depending on the nature of the polymer.

(v) Charge neutralizers

Particles generated from nebulizers or dust generators usually carry electrostatic charges, which is advisable to be removed. A commercially available aerosol neutralizer (TSI, USA) containing ^{85}Kr can be used to neutralize the electrostatic charges. This device is usually placed before the exposure chamber.

2.2 Animal Exposure Chambers

(i) Exposure techniques

There are two modes of operation of an inhalation exposure chamber.

(a) Static system

If a liquid is highly volatile, highly toxic or the quantity is very small a static method of operation is convenient. In this method, the animal is kept in a closed chamber. The agent is also placed in the chamber and is released by an external control. A fan or a closed circuit pump operated briefly can ensure mixing of the toxicant. Nemery et al.[13] and Pant et al.[14] studied the toxic effects of methyl isocyanate using this technique (Fig.2).

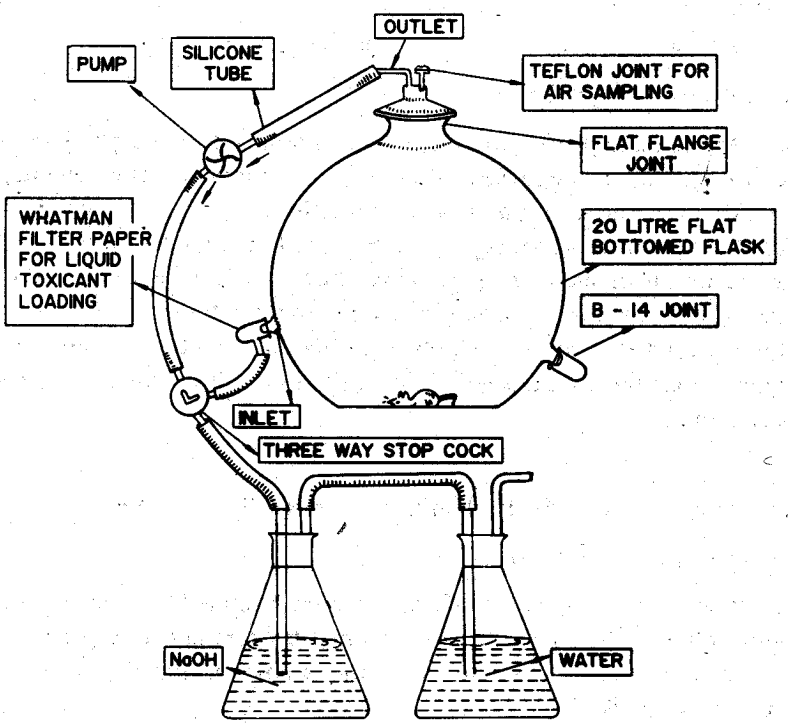

Figure 2. Assembly for inhalation exposure – static type.

But the disadvantage of this method is that it can be operated only for a short time, since as time passes the partial pressure of oxygen will fall and that of carbon dioxide will increase as also the relative humidity. Because of simplicity in design and operation it can be used for pilot studies.[15]

This system has also been used for testing the toxicity of thermal degradation products of polymers.

(b) Dynamic system

A dynamic system is an open system and many investigators prefer this mode of operation. In this system, the toxicant in the atmosphere of the chamber is continuously replinished. The advantage of this method is that partial pressure of oxygen,

carbon-di-oxide, relative humidity and concentration of the toxicant are always maintained. Another advantage is that this system can be used for any length of time. But the disadvantage is that large amount of the toxicant is required. Another disadvantage is the 'build-up time' which varies depending upon the capacity of the exposure chamber and the volume of air delivered per minute. A suitably adapted intoxicant delivery system and set of animal exposure chambers are used to study the effect of chronic exposure. This procedure is of special utility in the study of effect of industrial gases.

(ii)Type of exposure chambers

Three tupes of exposure chambers are in common use.

(a) Whole body exposure chamber

Most of the inhalation toxicity studies are conducted in chambers in which the whole body of the animal is exposed to the toxic environment. The advantage of this chamber is that no surgical preparation or anaesthesia is required and the animal is not subjected to any physical stress (like restraining the animal as in the case of other types); but the disadvantage is the possibility of aerosols getting deposited on the fur of the animals, which will be ingested by the preening nature of the animals. Highly lipid soluble materials can be appreciably absorbed through the skin also. Thus there is every chance that the toxicant will enter through all three routes viz, respiratory oral and cutaneous.

An example of a whole body chamber is the Rochester chamber.[16]

(b) Head only exposure chamber

In this type only the head of the experimental animal will be exposed to the toxicant atmosphere.[17] Specially designed animal holders are used for this purpose. However, the movement of the head of the animal is physically restrained by compression of the body.

(c) Nose only exposure chambers

In this type, only the muzzle, external nares and the mouth will be exposed to the toxicant atmosphere. The advantage of this method is that the toxicant can enter the body only through the respiratory route. But the disadvantage is that as the animal is restrained, the respiratory rate and metabolic rate will be increased. Primates and dogs are preferred as experimental animals in this technique.

(d) Special methods

Fine dust powders suspended in saline can also be introduced into the lungs.[18] The trachea is opened surgically under anaesthesia. A small quantity of the test material contained in a liquid media (generally saline) is instilled into the trachea by a syringe. The wound is stitched and the animal is allowed to recover from anaesthesia. The technique is considered useful for long term post instillation studies. Besides minute quantity of dust is required to treat the animals. Since the reaction of the upper respiratory tract is bypassed in this technique, it remained of limited application.

A modified technique with tracheal intubation has been used to differentiate respiratory irritants into sensory irritants and pulmonary irritants.[19]

2.3 Analysis of atmosphere of inhalation chamber

Accurate measurement of the concentration and the particle size analysis (specially dust and aerosols) is necessary to assess the entry of the intoxicant into the lungs. Various techniques have been reported in the literature.

(i) Particle size analysis

Particle size analysis is one of the most important parameters in inhalation toxicity studies. The deposition pattern of the particles at various regions of the respiratory tract[20] is shown in Fig. 3. Hence for producing desirable concentration of inhaled particulate matter, diameter of the particles should not be more than 5 microns.

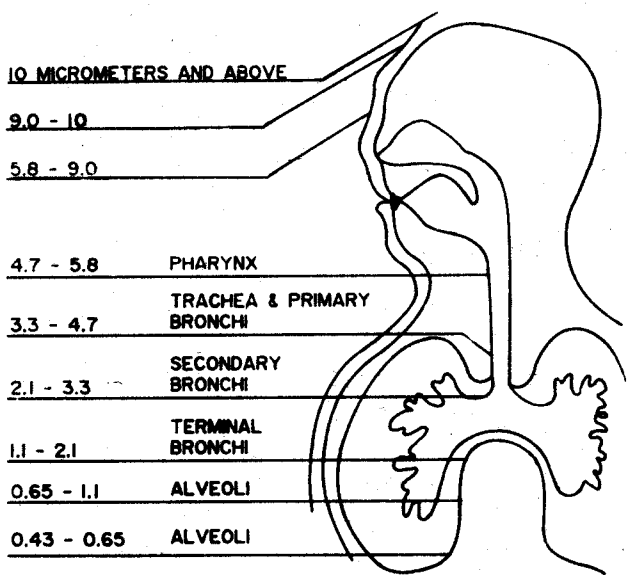

Figure 3. Site of deposition of inhaled particles in the lungs.

There are a number of methods available for the determination of particle size. Among them four methods are important (a) Cascade impactors, (b) Light and electron microscopic analysis, (c) optical particle counters and (d) electrical particle mobility analysers.[21]

(a) Cascade impactors

The cascade impactors draws a sample of test atmosphere through a succession of jets which is projected onto an impaction surface. Each successive jet is smaller than the preceding one, thereby the velocity of the air steam is increased. Smaller particles will get enough momentum to impact on a collection surface. This method will give the aerodynamic diameter. The May's cascade impactor and Casella's cascade

impactor are some of the instruments utilizing this principle. The Anderson Sampler[22] also works on this principle but it has the added advantage that the different stages represent the human respiratory tree.

(b) Optical Microscopic Technique

In this method, the samples can be collected in a filter thimble or other dry dust collector and dispersed on a slide. Using a calibrated graticule, the size of the particles can be determined.[21] This method is convenient because the technique can be adapted at a low cost and the diameters of the particles can be approximated by a simple measurement. A semi-automatic instrument for particle size analysis of photo-micrographic particle images has also been described.[23]

(c) Optical particle counters

In this method, the aerosol particles are passed through a sensitive volume, through which light from a lamp is focussed by a series of lenses on a photomultiplier. When particles pass through the sensitive volume the light scattered is detected by the photomultiplier. There are several instruments available for the direct counting of particles, with multi-channel facilities.[21] Since in these instruments, the range is a limiting factor, different instruments are needed to measure the particles even within the respirable range. Another sophisticated method using a similar principle is the laser aerosol counters.

(d) Electrical particle mobility analyser

This method employs initial electrostatic charging of all particles followed by subsequent measurement of the number and magnitude of the electrical impulses transmitted to conductive particle collecting surfaces.[24]

A more promising technique involving the use of electron microscopy and the scanning electron microscope (SEM) have also been described for the study of submicron dusts and fumes of concern in industrial hygiene, air pollution and general small particle technology.

(ii) Concentration analysis

The analysis of concentration of airborne contaminant in animal exposure chamber is an important parameter for the proper assessment of like effects on biological system. Concentration measured in terms of mg/m^3 or ppm is used to calculate the dose in the dosimetry expression. Dose = $C \times t$. Factors like deposition of the dispersed material on the walls of the chamber and poor stability of a chemical in gaseous/vapour or aerosol form may differ from its original stability. Therefore, there is a need for accurate and frequent analysis of concentration of the dispersed chemical.

Several methods are available for the continuous monitoring and analysis of the atmosphere in the animal chamber.

(a) Gas and liquid aerosols

Samples of air from the chamber can be collected using a suction pump. A known volume of the chamber atmosphere is passed through a series of impingers with suitable solvent to absorb the pollutant. This can then be analysed using colorimetry,

U-V spectrophotometry, gas chromatography or high performance liquid chromatography methods.

A more sophisticated technique is now available which ensures not only periodical detection of the contaminant but also helps in maintaining the predetermined concentration by incorporating a computer.

(b) Dusts

Dust concentration can be calculated by using gravimetric samplers or even by cascade impactors. Light scattering photometry can also be utilized for the concentration analysis of dusts. Similar to liquid aerosols, organic dusts can be taken in a suitable solvent and then analysed as mentioned above.

(c) Smoke

Inhalation toxicity studies of smoke (pyrolysis products and ignition products) are complicated not only by the toxic products emitted by the burning of the material but also due to immediate and intense physiological responses evoked by inhalation of *CO* and CO_2. The atmosphere of the animal exposure chamber, has to be analysed for the concentration of these gases in addition to the toxicants emitted due to chemical decomposition.[9] Thus depending on the nature of the polymer, formaldehyde, hydrogen cyanide and hydrogen chloride are likely to be evolved.

2.4 Dose Determination

The effects of a chemical (including drugs) is dependent on the amount of the chemical that enters the body. In the context of inhalation studies the concentration multiplied by the time ($C \times t$) denotes the quantity of the substance 'offered' and not the dose delivered. Thus the $C \times t$ product does not necessarily equal to K (the biological effect) in the Haber's expression of $C \times t = K$. The entry of inhaled material into the lungs and its subsequent retention is governed by the respiratory frequency and volume, physical barriers (repeatedly spliting airways), cellular secretions, physical forces such as sedimentation, impaction, diffusion and finally clearance from the lungs by mucocilliary escalator system and lymphatic drainage.

Concentration of the intoxicant in the environment is variable due to dacay caused by humidity, temperature and wind velocity. To overcome this difficulty, it has been suggested to plot a curve of concentration and time of exposure at regular intervals during the exposure and concentration may be computed from the 'area' covered in the graph. Yet another improvement has been suggested to express the dose by the expression 'Exposure Index' (*E.I.*) and to include respiratory minute volume and to standardise in terms of body weight. Thus the expression is denoted by the following equation :

$$E.I. = ppm \times V_1 \times min \times Kg^{-1}$$

where *ppm* is concentration parts per million; V_1 = minute volume; *min* = duration of exposure in minutes and Kg^{-1} = per kg body weight.

This expression seems to be more meaningful as it takes into account the effect of the intoxicant on respiration. Many sensory irritants produce respiratory depression due to reflex inhibition on there may be voluntary holding of breath.

A practical approach in experimental studies with laboratory animal is to express the effects such as LC_{50}, LC_{30} in mg.min/m^3. The amount of substance present in one m^3 when inhaled which is expected to kill 50 per cent and 30 per cent population respectively. Other expression used is the threshold limit value (TLV).

3. ASSESSMENT OF TOXIC EFFECTS ON BIOLOGICAL TISSUES

Injury to lung and other tissues in the body is largely dependent on the chemical nature of the inhaled intoxicants. The reactive substances like sulphur dioxide, chlorine, phosgene and methyl isocyanate act directly on the lung tissue. This is the primary site of action. Inert substances, do not interact with the lung tissue but produce effects like fibrosis (Asbestos) and dust induced pneumoconiosis. The third category of intoxicants undergo a metabolic change to produce lung injury.

Recently, Boyd[25] has reviewed schemes showing three different mechanisms by which chemicals can induce pulmonary toxicity after metabolic activation. In mechanism-I a relatively unreactive parent compound undergoes bioactivation in the lungs to produce a reactive metabolite that is toxic to the system e.g. CCl_4. In mechanism-II the parent substance after being absorbed from the lungs into the systemic circulation undergoes metabolic changes in the liver and then re-enters the pulmonary circulation as a reactive metabolite and thus cause damage to the lungs. In mechanism-III, the parent compound undergoes oxidation (or auto-oxidation) which results in the generation of various activated oxygen species which either directly or indirectly lead to pulmonary cell damage. Paraquat is a classical example of this category of chemicals. It produces pulmonary damage by producing oxygen free radicals and/or stimulating depletion of energy stores thus resulting in cell damage.

Lung injury induced by inhaled intoxicants may manifest itself by (i) damage to lung geometry e.g. increased resistance to air flow or loss of tissue recoil at the alveolar site, (ii) chemicals that alter lung biochemistry e.g. ozone and nitrogen oxide, and (iii) morphologic toxic lung damage that cause alterations in the gross and fine structure of lung function. These adverse effects may set in motion a sequence of events that ultimately will interfere with or even cripple gas exchange.

Studies on lung compliance, specific compliance and hysteresis of volume-pressure diagrams of air and liquid filled excised lungs are some of the parameters which yield information relevant to lung damage. It has been reported that phosgene adversely affects the flexibility of the alveolar wall resulting in the loss of distensibility (the lining becomes stiffer and compliance decreases) of the alveoli during inspiration.[26] The lung compliance is also markedly reduced by inhaled aerosols of surface active substances. Inhalation of fumes of hydrocarbons[27] and SO_2[28] evoke severe alveolar atelectasis and alter mechanical properties of the lungs. As a consequence of altered compliance and alveolar stability, the respiratory rate, minute volume, vital capacity, respiratory resistance paO_2, $paCO_2$ have been shown to be adversely affected by inhaled intoxicants resulting in gross impairment of lung function[29].

3.1 Biochemical Lung Injury

Studies designed to elucidate biochemical mechanisms of toxic lung damage follow essentially two approaches : to see whether a given agent interferes with a key metabolic reaction in lung cell metabolism or whether the agent interacts with and chemically modifies selected component of pulmonary tissue. The lung lipid peroxidation may be caused by the oxidant gases ozone and nitrogen dioxide[30] and possibly even by oxygen.[31] Studies have been carried out to assess the effect of inhaled intoxicants on the surface-active phospholipids in the lungs. SO_2, cigarette smoke, aerosols of paraquat selectively inhibit the synthesis of phosphatidylcholine resulting in alveolar atelectasis. A similar effect has been reported on inhalation of vapours of petroleum distillates[27] and with phosgene.[32] A new approach to study the release of lung phospholipids was made by the authors. Based on the knowledge that a cholinergic mechanism is involved in the release of phospholipids, the investigators exposed the rats to single and repeated exposures to aerosols of organophosphorous cholinesterase inhibitors. Total phospholipids (TPL), phosphatidylcholine (PC) and phosphatidyl ethanolamine (PE) and sphingomyecin (Sphg) were studied. It was found that single exposure to a concentration of 50 mg/m^3 and 100 mg/m^3 for 30 minutes to Di-isopropyl fluoro phosphonate (DFP) aerosols or repeated exposure to a concentration of 50 mg/m^3 for 30 minutes for six days daily did not alter significantly total phospholipid or its fractions (unpublished observation). Witschi[33] has made a comprehensive review of models and tools to study the biochemistry of toxic lung damage. Availability of isolated perfused lung preparation techniques has immensely helped in understanding the mechanisms involved in activation, inactivation, accumulation and biotransformation of chemicals by the lungs.[34]

Attention has also been drawn of the investigators to evaluate the effects of inhaled intoxicants on ultra structural level. Phosgene poisoning caused excessive release of lactate dehydrogenase (LDH) into the serum possibly due to anoxemia and cellular dacay.[35] Witschi[36] has reviewed data on the altered *in vivo* synthesis of RNA & DNA induced by environmental pollutants. Information on the synthesis, structure and degradation of cellular DNA & RNA with specific and potent inhaled intoxicants is required to facilitate full and thorough understanding of the pathology of transcription and translation.[37] Many relevant reviews have recently appeared in the literature which clearly show that lung is a potential target organ for toxic chemicals not only for inhaled contaminants but also for chemicals requiring metabolic activation[25] and that this organ is actively engaged in the uptake, accumulation and metabolism of xenobiotics.[38] It may be emphasized that the biochemical changes induced by acute or chronic exposure to inhaled intoxicants are finally determined on the ability of clearance, adaptibility and repair to damaged process residing in the lung tissue.

3.2 Pulmonary Pathology

The primary morphologic damage caused by inhaled intoxicants may be studied under two distinct classes of materials, the reactive substances and the inert dusts. There is yet another class of environmental pollutant classified as nuisance dusts that

are invariably present in the atmosphere but their presence is felt when the concentration in the environment increases abruptly.

The damage caused by 'reactive' substances is felt immediately on inhalation as these compounds may produce irritant effects on sensory and pulmonary sites of the airway like chlorine and methyl isocyanate (MIC). However, this does not seem to be always the case. For instance phosgene which is a highly reactive chemical with potential industrial pollutant capability produces gross pathological changes only after a few hours. The intricate mechanism of action of phosgene is the acylation reactions with $-NH_2$, $-OH$, $-SH$ groups.[39] However, thickening of alveolar septa and air ducts may be seen in four hours time by histopathological studies.[40] The histological changes occuring more distally at the level of blood air barrier, edematous swelling and palicated surfaces of alveolar cells, lamellar inclusions in type II septal cells seems to be the most damaging effect produced by phosgene.[41] Later anatomical defects include membrane rupture of single endothelial cells at the blood air barrier. Paraquat induces intense morphologic alterations as early as four hours causing cell death in the pulmonary epithelium. Swelling and vacuolization of the cytoplasm of type I alveolar cells are in fact early signs of acute paraquat poisoning in rats[42] and mice.[43] Recently extensive studies have been carried out to assess the morphological lung damage in laboratory animals exposed to varying concentration of methyl isocyanate (MIC). Multiple cellular damage including desquamation of epithelial lining of the bronchioles, alveolar edema and inflammatory reactions i.e. thickening of alveolar septa were caused in rabbits exposed to MIC. The most interesting finding was the infiltration of RBC in the alveolar air spaces and emphysema in rats exposed to sublethal concentration[14] of MIC. Extensive necrosis and loss of epithelial cells have subsequently been reported in rats[13], mice and guineapigs.[44]

Pulmonary pathology evoked by 'inert dusts' has been studied in the context of occupational health hazards. Crystalline silica, carbonaceous dust and asbestos dust are classical examples of this class of compounds. In general, the inhalation of dusts evokes mobilization of macrophages. Particles of the dusts in the respirable range (0.3–5 μm) get distributed within the alveoli, interestitial tissue supporting the alveoli, airways blood vessels and lymphoidal tissue scattered throughout the lung.

The inhaled particles of crystalline silica cause lung fibrogenesis leading to emphysema.[45] In acute silicosis the interestitial fibrosis is associated with lipoproteinosis—like lesions in which the alveoli are filled with a pink staining, relatively a cellular material.

Exposure to carbonaceous dust is more severe in persons engaged in mining, processing and handling of coal. It produces dust foci in the lungs. Severe emphysema and chronic bronchitis are the most commonly occuring ill effects of carbon dust.[18]

Diffused non-nodular type of fibrosis evoked by inhaling asbestos fibres (5–10 μm) may subsequently lead to silicosis. In contrast to the experience with exposure to inert particles, to free crystalline silica and coal dust, exposure to respirable asbestos fiber is associated with an excess risk of cancer.[46] Inflammatory changes, phagocytosis and ecasement of the dust without significant stormal proliferation has been reported in rats with intratracheally injected polyvinyl chloride dust.[47]

4. CONCLUSION

Exposure to airborne toxicants can occur in farm workers engaged in insecticide spraying of crops (Jagier, Wolfe) in occupation exposure of factory (Kolmodin) and miners. Besides, the general population may be exposed to accidentally released gases as happened in Bhopal and Cameroon. Deliberately released highly toxic chemicals in the environment in wars pose a grave health hazard not only to fighting forces but public in general also may be a target to these gases. Therefore, identification of problems associated with inhalation toxicity is of paramount importance to predict the likely extent and nature of damage.

Inhalation toxicity study is a multi-disciplinary exercise and needs a close coordination between biophysicists, biochemists, histopathologists and physicians.

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