

Asbestos

Toxicological overview

Key Points

Kinetics and metabolism

- Short asbestos fibres are deposited in the upper respiratory tract where they are cleared by mucociliary action
- Longer fibres are carried into the alveolar regions and are cleared much slower thereby being retained in the lungs for longer periods
- Some fibres may be swallowed during inhalation due to the mucociliary action
- The properties of the fibres play a role in their toxicity; shorter fibres such as chrysotile are generally less potent than amphibole fibres

Health effects of acute exposure

- The major route of exposure is through inhalation and to a lesser extent ingestion
- In general asbestos is not considered acutely toxic
- Acute high level exposure may cause pleural disorders, mesothelioma or lung cancer after a long latency period

Health effects of chronic exposure

- Chronic low level inhalation exposure may cause pleural disorders, mesothelioma or lung cancer; chronic high dose exposure may cause asbestosis
- Asbestos is a category 1 carcinogen i.e. is carcinogenic to humans
- Asbestos has not been linked with any adverse reproductive outcomes in humans

Toxicological Overview

Summary of Health Effects

The main route of exposure of asbestos fibres is through inhalation and to a lesser extent ingestion.

Short thick fibres are deposited in the upper respiratory tract and are cleared by mucociliary action to the pharynx where they are swallowed. Longer thinner fibres are carried deeper into the distal airways and alveolar regions and are cleared at a much slower rate, thereby being retained in the lung for longer periods. The size and shape of the asbestos fibres can therefore determine the effect caused by their inhalation, as asbestosis is related to the number of shorter, thicker fibres, whereas mesothelioma and lung cancer are related to longer thinner fibres.

Chrysotile fibres (white asbestos) are generally $< 5 \mu\text{m}$ and crocidolite (blue asbestos), amosite (brown asbestos), anthophyllite and tremolite fibres are approximately $5 - 10 \mu\text{m}$. In general, chrysotile is recognized to be less potent regarding carcinogenicity than amosite or crocidolite.

Asbestos is generally not considered to be acutely toxic, as few immediate effects are observed following exposure. Short-term high level inhalation exposure to asbestos has been associated with lung cancer, mesothelioma and pleural disorders such as pleural plaques. Such effects may be observed following a latency period of approximately 30 years.

Epidemiology studies have shown that chronic inhalation of all types of asbestos fibres is associated with asbestosis, pleural abnormalities, mesothelioma and lung cancer. Parenchymal asbestosis is considered to be a feature of high occupational exposure whereas pleural disorders, mesothelioma and lung cancers are more commonly associated with long-term to low levels.

Clinical signs and symptoms of asbestosis include basal crackles on auscultation, dyspnoea, rales, cough and abnormal gaseous exchange, which may ultimately lead to death. Hypoxia with cor pulmonale may occur in severe cases. Although asbestosis is non-malignant, its occurrence increases the risk of lung cancer, especially in smokers.

Mesothelioma is a rare malignant tumour of the pleura or the peritoneum, induced mainly by amphibole asbestos and to a lesser extent chrysotile. Signs and symptoms of pleural mesothelioma include weight loss, fever, chest pain, breathlessness on exertion and pleural effusion whereas peritoneal mesothelioma may cause abdominal pain, change in bowel habit and weight loss. Both are usually incurable when diagnosed. The incidence of mesothelioma appears to be independent of smoking.

Lung cancer may be caused by chronic inhalation of chrysotile, amosite, anthophyllite, and mixed fibres containing crocidolite, tremolite and actinolite or tremolite with anthophyllite, although it is unknown if different fibres differ in their potency. As with mesothelioma, a latency period of approximately 30 years may occur between the initial exposure and onset of disease. Unlike mesothelioma, the incidence of lung cancer is related to smoking as asbestos and smoking act synergistically to exert their carcinogenic effect.

Conflicting data exist regarding whether the inhalation of asbestos fibres may also cause cancer at other sites, such as stomach, oesophagus, colon or rectum. Overall, following a

meta-analysis it was concluded that a causal relationship between asbestos exposure and gastrointestinal cancers could not be established.

The World Health Organisation (WHO) concluded that there was little evidence that ingested asbestos is hazardous to health and therefore did not feel it necessary to establish a health-based guideline value for drinking water.

The International Agency for Research on Cancer (IARC) reviewed available data on the carcinogenicity of asbestos. Overall, there was sufficient evidence for carcinogenicity and asbestos was classified as group 1, namely carcinogenic to humans. Although not entirely established, asbestos may be considered a genotoxic carcinogen hence is thought not to exhibit a threshold under which adverse effects are seen. There is evidence that chrysotile is less potent than the amphiboles, but as a precaution chrysotile has been attributed the same risk estimates, although no threshold has been identified for carcinogenic risks of chrysotile.

Kinetics and metabolism

Asbestos consists largely of fibres that are generally insoluble and do not undergo absorption, distribution and metabolism as do most other non-fibrous chemicals.

The main route of exposure of asbestos fibres is through inhalation and to a lesser extent ingestion. It is unlikely that appreciable amounts of asbestos will be absorbed following dermal exposure [1].

Following inhalation, asbestos fibres are deposited on the epithelial surface of the respiratory tract. The fate of the asbestos fibres depends on the site of deposition and the aerodynamic characteristics [1-2]. Shorter thicker fibres (> 3µm) are deposited in the upper respiratory tract, whereas longer thinner fibres are carried deeper into the distal airways and alveolar regions [1-2]. Most of the fibres that are deposited in the upper airway are transported by mucociliary action to the pharynx, where they are swallowed. Fibres that are short enough to be ingested by macrophages are thought to be removed through phagocytosis [3].

Longer fibres are cleared at a much slower rate and may undergo fragmentation, splitting or dissolution. Therefore a higher proportion of longer fibres is retained in the lungs [3]. Due to the differences in structure and its longer fibre length, chrysotile is more likely to be deposited in the upper airways of the respiratory tract and is therefore cleared more efficiently from the lungs compared with amphibole fibres [2-3].

A small fraction of shorter fibres may also remain in the lungs for a longer period of time, and may penetrate through the epithelial layer of the lungs into the lymphatic system or the blood. Fibres that reach the lymphatic system are then able to reach other tissues of the body and those that enter the gastrointestinal tract, either by ingestion following inhalation or mucociliary transport from the lungs are mostly excreted in the faeces [1-2].

Ingestion of asbestos is not a major route of exposure. Ingestion of asbestos may accompany inhalation due to fibres being cleared from the respiratory tract by mucociliary action. Few ingested fibres pass through the wall of the gastrointestinal tract and reach the blood, lymph and urine hence most will be excreted in the faeces. Therefore the risk of non-carcinogenic injury to the lungs, heart, liver, kidney or skin following absorption from the GI tract is minimal [2, 4]. However, animal studies reported fibres in kidney, liver, brain, heart and spleen of rats fed only an asbestos-containing diet, supporting the hypothesis that fibres may pass through the gastrointestinal tract [1].

Asbestos fibres can pass through the skin. However, no studies have shown that fibres enter systemic circulation following dermal exposure [2].

Sources and route of human exposure

Asbestos is a group of naturally occurring fibrous serpentine (chrysotile) or amphibole (crocidolite, amosite, anthophyllite, tremolite and actinolite) minerals. Asbestos minerals are widely spread throughout the earth's crust. Chrysotile, the most abundant and commercially important form, is present in most serpentine rock formations and in many soils [5].

The main route of exposure of asbestos fibres is through inhalation and to a lesser extent ingestion [4, 6].

Human exposure to asbestos underwent a rapid increase over the past 100 years as it was used, due to its specific characteristics, in >3000 products. Therefore asbestos fibres are ubiquitous in the environment. Commercial use of asbestos peaked in the 1970s but bans on importation, supply and use of blue and brown fibres in 1985 and chrysotile in 1999 have contributed to the declining presence of asbestos. However, insulating materials in buildings and products manufactured before the ban may still exist [4, 6].

Asbestos is prevalent in the three main environmental media, namely air, water and soil. The majority of asbestos exposure arises from air due to natural weathering of asbestos-containing rock, which may be enhanced by human activity. It has been suggested that the amount emitted from natural sources may be greater than that emitted from industrial sources but overall, very little is known about the amounts arising from natural sources [4-6].

Emission of asbestos from human activities in the past resulting in potential human exposure may be separated into four main categories [5-6]:

- Product manufacture (thermal insulation, brake shoes, floor tiles, cement);
- Construction activities (removal or maintenance of previously installed asbestos in buildings and demolition of such buildings);
- Transport, use and disposal of products containing asbestos.

Indoor air may become contaminated with asbestos fibres from building materials, especially if damaged, including asbestos pipe insulation, boiler coverings and floor and ceiling tiles [4]. A summary of asbestos in air measurements reported asbestos concentrations in different environments [4];

- Rural areas (outdoors – remote from asbestos emission sources): below 0.0001 fibres ml⁻¹
- Urban areas (outdoors) – general levels may vary from below 0.0001 fibres ml⁻¹
- In buildings without specific asbestos sources – generally below 0.001 fibres ml⁻¹

Drinking water may become contaminated with asbestos fibres from natural sources such as erosion of rock, or man-made sources such as industrial effluents, atmospheric pollution, disintegration of asbestos-containing products and asbestos cement pipes in the distribution system [5, 7]. Exfoliation of asbestos from asbestos-cement pipes is related to the aggressiveness of the water supply [7]. Surveys of asbestos concentrations in raw and treated water in the United Kingdom suggest that most drinking water contains asbestos fibres, the concentration of which varies between none detectable and 1 million fibres L⁻¹ [8]. The limited data available suggest that exposure to airborne asbestos released from tap water during showering and bathing is negligible [7].

Soil may also be contaminated with asbestos due to the weathering of natural asbestos deposits or by land-based disposal of waste materials containing asbestos, although current regulations now restrict the disposal into landfills [1].

Once liberated in the environment asbestos persists for an unknown period of time [5].

Health Effects of Acute / Single Exposure

Human Data

General toxicity

The size and shape of the asbestos fibre appear to play a major role in the toxicity, as both affect the capacity of the lung to effectively remove them from the body. Asbestosis is related to the number of shorter, thicker fibres, whereas mesothelioma and lung cancer are related to longer thinner fibres (table 1). Chrysotile fibres (white asbestos) are generally $< 5 \mu\text{m}$ whereas crocidolite (blue asbestos), amosite, anthophyllite and tremolite fibres are approximately $5 - 10 \mu\text{m}$. It is recognized that chrysotile is generally less potent than amosite or crocidolite [3-4, 9].

Table 1. Effect of inhalation of different size asbestos fibres

Asbestos-induced effect	Length of fibre (μm)	Width of fibre (μm)
Asbestosis	$> 2 \mu\text{m}$	$> 0.15 \mu\text{m}$
Mesothelioma	$> 5 \mu\text{m}$	$< 0.1 \mu\text{m}$
Lung cancer	$> 10 \mu\text{m}$	$< 0.15 \mu\text{m}$

Acute, high level exposure to asbestos fibres can cause pleural disorders, mesothelioma and lung cancer after a long latency period, whereas chronic exposure to higher doses (concentrations not given) are more likely to be related to parenchymal asbestosis as well as lung cancer [4].

Inhalation

Acute exposure to asbestos fibres does not produce immediate acute effects other than some irritancy of skin, eyes and lungs with high concentrations. Temporary breathing difficulties have been reported in individuals exposed to high concentrations of asbestos dust [2].

Short-term high level exposure to asbestos has been associated with lung cancer, mesothelioma and pleural disorders such as pleural plaques although risks are likely to be very low [4].

Ingestion

No data on acute toxicity in humans following oral exposure was available.

Dermal / ocular exposure

Asbestos fibres may penetrate the skin and cause benign lesions around the implanted fibres, such as warts and corns, known as asbestos corns. Approximately 60 % of workers installing amosite insulation in the past reported lesions on the hands within 10 days [2].

Delayed effects following an acute exposure

Most health effects caused by asbestos occur after a latent period following exposure. Asbestos is carcinogenic by inhalation, and does not produce acute effects, but lung toxicity (the target organ) may be manifest after many years. Clinical manifestations often occur approximately 30 years after the first exposure. However, the risks of serious long-term health effects from a single exposure are judged to be very low [6].

Animal and In-Vitro Data

Inhalation

Rats exposed to asbestos (concentration not stated) for 14 days developed local inflammatory lesions in the terminal bronchioles and progressive fibrosis occurred within a few weeks of exposure [2].

Ingestion

A single oral exposure of rats to chrysotile (5 – 100 mg kg⁻¹) produced an increase in thymidine in the stomach, jejunum and duodenum, suggestive of an immediate response of cellular proliferation and DNA synthesis [2].

Dermal / ocular exposure

No data on acute toxicity in animals following dermal or ocular exposure was available.

Health Effects of Chronic / Repeated Exposure

Human Data

Inhalation

Chronic inhalation of all types of asbestos fibres can cause a number of abnormalities such as;

- pleural asbestosis (now called asbestosis-related pleural abnormalities)
- parenchymal asbestosis
- mesothelioma of the pleura and peritoneum and
- bronchial carcinoma [3, 7, 10].

Pleural asbestosis (asbestosis-related pleural abnormalities)

Inhalation of asbestos can cause irreversible diffuse interstitial fibrosis of the lung, known as asbestosis. Pleural asbestosis or asbestosis-related pleural abnormalities include pleural plaques, mainly involving the parietal pleura, and pleural thickening involving the visceral pleura.

Pleural plaques are discrete fibrous or calcified thickened areas that arise from the surface of the parietal pleura. They are usually asymptomatic without clinically important findings and may be observed without parenchymal asbestosis. Pleural plaques are not precursors of lung cancer, although many affected people have an increased incidence of lung cancer. Pleural plaques may be observed in 20 – 60 % of individuals occupationally exposed to asbestos and are most likely caused by the migration of inhaled asbestos to the pleura [4, 10].

Pleural thickening by definition is a homogeneous uninterrupted pleural density. It can occur with or without pleural effusion and may or may not be associated with asbestosis. It is usually asymptomatic but in severe cases can cause signs and symptoms of restrictive lung disease [10-11].

Parenchymal asbestosis

Parenchymal asbestosis results from a prolonged inflammatory response stimulated by the presence of fibres in the lung, leading to fibrosis of the lung parenchyma or the pleural tissue [2]. Asbestos fibres are resistant to breakdown in the lungs, thereby initiating a continual inflammatory response, even after exposure has ceased. It is estimated that cumulative exposure of 17-75 fibres-year ml^{-1} could cause fibrotic lesions and 3.5-300 fibres-year ml^{-1} could be fatal [2, 10].

Clinical symptoms may take up to approximately 30 years to develop after onset of exposure, although radiological differences may be observed earlier [2, 4-5]. The main clinical symptoms of asbestosis are basal crackles on auscultation, dyspnoea, rales, cough, abnormal gaseous exchange and enlargement of the heart, which may ultimately lead to death [2, 10]. Hypoxia with cor pulmonale may occur in severe cases [6].

In a recent review of epidemiological data of asbestosis exposure-response relationships for chrysotile, it was concluded that 'asbestotic changes are common following prolonged exposures of 5 – 20 fibres ml^{-1} ' corresponding to cumulative exposures of 50 – 200 fibres

year ml⁻¹ for a 10-year exposure, and that 'the risk at lower exposure levels is not known' [1, 5].

Parenchymal asbestosis is considered to be a feature of high occupational exposure although cases have been reported following an acute exposure to high concentrations of asbestos (concentrations not specified) [4, 6]. In contrast, parietal pleural plaques are more commonly seen following low occupational exposure, or those that have undergone environmental exposure. However, as asbestosis is rarely observed in relation to non-occupational asbestos exposure WHO concluded that environmental concentrations of asbestos are not sufficient to cause asbestosis [6].

Although asbestosis is non-malignant, its occurrence increases the risk of lung cancer, especially in smokers. There is some disagreement as to whether asbestosis is merely a marker of high-dose exposure or whether the interstitial fibrosis seen in asbestosis induces cancer, although lung cancer may develop without asbestosis [6].

Mesothelioma

Mesothelioma is a rare malignant tumour of the pleura or the peritoneum. The majority of cases reported are a result of occupational or para-occupational exposure to asbestos [3, 6, 10].

The majority of cases of mesothelioma arise following exposure to crocidolite and less frequently to amosite. Chrysotile only seldom causes mesothelioma, unless mixed with amphibole fibres [12]. This is mainly due to the long, thin dust fibres that are produced during technical processes involving amphiboles. When inhaled, such fibres are more resistant in the body and have a lower lung clearance than chrysotile. It is interesting to note that one study of a large group of workers occupationally exposed to chrysotile alone showed no incidence mesothelioma [3, 6, 9, 12-13].

Mesothelioma, in general, may occur following chronic low asbestos exposure, and peritoneal mesothelioma is associated with higher levels of asbestos exposure than pleural mesothelioma. In some cases, a very short exposure period may be sufficient to initiate the onset of the tumour [4].

Pleural mesothelioma initially causes few or non-specific symptoms such as weight loss and fever. As the disease progresses chest pain, breathlessness on exertion and pleural effusion may occur. Peritoneal mesothelioma may cause abdominal pain, change in bowel habit and weight loss [10]. Both are usually incurable when diagnosed [6, 9].

As with asbestosis, mesothelioma has a long latency period. A minimum of ten years from initial exposure is usually required. In most cases however the latency period is between approximately 30 years, although higher exposures may shorten the time frame [4, 9].

Bronchial carcinoma.

Many studies have been carried out to investigate the carcinogenicity of inhaled asbestos fibres. Occupational exposure to chrysotile, amosite, anthophyllite and mixed fibres containing crocidolite has been reported to cause lung cancer, as have minerals containing tremolite and actinolite or tremolite mixed with anthophyllite [12]. Although all types of asbestos can cause lung cancer, it is unclear whether they differ in their potency. In some studies, exposure to chrysotile resulted in no increase in risk ratio or only a slightly elevated risk ratio for lung cancer [12]. In contrast, some studies have reported that fibres found in the lung are predominately amphibole fibres although a few cases reported that mainly or only chrysotile fibres were found [3-4, 12-13].

Exposure to asbestos fibres may cause all four major types of lung cancer, namely squamous cell carcinoma, adenocarcinoma, large-cell carcinoma and small-cell carcinoma [4]. A latency period of approximately 30 years or more may occur between the time of initial exposure and tumour occurrence [4, 12-13].

Both asbestos and smoking independently increase the incidence of lung cancer, but together they act in a synergistic manner, whereas the risk of mesothelioma appears to be independent of smoking [12-13].

Carcinoma of other sites

Several mortality studies have also revealed that inhalation of asbestos may cause small increases in the incidence of death due to cancer of the stomach, oesophagus, colon or rectum. Other mortality studies however, failed to show a significantly increased risk of cancer incidence [1]. Following a meta-analysis of available studies, it was concluded that the available data 'do not establish a causal relationship between occupational exposure to asbestos and the development of gastrointestinal cancers' [1]. Excess cases of kidney, brain, bladder, larynx or haematopoietic cancers have also been noted in a number of studies. However, overall it was concluded that the evidence for such cancers was not strong [1].

Cardiovascular effects

Asbestos does not exert a direct effect on the cardiovascular system following inhalation. However, increased cardiovascular disease in asbestos workers has been reported. Lung fibrosis (asbestosis) following asbestos inhalation may cause an increased resistance to capillary blood flow in the lungs, resulting in pulmonary hypertension and cor pulmonale. Such heart failure may also arise with less severe fibrosis in patients with chronic obstructive pulmonary disease (COPD) or those that smoke. Pulmonary hypertension can also arise, in most cases prior to the decreased lung function being clinically detectable. Chronic constrictive pericarditis has also been reported [1, 4, 11].

Gastrointestinal effects

The gastrointestinal tract is directly exposed to asbestos, as fibres which are deposited in the respiratory tract following inhalation, may be swallowed. However, there is no evidence to suggest that asbestos increases the risk of non-carcinogenic and carcinogenic effects in the gastrointestinal system following inhalation [1].

Immunologic effects

Immunological changes have been reported following occupational, but also environmental exposure [4].

As asbestos-induced fibrosis progresses, patients may have an altered immune response as they exhibit antinuclear antibodies and rheumatoid factors. In addition, cell-mediated immunity is commonly decreased in patients with asbestosis, including a progressive decrease in lymphocytes. Although not well understood, it is thought that such a depression in immune function may play a role in the aetiology of asbestos-induced carcinoma [1, 4].

Ingestion

Various studies in humans have reported that ingestion of asbestos causes little or no risk of non-carcinogenic illness [1].

Conflicting data have been reported regarding the carcinogenicity of ingested asbestos fibres. Mortality studies of asbestos workers have shown an increased incidence of cancer of the larynx, kidneys and gastrointestinal system, including the oesophagus, stomach, colon

and rectum. Authors hypothesised such an increase to be due to ingestion of fibres. In contrast, other epidemiological studies failed to show any significant association between asbestos exposure and extrathoracic tumours [4, 12].

Many epidemiology studies have also been carried out in populations that drink water with high concentrations of asbestos. Overall, there has been little convincing evidence of the carcinogenicity of ingested asbestos. The WHO concluded that there is no consistent evidence that ingested asbestos is hazardous to health and hence did not feel the need to establish a health-based guideline value for asbestos in drinking water [7].

Dermal

Small warts or corns may develop on the skin following dermal contact. Such lesions are thought to be due to penetration of the skin by a macroscopic spicule, although fibres could not be identified on histological examination of the corns [1].

Genotoxicity

Epidemiology studies of asbestos workers, residents in asbestos-rich areas and patients with mesothelioma or lung cancer suggest that asbestos is genotoxic as chromosomal aberrations and sister chromatid exchange were significantly higher in peripheral blood lymphocytes of exposed individuals, compared with non-exposed controls in a number of studies [1].

Carcinogenicity

The International Agency for Research on Cancer (IARC) reviewed available data. Overall, there was sufficient evidence for carcinogenicity and asbestos was classified as group 1, namely carcinogenic to humans [13].

Several authors have produced estimates indicating that a population, of which 30% are smokers, with a lifetime exposure to asbestos at concentrations of 1000 F m^{-3} (0.0005 F ml^{-1} or 500 F m^{-3} , optically measured) would have an excess risk of lung cancer in the order of 10^{-6} - 10^{-5} and the risk of mesothelioma would be in the range of 10^{-5} - 10^{-4} . These ranges were proposed to provide adequate health protection [6].

A WHO Task Group expressed concern over the reliability of estimating the risk to human health from asbestos. Risk estimates are based on a large set of epidemiology data from occupational studies. Such data have been extrapolated to concentrations found in the environment. It was felt that the risk estimates proposed could be used only to obtain an approximation of the risk of lung cancer or mesothelioma from environmental exposures to asbestos [6].

Although there is evidence that chrysotile is less potent than the amphiboles, as a precaution chrysotile has been attributed the same risk estimates. No threshold has been identified for carcinogenic risk of chrysotile [6].

Reproductive and developmental toxicity

Female workers exposed to asbestos cement dust via inhalation experienced reproductive disorders. In addition, male railway builders who inhaled asbestos had sex organ abnormalities. However, such workers were also exposed to other chemicals including carbon monoxide, nitrogen dioxide, acrolein and formaldehyde as well as asbestos [1].

Few studies were identified regarding the reproductive effects following oral exposure to asbestos [1].

Chrysotile fibres have been reported in lung, liver and placenta of still born infants hence transplacental transfer of asbestos is thought to occur, although this has not been linked with any adverse reproductive outcomes in humans [11].

Animal and In-Vitro Data

Inhalation

Many chronic inhalation studies have been carried out to investigate the toxicity of different asbestos fibres in laboratory animals.

Several species such as rats, hamsters, guinea pigs and monkeys developed fibrosis following exposure to chrysotile and amphibole asbestos, the incidence and severity of which were dose-related. In general, it was observed that shorter fibres were generally less fibrogenic [3].

Guinea pigs and monkeys were exposed to chrysotile and amosite dust (30000 particles ml⁻¹), for 8 hours day⁻¹, 5 days week⁻¹ for 49 weeks year⁻¹. Both chrysotile and amosite produced pulmonary fibrosis, interstitial pneumonitis, metaplasia of the epithelium of alveolar ducts and cor pulmonale in guinea pigs. Three of the monkeys died after exposure to both chrysotile and amosite [2]. In a further study, rats were exposed to amosite, anthophyllite, crocidolite and chrysotile dust (9.7 – 14.7 mg m⁻³) for 7 hours day⁻¹, 5 days week⁻¹ for 3, 6, 12 or 24 months. Results showed an increase in severity of asbestosis with increasing dose [2].

Other studies, in which rats were exposed to chrysotile, crocidolite or amosite at 2 or 10 mg m⁻¹ for 12 months reported that all malignant pulmonary tumours occurred due to the chrysotile fibres, predominantly those over 20 µm in length [3].

Several studies induced fibrosis in animals by inhalation or intratracheal exposure to chrysotile, amosite, anthophyllite, crocidolite or tremolite (concentrations not stated). Results showed that crocidolite causes more severe inflammation than chrysotile and is retained in the lungs for longer periods [1]. Although fibrosis has been reported in several animal species an increased incidence of bronchial carcinoma and mesothelioma has only been documented in the rat [3].

Overall, data have shown that fibrosis, bronchial carcinoma and pleural mesothelioma may arise following inhalation of chrysotile and amphibole fibres, but there was no increase in tumours at other sites [3].

Ingestion

Several studies investigating the toxic potential of ingested asbestos have been carried out.

In a National Toxicology Program (NTP) study, male and female rats and Syrian Golden hamsters were administered 1% short and intermediate length chrysotile in the diet over their lifetime, equating to approximately 500 or 830 mg kg⁻¹ day⁻¹ for rats and hamsters, respectively. A similar study was also carried out by exposing male and female rats to 1% crocidolite, amosite or tremolite for life. None of the different forms of asbestos affected survival or induced any signs of toxicity [1-2].

Similarly, rats were administered 0.5 or 50 mg chrysotile for 14 months, after which time no adverse effects were observed in the gastrointestinal tract, although structural changes in the villi of the ileum were noted. Moreover, following a significant increase in [³H] thymidine incorporation in the gastrointestinal tract it was suggested that asbestos interferes with DNA metabolism in the rat [2].

Rats fed margarine containing 5 mg g⁻¹ amosite, crocidolite or chrysotile (250 mg week⁻¹) for 25 months did not show signs of gastrointestinal damage, although occasional asbestos fibres were seen in several tissues [2].

Most ingested asbestos fibres are not absorbed into the body hence the GI epithelium is the most directly exposed. A few studies in rats showed biochemical changes in cells following chronic oral exposure to 20 – 140 mg kg⁻¹ day⁻¹ chrysotile. However, no non-neoplastic regions were identified in several animal studies, including the NTP studies on lifetime exposure of rats and hamsters to asbestos [1].

Overall, there was no conclusive evidence from the toxicological studies carried out that ingested asbestos is carcinogenic [3, 5].

Genotoxicity

Many studies have been carried out to investigate whether asbestos fibres interact with DNA directly or indirectly via the induction of oxidative stress. Cell free assays have demonstrated that chrysotile, amosite and crocidolite all cause lipid peroxidation. Moreover, chrysotile causes the breakage of isolated DNA but it has been hypothesised that this may be due to the generation of reactive oxygen species attributed to the surface area of the fibres [5].

Data from several *in-vitro* assays demonstrated sister chromatid exchanges, chromosomal aberrations and anaphase abnormalities in Chinese hamster cells thus authors reported chrysotile, amosite and crocidolite to be weakly mutagenic. In contrast, chrysotile and crocidolite did not cause DNA breakage in tracheal epithelial cells [3, 5].

In-vivo and *in-vitro* mutagenicity studies have given equivocal results. Asbestos was not mutagenic in *Salmonella typhimurium* and *Escherichia coli*, but gave a mutagenic response in the *S. typhimurium* TA 102 strain, which is sensitive to reactive oxygen species. Similarly, *in-vitro* genotoxicity assays using mammalian cells reported both negative and positive data [1]. Moreover, the UICC reference samples of asbestos did not show mutagenic activity in bacterial assays [3]. Overall, data suggest that asbestos may have mutagenic potential.

Asbestos was assessed by WHO Europe as part of the work on air quality guidelines. It was noted that it is prudent to assume that there is no threshold below which effects are not observed and hence exposure should be kept as low as reasonably practicable [6].

Carcinogenicity

The NTP study in which male and female rats and Syrian Golden hamsters were administered 1% short and intermediate length chrysotile in the diet over their lifetime, or 1% crocidolite, amosite or tremolite (see 'ingestion'), reported mainly negative results. Some increased frequencies of tumours were seen in the large intestine of male rats exposed to intermediate length chrysotile ($500 \text{ mg kg}^{-1} \text{ day}^{-1}$). However, the significance of this is unclear [1].

The carcinogenic mechanism induced by asbestos fibres is not completely understood. Fibres may induce reactive oxygen species that may damage DNA; physical interactions between fibres and target cells may occur, causing DNA damage; fibres may induce cell proliferation or fibres may induce chronic inflammatory reactions. It is likely that several mechanisms contribute to the carcinogenicity [5].

Overall, data from inhalation studies provide adequate evidence that asbestos fibres are a carcinogenic hazard to humans. However, the data are not adequate to provide quantitative estimates of the risk to humans, as the exposure-response data from inhalation studies are not sufficient and the sensitivity of animals to predict risk to humans is uncertain [5].

Reproductive and developmental toxicity

In a National Toxicology Program study, male and female rats were administered 1% short and intermediate length chrysotile in the diet over their lifetime, equating to approximately $500 \text{ mg kg}^{-1} \text{ day}^{-1}$ starting with the dams of the test animals. Neither fibre affected the fertility of the dams or the litter size [1-2].

In a similar study male and female rats were fed 1% crocidolite in feed, beginning with the dams before and during gestation [2]. Exposure to crocidolite did not affect fertility or litter size, but average weight gain of the pups at weaning was lower compared to offspring from non-exposed rats. Similar results were also observed in other NTP studies with tremolite and amosite [1-2].

Offspring from mice given up to $33 \text{ mg kg}^{-1} \text{ day}^{-1}$ chrysotile during gestation did not show any teratogenic abnormalities [1-2].

Asbestos given to rats in drinking water (concentration not specified) did not cause any effects on embryo survival or any teratogenic effects [11].

Asbestos was shown to cross the placenta in rats following maternal intravenous injection [11].

Mice given chrysotile asbestos in drinking water ($20 \text{ mg kg}^{-1} \text{ day}^{-1}$) did not show any abnormalities in sperm [11].

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