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EVIDENCE FOR VARIATIONS IN THE PATHOGENIC EFFECTS OF THE DIFFERENT FORMS OF COMMERCIALLY USED ASBESTOS

A Review of the Literature

J.M.G. DAVIS

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INSTITUTE OF OCCUPATIONAL MEDICINE

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SUMMARY

The main commercially used types of asbestos are chrysotile, amosite and crocidolite although relatively small amounts of anthophyllite and tremolite are also used by industry. Since the use of asbestos is subject to strict controls in most countries it is most important to know if there are differences in the potential harmfulness between the different types. Unfortunately, the available evidence is fragmentary and to some extent contradictory.

Evidence from human epidemiological studies indicates that exposure to crocidolite asbestos results in a much greater likelihood of developing mesotheliomas than exposure to other asbestos types. However, it appears certain that both chrysotile and amosite can produce these tumours in humans although anthophyllite may not be able to do so. There is also some evidence to suggest that crocidolite exposure may be more likely to produce bronchial carcinomas than chrysotile.

Extraction of asbestos dust from human lung tissue indicates that levels of amphibole asbestos are higher and chrysotile lower than would be expected from exposure data. However, two papers from France suggest that chrysotile predominates in the pleural tissues and in mesotheliomas.

In vivo experimental studies mostly using rats have used the techniques of intrapleural or intraperitoneal injection of dust or inhalation to administer different varieties of asbestos. Almost all the injection studies showed that chrysotile was at least as carcinogenic as the amphibole dusts and usually more so.

In one publication only, UICC crocidolite had produced more mesotheliomas than UICC chrysotile but a "superfine" sample of chrysotile had produced even more. All inhalation studies where tumours developed have found chrysotile more effective in producing bronchial carcinomas than amphibole dusts and chrysotile also produced at least as many mesotheliomas.

With one exception all *in vitro* studies using phagocytic cells have found chrysotile more cytotoxic than amphibole samples although one group of workers using non-phagocytic cells did find that amphibole samples killed a higher proportion of cells than chrysotile. Without exception a series of studies examining the haemolytic effects of asbestos have reported that while chrysotile is highly haemolytic, the amphiboles show very little effect.

Possible reasons for the inconsistencies between results from humans and animal experiments are discussed. For the purposes of protection of individuals exposed to asbestos, epidemiological evidence must take priority over that from animal *in vitro* experiments. However, it is important to reconcile the differences and further studies using all available techniques are required.

1. INTRODUCTION

Asbestos has been used sporadically by mankind for thousands of years although for much of the time it was little more than a curiosity. Industrial production was hardly attempted before the 1870's and expanded slowly so that it was only at the end of the 19th Century that the use of asbestos became widespread. As early as 1906 MONTAGU MURRAY in England discussed a case of pulmonary fibrosis in an asbestos worker but the recognition that this constituted a definite industrial disease was slow to develop. An account of Murray's case was not published and it was not until 1924 that COOKE reported a second known death from pulmonary fibrosis in an asbestos worker. By 1930, however, WOOD and GLOYNE were able to review 37 cases of "asbestosis". In 1935, LYNCH and SMITH reported a case of asbestosis with associated bronchial carcinoma and in the same year GLOYNE reported on two similar cases. A definite association between the two conditions was not immediately recognised, however, and as late as 1951 GLOYNE, while recording that many asbestos workers did develop bronchial carcinoma, was still uncertain whether or not this incidence was above that for the normal population. In 1955, however, DOLL reviewed all coroners' autopsies performed over a 20-year period on asbestos workers from a large factory and concluded that the incidence of bronchial carcinoma in this group was ten times higher than in the general population. Although a later paper by KNOX et al. (1965) indicated that excess bronchial carcinoma could be largely eliminated by good dust control, this hazard is now well accepted as a potential for all asbestos exposed groups. In 1960, WAGNER et al. reported a third specific hazard of asbestos exposure. They had found that numbers of the normally extremely rare tumour, the mesothelioma, were occurring in the area of Cape Province in South Africa where blue asbestos or crocidolite was mined. They had failed to find cases in areas where either chrysotile or amosite was mined and even in a second crocidolite mining area in the Transvaal. Until this date there was no evidence that variations in hazard were associated with exposure to different asbestos types and as late as 1935 LANZA et al. in an early epidemiological study made the inaccurate generalisation that "the asbestos of commerce is chrysotile". The most disturbing aspect of WAGNER's report was the statement that some mesothelioma cases had received what appeared to be extremely low

exposure to crocidolite. This and the subsequent finding of mesotheliomas in asbestos factory workers in Europe and the United States of America, some of whom have been exposed to crocidolite in addition to other dusts, gave rise to the suggestion that crocidolite exposure constituted an especially grave hazard. As a result of this, new British regulations by HM Factory Inspectorate in 1970 introduced a hygiene standard for crocidolite dust ten times lower than that for other forms of asbestos. Some other countries including Sweden have singled out crocidolite as requiring especially careful handling and are currently considering the possibility of differential standards.

Unfortunately, it has proved extremely difficult to obtain accurate human data on the relative harmful effects of the different asbestos types since as BECKLAKE pointed out in 1976 "exposure to one fibre type only is rare (usually in mining) and most production workers have mixed exposure". Many epidemiological studies on groups of asbestos exposed workers have, however, been produced and while these report in detail on the level of asbestos health hazards, it is accepted that exposure to different types of asbestos has probably occurred. Studies of this type include those by SELIKOFF et al. (1965); HILL et al. (1966); HARRIES (1968) and (1976); ELMES and SIMPSON (1971) and NEWHOUSE et al. (1972); ENTERLINE et al. (1972).

6. CONCLUSIONS

Human epidemiological data show that crocidolite has been the form of asbestos most liable to cause mesothelioma and perhaps bronchial carcinoma as well. Animal experimental studies suggest that chrysotile is more fibrogenic and produces more bronchial carcinomas following inhalation than the amphibole varieties. Whether administered by injection or inhalation, chrysotile appears to produce at least as many mesotheliomas in experimental animals as crocidolite and more than amosite or anthophyllite. In vitro studies also suggest that chrysotile is more cytotoxic and haemolytic than amphiboles in almost all cell systems examined. At present there is no definite explanation for these inconsistencies but a number of possibilities deserve consideration.

(i) It could be that rats, the most frequently used experimental animal, react differently to the various asbestos types than humans especially in relation to tumour production. However, rats are used routinely in toxicology to screen substances for carcinogenic potential and do show the same three general toxic effects of asbestos as humans, viz. fibrosis, bronchial carcinoma and mesothelioma. A better animal model is unlikely to be found.

(ii) It is possible that for all species tumour induction requires a large fraction of the lifespan. Chrysotile could well be the most chemically unstable and the most likely to dissolve in lung fluids. Chrysotile may be able to survive in rat lungs long enough to exert its full carcinogenic potential but be removed from human lungs over a period of many years. Amphibole fibres may remain in human lung sufficiently long and in sufficient numbers to provoke mesothelioma.

(iii) While in most experimental studies the dust dose was accurately known, at least by mass and more recently by fibre number and length, the levels of industrial exposure more than 30 years ago are not known with any certainty. In the experimental situation crocidolite asbestos is certainly the easiest of the asbestos types with which to generate a dense cloud. Chrysotile requires much more severe mechanical treatment to generate a cloud and the fibres tend to flocculate and produce visible

but non-respirable masses. It may be therefore that workers exposed to crocidolite in the past received doses far in excess of those applicable in chrysotile usage. There is some evidence to support this idea in the work of GIBBS and DU TOIT (1973) who reported on the levels of dust in crocidolite, amosite and chrysotile mines and mills from South Africa and Canada. These findings unfortunately were produced either by konimeter or thermal precipitator and represent both fibres and particles but it is obvious that in the past the crocidolite operation in the North West Cape was far dustier than work with amosite or chrysotile. WEILL (1979) found no evidence for increased dustiness of crocidolite operations in an American asbestos cement factory compared to processes where chrysotile only was used. However, in this case also the midget impinger was used for dust estimation and dust was expressed as particles per cubic foot of air rather than as fibres.

(iv) Another major possibility that could explain the difference between human experience and experimental studies is that the exact particle size and shape is the important factor in disease rather than fibre chemistry. It is possible that experimentalists working with crocidolite and other amphiboles were in fact using materials with different characteristics to that found in industry. This is especiall likely in the case of the gas-mask workers studied by JONES et al. (1976 who were exposed to Australian crocidolite which was little used in industry and has never been used in experimental studies. TIMBRELL (1973) suggested that the lack of mesotheliomas in the Transvaal crocidolite mining areas could be explained because the crocidolite from this area had thicker fibres than found in North West Cape Province. I was assumed that the thin fibres penetrated more easily to the pleura. Following the work of STANTON et al. (1972) and (1977) it is now generally accepted that the most carcinogenic fibre size is a length in excess of 10 microns and a diameter of less than one micron. Experimental studies have, however, indicated that all mineral fibres in this size range may be equally carcinogenic.

Some evidence for the importance of fibre size arises from the work of W & BERRY. In 1969 when they reported injection studies showing chrysoti more carcinogenic than crocidolite, the published electron microscope

photographs of the dust samples used showed that the laboratory processed crocidolite contained fewer long thin fibres than the chrysotile. In 1973, however, UICC crocidolite was used containing many more long fibres. In this case the crocidolite produced more mesotheliomas than UICC chrysotile. Only the artificially separated "superfine" chrysotile appeared more dangerous. However, both the inhalation studies of WAGNER et al. (1974) and DAVIS et al. (1978) used UICC crocidolite. In the former study it appeared no more dangerous than UICC chrysotile and in the latter it appeared much less dangerous.

From the point of view of protection of the workforce, reliable epidemiological evidence must take priority over that obtained from animal experiments. There is very strong evidence that exposure to crocidolite in the past has had a far greater potential to cause mesothelioma than has exposure to chrysotile or amosite and crocidolite should be used by industry with considerable caution if at all.

From the biological point of view, however, it is most important to determine why experimental studies have not shown an increased level of hazard with crocidolite. Until these differences have been fully explained the hazards involved in the use of the different asbestos types will not be completely understood. It is essential that further work should be carried out to identify the factors responsible for carcinogenicity. This is particularly important because, for new types of asbestos products, human epidemiological evidence cannot be available for many years and animal studies represent the only possible way of obtaining advanced warning of increased hazard. Further examination of the characteristics of dust clouds produced in the asbestos industry in all phases of production and use and the relationships between these characteristics and epidemiological, animal and cell toxicity data is required to elucidate these problems.