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

A Review of the Literature

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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).

2. EPIDEMIOLOGICAL EVIDENCE RELATING TO THE RISK OF ASBESTOS EXPOSURE IN HUMANS

2.1 Evidence from exposure to one dust type

For the most part the only asbestos workers to be exposed to a single dust type are miners and millers and epidemiological studies of some of these groups have provided a little information on the relative effects of the different asbestos types. In 1960 WAGNER et al. published a report of 33 cases of pleural mesothelioma from South Africa. All but one of these were shown to have had some exposure to crocidolite asbestos. In 25 out of the 33, however, the exposure to crocidolite had not been industrial, but the people involved had lived in the mining areas, in some cases for only a few years as children. It was concluded, therefore, that the latent period for mesothelioma induction by asbestos was long but that a low dose might be sufficient for carcinogenesis.

McDONALD et al. in 1971 reported studies on a population of over 11,000 workers in the Quebec Asbestos Mining Industry where chrysotile is exclusively mined. The overall mortality of this group was lower than expected for the population of Quebec but in the highest dust exposure category comprising 5% of the cohort, the age standardised death rate was 20% higher than in other groups. This increase was largely accounted for by an excess of bronchial carcinomas but three mesotheliomas were also found. In 1974 McDONALD et al. enlarged the previous study to include a total of 28,000 men and confirmed their previous findings. Respiratory cancers appeared related to dust exposure but the overall excess of deaths from this cause was at most 50% more than expected. Five mesotheliomas were recorded.

WEBSTER in 1973 updated the information on the occurrence of mesotheliomas in South Africa. It was reported that 158 out of 360 recorded cases had had definite exposure to asbestos but only 88 of these came from the mining areas where exposure to only one type of asbestos could be assumed. Of the 88 cases 84 had been exposed to crocidolite and four to amosite.

In 1979 IRWIG et al. reported studies on 1,144 men from the South African crocidolite mines and 548 who were involved in the mining of amosite. It was claimed that pleural abnormalities visible on chest radiographs were significantly more frequent (at the 10% level) among the amosite miners than among those who had worked with crocidolite. There were

no other differences in recorded pathology between the two groups.

In 1973 both AHLMAN et al. and MEURMAN et al. in separate publications reported on the incidence of disease in Finnish anthophyllite workers. AHLMAN studied a population of 1,249 who had worked between 1936 and 1972 but only 170 of these had an exposure history of over 11 years. Among the whole group there were 105 cases of asbestosis. The population studied by MEURMAN et al. consisted of 1,041 individuals. Of 248 who were deceased, 21 had lung cancer compared to 13 expected but this difference was not statistically significant. No mesotheliomas were found.

Apart from the mining industry a few studies do exist of groups of workers where it is claimed that exposure was to a single asbestos type. In 1972 SELIKOFF et al. examined the mortality experience of a group of 230 men employed in a factory that used only amosite. Total deaths were more than twice the number expected. There were 14 cases of asbestosis and 25 cases of lung cancer where only two to three were expected. There were five deaths from mesothelioma.

JONES et al. (1976) discussed the occurrence of mesotheliomas among women who had worked on gas-mask manufacture in Britain during World War II. No more than 1,600 had been involved, many for short periods of time, yet 26 mesotheliomas had been recorded. The asbestos type used in this gas-mask production had been only Australian crocidolite.

A similar study was reported by McDONALD and McDONALD in 1978. This involved Canadian gas-mask manufacturing during World War II. The same type of Australian crocidolite was used as in Britain. Out of 199 workers who had been traced, 56 had died by 1975. Of these, nine had a mesothelioma.

2.2 Evidence from exposure to more than one asbestos dust type

Some studies on groups of people exposed to a mixture of asbestos types have attempted to distinguish between the harmful effects of each dust. Thus, ENTERLINE and WEILL (1973); ENTERLINE (1973) and WEILL et al. (1979) have reported on workers in the American asbestos cement industry. The final cohort size was 5,645 people with a 20-year

follow-up time. Exposure levels to either chrysotile or crocidolite did not appear to differ between the dusts but the standardised mortality ratios from respiratory cancer for the highest exposed groups were significantly higher for those who had had steady exposure to crocidolite and chrysotile than for those exposed to chrysotile alone. Rather surprisingly no mesotheliomas were found in this cohort although two had occurred in men with less than a 20-year follow-up period. One of these had mixed exposure including crocidolite but the other appeared to have been exposed only to chrysotile.

3. ANALYSIS OF DUST LEVELS IN THE LUNGS OF HUMANS EXPOSED TO ASBESTOS

A number of studies have been published which have involved the extraction, recognition and quantification of asbestos from human lungs and the relating of dust content to pathology. Thus, POOLEY in 1973 examined the lungs from 120 European cases of mesothelioma. He found that 37 cases contained only amphibole, 27 contained only chrysotile and the rest contained a mixture. It was reported that all the chrysotile cases had low dust levels although some of those containing amphibole had quite a high dust content. No distinction was made between the amphibole types.

SEBASTIEN et al. in 1977 examined a small series of 18 autopsy cases with varying recorded exposure. Most cases had been exposed to both amphibole and chrysotile but unless exposure had been recent, more amphibole than chrysotile was always found in the lung parenchyma. Chrysotile on the other hand was the most commonly found asbestos variety in pleural plaques. Most of this occurred as short ultimate fibrils.

In 1976 HEIDERMANNS et al. examined the lungs of 17 people with asbestosis and some cases not occupationally exposed. Fibre levels were between 1.1×10^9 and 2.7×10^{10} for asbestosis cases and 4×10^7 and 9×10^8 for controls. Fibre recognition was attempted with varying success. Among the asbestotics, amphibole was positively identified in only three cases with fairly certain identification in a further six. In no case was chrysotile identified.

LE BOUFFANT et al. also in 1976 looked at the relative amounts of amphibole and chrysotile in lung and pleural tissues obtained from 200 cases either by surgical section or at autopsy. They reported that while amphibole fibres predominated in the lung parenchyma with the amphibole/chrysotile ratio being 2.9, chrysotile predominated in the tissues of the visceral pleura. Here the amphibole/chrysotile ratio was 0.3. In the parietal pleura or in mesothelioma tissue no amphibole was found but quite large levels of chrysotile fibrils occurred almost all of which were less than 5 microns in length.

In a study on the types of asbestos fibre forming the central cores of asbestos bodies, CHURG and WARNOCK (1979) found that all of the 123 bodies examined from 21 patients contained amphibole.

The reason why most workers have found relatively more amphibole fibres than chrysotile in human lung specimens in spite of the fact that chrysotile makes up the bulk of industrial asbestos usage was probably indicated by JAURAND et al. in 1976. This group produced evidence for the chemical dissolution of chrysotile in the lung tissue and rather surprisingly found that this was most marked in the fibre core of asbestos bodies.

4. EVIDENCE ON DIFFERENCES IN ASBESTOS PATHOGENICITY DERIVED FROM ANIMAL STUDIES

4.1 Injection studies

Following his report of an association with blue asbestos exposure and mesotheliomas in humans, WAGNER (1962) showed that similar tumours could be produced by the intrapleural injection of asbestos dust in experimental animals. However, when the results of a very large study involving the injection of amosite, chrysotile and crocidolite into rats was published (WAGNER and BERRY, 1969) it was found that chrysotile produced slightly more tumours than crocidolite with only amosite showing significantly lower figures. In this study groups of approximately 100 SPF rats and a similar number of standard rats were injected with the three main asbestos types at a dose level of 20 mg. Tumour levels for the SPF and standard rats injected with chrysotile were respectively 63% and 69% while corresponding figures for crocidolite were 58% and 68% and amosite 39% and 31%.

In similar studies (WAGNER et al., 1970) the effects of varying doses of asbestos were also examined. In this case groups of 12 SPF rats were injected with doses of 0.5, 1, 2, 4 and 8 mgs of either chrysotile or crocidolite. Averaged over the doses, 36% and 19% of rats developed mesotheliomas from chrysotile and crocidolite respectively. The induction period was 100 days lower for chrysotile than crocidolite.

In a later paper (WAGNER et al., 1973) it was confirmed that crocidolite dust specially prepared from bulk samples received from Cape Province in South Africa was in general no more carcinogenic than most samples of chrysotile. A sample of specially prepared "superfine" chrysotile was, however, the most carcinogenic dust tested. This paper did include a direct comparison between the standard UICC reference samples of amosite, anthophyllite, chrysotile and crocidolite. Thirty-two rats were injected with each sample and the mesothelioma induction rates were as follows: amosite 38%, anthophyllite 25%, Canadian chrysotile 31%, Rhodesian chrysotile 23% and crocidolite 59%. The authors treated all the data relating to the animals in the different groups by a complex method of statistical analysis which they claimed gave clearer results. This produced a "carcinogenicity factor" for the different dusts of: amosite 0.66, anthophyllite 0.33, Canadian chrysotile 0.50, Rhodesian chrysotile 0.44 and crocidolite 1.45. This publication

remains the only one in which amosite has ever produced more tumours than chrysotile.

These results of WAGNER et al. were not confirmed by STANTON and WRENCH in 1972. These workers implanted a number of samples of mineral fibre including UICC amosite, chrysotile 'A' and crocidolite into groups of 30 rats. These groups developed 58%, 60% and 61% of mesotheliomas respectively. In a recent study (BOLTON et al. (in press)) intraperitoneal injection was used to compare the carcinogenic effects of a number of asbestos samples. This site proved more sensitive than the pleural cavity and the dose used (25 mgs) produced tumours in almost 100% of animals. However, there were significant differences between the tumour induction periods for chrysotile and amosite samples. Crocidolite was not used in this study. The dust samples were injected into groups of 72 rats and for four chrysotile samples the main tumour induction period was 312, 373, 400 and 438 days respectively. For two amosite samples the corresponding figures were 505 and 566 days.

A number of other workers including PEACOCK and PEACOCK (1968); REEVES et al. (1971); POTT and FRIEDRICHS (1972); POTT et al., (1976) and WIRTH (1975) have undertaken intrapleural or intraperitoneal injection studies using different varieties of asbestos and other minerals. Not all of these studies were designed specifically to compare the carcinogenic effects of asbestos samples alone and those that did use more than one asbestos type produced results that were insufficiently clear-cut to make definite comparisons.

WAGNER in 1979 adopted a new approach by examining the short-term effects of asbestos on lymph nodes following intraperitoneal injection into groups of 12 rats. Three dose levels were used, 5, 10 and 15 mgs. Five animals were examined from each group after three months and seven after six months. It was found that crocidolite produced a greater increase in lymph node weight than chrysotile. Mean lymph node weights from animals treated with chrysotile and crocidolite respectively were at the different dose levels, 24, 29 and 26 mgs, and 34, 53 and 53 mgs for the mediastinal lymph nodes and 32, 42 and 39 mgs and 55, 53 and 62 mgs for the cranial mesenteric lymph nodes.

As far as the effects of different varieties of asbestos on lung tissue are concerned, KLOSTERKÖTTER (1968) used intratracheal injection to administer long and short fibre samples of chrysotile, crocidolite or amosite to rats. Groups of 25 rats were used with each asbestos type and the dose was 30 mgs of dust. In all cases the short fibre samples produced almost no fibrosis while the long fibre samples did stimulate the production of fibrous tissue. No figures for levels of fibrosis were given but it was reported that "long asbestos fibres were strongly fibrogenic in the following order of magnitude: chrysotile, amosite, crocidolite.

4.2 Inhalation studies

Inhalation studies in animals represent the most natural approach to the study of asbestos related disease and a number of publications have reported experiments involving different varieties of asbestos, used in order to determine relative levels of fibrogenicity and carcinogenicity. Thus, HOLT et al. in 1965 reported studies in which guinea pigs were given a short but heavy exposure of either amosite, anthophyllite, chrysotile or crocidolite. The dose levels of each dust were not accurately recorded and animals were followed up for only a few months. Widespread pulmonary fibrosis was reported and no quantitative differences in reaction were noticed between the different dust types.

REEVES et al. in 1971 and 1974 treated by inhalation five different animal species with either chrysotile, crocidolite or amosite. The sizes of the various animal groups varied from 20 rabbits, to 30 mice and guinea pigs or 70 gerbils and rats. Dust exposure was at a level of approximately 50 mg/m^3 of air but it was admitted that the hammer-milling process used in dust generation resulted in much destruction of asbestos fibres and less than 2% of dust particles had an aspect ratio of more than 3:1. All species produced pulmonary fibrosis with some asbestos types. Although no methods of quantification were reported it was stated that crocidolite and amosite tended to produce more fibrous tissue than chrysotile. Only rats produced any tumours in these studies. There were two bronchial carcinomas and one pleural mesothelioma following chrysotile inhalation, one bronchial carcinoma and two pleural mesotheliomas following amosite inhalation and four bronchial carcinomas but no mesotheliomas after treatment with crocidolite.

In 1963 WAGNER had reported an inhalation study which had attempted to compare the pathogenic effects of chrysotile, crocidolite and amosite on guinea pigs and vervet monkeys. However, while the chrysotile and amosite dust samples were relatively pure, the crocidolite sample contained less than 10% asbestos and the results were not, therefore, comparable. In 1974, however, WAGNER et al. published the results of a large inhalation experiment in which rats had been treated with the UICC standard reference samples of either amosite, anthophyllite, chrysotile or crocidolite. Dose levels were approximately 10 mg/m^3 of air and a number of different dose periods were used. Groups of approximately 50 animals were exposed for either one day or three months and groups of approximately 25 animals for either six months, 12 months or 24 months. There were significant differences between the levels of pulmonary fibrosis caused by the different asbestos types ($P < 0.01$). Amosite gave the least fibrosis and anthophyllite and Canadian chrysotile the most. Crocidolite and Rhodesian chrysotile were intermediate. The overall numbers of malignant pulmonary tumours were: Rhodesian chrysotile 30, Canadian chrysotile 17, crocidolite 16, anthophyllite 16 and amosite 11. The number of pleural mesotheliomas produced were: Rhodesian chrysotile 0, Canadian chrysotile 4, crocidolite 4, anthophyllite 2 and amosite 1.

In most of the experimental studies involving asbestos inhalation there has been relatively poor characterisation of the dust cloud in terms of fibre size and shape. In 1978, however, DAVIS et al. published a report of a study in which the UICC standard reference samples of amosite, chrysotile and crocidolite have been compared at equivalent dust mass or equivalent fibre number in the dust clouds. Groups of 48 rats were used. These results indicated that chrysotile was more fibrogenic and carcinogenic than the other asbestos types. For animals examined 17 months after the end of dusting, the equal mass (10 mg/m^3) chrysotile cloud had produced more than double the pulmonary fibrosis of any other treatment ($P < 0.001$). The differences between the other four asbestos clouds were less dramatic but there appeared to be a definite gradation with the lower (2 mg/m^3) chrysotile cloud having produced more interstitial fibrosis than any of the amphiboles ($P < 0.01$). At the same time amosite appeared to have produced more damage than crocidolite but the differences were not significant. All malignant lung tumours found in this study

occurred in animals treated with chrysotile, eight and two in the high and low dose groups respectively. This finding was significant ($P < 0.001$).

5. IN VITRO STUDIES USING DIFFERENT VARIETIES OF ASBESTOS

In vitro studies have been used as an alternative approach to animal experiments for the comparison of the biological effects of different asbestos types. These studies produce results much more quickly and cheaply and it is hoped that eventually sufficient data will be available from comparisons between the two systems to be certain whether or not in vitro work can predict with accuracy the fibrogenic and carcinogenic potential of dusts. This stage has not yet been reached but data from a considerable number of studies is available. Most workers have used phagocytic cells maintained in culture but some non-phagocytic cell lines have been used as well as red blood cells.

5.1 Tests with nucleated cells

In 1968 PARAZZI et al. treated guinea pig peritoneal macrophages with both chrysotile and crocidolite. The crocidolite was a standard sample from South Africa but the chrysotile came from Balangero in Italy. This is the only occasion that this type of chrysotile has been used in experimental studies. Dose levels were 400 μg of dust to 1 x 10^6 cells. Toxicity was estimated by a fluorochromatic staining technique and by the production of lactic acid. The tests were run for a maximum of seven hours at the end of which all cells treated with crocidolite had lost their fluorochromasia but only 63% of cells treated with chrysotile. Similarly, all lactic acid production had ceased in cells treated with crocidolite within one hour of dusting. With chrysotile, production continued for almost all of the seven hours.

In 1973 ALLISON using mouse peritoneal macrophages reported that chrysotile was much more cytotoxic than crocidolite or amosite. Dose levels were 100 μg/1 x 10^6 cells and after 48 hours the percentages of viable cells were 18% (chrysotile), 62% (crocidolite) and 73% (amosite). It was suggested that with chrysotile in the absence of serum there was an immediate toxic effect when the dust particles came into contact with cells but that this was delayed by several hours if the cells were grown in a medium containing serum. No such effect was seen with amphibole dusts.

Similar results were obtained using hamster macrophages by BEY and

HARINGTON (1971) and HILLER and HARINGTON (1972). This group used dose levels of between 36 and 144 μg of dust/1 x 10^5 cells. With amosite and crocidolite the various dust doses produced little variation and at 72 hours the number of surviving cells expressed as a percentage of the undusted control figure was approximately 70% for all amosite cultures and 50% for crocidolite. Chrysotile was more cytotoxic and a dose effect was observed. The percentage of surviving cells at 72 hours was 60% for a dose level of 36 μg of dust, 35% for 72 μg and 0% for 144 μg.

ROBOCK and KLOSTERKÖTTER (1971) and (1973) treated guinea pig macrophages with the different UICC asbestos types and estimated the ability of the treated cells to reduce triphenyltetrazolium chloride (TTC). The dose level was 1.2 mg of dust to 8 x 10^6 cells. The results, which were expressed as a percentage of the very cytotoxic effect of DQ12 quartz were as follows: chrysotile 'A' 61%, anthophyllite 64%, amosite 40%, crocidolite 32% and chrysotile 'B' 30%.

Both WADE in 1976 and WRIGHT et al. in 1980 adopted a slightly different approach. In these studies the macrophage-like cell line $P388D_1$ (DAWE and POTTER, 1957) was used to improve reproducibility between experiments. Both workers reported that chrysotile samples were more cytotoxic than amphibole. WADE used chrysotile and amosite at dose levels of 10, 50 and 100 μg of dust for an initial cell concentration of 4 x 10^5. After 72 hours the percentage viability was 95.3%, 61.4% and 46% for the amosite doses and 45%, 5.7% and 0.9% for chrysotile. WRIGHT tested a series of chrysotile and amphibole samples at dose levels of 10 and 50 μg/5 x 10^5 cells. After 48 hours the percentage viability ranged between 8.4% and 25.8% for the various chrysotile samples, between 52.4% and 60% for amosite samples and was 96.4% for UICC crocidolite.

NEUGUT et al. (1978) used CHO cells, an epitheloid line derived from Chinese hamster ovary and K22 cells, an epithelial cell line derived from rat liver. In this case the results were given as growth curves rather than percentage viability at a fixed time point. It was found, however, that for both cell lines a 10 μg dose of chrysotile was more cytotoxic than either amosite or crocidolite.

Similar results have been obtained in 1968 by SCHLIPKOTER using a number of asbestos type and L cells which are a fibroblastic cell line. Results had also been expressed as growth curves and a dose level of 2.4 mgs/1 x 10^6 was used. The asbestos types in descending order of cytotoxicity were chrysotile, amosite, crocidolite and anthophyllite.

CHAMBERLAIN and BROWN (1978) tested the effects of a series of dusts including UICC asbestos samples on two non-phagocytic cell lines. These were the V79-4 line originally obtained from Chinese hamster lung and the A549 line which appears to have the characteristics of type II alveolar epithelial cells. While quartz dust had little effect on these cells all the asbestos varieties were cytotoxic. In these experiments amosite was the most cytotoxic followed by crocidolite, UICC chrysotile 'B', anthophyllite and "superfine" chrysotile. It was suggested that while this test system gave little information on the fibrogenicity of a dust it might give a better idea of carcinogenic potential. It was pointed out, however, that in animal experiments the "superfine" variety of chrysotile had proved more carcinogenic than any other asbestos type.

5.2 Tests involving the haemolysis of erythrocytes

The following workers have tested the ability of asbestos dust samples to haemolyse erythrocytes. In 1967 MacNAB and HARINGTON tested a 2% suspension of sheep erythrocytes with a number of dusts including the main asbestos types. Incubation was for a period of 50 min at 37°C. While chrysotile caused 78% haemolysis in this time amosite, anthophyllite and crocidolite asbestos lysed erythrocytes only after prolonged incubation.

In 1968 SCHLIPKOTER examined the ability of different asbestos types to lyse human red cells in different buffers at a variety of pH values. Results were expressed as the amount of asbestos by weight needed to produce 30% haemolysis. While the amount of chrysotile was very low, the figures for anthophyllite, amosite and crocidolite were at least in order of magnitude greater.

Also in 1978 VAILLE and SOUCHARD tested the haemolytic effect of three samples of chrysotile and three amphibole varieties. While chrysotile

samples produced between 92 and 94% haemolysis, anthophyllite produced 26%, chrysotile 9% and amosite 6%.

Very similar results were obtained in 1970 by SCHNITZER and PUNDSACK. These workers also tested the haemolytic effects of a number of asbestos samples on a 2% suspension of sheep red cells. After two hours' incubation, all of a series of chrysotile samples had caused marked haemolysis, usually over 95%. No figures were given for the results of tests using naturally occurring UICC samples of amosite, crocidolite, anthophyllite and tremolite but it was stated that "none of the samples of amphibole asbestos minerals was substantially active".

WRIGHT et al. in 1980 reported a study of the same type in which the haemolytic activity of a number of chrysotile samples ranged from 44% to 85%. The corresponding figure for UICC amosite was 2.7% while the other amosite samples and crocidolite were less than 1%.

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 especially 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. It 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 WAGNER & BERRY. In 1969 when they reported injection studies showing chrysotile 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.

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ASBESTOS INTERNATIONAL ASSOCIATION
(Limited by Guarantee)

68 GLOUCESTER PLACE, LONDON W1H 3HL

MEMORANDUM

AIA/8/PAC

TO: Member Associations

28 January 1982

FROM: Director General

Subject: Summary of Main Features of Warning Labels

Enclosed is a copy of our schedule "Summary of Main Features of Warning Labels" which incorporates all amendments notified up to 15 January 1982.

Will you please let us know if you wish any alterations to be made.

for DIRECTOR GENERAL

AIA Information Memorandum No 4/81

ASBESTOS INTERNATIONAL ASSOCIATION

AIA/8/PAC
15th January 1982

Summary of Main Features of Warning Labels

JNTRY (1)	AIA LOGO (2)	LOGO WORDING (3)	ADDITIONAL INFORMATION FOR CONSUMER (4)	VOLUNTARY/ COMPULSORY (5)	PRODUCT CONCERNED (6)	START DATE (7)
\C* recomended)	Yes	Attention Contains asbestos. Observe safety rules. Avoid breathing dust (See Annex 1 for language of concerned country).	To suit country and product. Some countries are producing regulations making labelling compulsory.	Varies	All possible.	Various
ıtralia ames Hardie l others. l States)	Yes	Caution This product contains asbestos. Breathing asbestos dust can damage health. Keep dust down.	Where possible part of label. Otherwise in brochures or on outside of container.	Voluntary	All unless no work done on them before use. Tie-on labels.	Operating
ıtria	Yes	Attention Contains asbestos. Observe safety rules. Avoid breathing fine dust.	Information leaflet incorporating logo and pictures about dust suppressed tools.	Voluntary	Asbestos cement sheet and pipes.	Operating
lgium ternit)	Yes	Attention Contains asbestos. Observe safety rules. Avoid breathing dust. (In French, German & Dutch)	On a leaflet in three languages. Logo wording on back until logo and wording are produced separately.	Voluntary	Asbestos cememt sheets and pipes, brake linings.	Operating
nada ll mines)	Yes	None	Separate full warning label on outside of package. Logo to be alongside where possible.	Voluntary	Raw fibre.	Operating

Advisory Council of the AIA.

INTRY (1)	AIA LOGO (2)	LOGO WORDING (3)	ADDITIONAL INFORMATION FOR CONSUMER (4)	VOLUNTARY/ COMPULSORY (5)	PRODUCT CONCERNED (6)	START DATE (7)
ırus	Yes			Voluntary	Raw fibre.	Operating
ımark	Yes	See EEC		Voluntary	Asbestos cement sheets.	To start soon
ıland	Yes		Recommendation to use dust-free tools.	Voluntary	All except asbestos cement.	Operating
ınce	Yes	Contents asbestos. Avoid breathing dust during cutting. Observe instructions for use.	The label sizes and colours are as used in UK.	Voluntary	Effective 1st April 1982, all products containing asbestos.	a/c products operating
:many	Yes	Attention Contains asbestos. Avoid breathing fine dust. Health Hazard. Observe Safety Rules (in German).	<u>The following information has to be attached to asbestos-containing products</u> 1. "Contains asbestos" 2. Name & address of producer 3. "Observe the Directive for handling dangerous substances. Appendix II Carcinogenic Substances" <u>Exporters to FRG should attach the following label:</u> Enhalt Asbest Arbeitsstoff-Verordnung, Abschitt krebserzeugende. Arbeitsstoffe der Gruppe II beachten.	Columns 2 & 3 are voluntary but 4 is compulsory	a/c sheets & pipes. Textiles (yarns, cloth, etc, as well as packings & compensator).	Operating
ıece	Yes	Contains asbestos. Observe Safety Rules. Avoid breathing dust.	On bags of fibre from Mabe mines by end of 1981. Others in near future.	Voluntary	Initially asbestos fibres then a/c products.	By end 1981

UNTRY (1)	AIA LOGO (2)	LOGO WORDING (3)	ADDITIONAL INFORMATION FOR CONSUMER (4)	VOLUNTARY/ COMPULSORY (5)	PRODUCT CONCERNED (6)	START DATE (7)
aly	Yes	Attention Contains asbestos. Avoid breathing dust. Follow instructions for use.	Balangero mine only on voluntary basis. No-one else using it.	Voluntary	Raw fibre.	Operating
aland	Yes	Take care with asbestos. Warning. Breathing asbestos can damage health. Observe the safety rules.		Voluntary	50% of all products.	Operating
pan	No	N/A	Leaflet instructions, when product contains 5% or more asbestos by weight. All exports have label in English.	Compulsory		Operating
herlands	Yes		Consumer goods only by 1982 (ie goods sold through shops and similar channels to persons for their own use)	Compulsory	a/c sheets.	Operating
public of th Africa	Yes	Caution. Contains asbestos fibres. Avoid making dust. Breathing asbestos dust may cause serious bodily harm.		Voluntary	Raw fibre.	Operating

JNTRY (1)	AIA LOGO (2)	LOGO WORDING (3)	ADDITIONAL INFORMATION FOR CONSUMER (4)	VOLUNTARY/ COMPULSORY (5)	PRODUCT CONCERNED (6)	START DATE (7)
ɜden	on some warning labels	N/A	1. FOR YOUR INFORMATION This item contains asbestos but has been processed with a dust inhibitor which, with normal handling, prevents the spreading of asbestos fibres. 2. THIS PART CONTAINS ASBESTOS Avoid dust generating handling as asbestos fibres are dangerous to health if inhaled. Dust producing machining must take place under high power extraction. 3. FRICTION MATERIALS (only in Swedish)	Compulsory	All asbestos containing products.	Operating
itzerland	No	N/A	Red stick-on label and blue stick-on leaflet with instructions.	Voluntary		Operating
ited States	No	N/A	Warning notice required as per Federal register "Caution. Contains asbestos fibres. Avoid breathing dust. Breathing asbestos dust may cause serious bodily harm.	Compulsory	Raw materials, mixtures, scrap, waste, debris & other products containing asbestos fibres except where fibres are modified by a bonding agent.	Operating
ited Kingdom	Yes	Yes	Take care with asbestos. Warning: breathing asbestos dust can damage health. Observe the safety rules.	Voluntary	90% of all products on agreed list for Home & Export markets.	Operating

Annex 1 to AIA Schedule "Summary of Main Features of Warning Labels" (see item 1)

AIA ASBESTOS LABEL

Wording recommended to Member Associations

ɴGLISH	FRENCH	GERMAN	ITALIAN	DANISH	DUTCH	GREEK
ITENTION	ATTENTION	ACHTUNG	ATTENZIONE	-	ATTENTIE	ΠΡΟΣΟΧΗ
ɔNTAINS ɜBESTOS	CONTIENT DE L'AMIANTE	ENTHALT ASBEST	CONTIENE ASBESTO	INDEHOLDER ASBEST	BEVAT ASBEST	ΠΕΡΙΕΧΕΙ ΑΜΙΑΝΤΟ
ɜSERVE ɦE SAFETY JLES	OBSERVER LES REGLES DE SECURITE	BEACHTE UMGANGSVOR- SCHRIFTEN	OSSERVARE LE REGOLE DI SICUREZZA	FØLG SIKKERHEDS- FORSKRIFTERNE	VOLG DE VEILIGHEIDS VOORSCHRIFTEN	ΤΗΡΕΙΤΕ ΤΟΥΣ ΚΑΝΟΝΕΣ ΑΣΦΑΛΕΙΑΣ
VOID ʀEATHING JST	EVITER D'INHALER LA POUSSIERE	VERMEIDE STAUB EINZUATMEN	EVITARE DI RESPIRARE LA POLVERE	UNGDÅ INDÅNDING AF STØV	VERMIJD INADEMMING VAN STOF	ΑΠΟΦΕΥΓΕΤΕ ΤΗΝ ΕΙΣΠΝΟΗ ΣΚΟΝΗΣ