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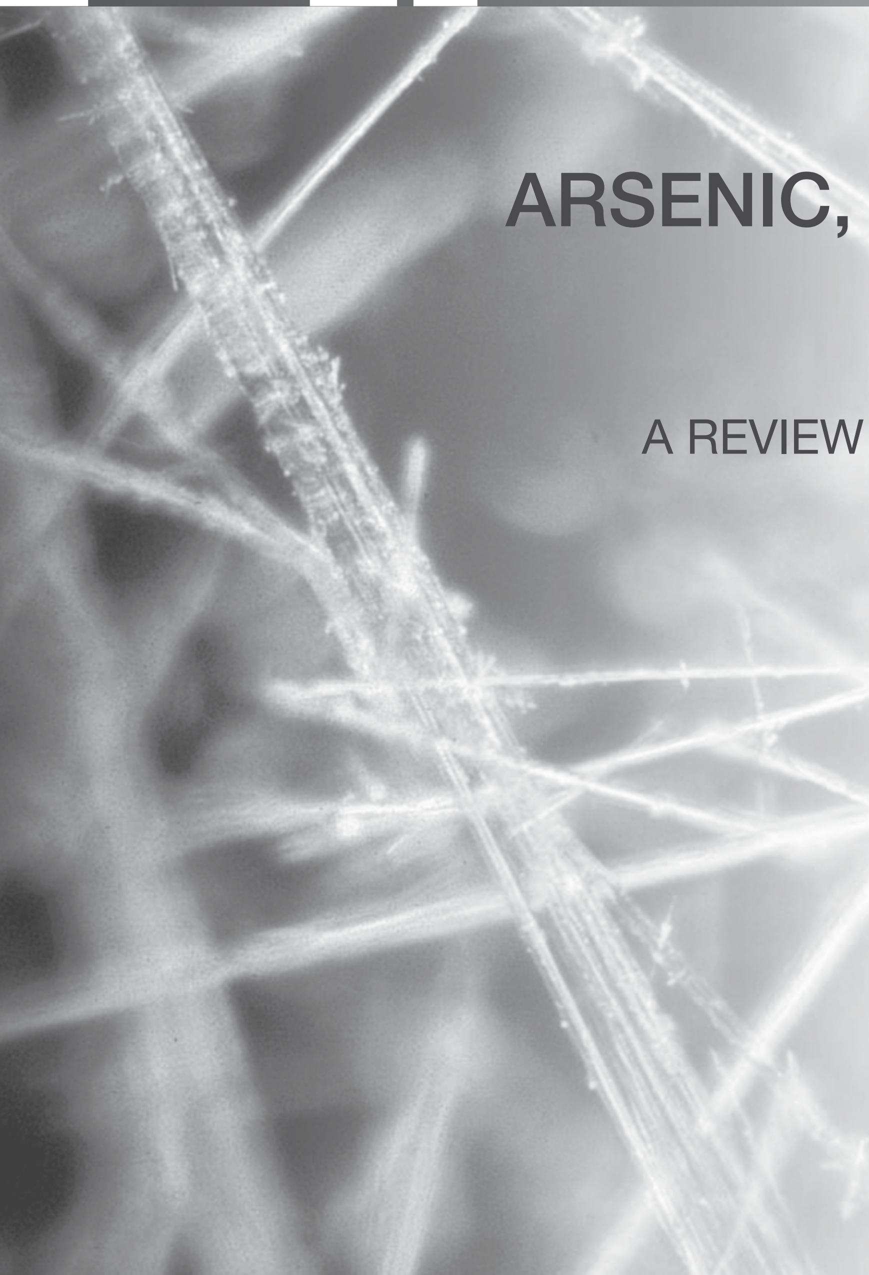

ARSENIC, METALS, FIBRES, AND DUSTS

VOLUME 100 C
A REVIEW OF HUMAN CARCINOGENS

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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

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ERIONITE

Erionite was considered by previous IARC Working Groups in 1987 (IARC, 1987a, b). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

Erionite (CAS Registry No.: 66733-21-9) is a naturally occurring fibrous mineral that belongs to a group of hydrated aluminosilicate minerals called zeolites (NTP, 2004). Its molecular formula is $(Na_2, K_2, Ca, Mg)_{4.5}Al_9Si_{27}O_{72}\bullet 27H_2O$) (IARC, 1987a).

1.2 Chemical and physical properties of the agent

Erionite is a natural fibrous zeolite, found in certain volcanic tuffs as an environmental contaminant. The basic structure of erionite series minerals is an aluminosilicate tetrahedron ($(Si,Al)O_4$) with oxygen atoms shared between two tetrahedra. Erionite is a 'chain silicate' composed of six tetrahedra on each edge of the unit (NTP, 2004). Although erionite has a similar morphology to that of amphibole asbestos (i.e. it has a chain-like structure), it has different chemical and physical properties (Metintas *et al.*, 1999). Erionite occurs as finely fibrous or wool-like white prismatic crystals, with a hexagonal physical structure, and an internal surface area approximately 20 times larger than that of crocidolite asbestos (IARC, 1987a; Metintas *et al.*, 1999; NTP, 2004). It has a density between 2.02–2.08, and absorbs up to 20% of its weight in water. Its gas absorption, ion exchange, and catalytic properties are highly selective and dependent upon the molecular or ionic size of the sorbed compounds as well as upon the cation content of erionite itself (IARC, 1987a). Erionite is not known to occur in other than fibrous form; however, the detailed morphology of erionite 'bundles' that are composed of many 'fibres' and 'fibrils' enhances its surface-area-to-volume ratio drastically (Dogan *et al.*, 2008).

1.3 Use of the agent

Natural zeolites have many commercial uses, most of which are based on the ability of these minerals to selectively absorb molecules from air or liquids. Erionite has been used as a noble-metal-doping catalyst in a hydrocarbon-cracking process, and studied for its use in agricultural applications (i.e. in fertilizers and odour control in livestock production) (IARC, 1987a; NTP, 2004). Erionite-rich blocks were historically quarried in the western United States of America for house-building materials, but this use was considered very minor, and not an intentional use of erionite itself (IARC, 1987a). Natural erionite has not been mined or marketed for commercial purposes since the late 1980s, and has been replaced by synthetic non-fibrous zeolites (Dogan & Dogan, 2008).

1.4 Environmental occurrence

1.4.1 Natural occurrence

Zeolite minerals are found as major constituents in numerous sedimentary volcanic tuffs, especially where these have been deposited and altered by the action of saline lake water (either by percolation or immersion). Erionite minerals occur as deposits of prismatic-to-acicular crystals in several different types of rock (e.g. rhyolite tuff), and in a wide range of geological settings. They rarely occur in pure form and are normally associated with other zeolite minerals (e.g. clinoptilolite, clinoptilolite-phillipsite). Erionite occurs as two major morphotypes: a short fibre form (named after the original Greek word for wool), and a long fibre form. When ground to powder, erionite fibres resemble amphibole asbestos fibres morphologically (IARC, 1987a; Dogan & Dogan, 2008).

Deposits of erionite have been recorded in Antarctica, Europe (Austria, the Czech Republic, France, Germany, Italy), Africa (Kenya, United Republic of Tanzania), Asia (the Republic of Korea, Japan), North America (USA, Canada, Mexico), as well as Georgia, Iceland, New Zealand, the Russian Federation, Scotland, and Turkey (Dogan & Dogan, 2008; Ilgren *et al.*, 2008).

The fibre size distribution of erionite from different deposits vary. Turkish erionite from Karain contains a higher proportion (32%) of longer fibres (> 4 µm) than erionite from Oregon, USA (11%) or New Zealand (8%). New Zealand and Oregon erionites contain 2–3% of thicker fibres (> 1 µm), whereas Karain erionite does not contain any such fibres (Ilgren *et al.*, 2008).

1.5 Human exposure

1.5.1 Exposure of the general population

Most of the non-occupational data on exposure to erionite refers to certain villages of the Cappadocia region, Turkey, where people are exposed to erionite throughout their lives. Erionite deposits in the USA are in remote desert regions where there is no stable population (Dogan *et al.*, 2008).

Dumortier *et al.* (2001) evaluated the fibre burden in bronchoalveolar lavage fluid (BALF) of 16 inhabitants of Tuzköy, an erionite-exposed village in the Cappadocia region of Turkey. All subjects were considered to have environmental exposure to erionite (because they were born in the village and had lived there for 10 years). Their fibre burden was compared to that of subjects with (n = 59) and without (n = 16) environmental exposure to tremolite asbestos. Ferruginous bodies (FBs) and fibres in the BALF were measured and analysed by phase–contrast light and transmission electron microscopy (TEM). FBs were detected by light microscopy in the BALF of 12 subjects; of these, seven had concentrations above 1 FB/mL. The geometric mean concentration of FBs was 1.33 FB/mL (95%CI: 0.35–3.04). In the TEM analysis, erionite accounted for 95.7% of the FBs. Erionite fibres were found in the BALF of all 16 subjects; nine subjects had concentrations higher than 300 f/mL. The mean concentration of erionite fibres in BALF was similar to that of tremolite fibres in subjects with environmental exposure to tremolite. Erionite accounted for 35.6% of fibres longer than 8 µm in BALF. Tremolite, in contrast, accounted for 14.0%. The asbestos fibre concentrations in erionite villagers was not different from that in subjects without environmental exposure to tremolite.

1.5.2 Occupational exposure

Historically, occupational exposure occurred from the mining and production of erionite. Erionite has also been reported to be a minor component in some commercial zeolites. Although erionite has not been mined for commercial purposes since the late 1980s, occupational exposure to erionite may still occur during the mining, production, and use of other zeolites (NTP, 2004).

2. Cancer in Humans

2.1 Pleural and peritoneal mesothelioma

At the end of the 1970s, a very high incidence of pleural mesothelioma was observed in one of the regions of Turkey, in three villages in Cappadocia where erionite was present (Sarihidir, Tuzköy, and Karain). During 1970–87, 108 cases of pleural mesothelioma were recorded in the small village of Karain (604 inhabitants in 1974) – equivalent to an annual incidence of more than 800 cases/100000, that is, about 1000 times the rate observed in the general population of industrialized countries. These cases were responsible for nearly half the deaths reported in this village. In Tuzköy, the annual incidence was estimated at 220 cases/100000. Overall, it was identical for men and women, the ratio of men/women was in the range of 1–2, according to series and village, and the mean age was roughly 50, with a range of 26–75 years (Bariş *et al.*, 1978; Simonato *et al.*, 1989). Artvinli & Bariş (1979) suggested that the presence of erionite in the soil, road dust and building stones of Tuzköy was probably the cause of the high incidence of mesothelioma, and other respiratory abnormalities. It was estimated that a cumulative yearly dose of 1 f/mL induces a pleural mesothelioma rate of 996/100000 persons–year in erionite villages (Simonato *et al.*, 1989).

Bariş & Grandjean (2006) extended the follow-up of the inhabitants of Sarihidir and Karain and another village without known exposure to erionite during 1979–2003. A total of 891 men and women, aged 20 years or older, were included, 230 of them from the village without exposure. During the 23-year follow-up, 372 deaths occurred; 119 of these from mesothelioma, which was the cause of 44.5% of all deaths in the exposed villages. Seventeen patients had peritoneal mesothelioma; the rest had pleural mesothelioma. Only two cases of mesothelioma, one of each type, occurred in the control village—both in women born elsewhere. When standardized to the world population, the pleural mesothelioma incidence was approximately 700 and 200 cases per 100000 people annually in the two exposed villages, respectively, and about 10 cases per 100000 people in the control village.

Other studies were published on a cohort of nearly 100 Karain natives who had emigrated to Sweden from the 1960s onwards. In the first of these, seven cases (four women, three men) of mesothelioma were observed (Özesmi *et al.*, 1990). In a follow-up to 1997 including 162 subjects (87 men and 75 women), Metintas *et al.* (1999) reported 14 (78%) deaths due to mesothelioma among the overall 18 deaths during 1965–97; this proportion was even higher than the proportion found in a Turkish study (49%) (Bariş *et al.*, 1996). The fact that the immigrant community was stable, and the diagnoses of mesothelioma were all histopathologically proven, gives strength to the findings. The average annual mesothelioma incidence rates in this cohort were about 135 times higher among the men and 1336 times higher among the women compared with the general population of Sweden during 1965–67. The total observed number of malignant pleural mesotheliomas (eight men and ten women) in this group resulted in a risk (mesothelioma standardized incidence ratio) in the men and women subjects of about 265 and 1992 times higher, respectively, than that of the

Swedish population (Metintas *et al.*, 1999). The men/women ratio of pleural mesothelioma in the cohort (0.8) was different from that of industrialized countries, where mesothelioma mostly occurs due to occupational exposure. Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-07-Table2.1.pdf presents the main results of pleural mesothelioma incidence and mortality in populations exposed to erionite in Cappadocia, Turkey.

Selçuk *et al.* (1992) studied 135 mesothelioma cases in Turkey from erionite (n = 58) and tremolite (n = 77) villages. The clinico-anatomical appearance of the malignancies was similar in subjects exposed to asbestos or erionite fibres, and pleural plaques were observed in all subjects. In both the erionite- and the asbestos-exposed groups, one quarter of the patients were less than 40 years of age, and the mean ages were not significantly different between the two groups (respectively, 46.4 and 49.7 years); the ages of the patients were in the range of 27–67 years in the erionite group and 26–75 years in the asbestos group, suggesting that the latent period was not specific to the type of fibre that patients were exposed to. Men and women were approximately equal in number in the erionite group (men/women ratio: 31:27); and men were the predominant gender in the asbestos group (men/women ratio: 51:26). However, this may be explained in part by referral bias, as populations from the three erionite villages were known as a high-risk group, and the patients were referred as soon as a presumptive diagnosis was made; in contrast, there was no equivalent system of survey in the asbestos villages where patients were not actively surveyed, but were admitted after presentation.

Gulmez *et al.* (2004) retrospectively evaluated 67 patients with mesothelioma observed during 1990–2001 in central Anatolia, Turkey. In 51 patients (76.1%), the mesothelioma was confined to the pleura, in 14 patients it was exclusively peritoneal, and in two patients, it involved both areas. Of the 67 cases, 35 (52.2%) were women; the mean age for all cases was 57.6 years. Environmental exposure to erionite and asbestos was found in 50.7% and 25.4% of the cases, respectively.

Some of the studies of erionite-induced mesothelioma in Turkey could not rely on full diagnosis assessment. X-rays and biopsy histology were available for many cases, but not for all. However, some studies were able to perform full histopathological examinations, such as the Selçuk *et al.* (1992) study, or the Swedish study of Karain emigrants (Özesmi *et al.*, 1990; Metintas *et al.*, 1999), and found associations of the same order of magnitude between erionite exposure and the risk of mesothelioma, giving strong confidence in the Turkish findings.

Some reports suggested that the simian virus 40 (SV40) could act as a co-carcinogen to induce mesothelioma (Carbone *et al.*, 2002). This is a controversial issue; however, this hypothesis can be excluded regarding erionite because SV40 DNA was never found in the specimen of Turkish patients (Emri *et al.*, 2000; Carbone *et al.*, 2007). Based on the fact that not all exposed villagers died from mesothelioma and that some families in erionite villages seemed to be at particularly high risk, the cause of the high incidence of mesothelioma was hypothetically attributed to the interaction of erionite exposure and genetic factors (Carbone *et al.*, 2007). Although it is not possible to exclude some genetic susceptibility, this hypothesis remains largely speculative and is not substantiated by sound data, because all relatives shared the same exposure to erionite since birth, except for some women who came from other villages, and because some mesotheliomas occurred in patients whose parents died from other causes, and vice versa (Bariş & Grandjean, 2006).

2.2 Other cancers

Bariş *et al.* (1996) also studied the cancer-specific mortality in the three Turkish erionite villages of Karain, Tuzköy, and Sarihidir. During 1970–94, 305 deaths were reported in Karain; of these, 177 (58%) were cancers, and included 150 cases (49.2%) of malignant pleural mesothelioma, seven cases (2.3%) of malignant peritoneal mesothelioma, and six (1%) of gastroesophageal carcinoma; four deaths (1.3%) from cancer of the lung included two non-smoking women; there were also three cases (1%) of leukaemia, and six of other malignancies (1.9%). During 1980–94, 519 deaths were reported in Tuzköy and Sarihidir (432 and 87, respectively); of these, 257 were cancers, and included 120 cases of malignant pleural mesothelioma, and 64 cases of malignant peritoneal mesothelioma; 30 patients had "intra-abdominal carcinoma" (according to the authors, some of them might have been peritoneal mesothelioma or ovarian carcinoma), and 14 patients had cancer of the lung (four of whom were non-smoking women); there were five cases of gastroesophageal cancer, five deaths due to leukaemia, and 16 cases of various malignancies including ovarian cancer, mesenchymal tumours, and leiomyosarcoma of the colon. These mortality figures lend some support to the hypothesis that erionite fibres also cause cancer other than mesothelioma and cancer of the lung; however, no statistical comparisons and no mineralogical analyses of the tissues were performed to demonstrate this relationship. Another difficulty is the uncertain validity of diagnoses. Bariş & Grandjean (2006) also looked at other cancers in their follow-up of the inhabitants of Sarihidir and Karain, but the small number of these cancers (n = 32, accounting for 9% of the total deaths) precluded a detailed analysis.

2.3 Synthesis

Studies of villages in Turkey where inhabitants were exposed from environmental sources from birth as well as the follow-up of a cohort of emigrants from one of the exposed villages in Sweden showed an extremely high incidence of pleural and peritoneal mesothelioma that can be causally associated with erionite exposure. The potency of erionite to induce mesothelioma seems much higher than for any type of asbestos.

3. Cancer in Experimental Animals

See Section 3 of the *Monograph* on Asbestos in this volume.

4. Other Relevant Data

See Section 4 of the *Monograph* on Asbestos in this volume.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of erionite. Erionite causes mesothelioma.

There is *sufficient evidence* in experimental animals for the carcinogenicity of erionite.

Erionite is *carcinogenic to humans (Group 1).*

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