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Carcinogenicity of fluoro-edenite, silicon carbide fibres and whiskers, and carbon nanotubes

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In October, 2014, 21 experts from ten countries met at the International Agency for Research on Cancer (IARC; Lyon, France) to assess the carcinogenicity of fluoro-edenite, silicon carbide (SiC) fibres and whiskers, and carbon nanotubes (CNTs) including singlewalled (SWCNTs) and multi-walled (MWCNTs) types. These assessments will be published as Volume 111 of the IARC Monographs.¹ Fluoro-edenite was first identified around the Etna volcano near Biancavilla, Italy; a similar mineral was also reported from the Kimpo volcano in Japan. Fluoro-edenite can occur as asbestiform fibres. Unpaved roads made from local quarry products from Biancavilla, used since the 1950s, are a source for airborne fluoro-edenite fibres; additionally indoor air was also contaminated from the use of the quarry's products in building materials. Several surveillance studies reported an excess of mesothelioma incidence and mortality in the regional population of Biancavilla.² Since the rate ratios for mesothelioma were large and stable, chance was unlikely to explain these findings. The excess was similar in men and women, and most prominent in young adults, suggesting an environmental rather than occupational cause. Moreover, most of the cases had no history of occupational exposure to asbestos. Fluoro-edenite fibrous amphibole was classified as carcinogenic to humans (Group 1) on the basis of sufficient evidence in humans that exposure to fluoro-edenite causes mesothelioma. Sufficient evidence of carcinogenicity was also reported in experimental animals, with increased incidences of mesotheliomas observed in one study in male and female rats given fibrous fluoro-edenite by intraperitoneal or intrapleural injection.³ The results of the few available mechanistic studies were consistent with proposed mechanisms of fibre carcinogenicity.⁴ SiC occurs in several forms: particles, fibres, and whiskers. SiC particles are manufactured (mostly for use as industrial abrasive) mainly by the Acheson process, with SiC fibres being unwanted by-products. SiC fibres are generally poly-crystalline; of variable length and diameter, and may include fibres that are indistinguishable from whiskers. SiC whiskers are intentionally produced by different processes as durable industrial substitutes for asbestos; they

are physically homogeneous and monocrystalline, and their dimensions are similar to asbestos amphiboles. The carcinogenicity of SiC fibres was investigated in two cohorts of Acheson process workers who were exposed to fibrous and non-fibrous SiC, quartz, and cristobalite. In a Canadian cohort study,⁵ an excess of lung cancer mortality was observed. An excess of lung cancer and an exposure–response relationship with SiC fibres was described in the most detailed report from a series of studies on cancer incidence in a Norwegian cohort.⁶ The analyses were limited to workers with at least 3 years of employment in the plant and based on a detailed jobexposure matrix taking into account multiple exposures. The exposure–response relationship was somewhat weakened after adjustment for exposure to cristobalite. Occupational exposures associated with the Acheson process were classified as carcinogenic to humans (Group 1) on the basis of sufficient evidence in humans that they cause lung cancer. Since the correlation between exposures to SiC fibres and cristobalite made it difficult to disentangle their independent effects, the Working Group concluded that fibrous SiC is possibly carcinogenic to humans (Group 2B) based on limited evidence in humans that it causes lung cancer. No data on cancer in humans exposed to SiC whiskers were available. In experimental animals, there was sufficient evidence for the carcinogenicity of SiC whiskers, with mesotheliomas observed in three studies in female rats treated by intrapleural implantation,⁷ intrapleural injection, or intraperitoneal injection, and in one inhalation study in rats that did not include concurrent controls. Although not unanimous, the Working Group classified SiC whiskers as probably carcinogenic to humans (Group 2A) rather than possibly carcinogenic to humans (Group 2B), on the basis that the physical properties of the whiskers resemble those of asbestos and erionite fibres, which are known carcinogens. In addition, the results of available mechanistic studies were consistent with proposed mechanisms of fibre carcinogenicity.⁴ The majority of the Working Group considered that differences in the nature of SiC fibres and SiC whiskers warranted separate evaluations. Carbon nanotubes may consist of either a single graphene cylinder (SWCNTs) with an outer diameter of 1–3 nm, or of multiple graphene cylinders arranged in concentric layers (MWCNTs) with diameters of 10–200 nm. CNTs are typically few micrometres in length, ranging from a few hundreds of nanometres to several tens of micrometres; their physical and chemical characteristics vary depending on the production technique. Applications include improving the structural properties of fabrics, plastics, rubbers, electronics, and composite materials. The highest release of CNTs, usually as entangled agglomerates which can be respirable, is observed during production and handling, and in cleaning of the production reactor. Measurement of occupational exposure is limited, Carcinogenicity

and consumer exposure was not quantified. No human cancer data were available to the Working Group, indicating inadequate evidence for the carcinogenicity of CNTs in humans. Some CNTs were tested in rodents. MWCNT-7 caused peritoneal mesotheliomas in male and female rats in one intraperitoneal injection study⁸ and one intrascrotal injection study,⁹ and in male *p53*^{+/-} mice in two intraperitoneal injection studies.¹⁰ Inhalation of MWCNT-7 promoted bronchioloalveolar adenoma and carcinoma in male mice.¹¹ In one intraperitoneal study, two other types of MWCNTs with physical dimensions similar to those of MWCNT-7 (length, 1–19 µm; diameter, 40–170 nm) caused mesotheliomas in male and female rats.⁸ Two studies with SWCNTs in rats were inconclusive. Regarding carcinogenicity in experimental animals, the Working Group concluded that there was sufficient evidence for MWCNT-7, limited evidence for the two other types of MWCNTs with dimensions similar to MWCNT-7, and inadequate evidence for SWCNTs. Mechanistic and other data in rodents provided evidence of translocation of three types of MWCNTs (including MWCNT-7) to the pleura.¹² Additionally, inhalation of some MWCNTs or SWCNTs induced acute or persistent pulmonary inflammation, granuloma formation, fibrosis, and bronchiolar or bronchioloalveolar hyperplasia in rodents.^{13,14} Studies in rodents (eg, Shvedova et al¹⁵) and in cultured human lung or mesothelial cells showed that MWCNTs, SWCNTs, or both induce genetic lesions such as DNA strand breaks, oxidised DNA bases, mutations, micronucleus formation, and chromosomal aberrations. SWCNTs and MWCNTs also perturb the cellular mitotic apparatus, including microtubules and centrosomes, in human lung epithelial cells.^{16,17} As a whole, the Working Group acknowledged that the above mechanisms are all relevant to humans. However, a majority did not consider the mechanistic evidence for carcinogenicity—especially concerning chronic endpoints—to be strong for any specific CNT. Furthermore, the lack of coherent evidence across the various distinct CNTs precluded generalisation to other types of CNTs. Thus, MWCNT-7 was classified as possibly carcinogenic to humans (Group 2B); and SWCNTs and MWCNTs excluding MWCNT-7 were categorised as not classifiable as to their carcinogenicity to humans (Group 3).

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