ANAESTHETICS, VOLATILE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

Data from postal surveys of cancer incidence among working populations showed a higher rate of cancer among female operating-room personnel than among controls[1-4], partly reflecting an excess of leukaemia and lymphoma[2]. In one of the studies[4], a higher rate of cancer was reported among dental assistants with relatively heavy exposure to anaesthetics, reflecting a higher prevalence of cervical and uterine cancer in women with heavier exposure to anaesthetics than in those with a lighter exposure (significant only for cancer of the cervix). All of these postal surveys had major shortcomings[5], with response rates varying from 40-82%. Five mortality studies were carried out on anaesthetists[6-10]. A deficiency of deaths from cancer was seen in four[6,8-10]; however, in one study[6], there was an excess of deaths from lymphoma and myeloma (17 observed, 8.9 expected, with a ratio of 1.9 [95% confidence interval, 1.2-2.6]) and, in another, a possible excess of cancer of the pancreas[7]. Cancer incidence was also studied in 28 235 registered nurses. Minor excesses of breast cancer, lymphoma and acute myelogenous leukaemia were balanced by deficits in cancers at other sites. No significant difference was found for active operation and

anaesthetic nurses as compared to the female Norwegian population[11]. In a study of the incidence of cancer among offspring born to nurse anaesthetists, three neoplasms occurred in two of 434 children born to anaesthetists who had worked during pregnancy (a neuroblastoma and a carcinoma of the thyroid in one, and a carcinoma of the parotid in the other) and one leukaemia among the 261 children born to anaesthetists who had not worked during pregnancy[12].

It is not possible to consider exposure to different volatile anaesthetics separately, although the study of US anaesthesiologists working during 1930-1946[10] concerned the period before fluorinated anaesthetic agents were introduced in the 1950s.

B. Evidence for carcinogenicity to animals (*inadequate* for enflurane, halothane, isoflurane, methoxyflurane and nitrous oxide)

Enflurane was tested for carcinogenicity by inhalation in one strain of mice at the maximum tolerated dose[13] and at several dose levels in a limited study in which treatment started *in utero*[14]. No treatment-related neoplasm was observed.

Halothane was tested for carcinogenicity by inhalation in mice and rats. When mice were exposed *in utero* and then three times weekly for 78 weeks at the maximum tolerated dose[15] or 24 times at several dose levels[14], no treatment-related neoplasm was observed. No carcinogenic effect was seen in rats exposed to a low level of halothane alone or in combination with nitrous oxide[16].

Isoflurane was tested for carcinogenicity by inhalation in one strain of mice. It induced liver tumours in one experiment[1] but no treatment-related neoplasm in another[14]. Both experiments had limitations.

Methoxyflurane was tested for carcinogenicity in mice by inhalation *in utero* in one limited study. No treatment-related neoplasm was observed[14].

Nitrous oxide was tested for carcinogencity by inhalation in mice and rats. In one limited study in mice in which exposure started *in utero*, no treatment-related neoplasm was observed[14]. No carcinogenic effect was seen in rats exposed chronically to a low dose of nitrous oxide alone or in combination with halothane[16].

C. Other relevant data

Studies in hospital personnel exposed to inhalation anaesthetics showed an increased frequency of chromosomal aberrations but not of sister chromatid exchanges in peripheral blood lymphocytes[17,18].

Neither enflurane nor halothane induced dominant lethal mutations in rodents *in vivo*, and halothane did not induce chromosomal aberrations, micronuclei or sister chromatid exchanges in rodents treated *in vivo*[19].

Divinyl ether and fluroxene induced sister chromatid exchanges in cultured Chinese hamster ovary cells and mutation in bacteria. Negative results were obtained in these tests with halothane, enflurane, diethyl ether, isoflurane, methoxyflurane and nitrous oxide. Halothane caused gene conversion and mutation in yeast under conditions that enhanced endogenous levels of cytochrome P450. Diethyl ether was not mutagenic to fungi. Cyclopropane was not mutagenic to bacteria[19].

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