4. STUDIES OF CANCER IN EXPERIMENTAL ANIMALS

4A. Metallic medical and dental materials

4A.1 Metallic chromium

4A.1.1 *Intrapleural administration*

Mouse: A group of 50 male C57BL mice, approximately six weeks of age, received six intrapleural injections of 10 μg per mouse of chromium powder in 0.2 mL of a 2.5% gelatin–saline solution every other week; 32 mice lived for up to 14 months, at which time no tumour was observed (Hueper, 1955a). [The Working Group noted the relatively short period of exposure and the low dose.]

Rat: Groups of 17 female and eight male Osborne-Mendel rats, approximately four months of age, were given six monthly intrapleural injections of 16.8 mg per rat of chromium powder in 50 μL lanolin; 25 male Wistar rats, of approximately the same age, received six weekly intrapleural injections of 0.5 mg per rat of chromium powder suspended in 0.1 mL of a 2.5% gelatin–saline solution. Six Osborne-Mendel rats survived up to 19–24 months and 12 Wistar rats up to 25–30 months. Three female Osborne-Mendel rats developed adenofibromas of the thoracic wall; in addition, one of these rats also had a retroperitoneal haemangioma. Two other rats [group unspecified] had a haemangioma and an angiosarcoma, and another rat [group unspecified] had an intra-abdominal round-cell sarcoma. No Osborne-Mendel control rats were used. Of 12 male Wistar rats receiving gelatin alone, three developed intra-abdominal round-cell sarcoma (Hueper, 1955a).

4A.1.2 *Intramuscular administration*

Rat: A group of 25 male and 25 female weanling Fischer 344 rats received monthly intramuscular injections of 100 mg per rat of chromium powder (99.9% pure) in 0.2 mL tricaprylin. Treatment was continued until definite nodules appeared at the injection site in more than one animal [time unspecified]. The study was terminated at 644 days [survival figures not given]. A single injection-site fibrosarcoma was reported in a male rat. No local tumour was seen in 50 vehicle control rats (Furst, 1971).

4A.1.3 *Intraperitoneal administration*

Mouse: A group of 50 male C57BL mice, approximately six weeks of age, was given weekly intraperitoneal injections for four consecutive weeks of 10 μg per mouse of chromium powder (diameter, >100 μm to colloidal particle size) suspended in 0.2 mL of a 2.5% gelatin–saline solution. Forty mice survived up to 21 months, at which time the

experiment was terminated. One mouse developed myeloid leukaemia; no other tumour was noted (Hueper, 1955a). [The Working Group noted the low dose given and the absence of controls.]

Rat: A group of 25 male Wistar rats, 3–4 months of age, was given weekly intraperitoneal injections for six consecutive weeks of 50 μg per rat of chromium powder in 0.1 mL of a 2.5% gelatin–saline solution. One rat developed a scirrhous carcinoma of the caecal submucosa, two rats developed intra-abdominal round-cell sarcomas, one rat had both a sarcoma of the leg of cartilaginous osteoid origin and an insulinoma of the pancreas, and one rat had an insulinoma (Hueper, 1955a). [The Working Group noted that no vehicle control group was reported and that the authors stated that, although round-cell sarcomas also occurred in controls, insulinomas were found only in treated rats.]

4A.1.4 *Intravenous administration*

Mouse: A group of 25 C57BL mice [sex unspecified], approximately eight weeks of age, received six weekly injections into the tail vein of 2.5 μg per mouse of chromium powder (particle size, ≤ 4 μm) in 0.05 mL of a gelatin–saline solution. Six animals lived up to 12 months, but none to 18 months. No tumour was observed (Hueper, 1955a). [The Working Group noted the small number of animals and the low dose.]

Rat: A group of 25 male Wistar rats, approximately seven months of age, was given six weekly injections of 90 μg per rat of chromium powder in 0.18 mL of a 2.5% gelatin–saline solution into the left saphenous vein. Fifteen were still alive at one year and 13 at two years, at which time the study was terminated. Round-cell sarcomas were observed in four rats—three in the ileocaecal region and one in the intrathoracic region. One rat had a haemangioma of the renal medulla and two rats had papillary adenomas of the lungs, one of which showed extensive squamous-cell carcinomatous changes. Use of vehicle-treated controls was not reported. The author stated that, although round-cell sarcomas also occurred in groups of control rats in this series of studies, lung adenomas were found only in treated rats (Hueper, 1955a).

Rabbit: Eight albino rabbits [sex unspecified], approximately six months of age, received six weekly intravenous injections of 25 mg/kg bw of chromium powder in 0.5 mL of a 2.5% gelatin–saline solution into the ear vein. The same course of treatment was given four months later, and three years after the first injection, a third series of injections was given to the three surviving rabbits. Four rabbits given intravenous injections of the vehicle alone served as controls. One of three treated rabbits that survived six months after the last injection developed a tumour of uncertain origin (evidently an immature carcinoma) involving various lymph nodes, but no tumour occurred in controls (Hueper, 1955a).

4A.1.5 *Intrarenal administration*

Rat: Six groups of 20 or 18 female Sprague-Dawley rats (weighing 120–140 g) received an injection of 5 mg of various metallic powders [reagent grade, particle size

unspecified] into each pole of the right kidney (total dose, 10 mg per rat). The metallic powders, which included cadmium, chromium, cobalt, gold, lead and nickel, were suspended in 0.05 mL glycerine for injection. A group of 16 females receiving an injection of 0.05 mL glycerine into each pole of the kidney served as negative controls; a further group of 16 females receiving an injection of 5 mg of nickel subsulfide powder into each pole of the right kidney (total dose, 10 mg per rat) served as positive controls. No renal tumour developed within the 12-month period of observation in the six groups of rats that received intrarenal injection of metallic powders, although 1/20 rats treated with metallic nickel powder developed a rhabdomyosarcoma involving the injected kidney and mesentery. No renal tumour was observed in the negative control group, but renal carcinomas were found in 7/20 rats in the positive control group which received nickel subsulfide by intrarenal injection (Jasmin & Riopelle, 1976). [The Working Group noted the short duration and inadequate reporting of the experiment.]

4A1.6 *Intraosseous administration*

Rat: A group of 25 male Wistar rats, approximately five months of age, received an intramedullary injection into the femur of 0.2 mL of a 50% (by weight) suspension of chromium powder (approximately 45 mg) in 20% gelatin–saline and was observed for 24 months; 19 survived over one year. No tumour developed at the injection site. Similarly, a group of 25 male Osborne-Mendel rats, approximately five months of age, received a similar dose of chromium powder in 0.2 mL lanolin injected into the femur and was observed for 24 months; 14 rats survived for one year, and one developed a fibroma at the injection site (Hueper, 1955a).

Rabbit: Two groups of 15–20 rabbits [strain, sex and age unspecified] received an implantation in the femoral cavity of metallic chromium dust or metallic cobalt dust [purity and particle size unspecified]. Physical examination by palpation and X-ray examination at three years after implantation revealed no implantation-site tumour in 11 survivors of the chromium-treated group or six survivors of the cobalt-treated group (Vollmann, 1938). In a follow-up study of survivors [number unspecified] at intervals up to six years after implantation, sarcomas were observed at the implantation site in three chromium-treated rabbits and two cobalt-treated rabbits (Schinz & Uehlinger, 1942). [The Working Group noted the limited reporting.]

4A.2 Metallic cobalt

4A.2.1 *Intramuscular administration*

Rat: A group of 10 male and 10 female hooded rats, 2–3 months of age, received a single intramuscular injection of 28 mg per rat of cobalt metal powder (spectrographically pure with particle sizes of 3.5 μm × 3.5 μm to 17 μm × 12 μm, with large numbers of long narrow particles of the order of 10 μm × 4 μm) in 0.4 mL fowl serum into the thigh; a control group of 10 males and 10 females received fowl serum only. Average survival times were 71 weeks in treated males and 61 weeks in treated females; survival

of controls was not specified. During the observation period of up to 122 weeks, 4/10 male and 5/10 female treated rats developed a sarcoma (mostly rhabdomyosarcoma) at the injection site compared with 0/20 controls. A further group of 10 female rats received a single intramuscular injection of 28 mg cobalt metal powder in 0.4 mL fowl serum; others received injections of 28 mg zinc powder (5 rats) or 28 mg tungsten powder (5 rats). Average survival time for cobalt-treated rats was 43 weeks. During the observation period of up to 105 weeks, sarcomas (mostly rhabdomyosarcoma) developed in 8/10 cobalt powder-treated rats; none occurred in the zinc powder- or tungsten powder-treated rats. No other tumour occurred in the cobalt-treated or other rats, except one malignant lymphoma in a zinc-treated rat (Heath, 1954, 1956).

4A.2.2 *Intrarenal administration*

Rat: Six groups of 20 or 18 female Sprague-Dawley rats (weighing 120–140 g) received an injection of 5 mg of various metallic powders [reagent grade, particle size unspecified] into each pole of the right kidney (total dose, 10 mg per rat). The metallic powders, which included cadmium, chromium, cobalt, gold, lead and nickel, were suspended in 0.05 mL glycerine for injection. A group of 16 females receiving an injection of 0.05 mL glycerine into each pole of the kidney served as negative controls; a further group of 16 females receiving an injection of 5 mg nickel subsulfide powder into each pole of the right kidney (total dose, 10 mg per rat) served as positive controls. No renal tumour developed within the 12-month period of observation in the six groups of rats that received intrarenal injection of metallic powders, although 1/20 rats treated with metallic nickel powder developed a rhabdomyosarcoma involving the injected kidney and mesentery. No renal tumour was observed in the negative control group, but renal carcinomas were found in 7/20 rats in the positive control group which received nickel subsulfide by intrarenal injection (Jasmin & Riopelle, 1976). [The Working Group noted the short duration and inadequate reporting of the experiment.]

4A.2.3 *Intrathoracic administration*

Rat: Two groups of 10 female hooded rats, 2–3 months of age, received intrathoracic injections of 28 mg cobalt metal powder (spectrographically pure with particle sizes of 3.5 μm × 3.5 μm to 17 μm × 12 μm, with many long narrow particles of the order of 10 μm × 4 μm) in fowl serum through the right dome of the diaphragm (first group) or through the fourth left intercostal space (second group) and were observed for up to 28 months. Death occurred within three days of the treatment in 6/10 rats injected through the diaphragm and in 2/10 rats injected through the intercostal space. The remaining rats in the first group (diaphragm) survived 11–28 months and those in the second group (intercostal space) survived 7.5–17.5 months. Of the 12 rats that survived the injection, four developed intrathoracic sarcomas (three of mixed origin, including rhabdomyosarcomatous elements, one rhabdomyosarcoma arising in the intercostal muscles). No controls were used (Heath & Daniel, 1962).

4A.2.4 *Intraosseous administration*

Rabbit: Two groups of 15–20 rabbits [strain, sex and age unspecified] received an implantation in the femoral cavity of metallic chromium dust or metallic cobalt dust [purity and particle size unspecified]. Physical examination by palpation and X-ray examination three years after implantation revealed no implantation-site tumour in 11 survivors of the chromium-treated group or six survivors of the cobalt-treated group (Vollmann, 1938). In a follow-up study of survivors [number unspecified] at intervals up to six years after implantation, sarcomas were observed at the implantation site in three chromium-treated rabbits and two cobalt-treated rabbits (Schinz & Uehlinger, 1942). [The Working Group noted the limited reporting.]

4A.3 Metallic nickel

4A.3.1 *Inhalation exposure*

Mouse: A group of 20 female C57BL mice, two months of age, was exposed by inhalation to 15 mg/m^3 metallic nickel powder (> 99% pure nickel; particle diameter, ≤ 4 μm) for 6 h per day on four or five days per week for up to 21 months. All mice had died by the end of the experiment. No lung tumour was observed. No control group was available (Hueper, 1958).

Rat: Groups of 50 male and 50 female Wistar rats and 60 female Bethesda black rats, 2–3 months of age, were exposed by inhalation to 15 mg/m^3 metallic nickel powder (> 99% pure nickel; particle diameter, ≤ 4 μm) for 6 h per day on four or five days per week for 21 months, when the experiment was terminated. Histological examination of the lungs of 50 rats showed numerous multicentric, adenomatoid alveolar lesions and bronchial proliferations that were considered by the author as benign neoplasms. No control group was included in the study (Hueper, 1958).

A group of 60 male and 60 female Bethesda black rats [age unspecified] was exposed by inhalation to metallic nickel powder (98.95% nickel; particle diameter, 1–3 μm) [concentration unspecified] in combination with 20–35 ppm (50–90 mg/m^3) sulfur dioxide as a mucosal irritant; powdered chalk (1:1) was added to the nickel to prevent clumping. Exposure was for 5–6 h per day. Forty-six of 120 rats lived longer than 18 months. No lung tumour was observed, but many rats developed squamous metaplasia and peribronchial adenomatoses (Hueper & Payne, 1962).

Guinea-pig: A group of 32 male and 10 female guinea-pigs (Strain 13), approximately three months of age, was exposed by inhalation to 15 mg/m^3 metallic nickel powder (> 99% nickel; particle diameter, ≤ 4 μm) for 6 h per day on four or five days per week for up to 21 months. Mortality was high; only 23 animals survived to 12 months and all animals had died by 21 months. Almost all animals developed adenomatoid alveolar lesions and terminal bronchiolar proliferations. No such lesion was observed in nine controls. One treated guinea-pig had an anaplastic intra-alveolar carcinoma, and another had an apparent adenocarcinoma metastasis in an adrenal node, although the primary tumour was not identified (Hueper, 1958).

4A.3.2 *Intratracheal administration*

Rat: Two groups of 39 and 32 female Wistar rats, 11 weeks of age, received either 20 or 10 weekly intratracheal instillations, respectively, of 0.3 or 0.9 mg metallic nickel powder [purity unspecified] in 0.3 mL saline (total doses, 6 mg and 9 mg, respectively) and were observed for almost 2.5 years. Lung tumour incidence in the two groups was 10/39 (nine carcinomas, one adenoma) and 8/32 (seven carcinomas, one mixed), respectively; no lung tumour developed in 40 saline-treated controls maintained for up to 124 weeks. Pathological classification of the tumours in the two groups combined revealed one adenoma, four adenocarcinomas, 12 squamous-cell carcinomas and one mixed tumour. Average time to observation of the tumours was 120 weeks, the first tumour being observed after 98 weeks (Pott *et al*., 1987).

Hamster: A group of 27 male and 31 female Syrian golden hamsters (strain Cpb-ShGa51), 10–12 weeks of age, received 12 intratracheal instillations of 0.8 mg metallic nickel powder (99.9% nickel; mass median aerodynamic diameter, 9 μm) in 0.15 mL saline at two-week intervals (total dose, 9.6 mg). Median lifetime was 111 weeks for males and 100 weeks for females. One lung tumour, an adenocarcinoma, was observed in females that received nickel powder. No lung tumour was observed in males or in vehicle-treated controls (Muhle *et al*., 1992).

4A.3.3 *Intrapleural administration*

Rat: A group of 25 female Osborne-Mendel rats, six months of age, received five injections of a 12.5% suspension of metallic nickel powder in 0.05 mL lanolin into the right pleural cavity [6.25 mg nickel powder] once a month for five months. A group of 70 rats received injections of lanolin only. The experiment was terminated after 16 months. Four of the 12 nickel-treated rats that were examined developed round-cell and spindle-cell sarcomas at the site of injection; no control animal developed a local tumour (Hueper, 1952).

A group of five male and five female Fischer 344 rats, 14 weeks of age, received injections of 5 mg metallic nickel powder suspended in 0.2 mL saline into the pleura once a month for five months (total dose, 25 mg nickel). Two nickel-treated rats developed mesotheliomas within slightly over 100 days; no tumour occurred in 20 controls (Furst *et al*., 1973). [The Working Group noted the small number of animals and the limited reporting of the experiment.]

4A.3.4 *Subcutaneous administration*

Rat: A group of five male and five female Wistar rats, 4–6 weeks of age, received subcutaneous implantation of four pellets (approximately 2 mm in diameter) of metallic nickel. [No control group of sham-operated rats was available.] The animals were observed for 27 months. Sarcomas (fibrosarcoma or rhabdomyosarcoma) developed within 7–23 months around the implants in 5/10 rats that received metallic nickel pellets (Mitchell *et al*., 1960).

4A.3.5 *Intramuscular administration*

Rat: Groups of 25 male and 25 female Fischer 344 rats [age unspecified] received five monthly intramuscular injections of 5 mg metallic nickel powder in 0.2 mL trioctanoin. Fibrosarcomas occurred in 38/50 nickel-treated animals but in none of a group of 25 male and 25 female controls given trioctanoin alone (Furst & Schlauder, 1971).

Groups of 20 or 16 male Fischer 344 rats, 2–3 months old, received a single intramuscular injection of 14 mg metallic nickel powder (99.5% nickel) in 0.3–0.5 mL penicillin G procaine vehicle into the right thigh. The metal was ground to median particle diameter of < 2 μm. Of the 20 rats receiving nickel powder, 13 developed tumours (mainly rhabdomyosarcomas) at the site of injection, with an average latency of 34 weeks. No local tumour developed in 44 controls given penicillin G procaine or in 40 controls given an injection of glycerol (Sunderman, 1984).

Two groups of 10 male Fischer 344 rats, three months of age, received a single intramuscular injection of 3.6 or 14.4 mg per rat of metallic nickel powder in 0.5 mL penicillin G procaine suspension. Surviving rats were killed 24 months after the injection. Sarcomas at the injection site were found in 0/10 and 2/9 nickel-treated rats, respectively, compared with 0/20 vehicle controls (Sunderman & Maenza, 1976). [The Working Group noted the small number of animals.]

Groups of 20 WAG rats [sex and age unspecified] received a single intramuscular injection of 20 mg metallic nickel powder in an oil vehicle [type unspecified]. A group of 56 control rats received 0.3 mL of the vehicle alone. Local sarcomas developed in 17/20 nickel-treated and 0/56 control rats injected with oil (Berry *et al*., 1984). [The Working Group noted the inadequate reporting.]

A group of 40 male WAG rats, 10–15 weeks of age, received a single intramuscular injection of 20 mg metallic nickel in paraffin oil; 10 of these rats also received intramuscular injections of 50 000 U interferon per rat twice a week beginning in the 10th week after nickel treatment. Rhabdomyosarcomas occurred in 14/30 and 5/10 rats in the two groups, respectively. No local tumour occurred in 60 control rats that received the vehicle (Judde *et al*., 1987).

Hamster: Furst and Schlauder (1971) studied the local tumour response to metallic nickel powder in Syrian hamsters compared with that in Fischer 344 rats (see above). Groups of 25 male and 25 female hamsters, 3–4 weeks of age, received five monthly intramuscular injections of 5 mg nickel powder in 0.2 mL trioctanoin. Two fibrosarcomas at the injection site occurred in males. No local tumours occurred in 25 male and 25 female controls injected with trioctanoin alone.

4A.3.6 *Intraperitoneal administration*

Rat: In a study reported in an abstract, a group of male and female Fischer rats [number and age unspecified] (weighing 80–100 g) received 16 intraperitoneal injections of 5 mg metallic nickel powder in 0.3 mL corn oil twice per month for eight months. A control group received injections of corn oil only. In the nickel-treated

group, 30–50% of rats were reported to develop intraperitoneal tumours (Furst & Cassetta, 1973).

A group of 50 female Wistar rats, 12 weeks of age, received 10 weekly intraperitoneal injections of 7.5 mg metallic nickel powder [purity and particle size unspecified] (total dose, 75 mg nickel). Abdominal tumours (sarcoma, mesothelioma or carcinoma) developed in 46/48 (96%) nickel-treated rats, with an average tumour latency of approximately eight months. Concurrent controls were not reported, but in non-concurrent groups of saline controls, abdominal tumours were found in 0–6% of animals (Pott *et al*., 1987).

4A.3.7 *Intraosseous administration*

Rat: In groups of 20 WAG rats [sex and age unspecified], subperiosteal injection of 20 mg metallic nickel powder resulted in local tumours in 11/20 rats; intramedullary injection of 20 mg metallic nickel powder resulted in local tumours in 9/20 rats (Berry *et al*., 1984). [The Working Group noted the absence of controls and the inadequate reporting of tumour induction.]

4A.3.8 *Intrarenal administration*

Rat: A group of male Fischer 344 rats, approximately two months of age, received an intrarenal injection of 7 mg metallic nickel powder in 0.1 mL saline solution into each pole of the right kidney (total dose, 14 mg nickel per rat). The study was terminated after two years; the median survival time was 100 weeks compared with 91 weeks in a group of saline-treated controls. Renal tumours occurred in 0/18 rats compared with 0/46 saline-treated controls (Sunderman *et al*., 1984).

4A.3.9 *Intravenous administration*

Mouse: A group of 25 male C57BL mice, six weeks of age, received two intravenous injections of 0.05 mL of a 0.005% suspension of metallic nickel powder in 2.5% gelatin into the tail vein (2.5 μg nickel). Nineteen animals survived more than 52 weeks, and six survived over 60 weeks. No tumour was observed. No control group was used (Hueper, 1955b). [The Working Group noted the short period of observation.]

Rat: A group of 25 Wistar rats [sex unspecified], 24 weeks of age, received intravenous injections of 0.5 mL/kg bw (0.1–0.18 mL) of a 0.5% suspension of nickel powder in saline into the saphenous vein once a week for six weeks. Seven rats developed sarcomas in the groin region along the injection route [probably from seepage at the time of treatment]. No control group was used (Hueper, 1955b).

4A.4 Metallic titanium

4A.4.1 *Intramuscular administration*

Rat: Groups of 15 male and 15 female Sprague-Dawley rats, 20–30 days old, received intramuscular implants of polished rods (1.6 mm in diameter, 8 mm in length) of metallic titanium (> 99% titanium) and were observed for up to two years [survival

unspecified]. Two groups of 15 male and 15 female untreated or sham-operated control animals were available. No benign or malignant tumour developed at the implantation site or in the sham-operated control group. The incidences of malignant tumours at distant sites did not differ significantly between control and treated rats (Gaechter *et al*., 1977).

4A.4.2 *Intraosseous administration*

Rat: Four groups of 11–15 male and 11–15 female Sprague-Dawley rats, 30–43 days of age, received implants in the femoral bone of metallic titanium as small rods (1.8 mm in diameter, 4 mm in length), as powders (fine, diameter < 28 μm; coarse, diameter 28–44 μm) or as compacted wire (4 × 2.8 mm). A total of 77 rats in three groups of 12–13 male and 13 female untreated or sham-operated controls were available. Average survival in all groups exceeded 21 months; the animals were observed for up to 30 months. No sarcoma at the implantation site was observed in rats that received titanium implants or in two groups of 25 and 26 untreated rats or in a group of 26 sham-treated control rats. Two implant site-associated lymphomas were observed in the groups receiving titanium powder, but none in sham-operated controls (Memoli *et al*., 1986).

4A.5 Metallic foils

4A.5.1 *Subcutaneous administration*

Rat: Three groups of Wistar rats [initial number, sex and age unspecified] were given subcutaneous implants of gold, silver or platinum foils as discs (17 mm diameter [thickness unspecified]) and observed for 23 months. The total number of sarcomas at the implantation site was 68/77 (88.3%) for gold foil, 65/84 (77.4%) for silver foil and 39/73 (53.4%) for platinum foil (Nothdurft, 1956). [The Working Group noted that no sham-operated controls were available.]

Five groups of 25 male Wistar rats [age unspecified] were given subcutaneous implants of silver, tin, tantalum, Vitallium or stainless steel foils as discs or squares (1.5 cm; two discs or squares per rat) and observed for > 596 days. Local sarcomas were found in 14/25 (56%) rats with silver foil, 5/21 (24%) rats with steel foil, 2/23 (8.7%) rats with tantalum foil, 0/25 (0%) rats with tin foil and 5/23 (21.7%) rats with Vitallium foil (Oppenheimer *et al*., 1956). [The Working Group noted that no sham-operated controls were available and that the composition of the stainless steel was not specified.]

4A.5.2 *Intraperitoneal administration*

Mouse: A group of 43 female Marsh mice, three months of age, received intraperitoneal implants of open-end tin foil cylinders (2 × 4 mm; 151 mm^2 surface area). A control group of 39 female mice was sham-operated. The animals were observed for 18 months. Local sarcomas were found in 8/31 test animals versus 1/23 controls. [The low effective numbers of test and control rats reflect the occurrence of pneumonia.] (Bischoff & Bryson, 1977).

Rat: Groups of 31 male and 29 female Evans rats, five to six weeks of age, received intraperitoneal implants of open-end tin foil cylinders (25 × 8 mm; 628 mm^2 surface area). Four control groups of 29–31 male and female mice were sham-operated. The animals were observed for 18–24 months. Local sarcomas were found in the four groups of effective animals as follows: experiment 1, males, 10/16; females 8/13 and experiment 2, males 7/8; females 9/12. In controls the corresponding incidences were 0/16, 0/21, 0/8 and 0/14. Histiocytic lymphomas appeared sporadically in all groups of test and control animals (Bischoff & Bryson, 1977).

4A.6 Metal alloys

The results of experimental carcinogenicity studies on metal alloys are tabulated in Table 40. Alloy composition is specified by the chemical symbol of each metal followed by its percentage. Silica, carbon and other elements are not always given.

4A.6.1 *Intratracheal administration*

Hamster: Groups of 50 male and 50 female Syrian golden hamsters, three months of age, received a single intratracheal instillation of 10, 20 or 40 mg metallic nickel powder (particle diameter, 3–8 μm) or powders of nickel-containing alloys (particle diameter, 0.5–2.5 μm; alloy I: Fe39Ni27Cr16; alloy II: Ni67Cr13Fe7) or four intratracheal instillations of 20 mg of each of the substances every six months (total dose, 80 mg). In the groups receiving single instillations of alloy II, the incidences of malignant intrathoracic tumours were reported to be 1, 8 and 12%, respectively, suggesting a dose–response relationship. In the group receiving repeated instillations of alloy II, 10% of animals developed an intrathoracic malignant neoplasm (fibrosarcoma, mesothelioma or rhabdomyosarcoma). Metallic nickel induced comparable numbers and types of intrathoracic neoplasms, but no tumour was observed in animals treated with alloy I or in control animals (Ivankovic *et al*., 1987, 1988).

A group of 27 male and 31 female Syrian golden hamsters (strain Cpb-ShGa51), 10–12 weeks of age, received 12 intratracheal instillations of 0.8 mg metallic nickel powder (99.9% nickel; mass median aerodynamic diameter, 9 μm) in 0.15 mL saline at two-week intervals (total dose, 9.6 mg). Three additional groups (28–31 animals of each sex per group) were treated with 12 intratracheal instillations of 3 or 9 mg nickel stainless-steel dust (Fe59Cr14Ni7C4Al2Mn1; mass median aerodynamic diameter, 3–5 μm) or 9 mg chromium stainless-steel dust (Fe68Cr13C3Al2; mass median aerodynamic diameter, 3–5 μm). The observation period was 26 months for females and 30 months for males. The median lifespan was 90–111 weeks in the various groups. One lung tumour was observed: an adenocarcinoma in the group that received nickel powder. No lung tumour was observed in vehicle-treated controls or in the groups treated with the stainless-steel powders (Muhle *et al*., 1992).

Table 40. Studies of cancer in animals given implants of metallic alloy medical and dental materials

Implant material/composition (wt %)	Route/size/amount	Species	Duration of observation	Local tumour outcome		Reference	Comments
				No.	%		
Nickel-containing alloys except stainless steels							
Ni67Cr13Fe7	Intratracheal/powder 0.5–2.5 μm/	Hamster				Ivankovic *et al*. (1987,	
	10 mg			1/100	1	1988)	Single instillation
	20 mg			8/100	8		
	40 mg			12/102	12		
	20 mg × 4			10/100	10		Repeated instillation
Ni27Fe39Cr16	Intratracheal/powder 0.5–2.5 μm/	Hamster				Ivankovic *et al*. (1987,	
	10 mg			0/100	0	1988)	Single instillation
	20 mg			0/100	0		
	40 mg			0/100	0		
	20 mg × 4			0/100	0		Repeated instillation
Ni60Ga40	Subcutaneous/pellets (~ 2 mm diameter)/ 4 pellets	Rat	27 months	9/10	90	Mitchell *et al*. (1960)	
Ni35Co35Cr20Mo10 (MP35N alloy)	Intramuscular/rod (8 × 1.6 mm diameter)/ 1 rod	Rat	2 years	0/30	0	Gaechter *et al*. (1977)	
Ni35–36Co33Cr20–22Mo9 (MP35N alloy)	Intraosseous/rod (4 × 1.6 mm diameter)	Rat	30 months	0/26	0	Memoli *et al*. (1986)	
	powder (< 28 μm)/43 g			3/26	12		
Ni38Fe62	Intramuscular/particles (< 2 μm)/14 mg as Ni	Rat	2 years	0/16	0	Sunderman (1984)	In penicillin G procaine vehicle

Table 40 (contd)

Implant material/composition (wt %)	Route/size/amount	Species	Duration of observation	Local tumour outcome		Reference	Comments
				No.	%		
Nickel-containing alloys except stainless steels (contd)							
Ni50Al50	Intraperitoneal/powder (< 10 μm)/50 mg (as Ni) 3 × 50 mg (as Ni)	Rat	30 months	 8/35 13/35	 23 37	Pott *et al*. (1989, 1992)	52% Ni after milling
Ni32Fe55Cr21Mn1	50 mg (as Ni) 2 × 50 mg (as Ni)			2/33 1/36	6.1 2.8		29% Ni after milling
Ni74Cr16Fe7	50 mg (as Ni) 3 × 50 mg (as Ni)			12/35 22/33	34 66.7		66% Ni after milling
Ni38Fe62	Intrarenal/powder/ 14 mg (as Ni)	Rat	2 years	1/14	7	Sunderman *et al*. (1984)	
Ni67Cu30Fe2Mn1	Ear tag	Rat	2 years	14/168 2/193	8.3 1.0	Waalkes *et al*. (1987)	Observed in a carcinogenicity study on cadmium compounds
Cobalt-based alloys							
Vitallium (CoCrMo)	Subcutaneous/pellet (~ 2 mm diameter)/ 4 pellets	Rat	27 months	0/10	0	Mitchell *et al*. (1960)	
Co67Cr26Mo7Mn1	Intramuscular/particles (0.1~1 μm)/2 mg	Rat	29 months	3/16 4/14 15/50	18.8 25.0 30.0	Heath *et al*. (1971); Swanson *et al*. (1973)	Obtained by frictional movement of prostheses in Ringer's solution

Table 40 (contd)

Implant material/composition (wt %)	Route/size/amount	Species	Duration of observation	Local tumour outcome		Reference	Comments
				No.	%		
Cobalt-based alloys (contd)							
Co68Cr28Mo4	Intramuscular/powder (100–250 µm)/28 mg	Rat	2 years	0/51	0	Meachim *et al.* (1982)	
	powder (0.5~50 µm)/ 28 mg			0/61	0		
Co53Cr19W15Ni10 (wrought Vitallium)	Intramuscular/rod (8 × 1.6 mm diameter)/ 1 rod	Rat	2 years	0/30	0	Gaechter *et al.* (1977)	
Co63Cr29Mo6Ni2 (cast Vitallium)	Intramuscular/rod (8 × 1.6 mm diameter)/ 1 rod	Rat	2 years	0/30	0	Gaechter *et al.* (1977)	
Co68Cr28Mo4	Intramuscular/powder (0.5~50 µm)/28 mg	Guinea-pig	Lifetime	0/46	0	Meachim *et al.* (1982)	
Co41Cr18Zr16Si11	Intraosseous/powder (< 28 µm)/42 mg	Rat	30 months	1/18	5.6	Memoli *et al.* (1986)	
Co51Cr20W14Ni10 Fe2Mn2	Wire			3/32	9.4		
Co70Cr25Mo5	Rod (4 × 1.6 mm diameter)			0/25	0		
Co47Cr20W14Ni12	Rod (4 × 1.6 mm diameter)			0/26	0		

Table 40 (contd)

Implant material/composition (wt %)	Route/size/amount	Species	Duration of observation	Local tumour outcome		Reference	Comments
				No.	%		
Cobalt-based alloys (contd)							
Co67Cr27Mo6 (F 75 alloy)	Smooth, solid extra-osseous half-cylinder (5 mm diameter × 13 mm) on lateral femur	Rat	24 months	14/101	14.0	Bouchard *et al*. (1996)	Not sintered
	Sintered porous extraosseous half-cylinder (5 mm diameter × 13 mm) on lateral femur	Rat		3/102	3.0		Sintered
	Injection of a suspension of microspheres (50–80 µm diameter) in the dorsal subcutis	Rat		15/103	15.0		
Co59Cr29Mo6Mn1Si1 (F 75-82)	Intra-articular/wear debris (1.5–50 µm)/20 mg	Rat	24 months	0/12	0	Lewis *et al*. (1995)	In saline vehicle
Titanium-based alloys							
Ti75V8Cr6Mo4Zr4Al3 (RMI alloy)	Intramuscular/rod (8 × 1.6 mm diameter)/ 1 rod	Rat	2 years	0/30	0	Gaechter *et al*. (1977)	
Ti89Al6V4	As above	Rat	2 years	0/30	0		
Ti89Al6V4 (F 136 alloy)	Intraosseous/half-cylinder (33 mm × 5 mm diameter)	Rat	24 months	23/102	22.5	Bouchard *et al*. (1996)	Not sintered
Ti89Al6V4 (F 136 alloy)	Intra-articular/wear debris (20–650 µm)/20 mg	Rat	24 months	0/8	0	Lewis *et al*. (1995)	In 50% glycerol vehicle

Table 40 (contd)

Implant material/composition (wt %)	Route/size/amount	Species	Duration of observation	Local tumour outcome		Reference	Comments
				No.	%		
Stainless steels							
Fe59Cr14Ni7C4Al2Mn1	Intratracheal/dust (3–5 µm)/12 × 3 mg	Hamster	26–30 months	0/63	0	Muhle *et al.* (1992)	
	(3–5 µm)/12 × 9 mg	Hamster		0/62			
Fe68Cr13C3Al2	(3–5 µm)/12 × 9 mg	Hamster		0/56	0	Muhle *et al.* (1992)	
Stainless steel[a]	Intramuscular/discs 18-, 12- and 4-mm diameter; 1.5 mm thick	Guinea-pig Rat	> 30 months	0/47 6/59	0 10	Stinson (1964)	
Fe65Cr17Ni14Mo2	Intramuscular/rod (8 × 1.6 mm diameter)/ 1 rod	Rat	2 years	0/40	0	Gaechter *et al.* (1977)	
Fe65Cr17Ni14 (316L solid)	Intraosseous/rod (4 × 1.6 mm diameter)	Rat	30 months	0/26	0	Memoli *et al.* (1986)	
Fe68Cr16Ni13 (316L powder)	Powder (< 2 µm)/40 mg			0/52	0		
Fe70 Cr15 Ni12	Intrabronchial/wire (28 gauge, approx. 10 mm long)	Rat (35)	24 months	0/32	0	Autian *et al.* (1976)	

[a] Metal composition unspecified

4A.6.2 *Intrabronchial administration*

Rat: A group of 35 male Bethesda black rats, approximately three months old, received implants via tracheotomy into the left inferior bronchus of a coiled wire fabricated of surgical-grade stainless steel suture material (Fe70Cr15Ni12, 28 gauge, approximately 1 cm long). Thirty-two of the rats survived for two years; none developed a lung tumour at the implant site. In contrast, three squamous-cell carcinomas were observed after 17–21 months in another group of rats that received intrabronchial implants of a polyether chlorinated polyurethane sheet (1 × 1 × 10 mm) (Autian *et al*., 1976).

4A.6.3 *Subcutaneous administration*

Rat: Six groups of five male and five female Wistar rats, 4–6 weeks of age, received subcutaneous implants of four pellets (~2 mm diameter) of: (*a*) Vitallium alloy, (*b*) metallic nickel, (*c*) metallic copper, (*d*) Ni60Ga40 alloy, (*e*) metallic silver or (*f*) AgHg dental amalgam. [The percentage compositions of the metal constituents of the Vitallium alloy and the dental amalgam were unclear. No control group of sham-operated rats was available.] The animals were observed for 27 months. Sarcomas (fibrosarcoma or rhabdomyosarcoma) developed around the implants in 5/10 rats that received metallic nickel pellets and in 9/10 rats that received Ni60Ga40 alloy pellets. No local tumour occurred in the other groups of treated rats (Mitchell *et al*., 1960).

4A.6.4 *Intramuscular administration*

Rat: A group of 59 female rats of the Chester-Beatty strain, three months old, received intramuscular implants of stainless steel discs (18-, 12- and 4-mm diameter, 1.5 mm thick). Each rat received one large (18-mm) disc into the left buttock and one small (4-mm) and one medium (12-mm) disc into the right buttock. Three animals were killed at 6, 12, 18, 24 and 30 months; the remainder were observed for their lifespan. Six rats developed a total of seven sarcomas in juxtaposition to the large discs or medium-sized discs. The minimum latent period was 332 days (Stinson, 1964). [The Working Group noted that no sham-operated controls were available.]

In a series of three experiments, a total of 80 female hooded rats, 7–9 weeks of age, received an intramuscular injection of 28 mg of wear particles (Co67Cr26Mo7Mn1; particle diameter, mostly 0.1–1 μm; obtained following repeated frictional movement in Ringer's solution of artificial hip or knee prostheses) in 0.4 mL horse serum and were observed for up to 29 months [survival not specified]. No control group was reported. Sarcomas developed at the injection site in 3/16, 4/14 and 15/50 rats in three series, respectively. Of the 22 tumours, 10 were rhabdomyosarcomas, 11 were fibrosarcomas and one was an unclassified sarcoma with giant cells. Distant metastases were found in 11/22 tumour-bearing rats (Heath *et al*., 1971; Swanson *et al*., 1973).

Groups of female Wistar and hooded Lister rats, weighing 190–310 and 175–220 g, respectively, received intramuscular implants of 28 mg of coarse (100–250 μm diameter; 51 Wistar rats) or medium (0.5–50 μm diameter, 85% 0.5–5 μm; 61 Wistar and 53

hooded rats) particles as dry powder (obtained by grinding Co68Cr28Mo4 alloy) and were observed for life. A sham-operated control group of 50 female Wistar rats was used. Survival at two years was 11/51 Wistar rats receiving the coarse particles, 7/61 Wistar rats receiving the fine particles, 0/53 hooded rats receiving the fine particles and 5/50 Wistar controls. No tumour was noted at the implantation site in rats treated with either type of alloy particles or in sham-operated control animals (Meachim *et al*., 1982).

[The Working Group noted in comparing these two studies that the particle size was smaller in the studies by Heath *et al.* and Swanson *et al*. than either of the dry powders tested by Meachim *et al*., and that the studies differed in the method of production of the test powders (the former being more relevant to the in-vivo situation), and that in the Heath *et al.* and Swanson *et al.* studies, horse serum was used as vehicle.]

Seven groups of 15 or 20 male and 15 or 20 female Sprague-Dawley rats, aged 20–30 days, received intramuscular implants of polished rods (1.6 mm in diameter, 8 mm in length) of one of seven alloys: (*a*) Fe65Cr17Ni14Mo2 alloy (stainless steel 316L); (*b*) Co53Cr19W15Ni10 alloy (wrought Vitallium); (*c*) Co63Cr29Mo6Ni2 alloy (cast Vitallium); (*d*) Ni35Co35Cr20Mo10 alloy (MP35N alloy); (*e*) metallic titanium (> 99% titanium), (*f*) Ti75V8Cr6Mo4Zr4Al3 alloy (RMI alloy) and (*g*) Ti89Al6V4 alloy. The animals were observed for up to two years [survival unspecified]. Two groups of 15 male and 15 female untreated or sham-operated control animals were available. No benign or malignant tumour developed at the implant site in any of the groups receiving metal implants or in the sham-operated control group. The incidence of malignant tumours at distant sites did not differ significantly between any of the treated and two control groups (Gaechter *et al*., 1977).

Groups of 20 or 16 male Fischer 344 rats, two to three months old, received a single intramuscular injection of 14 mg metallic nickel powder (99.5% nickel) or 14 mg (as nickel) of Fe62Ni38 alloy in 0.3–0.5 mL penicillin G procaine vehicle into the right thigh. Each compound was ground to a median particle diameter of < 2 μm. Of the 20 rats receiving nickel powder, 13 developed tumours (mainly rhabdomyosarcomas) at the site of injection, with an average latency of 34 weeks. No local tumour developed in the 16 rats given the Fe62Ni38 alloy, in 44 controls given penicillin G procaine or in 40 controls given an injection of glycerol (Sunderman, 1984).

Guinea-pig: A group of 47 female guinea-pigs of the Hartley strain, 4–6 months old, received intramuscular implants of stainless steel discs (18-, 12- and 4-mm diameter, 1.5 mm thick). Each guinea-pig received one large (18-mm) disc into the left gluteal muscle, and one small (4-mm) and one medium (12-mm) disc into the right. Three animals were killed at 6, 12, 18, 24 and 30 months; the remainder were observed for their lifespan. No local tumours developed (Stinson, 1964).

A group of 46 female Dunkin-Hartley guinea-pigs (weighing 550–930 g) received intramuscular implants of 28 mg of a dry powder (particle diameter, 0.5–50 μm, 85% 0.5–5 μm) obtained by grinding Co68Cr28Mo4 alloy. The guinea-pigs were observed for life and 12/46 animals were alive at three years. No control group was available.

No tumour was observed at the implantation site in any guinea-pig; nodular fibroblastic hyperplasia was noted in eight animals (Meachim *et al*., 1982).

4A.6.5 *Intraperitoneal administration*

Rat: Groups of female Wistar rats, 18 weeks of age, received single or repeated intraperitoneal injections of one of three nickel-containing alloys (milled to particle size < 10 μm) in 1 mL saline solution once or twice per week. The alloys were (*a*) Ni50Al50 alloy (nickel content 52% after milling), (*b*) Fe55Ni32Cr21Mn1 alloy (nickel content 29% after milling) and (*c*) Ni74Cr16Fe7 alloy (nickel content 66% after milling). All animals were killed 30 months after the first injection. The incidences of local sarcomas and mesotheliomas in the peritoneal cavity are shown in Table 41. A dose–response trend was apparent for metallic nickel and the tumour responses to the nickel alloys increased with the proportion of nickel present and the dose (Pott *et al*., 1989, 1992).

Table 41. Tumour responses of rats to intraperitoneal injection of nickel and nickel alloys

Compound	Total dose (mg as nickel)	Schedule	Meso-theliomas	Sarco-mas	Local tumours
Metallic nickel	6	Single injection	2	3	4/34*
	12	2 × 6 mg	3	2	5/34*
	25	25 × 1 mg	9	6	25/35*
Alloy (66% nickel after milling)	50	Single injection	0	12	12/35*
	150	3 × 50 mg	5	19	22/33*
Alloy (52% nickel after milling)	50	Single injection	1	7	8/35*
	150	3 × 50 mg	3	11	13/35*
Alloy (29% nickel after milling)	50	Single injection	1	1	2/33
	100	2 × 50 mg	0	1	1/36
Saline controls		3 × 1 mL	0	1	1/33
		50 × 1 mL	0	0	0/34

From Pott *et al*. (1989, 1992)
* $p < 0.05$

4A.6.6 *Intrarenal administration*

Rat: Groups of male Fischer 344 rats, approximately two months of age, received an intrarenal injection of 7 mg metallic nickel powder or 7 mg (as nickel) Fe62Ni38 alloy in 0.1 or 0.2 mL saline solution into each pole of the right kidney (total dose, 14 mg nickel per rat). The study was terminated after two years; the median survival time was 100 weeks in the two treated groups compared with 91 weeks in a group of saline-treated controls. Renal tumours occurred in 0/18 (nickel-treated) and 1/14

(alloy-treated) rats, compared with 0/46 saline-treated controls. The tumour, a nephroblastoma, was observed at 25 weeks (Sunderman *et al*., 1984).

4A.6.7 *Intraosseous administration*

Rat: Groups of 10–17 male and 8–15 female Sprague-Dawley rats (total number, 409), 30–43 days of age, received implants in the femoral bone of various metallic materials as small rods (1.6 mm diameter, 4 mm length), powders (fine, diameter < 28 μm; coarse, diameter 28–44 μm) or porous compacted wire. A total of 77 rats in groups of 12–13 male and 13 female untreated or sham-operated controls was available. Average survival in all groups exceeded 21 months; the animals were observed for up to 30 months. Sarcomas at the implantation site were observed in 1/18 rats given Co41Cr18Zr16Si11 powder, 3/32 rats given Co51Cr20W14Ni10Fe2Mn2 compacted wire and 3/26 rats given Ni35Co33Cr22Mo9Ti1 powder (MP35N alloy). No sarcoma at the implant site was observed in rats that received other metallic implants or in two groups of 25 and 26 untreated rats or in a group of 26 sham-treated control rats. A total of 12 implant site-associated lymphomas was observed sporadically in the test groups, but none in sham-operated controls (Memoli *et al*., 1986).

Four groups of 52 male and 52 female Sprague-Dawley rats, four weeks of age, were given implants of metal half-cylinders (5 mm in diameter, 13 mm in length) fixed on the left, lateral femur by an intraosseous cylindrical peg (1.5 mm diameter, 3 mm length) (groups 1, 2 and 3) or subcutaneous injections of metal microspheres (50–80 μm diameter, group 4). Group 1 received half-cylinders of Ti89Al6V4 alloy (F 136 alloy); group 2 received half-cylinders of Co67Cr27Mo6 alloy (F 75 alloy); group 3 received half-cylinders of sintered-porous Co67Cr27Mo6 alloy (F 75 alloy); and group 4 received microspheres of Co66Cr28Mo6 (F 75 alloy). No sham-operated or vehicle-injected control groups were available. The experiment was terminated 24 months after implantation [survival data not specified]. Implant-associated tumours were observed in 23/102, 14/101, 3/102 and 15/103 rats of Groups 1, 2, 3 and 4, respectively. The total of 55 implant-associated tumours included 52 malignant tumours (mostly sarcomas) and three benign tumours (lipomas, all in Group 4). Within Groups 1–3, 34/40 of the tumours were associated with loose implants, 3/40 with undetermined implant fixation status and 3/40 with implants fixed to the bone, supporting an association between implant looseness and implant-associated neoplasms ($p < 0.001$) (Bouchard *et al*., 1996).

4A.6.8 *Intra-articular administration*

Rat: Two groups of 12 and eight male Fischer 344 rats, 2–4 months old, received an intra-articular injection into the suprapatellar pouch of 20 mg wear-debris powders of either Co59Cr29Mo6Mn1Si1 alloy (F 75-82 alloy; particle dimensions, 1.5–50 μm; suspended in 0.1 mL saline vehicle) or Ti89Al6V4 alloy (F 136-84 alloy; particle dimensions, 20–650 μm; suspended in 0.1 mL 50% glycerol vehicle). Two control groups were available: a negative control group of 11 rats received a similar intra-articular injection of metallic manganese powder (Mn 94%, O 6%; median particle diameter, 1.5 μm;

suspended in 0.1 mL saline vehicle); a positive control group of 12 rats received a similar intra-articular injection of nickel subsulfide powder (median particle diameter, 1.5 μm; suspended in 0.1 mL saline vehicle). The animals were followed up to 24 months after injection. Median survival exceeded 18 months in the test groups and the negative control group, and was 10 months in the positive control group. Tumours (mostly malignant fibrous histiocytomas) developed at the injection site in 10/12 rats in the positive control group. No injection site tumour was observed in either test group or in the negative control group (Lewis *et al*., 1995).

4A.6.9 *Implantation of ear tags*

Rat: In two studies on the carcinogenicity of cadmium salts, groups of male Wistar rats, six weeks of age, received identification ear-tags made of a Ni67Cu30Fe2Mn1 alloy. In one study, a total of 14/168 rats surviving to two years developed a tumour (mostly osteosarcoma) at the site of ear-tag implantation. In the second study, 2/193 surviving rats developed a tumour (one osteosarcoma, one giant-cell tumour) at the site of ear-tag implantation within two years. The authors implicated nickel in the alloy as the probable causative agent and suggested that local microbial infection might be a contributory factor (Waalkes *et al*., 1987).

4B. Non-metallic Medical and Dental Materials

4B.1 Polydimethylsiloxanes (silicones)

4B.1.1 *Subcutaneous administration*

Mouse: Three groups of 50 male and female C57BL/6JN mice [age unspecified] received subcutaneous implants of a silicone rubber cube (prepared by heat-curing of linear gum (polysilicone gum) with silica powder and a catalyst (benzoyl peroxide)) (10 mm thickness, 200 mg), a polysilicone gum ball (200 mg) or silica powder (200 mg) into the nape of the neck. All animals were observed for a maximal period of 24 months. No tumour was found at the site of implantation with any sample (Hueper, 1961).

Rat: A group of Wistar rats [sex and age unspecified] was given subcutaneous implants of plain films of Silastic (15 × 15 mm × 0.25 mm). Of the 35 rats that survived at the minimal latent period, 14 animals developed malignant tumours at the implantation site within a latent period of 300–609 days (Oppenheimer *et al*., 1955).

Five groups of 25–30 male and female Wistar rats, weighing 60 g, received subcutaneous implants of Silastic 250, 450, 675, 2000 or 9711 (4 × 5 × 0.16 mm) and were observed for two years. At 300 days, 112 rats were still alive. Two malignant fibrosarcomas developed at the site of implantation of Silastic 250 and Silastic 2000 at 583 and 562 days, respectively (Russell *et al*., 1959). [The Working Group noted the small size of the film.]

Three groups of 30 female Bethesda black rats, three months of age, received subcutaneous implants of a Silastic cube (300 mg), a polysilicone gum ball (300 mg) or

silica powder [not characterized] (30 mg) into the nape of the neck. All animals were observed for a maximal period of 24 months. The total numbers of tumours at the site of implantation were 10/30 for Silastic, 1/30 for polysilicone gum and 0/30 for silica powder (Hueper, 1961).

A group of 20 male and 20 female Wistar rats [age unspecified] was given subcutaneous implants of silicone film ($10 \times 20 \times < 1$ mm); 1/14 males and 2/19 females developed malignant fibrous histiocytomas at the site of implantation during the two-year test period (Maekawa *et al*., 1984).

A group of male Wistar rats, five weeks of age, was given subcutaneous implants ($20 \times 10 \times 1$ mm) of a silicone film of known composition (methylvinylpolysiloxane was mixed with 25% of silica, a small amount of methylhydrogenpolysiloxane as curing agent and platinum catalyst, and rolled out to a 1-mm thick film and cured at 70°C for 3 h). The first tumour at the site of implantation was seen after 24 months, at which time 14 rats survived. Two local malignant fibrous histiocytomas were observed after 24 months (Nakamura *et al*., 1992).

A group of 50 Sprague-Dawley rats [age and sex unspecified] was given 0.1 mL of Bioplastique by subcutaneous injection. The Bioplastique contained 38% silicone, with particles as small as 5 μm, but mostly in the range 100–150 μm, in a hydrogel carrier. The animals were observed for two years. Thirty-four of the 48 animals examined had developed one or more tumours: breast adenomas (22), pituitary tumours (18), mediastinal hibernomas (2), retroperitoneal liposarcoma (1) and breast adenocarcinoma (1). There was no significant difference in the total number of breast and pituitary tumours between the treated group and a control group housed and fed under the same conditions as the injected animals. Three tumours associated with the injection site were found, all of which were poorly differentiated sarcomas (Dewan *et al.*, 1995).

4B.1.2 *Intraperitoneal administration*

Mouse: A group consisting of 50 male and female C57 BL/6JN mice [age unspecified] received implants of a silicone rubber cube (Silastic, produced by heat curing of linear polydimethylsiloxane gum (polysilicone gum) with silica powder and a catalyst (benzoyl peroxide); 200 mg), a polysilicone gum ball (200 mg) or silica powder (20 mg) into the abdominal cavity and were observed for 24 months. A spindle-cell sarcoma located in the lower abdominal cavity not connected with the Silastic implant was found in one of the 50 mice; one of the mice with a polysilicone gum pellet had a spindle-cell sarcoma in the right lower abdominal cavity and a second mouse in the polysilicone gum group developed a lymphatic leukaemia; among the mice given silica powder, two mice developed malignant lymphomas in the abdominal cavity (Hueper, 1961).

Rat: Three groups of female Bethesda black rats, three months of age, were given implants of a silicone rubber cube (Silastic, produced by heat curing of linear polydimethylsiloxane gum (polysilicone gum) with silica powder and a catalyst (benzoyl peroxide); 300 mg), a polysilicone gum ball (300 mg) or silica powder (25 mg) into the abdominal cavity. All animals were observed for maximal period of 24 months. No

tumour was found at the site of implantation with the Silastic, polysilicone gum or silica powder (Hueper, 1961).

4B.1.3 *Intraosseous implantation*

Rat: Cylinders (1.8 mm diameter, 4.0 mm length) of polydimethylsiloxane Silastic were implanted into a drill hole of about 2 mm diameter through the lateral cortex of the left distal femur of a group of 13 male and 13 female Sprague-Dawley rats. No tumour was found at the site of implantation during the 30-month experimental period (Memoli *et al*., 1986).

4B.2 Polyurethane

4B.2.1 *Subcutaneous and/or intraperitoneal administration*

Rat: Six groups of 30 female Bethesda black rats, three months of age, were given subcutaneous implants into the nape of the neck or into the right side of the abdominal cavity of one of three forms (a disc cut from a sheet, cubes cut from polyurethane foam or a powder derived from the foam by micropulverization, each sample weighing 65 mg) of polyurethane (made from toluene diisocyanate). A group of 30 control rats was given four intraperitoneal injections of saline. Animals were observed for up to 24 months. The discs gave rise to one subcutaneous tumour, the foam caused one subcutaneous and nine abdominal tumours and the powder gave rise to one abdominal tumour. The latency of tumour appearance was 10 months for the foam and 22 months for the disc. Tumours distant from the site of implantation were similar to those seen in controls (see Table 42; Hueper, 1960). [The Working Group noted that the effective numbers of rats were not reported.]

Groups of 30 female Bethesda black rats, three months of age, were given subcutaneous (in the nape of the neck) or intraperitoneal implants of polyurethane sheet,

Table 42. Sites and types of tumours observed in rats with implants of polyurethane

Type of polyurethane	Site of implantation	No. of tumours	
		Local	Distant
Disc	Subcutaneous	1	5
	Intraperitoneal	0	6
Foam	Subcutaneous	1	5
	Intraperitoneal	9	4
Powdered foam	Subcutaneous	0	4
	Intraperitoneal	1	6
Controls		0	4

From Hueper (1960)

foam cubes or powder. The sheet, made by reacting toluene diisocyanate 80/20, adipic acid and diethylene glycol, and containing the flame retardant tris(β-chloroethyl) phosphate, was cut into two discs (3 and 5 mm in diameter). The foam was cut into cubes measuring 25 × 20 × 3 mm; each cube was further subdivided into four pieces for subcutaneous implantation. Powder was obtained by micropulverizing the foam. Each sample weighed 65 mg. A group of 200 female rats served as controls. Polyurethane sheet and foam each produced only one subcutaneous sarcoma; however, intraperitoneal implantation of the foam produced eight adenocarcinomas of the caecum within a latency of 10–19 months. One subcutaneous sarcoma was found following subcutaneous implantation of the powdered form, and one invading adenocarcinoma of the caecum following intraperitoneal implantation. There was no indication of any excess of tumours at distant sites (Hueper, 1961).

Groups of 20 male and 15 female rats Bethesda black rats [age unspecified] were given subcutaneous implants into tissue of the nape of the neck and/or implants into the abdominal cavity (pericaecal or perigastric region) of two polyurethane foams (a linear polyester of adipic acid and diethylene glycol coupled with toluene diisocyanate, old or freshly prepared) and three rigid types of polyurethane. The 65-mg implants varied from 6 × 5 × 2 mm to 25 × 20 × 4 mm in size because of differences in density. Animals were observed for 24 months. Among the 210 rats given intraperitoneal implants of foam, 27 tumours related to the implants were detected (including five stomach sarcomas and 16 adenocarcinomas of the colon). Subcutaneous implants of rigid polyurethane foams resulted in nine sarcomas in 135 rats; the intraperitoneal implant of rigid foam produced two abdominal fibrosarcomas in 135 rats (Hueper, 1964).

Groups of 18 and 10 albino rats [sex and age unspecified] were given subcutaneous implants into the neck region of two polyurethane foams (Etheron, derived from diisocyanate polyethers, and Polyfoam, from toluene diisocyanate; 20 × 20 × 5 mm). Etheron induced two sarcomas in 18 animals that lived for 15–28 months. Polyfoam induced four local sarcomas in 10 animals, the average age at death being 22.5 months. The two foams disappeared almost entirely within two years after implantation (Walter & Chiaramonte, 1965).

Groups of about 30 male Bethesda black rats, three months of age, were given intraperitoneal implants of 17 isocyanate polyurethane samples containing various substituent groups (aromatic, alphatic or ester groups). Thirteen polyurethane samples were implanted as sheets and four as granular material. The sheets were cut into rectangular pieces with no side greater than 3 mm. Thirteen of the polyurethane samples were also implanted into females. Each rat received 1.5 g of test samples. Of the 1015 rats implanted with polyurethane samples, 292/577 males and 248/438 females developed malignant tumours at the implantation site during the 24-month study, about 90% of which were fibrosarcomas. Wide variations in tumour rates were observed among the 17 experimental groups. Local malignant tumours developed in 0/37 sham-operated male controls and 1/37 female controls (Autian *et al*., 1975). [The Working Group noted that incomplete pathological data were reported.]

A chlorinated poly(ether urethane) (Y-238, prepared from toluene diisocyanate and cured with 4,4′-methylenebis(*ortho*-chloroaniline) (MOCA)), which demonstrated the highest relative tumorigenicity of 17 polyurethane samples tested in the study by Autian *et al*. (1975), was selected for further evaluation. Five groups of 35 male Bethesda black rats, three months of age, were given intraperitoneal implants of discs (3.1 mm in diameter) resulting in doses of 93.8, 187.5, 375, 750 and 1500 mg per rat. The animals were observed for two years. The numbers of local fibrosarcomas observed in the five groups were 0, 1, 2, 8 and 24, respectively, suggesting a dose-related response (Autian *et al*., 1976).

Five groups of 20 male Wistar rats, six weeks of age, were given subcutaneous implants of five kinds of polyurethane (ether-type) films (15 × 15 × 0.2–0.25 mm) (Biomer, Cardiothane, TM-3 purified, TM-3 unpurified and a tailor-made dicyclohexylmethanediisocyanate-based segmented polyurethane (DCHMDI-SPU)). The first tumour at the site of implantation was seen after 14 months for Biomer, Cardiothane and TM-3 unpurified and after 11 months for TM-3 purified and DCHMDI-SPU. The total incidence of local tumours after 28 months was 4/13 for Biomer, 2/13 for Cardiothane, 1/11 for TM-3 purified, 6/18 for TM-3 unpurified and 3/11 for DCHMDI-SPU, respectively (Imai & Watanabe, 1987).

Four groups of 30 male Wistar rats, five weeks of age, were given subcutaneous implants of three kinds of polyurethane film (containing no additives) of different molecular weight (U-4, 220 000; U-6, 124 000; U-8, 55 600), synthesized from 4,4′-methylenediphenyl diisocyanate, poly(tetramethylene glycol) and 1,4-butanediol with molar ratio of 2: 1: 1, or silicone films (20 × 10 × 1 mm). The rats were observed for one year. As summarized in Table 43, histopathological evaluation showed no relationship

Table 43. Histopathological evaluation in one-year implantation study of polyurethanes of different molecular weight

Implant	No. of animals in rank				Total active incidence (A + B + C)	Capsule thickness (mm)	
	A	B	C	D		Mean	SD
U-4	2	3	9	16	14	0.32	0.12
U-6	0	0	2	28	2	0.32	0.14
U-8	0	1	5	24	6	0.37	0.21
Silicone	0	0	0	27	0	0.30	0.08

Criteria of ranking: A, local tumour was found; B, atypical cell proliferation accompanied by preneoplastic changes was observed at the inner layer of the capsule; C, cell proliferation but no preneoplastic change was observed; D, no cell proliferation was observed
From Nakamura *et al*. (1992)

between molecular weight and active tissue responses, including local malignant fibrous histiocytomas (Nakamura *et al*., 1992).

Groups of 30 male Wistar rats, five weeks of age, were given subcutaneous implants of polyurethane (U-6), silicone and a 1:1 blend (U-6/silicone films) (20 × 10 × 1 mm) and were held for two years. As shown in Table 44, the polyurethane content governed tissue responses, including tumour formation (Nakamura *et al*., 1992).

Table 44. Effects of polyurethane content on tissue responses in a two-year study

Implant	No. of animals in rank				Total active incidence (A + B + C)	Capsule thickness (mm)	
	A	B	C	D		Mean	SD
Silicone	2	1	4	21	7	0.27	0.08
U-6/silicone	2	0	9	18	11	0.29	0.10
U-6	11[a,b]	1	10	7	22[c]	0.29	0.11

Criteria of ranking: A, tumour was found; B, atypical cell proliferation accompanied by preneoplastic changes was observed at the inner layer of the capsule; C, cell proliferation but no preneoplastic change was observed; D, no cell proliferation was observed

[a] Significantly different from silicone (χ^2-test, $p < 0.01$)

[b] Trend test (Cochran-Armitage test, $p < 0.01$)

[c] Trend test (Cochran-Armitage test, $p < 0.0001$)

From Nakamura *et al*. (1992)

Seven groups of 30 male Wistar rats, five weeks of age, were given subcutaneous implants of poly(ether urethane) film (10 × 20 × 1 mm) with smooth or porous (pore size, 20–50 μm) surface morphology, containing different amounts of oligomers, or a silicone film of the same size as control. The poly(ether urethanes) used were: UN (unrefined; molecular weight, 220 000) prepared from 4,4′-methylenediphenyl diisocyanate, poly(tetramethylene glycol) and 1,4-butanediol with molar ratio of 2 : 1 : 1, having oligomer content of 5.6%; UR, refined UN to delete oligomers; and UA, oligomer-added UN, having oligomer content of 11%. Animals were observed for two years. The incidence of local tumours (malignant fibrous histiocytomas) at the site of implantation and the shortest latent period are summarized in Table 45. It was concluded that the amount of oligomers did not affect the local tumour incidence, whereas changing surface morphology from smooth to porous extended the latent period of tumour development and decreased the total incidence of local tumours. There was no increase in the incidence of tumours at sites distant from the implantation site (Nakamura *et al*., 1995).

Table 45. Injection-site tumours in rats given implants of different polyurethanes

Implant	Surface	Total no. of MFH-bearing animals	Shortest latent period (months)
UR	Smooth	6	12
UR	Porous	7	18
UN	Smooth	8	15
UN	Porous	4	21
UA	Smooth	8	12
UA	Porous	4	21
Silicone	Smooth	3	15

See text for definition of polyurethane types UA, UN and UR
MFH, malignant fibrous histiocytoma
From Nakamura *et al*. (1995)

4B.2.2 *Inhalation and/or intratracheal or intrabronchial administration*

Rat: Two groups of 39 and 45 Sprague-Dawley rats [sex and age unspecified] were exposed by inhalation to rigid isocyanate polyurethane foam powder [composition not specified] at concentrations of 3.6 and 20 mg/m^3, respectively, for 6 h per day on five days per week for six weeks. The median particle size was 0.5 μm. One bronchial squamous-cell carcinoma was observed in animals at each dose level after 544 and 349 days, respectively. The median lifespans were 50 and 62 weeks, and the durations of the experiments were 139 and 101 weeks. No tumours were found in 20 untreated rats (Laskin *et al*., 1972).

Groups of white rats [number, sex and strain unspecified] of different ages (2–3 months or 11–19 months) received intratracheal intubations of 5 mg of powder from an old polyurethane dust (the same product as that used by Laskin *et al*., 1972) or a freshly prepared polyurethane [composition not specified] suspended in 0.2 mL saline. This dose is the equivalent of inhalation for 8 h per day for 30 days of a concentration between the minimal and maximal levels used in the experiment by Laskin *et al*. (1972). Pulmonary fibrosis appeared after six months. A sub-pleural adenoma was seen in a rat given the old polymer, and four benign lesions reported to be intra-bronchial adenomas were observed 18 months after intubation among 15 young rats given the freshly prepared sample (Stemmer *et al*., 1975).

Two groups of 35 male Bethesda black rats, three months of age, were given implants via tracheotomy into the left inferior bronchus of a polyether chlorinated poly-urethane sheet (Y-238, a polymer formed by reaction of toluene diisocyanate with poly-ether and cured with MOCA) cut into strips of approximately 1 × 1 × 6 mm (5–8 mg) or 1 × 1 × 10 mm (9–10 mg), through which fine, stainless-steel surgical wire was

passed and bent to form two hooks. One squamous-cell carcinoma of the lung was observed after 21.5 months in the first group, in which 31 animals survived one year or more; and three squamous-cell carcinomas of the lung were observed after 17–21 months in the second group, in which 32 animals survived one year or more. No lung tumours were observed in 35 controls given implants of surgical wire alone; 33 animals survived more than one year (Autian *et al*., 1976).

Groups of 50 male and 50 female Sprague-Dawley rats, eight weeks of age, were exposed by inhalation to a freshly generated rigid polyurethane foam dust (particle diameter, 94% < 5 μm) synthesized from Desmophen FWFA/2 (polyol based on a sucrose-polyether) and Desmodur 44V20 (a polymeric isocyanate based on 4,4′-methylenediphenyl diisocyanate) at a concentration of 8.65 mg/m^3 air for 6 h per day on five days per week for 12 weeks; the experiment was terminated after 140 weeks. There was no difference in tumour incidence in the polyurethane group compared with controls exposed to titanium oxide or to air alone (Thyssen *et al*., 1978).

Hamster: Two groups of 40 and 50 male Syrian hamsters were exposed by inhalation to respirable dust (0.5–3 μm) generated from rigid polyurethane foam [composition not specified] at concentrations of 3.6 and 20 mg/m^3 in air, respectively, for 6 h per day on five days per week for six weeks. Median survival times were 76 and 87 weeks and the duration of exposure was 139 and 101 weeks, respectively. No lung tumour was reported (Laskin *et al*., 1972).

4B.3 Poly(methyl methacrylate)

4B.3.1 *Subcutaneous and/or intramuscular administration*

Mouse: A group of 50 Harlan albino Swiss mice [sex unspecified], six weeks of age, was given subcutaneous implants into the lateral abdominal wall of poly(methyl methacrylate) (PMMA) film (10 × 10 × 0.2 mm), prepared by polymerizing commercially obtained monomer liquid (containing 1.0 mg/kg (ppm) hydroquinone) and polymer powder (containing cadmium oxide pigments), similar to that used in making dentures. The first fibrosarcoma at the implantation site was found in mice given PMMA films 257 days after the operation, when 20/50 mice were still alive; four additional fibrosarcomas developed at 405, 438, 454 and 469 days after the implantation. A group of 50 control mice was given subcutaneous implants of cellophane film; one fibrosarcoma at the implantation site was found 400 days after the operation among the seven mice still alive at that time (Laskin *et al*., 1954).

Two groups of 50 Harlan albino Swiss mice [sex unspecified], six weeks of age, were given subcutaneous implants into the lateral abdominal wall of films (10 × 10 × 0.20–0.25 mm) of cold- or heat-cured polymerized PMMA. An equal number of control mice of the same age, sex and strain were given implants of cellophane film (0.1 mm thick) of identical size. Animals were observed weekly for 420 days. At the end of that time, 22, 13 and 25 mice, respectively, were still alive; one mammary carcinoma, considered to be ‘spontaneous’, was found near a heat-cured PMMA film implant. The study ended after 575 days, when surviving animals comprised two mice

that received heat-cured PMMA film, 10 that received cold-cured PMMA film and five controls. No neoplastic changes at the site of implantation were detected (Kydd & Sreebny, 1960).

Groups of female Swiss albino mice, 7–8 weeks of age, were given subcutaneous implants into the left flank of PMMA films of varying sizes (15 × 15 × 0.5 mm, 12 × 12 × 0.5 mm, 6 × 6 × 0.5 mm or 6 × 12 × 0.5 mm) and observed for 100 weeks. The incidences of sarcomas at the site of implantation were 3/18 (16%), 10/38 (26%), 1/15 (6.6%) and 1/15 (6.6%) (Tomatis, 1966a).

Rat: A group of 25 Wistar rats [sex and age unspecified] was given subcutaneous implants of films of PMMA (15 × 15 mm × 0.14 mm). At the time of appearance of the first tumour, 20/25 rats were still alive; among these, four sarcomas were found at the site of implantation (20%), with latent periods ranging from 581 to 685 days. Of 50 surviving rats given implants of glass coverslips, one developed a fibrosarcoma that appeared 659 days after implantation. Results from an experiment that was still in progress at the time of reporting indicated that 11/25 rats given implants of purified PMMA (instead of commercial grade) developed subcutaneous sarcomas. In this group, the first tumour developed at 447 days (Oppenheimer *et al*., 1953, 1955).

A group of 153 female Chester Beatty rats, three months of age, were given intramuscular implants of PMMA discs. Each animal received one large disc (18 mm in diameter, 1.5 mm thick) in the left thigh and one medium (12 mm in diameter) and one small (4 mm in diameter) disc in the right thigh. Thirty-four tumours, all spindle-cell sarcomas, were observed in association with the largest discs, with latent periods of 150–807 days; seven animals had metastases to the lungs and/or mesentery. Sarcomas associated with the medium-sized discs were found in 17/142 rats still alive at the minimum latent period (297 days); five animals had metastases to the lungs and mesentery. The 51 sarcomas observed occurred in a total of 46 rats. No tumours were found in association with the smallest discs (Stinson, 1964). [The Working Group noted that the number of animals at risk was not given.]

A group of 34 female Wistar rats, 9–12 weeks of age, was given subcutaneous implants of PMMA (Plexiglas) rings (24 mm in diameter with a hole of 21.5 mm); one fibroblastic sarcoma was detected in one rat after 112 weeks of observation (Zajdela, 1966).

Male Wistar rats weighing 175–200 g [age unspecified] were given implants of PMMA (Surgical Simplex P; cut into discs 18 mm in diameter and 0.14 mm thick) inserted subcutaneously in the abdominal region. One group of 22 rats received the discs bilaterally, and another group of 25 rats received the PMMA disc on one side and a glass disc on the other. Surviving animals were killed after 39 months. Only 22 rats with either bilateral or single PMMA discs were subjected to pathological examination. Two fibrosarcomas were found at the site of implantation of PMMA discs between 349 and 471 days after implantation, but no tumours were associated with the glass discs (Lavorgna *et al*., 1972).

Guinea-pig: A group of 86 female Hartley guinea-pigs, 4–6 months of age, was given intramuscular implants into the thigh of three PMMA discs (1.5 mm thick) of different diameter (18, 12 and 4 mm). Groups of three animals were killed at six, 12, 18, 24 and 30 months after implantation to examine the tissue reactions around the discs; the remaining guinea-pigs were observed throughout their lifespan. No tumours were detected, even though some animals were still alive 48 months after the implantation (Stinson, 1964). [The Working Group noted that the effective number of animals at risk was not given.]

4B.3.2 *Intraperitoneal administration*

Rat: Two groups of 25 male and 25 female rats [strain unspecified], 3–4 months of age, were given intraperitoneal implants of either glass or PMMA discs (about 20 mm in diameter) and a group of 50 sham-operated animals served as controls. No tumours were found after 21 months in the glass-implanted group (21 survivors at 11 months). In the PMMA-implanted group, 20 rats survived 11 months and two sarcomas were observed around the implant (at 13 and 14 months after implantation), one of which metastasized to the omentum and peritoneal cavity; a third tumour in the peritoneal cavity, found at 20 months, did not arise from the capsule enveloping the disc. One lipoma was observed at 11 months in the 23 sham-operated animals alive at that time (Brunner, 1959).

4B.3.3 *Other experimental systems*

Combined subcutaneous and intraperitoneal implantation: Six groups of 10 male and 10 female rats [strain and age unspecified] were given implants of PMMA discs (17 mm diameter, 1–2 mm thick); each rat received five discs intraperitoneally into the abdominal wall and two subcutaneously under the dorsal skin. The PMMA discs contained 0, 2, 5, 10, 25 and 50% fibrin (to produce increasing roughness of the disc surface). A control group of 30 sham-operated animals was available. The numbers of animals at risk at the time of appearance of the first tumour were 20, 13, 15, 18, 14 and 13, respectively, in the groups given PMMA implants, and 15 in the control group; all animals were killed 17 months after implantation. The numbers of sarcomas were 2 (10%), 5 (38%), 2 (13%), 3 (17%), 4 (29%) and 1 (8%) in the implanted groups. No tumours developed in the sham-operated rats. Overall, 13 intraperitoneal and four subcutaneous tumours were observed; the first tumour appeared after nine months. Tumour development was not related to fibrin concentration (Brunner, 1959).

A group of male and female outbred rats (weighing 100–170 g) [initial number and age unspecified] was given intraperitoneal implants of five discs and subcutaneous implants of two discs of PMMA (16 mm diameter, 0.2–0.4 mm thick). At six months, 13 treated animals and 27 sham-operated controls were still alive; these animals were observed up to 23 months. Of treated animals, one developed a sarcoma near an intraperitoneal implant, one developed a subcutaneous sarcoma (metastasizing

to the lung) and two others developed [unspecified] tumours (Klärner, 1962). [The Working Group noted that the time of tumour appearance was not stated.]

Intraosseous implantation: A group of 13 male and 13 female Sprague-Dawley rats, 30–43 days of age, was given an implant of a PMMA bone cement (2 mL, Simplex P) injected into a drill hole about 2 mm in diameter through the lateral cortex of the left distal femur and allowed to polymerize *in vivo*. No tumour was found at the site of injection during the 30-month experimental period (Memoli *et al*., 1986).

4B.4 Poly(2-hydroxyethyl methacrylate)

4B.4.1 *Subcutaneous administration*

Rat: A group of 15 male Wistar rats, weighing 200 g, was given subcutaneous implants of cross-linked poly(2-hydroxyethyl methacrylate) film (10 × 20 × 0.5 mm) and one animal was killed at three and six months after implantation, for histological examination. The remaining animals were kept until they were moribund, died or developed tumours. Five local tumours [unspecified] were found at the site of implantation in 10 rats that survived for more than 12 months (Imai & Masuhara, 1982).

A group of 20 male and 20 female Wistar rats [age unspecified] was given subcutaneous implants of poly(2-hydroxyethyl methacrylate) film (10 × 20 × < 1 mm); 7/19 males and 9/20 females developed malignant fibrous histiocytomas at the site of implantation during the two-year test period (Maekawa *et al*., 1984).

Hamster: A group of 11 male hamsters (weighing 120 g) [strain unspecified] was given subcutaneous implants of cross-linked poly(2-hydroxyethyl methacrylate) film (10 × 20 × 0.5 mm) and one animal was killed at three and six months after implantation, for histological examination. The remaining animals were kept until they were moribund, died or developed tumours. Among animals that survived for more than 12 months, no tumours were found at the site of implantation (Imai & Masuhara, 1982).

Guinea-pig: A group of eight male guinea-pigs [age and strain unspecified] was given subcutaneous implants of cross-linked poly(2-hydroxyethyl methacrylate) film (10 × 20 × 0.5 mm) and one animal was killed at three and six months after implantation, for histological examination. The remaining animals were kept until they were moribund, died or developed tumours. Among animals that survived for more than 12 months, no tumours were found at the site of implantation (Imai & Masuhara, 1982).

4B.5 Poly(ethylene terephthalate)

4B.5.1 *Subcutaneous administration*

Rat: Groups of male Wistar rats [initial number and age unspecified] were given subcutaneous implants of discs (15 mm diameter) of a material described as Dacron in various physical forms. The incidence of malignant tumours at the site of implantation is summarized in Table 46 (Oppenheimer *et al*., 1955).

Table 46. Injection-site tumours in rats given poly(ethylene terephthalate) (Dacron) implants

Material	Thickness (mm)	No. of rats surviving minimal latent period	No. of local tumours (%)	Latent period (days)
Plain film	0.02	41	8 (19.5)	330–693
Perforated film	0.02	42	2 (4.8)	327–651
Textile	0.05	38	0 (0)	–

From Oppenheimer *et al*. (1955)

4B.6 Polyethylene

4B.6.1 *Subcutaneous administration*

Mouse: A group of albino mice (Paris strain) [initial number, sex and age unspecified] was given subcutaneous implants of a polyethylene film (0.002 mm thick); 3/28 survivors developed local sarcomas (Oppenheimer *et al*., 1952).

A group of albino (Longacre) mice [initial number, sex and age unspecified] was given subcutaneous implants of a pure, plain polyethylene film (15 mm diameter, 0.02 mm thick); 3/29 survivors developed malignant tumours at the site of implantation (Oppenheimer *et al*., 1955).

Two groups of 42 male and 45 female or 41 male and 32 female BALB/c An mice, 1–3 months of age, were given subcutaneous implants of commercial polyethylene discs (20 mm diameter, 0.38 mm thick) with either a smooth or roughened surface. The first sarcoma at the site of implantation was seen after 7.5 months, at which time the numbers of survivors in the two groups were 71 and 60 mice. The total number of sarcomas after 13 months was 35/71 in the mice given smooth discs and 7/60 in mice given roughened discs (Bates & Klein, 1966).

Rat: A group of 98 Wistar rats [sex and age unspecified] was given a subcutaneous implant of a commercial polyethylene film (0.002 mm thick); 10/80 survivors developed sarcomas, the first tumour appearing after 392 days. In rats given a polyethylene film without plasticizer, 5/40 developed local sarcomas. No local sarcomas developed in five control rats given implants of surgical cotton (Oppenheimer *et al*., 1952).

Groups of 25 male and 25 female Wistar or 25 male and 25 female Hisaw rats [age unspecified] were given implants of pure polyethylene film (20 × 15 mm) without plasticizer in the abdominal wall and over the skull; 8/63 developed fibrosarcomas after 434 or more days (two associated with cranial and six with abdominal implants). No such tumours occurred among 28 Hisaw controls subjected to sham operations (Bering *et al*., 1955).

Groups of Wistar rats [initial number, sex and age unspecified] were given subcutaneous implants of polyethylene film (15 mm diameter) of varying thicknesses and physical state. The incidence of malignant tumours at the site of implantation is

summarized in Table 47. The minimal latent period was shorter with the plain films than with the perforated film or the textile (385 and 392 days versus 407 and 497 days, respectively) (Oppenheimer *et al*., 1955).

Table 47. Injection-site tumours in rats given implants of polyethylene

Type of polyethylene	Thickness (mm)	Effective no. of rats	No. of tumours (%)	Latent period (days)
Plain commercial film	0.05	80	10 (12.5)	392–722
Plain pure film	0.02	55	11 (20)	385–742
Perforated pure film	0.02	41	6 (14.6)	407–784
Textile	0.15	40	1 (2.5)	497
Plain film, high mol. wt	0.07	34	3 (8.8)	352–583
Powder	–	42	0 (0)	–

From Oppenheimer *et al*. (1955)

A group of 60 male and female Wistar rats (weighing 60 g) received a subcutaneous implant of a sheet of polyethylene measuring 4 × 5 × 0.16 mm and was observed for two years. At 300 days, 51 rats were still alive. No malignant tumour was found at the site of implantation (Russell *et al*., 1959). [The Working Group noted the small size of the film.]

A group of 90 Wistar rats [sex and age unspecified] was given subcutaneous implants of glass cover-slips (18 mm in diameter) into the left and right flanks. Four months later, in a group of 27 of these rats, polyethylene powder was inserted against the cover-slip on the right and glass powder against that on the left side. Five and six sarcomas developed, respectively, with mean latent periods of 570 and 547 days. In another group of 27 rats, the glass cover-slips were removed after four months and polyethylene powder was implanted into the empty pocket in one side and glass powder into the other; one sarcoma occurred on the side containing polyethylene and none on that containing glass powder. In a third group of 25 rats, the glass cover-slip on the right side was removed after four months and no sarcoma developed, whereas six sarcomas occurred on the left side in which the glass cover-slip was left in place, with a mean latent period of 503 days (Oppenheimer *et al*., 1961).

A group of 55 albino rats [sex and age unspecified] was given implants of polyethylene film (10 mm diameter) into the left abdominal subcutaneous tissue and of polyethylene mesh (10 mm diameter) on the right side. After 18–24 months, four sarcomas were found at 45 sites at which films had been implanted and one at 52 sites at which mesh had been implanted (Shulman *et al*., 1963).

Two groups of 20 male CB stock rats, eight weeks of age, were given subcutaneous implants of segments of polyethylene (620 mg) or a gelatin capsule containing 530 mg of the shredded plastic. Two groups of controls were given either a sham operation or

empty gelatin capsules. All survivors were killed after 93 weeks. Six sarcomas and one squamous-cell carcinoma developed at the implantation sites in seven rats treated with the solid implants; five sarcomas occurred in rats given the capsules containing shredded polyethylene. No implantation site tumour occurred in sham-operated controls or controls given gelatin capsules (Carter & Roe, 1969).

Groups of male Wistar rats [age unspecified] had high-density polyethylene discs (18 mm diameter, 0.14 mm thick) inserted subcutaneously in the abdominal region. One group of 22 rats received the discs bilaterally and another group of 120 rats received the polyethylene disc on one side and a glass disc on the other. Surviving animals were killed after 39 months. Only 55 rats with either bilateral or a single polyethylene disc were subjected to pathological examination. Five fibrosarcomas were found at the site of implantation of polyethylene discs between 347 and 644 days after implantation, but no local tumours were associated with the glass discs (Lavorgna *et al*., 1972).

No local sarcomas were reported in a group of 11 male and 21 female Fischer 344 rats given subcutaneous implants of polyethylene powder (particle size, 425–600 μm) and observed for 100–118 weeks (Behling & Spector, 1986).

A group of 12 male Wistar rats, eight weeks of age, was given subcutaneous implants of two porous polyethylene blocks (5 × 10 × 15 mm; average pore size, 400 μm) and two collagen-immobilized porous polyethylene blocks of the same size into the left and right flanks, respectively. All rats were killed one year after implantation. Eleven tumours developed among the 24 sites of implantation with the polyethylene sample, while one tumour developed among the 24 sites of implantation with the collagen-immobilized polyethylene sample (Kinoshita *et al*., 1993).

A group of 50 male Wistar rats, 11 weeks of age, was given subcutaneous implants of medical grade polyethylene film (20 × 10 × 1 mm); 21/41 survivors developed malignant tumours at the site of implantation during the 24-month experimental period. Most of the tumours were diagnosed as fibrosarcomas, and the minimal latency period was 320 days. No such tumour occurred among 30 controls subjected to sham operations (Nakamura *et al*., 1994).

Hamster: A group of 50 hamsters [sex and strain unspecified], one month of age, was given subcutaneous implants of polyethylene film (squares of 20 × 20 mm); two survived more than 442 days. Both developed tumours at the site of implantation, which were diagnosed as a malignant mesenchymal tumour and a fibrosarcoma, after 442 and 457 days, respectively (Bering & Handler, 1957). [The Working Group noted the poor survival.]

4B.6.2 *Intraperitoneal administration*

Rat: Four groups of 30 female Bethesda black rats, three months of age, were given intraperitoneal implants of polyethylene cubes (3.5 × 3.5 × 3 mm), discs (12 mm diameter), rolled film (10 × 1.75 cm) or powder (65 mg) and were observed for up to 24 months. Sarcomas associated with the implant were found in 6/25 rats given rolled

film, in 0/25 rats given cubes and in 1/22 rats given discs. In rats given polyethylene powder, multicystic foreign-body granulomas of the serosal surface of the liver, kidney, spleen and anterior abdominal wall were observed (Hueper, 1961).

Two groups of 20 and 19 male and female Wistar rats, weighing 55–75 g, were given implants of polyethylene rods (10 × 2 × 2 mm) or powder into the peritoneal cavity, respectively. No local tumours developed; 11 and five rats in the two groups survived up to 800 days (Simmers *et al*., 1963).

A group of 38 male and 36 female Bethesda black rats, three months of age, was given intraperitoneal implants of particles of polyethylene (> 3 mm diameter, weighing 1.5 g). Within two years, 24 males developed intraperitoneal fibrosarcomas and five other [unspecified] tumours, and 19 females developed intraperitoneal fibrosarcomas and one other [unspecified] tumour. The incidence of local tumours in control male rats was 0/37 and that in female controls was 1/37 (Autian *et al*., 1975). [The Working Group noted that incomplete pathology data were reported.]

4B.6.3 *Other experimental systems*

Combined subcutaneous and intraperitoneal implantation: A group of 23 BD rats [sex and age unspecified] was given subcutaneous and intraperitoneal implants of polyethylene film; among the 14 rats still alive at the time of appearance of the first tumour (15 months), eight developed subcutaneous sarcomas and one developed an intraperitoneal fibroma (Druckrey & Schmähl, 1954).

Intraosseous implantation: A group of 13 male and 13 female Sprague-Dawley rats [age unspecified] was given implants of ultra-high molecular weight polyethylene cylinders (1.8 mm diameter, 4.0 mm length) placed into a drill hole through the lateral cortex of the left distal femur. No local tumour was found. One case of myeloid leukaemia occurred among the effective number of 24 rats during the 23-month observation period, an incidence similar to that of spontaneously occurring tumours. A similar group of 13 males and 13 females was given implants of 4.8 mg polyethylene in powder form (particle size, 10–383 μm); no local tumour was found (Memoli *et al*., 1986).

4B.7 Polypropylene

4B.7.1 *Subcutaneous administration*

Rat: A group of 70 E3 rats [sex and age not specified] was given subcutaneous implants of eight polypropylene discs (20 mm diameter, 2 mm thick). The experiment was terminated after 14 months, when 35 animals were still alive. A total of 55 local fibrosarcomas were produced, the first appearing after seven months. In another group of 60 rats, which was given a total of 480 implants, the discs were removed eight months after the implantation. The experiment was terminated at 14 months, when 41 animals were still alive. Two fibrosarcomas were observed at the ninth month, and 32 further local tumours were detected during the following five months (Vollmar & Ott, 1961). [The Working Group noted that no controls were included in these experiments.]

A group of 67 rats [sex, strain and age unspecified] was given a combination of implantation of discs (a total of 536 implants) and X-irradiation (3 × 200 rad, two to three weeks after implantation) which led to reduced survival. When the experiment was terminated after 14 months, a total of 34 local tumours had been found and 18 animals were still alive. After implantation of a total of 560 samples of polypropylene powder to 70 rats, the first local fibrosarcoma was found at 11 months. When the experiment was terminated after 14 months, four rats had developed local sarcomas and 35 were still alive (Vollmar & Ott, 1961). [The Working Group noted that no controls were included in these experiments.]

A group of 20 male Wistar rats, six weeks of age, was given subcutaneous implants of a thin polypropylene film (15 × 15 × 0.1 mm). No local tumour was found among 18 animals that survived for more than 11 months, during a 28-month observation period (Imai & Watanabe, 1987).

A group of 50 Wistar male rats [age unspecified] was given subcutaneous implants of a medical-grade polypropylene film (20 × 10 × 1 mm); 17/50 survivors developed malignant tumours at the site of implantation during the 24-month experimental period. Most of the tumours were diagnosed as malignant fibrous histiocytoma, and the latency period was 512 ± 133 days. One fibroma occurred among 50 sham-operated controls (Nakamura *et al*., 1997).

4B.8 Polytetrafluoroethylene

4B.8.1 *Subcutaneous administration*

Mouse: A group of 89 random-bred female Swiss mice, 7–9 weeks of age, was given a subcutaneous implant in the left flank of a polytetrafluoroethylene (PTFE) sheet (12 × 12 × 1.2 mm). The first local tumour developed 25 weeks after implantation; a total of 11 (12.5%) fibrosarcomas were found after an average latent period of 54.5 weeks (Tomatis & Shubik, 1963). [The Working Group noted that since the implant was not retained in nine mice and since 70 mice were still alive at the appearance of the first tumour, the effective tumour incidence was 16%.]

Groups of random-bred Swiss mice, 7–9 weeks of age, were given a subcutaneous implant of a PTFE sheet (12 × 12 × 1.2 mm) (89 females and 61 males), a 15-mm diameter PTFE disc (103 females), a Teflon fragment corresponding to one disc [size not specified] (53 females) or a 20-mm diameter PTFE disc (54 females and 50 males). Tumours developed around the implant in 8/89 (10%) and 1/61 (2%), 23/103 (22.7%), 10/53 (21.2%) and 7/54 (15.2%) and 4/50 (8%) mice in the above groups, respectively. No similar tumours were seen in 200 and 100 untreated female and male mice. Of 50 female mice given implanted glass coverslips (12 × 12 × 1.2 mm), six developed sarcomas (13.6%) and of 48 females given implants of fragments of glass corresponding to one sheet, two developed sarcomas (4.3%). The average latent period for gross, palpable tumours was 55 weeks, with two tumours appearing as early as week 25 and nine at 65 weeks after implantation. All neoplasms were fibrosarcomas, and some had angiosarcomatous areas (Tomatis, 1963).

A group of 19 male and 27 female inbred C57BL mice, 7–9 weeks of age, was given subcutaneous implants of PTFE discs (15 mm diameter, 1.2 mm thick). At 50 weeks, 13 males and 13 females were still alive. Among 20 females that retained the implant and were considered to be at risk, four developed local sarcomas at weeks 39, 47, 52 and 58, and four local sarcomas were found in the 15 males considered to be at risk (26%) at weeks 49, 51, 60 and 91. Mice were observed for 90 weeks, at which time only three males and three females were still alive. Tumours always occurred around the discs; one sarcoma tested was found to be transplantable in syngeneic mice. Tumours unrelated to the implant developed in three females and one male. In a control group of 30 male and 33 female mice without implants that were observed for 100 weeks, no subcutaneous sarcoma was found; three females and two males developed spontaneous tumours (Tomatis, 1966b).

A group of 40 male and 40 female random-bred CTM albino mice, eight weeks of age, was given subcutaneous implants into the right flank of PTFE discs (15 mm diameter, 1.2 mm thick) and were observed for lifespan; 18 females and nine males developed sarcomas around the disc, giving a total incidence of 38% of the 69 mice still alive at the time of the appearance of the first tumour. Average ages of tumour-bearing animals at death were 72 and 69 weeks for females and males, respectively. No subcutaneous fibrosarcoma was found in 99 male and 98 female control mice of the same strain observed for lifespan (Tomatis & Parmi, 1971).

Three groups of 38, 38 and 39 female BALB/c, C3Hf/Dp and C57BL/He mice, 6–7 weeks of age, received subcutaneous implants of PTFE discs (15 mm diameter, 1.2 mm thick) in the dorsal area. Fibrosarcomas developed around the discs in 17/38 (44%) BALB/c, 36/38 (94%) C3Hf/Dp and 12/39 (30%) C57BL/He mice, within mean latent periods of 78, 61 and 82 weeks, respectively. All surviving mice were killed at 120 weeks of age. Of the 56 tumours examined histologically, two were rhabdomyosarcomas and the rest were fibrosarcomas (Menard & Della Porta, 1976). [The Working Group noted that the incidence of tumours was calculated on the basis of the number of mice treated initially.]

Rat: Two groups of Wistar rats [initial numbers, sex and age unspecified] were given subcutaneous implants of PTFE discs (15 mm diameter, 0.02 mm thick) in the abdominal wall; in one group, the discs were perforated. The numbers of rats that survived the minimum latent period were 34 and 32 for the groups implanted with plain and perforated discs, respectively. Eight sarcomas (23.5%) were observed in the first group and six sarcomas (18.7%) in the second group (Oppenheimer *et al*., 1955).

A group of 65 weanling male and female Wistar rats was given single subcutaneous implants of PTFE film ($4 \times 5 \times 0.16$ mm) in the abdominal wall; 55 rats were still alive after 300 days and 45 at the time of appearance of the first tumour (659 days). All rats were killed within 800 days. Two subcutaneous sarcomas were found; no tumour was observed in 20 control animals given glass implants of the same size, which survived 300 days and were observed for a similar period of time (Russell *et al*., 1959). [The Working Group noted the small size of the film.]

A group of 39 male Evans rats [age unspecified] was given subcutaneous implants of PTFE mesh surgical outflow patches (20 × 10 mm). A further 40 rats were given implants of the shredded material, and 41 rats without implants served as controls. The experiment was terminated 19 months later, and no local tumours were observed; at that time, 28 controls and 24 and 23 PTFE-implanted rats were still alive (Bryson & Bischoff, 1969).

A group of 50 Sprague-Dawley rats [age unspecified] was given 0.1 mL of Polytef by subcutaneous injection. The Polytef consisted of 50% PTFE particles of which 90% were < 40 μm in diameter; the remainder of the injection was a glycerol carrier, with a small amount of polysorbate. The animals were observed for two years. Of the 48 injected animals examined, 30 (63%) had one or more tumours: breast adenomas or fibrosarcomas (7/15), pituitary adenomas (18), breast adenocarcinomas (4), lymphoma (1), ovarian tumours (2), uterine carcinoma (1), and a hepatocellular carcinoma (1), respectively, but there was no significant difference in the total number of tumours or in the number of breast and pituitary tumours between the treated group and an untreated control group. No tumours were found in the region of the injection site (Dewan *et al.*, 1995).

4B.8.2 *Intraperitoneal administration*

Rat: Groups of male and female weanling Wistar rats were given intraperitoneal implants of PTFE rods (10 × 2 × 2 mm; 16 rats) or equivalent amounts of PTFE powder (17 rats). After 365 days, 13/16 and 10/17 animals were still alive in the two groups, respectively; after 800 days, 9/16 and 3/17 animals were still alive. Surviving animals were killed 27 months after implantation. No local tumours were found in rats with rod implants, whereas two sarcomas became palpable in the powder-treated animals at 354 and 476 days after implantation. Extraperitoneal tumours included one fibrosarcoma in the inguinal region in a rat with a rod implant and one liposarcoma in the upper part of the leg, one fibrosarcoma in the shoulder and one inguinal fibroadenoma in powder-treated rats. Among 25 untreated controls, one adenoma of the testis and a possible carcinoma in the inguinal region were observed (Simmers *et al*., 1963).

4B.9 Polyamide (nylon)

4B.9.1 *Subcutaneous administration*

Rat: Groups of male Wistar rats [initial number and age unspecified] were given subcutaneous implants of discs (15 mm diameter) of a material described as nylon in various physical forms. The incidence of malignant tumours at the site of implantation is given in Table 48 (Oppenheimer *et al*., 1955).

4B.9.2 *Intraperitoneal administration*

Rat: A group of nine BD rats [sex and age unspecified] was given intraperitoneal implants of five films of polycaprolactam (Nylon 6; about 10 mm diameter). Four out of six rats which survived for 360 days had local sarcomas (Druckrey & Schmähl, 1952).

Table 48. Injection-site tumours in rats given polyamide (nylon) implants

Material	Thickness (mm)	No. of rats surviving minimal latent period	No. of local tumours (%)	Latent period (days)
Plain film	0.06	26	7 (27.0)	441–651
Perforated film	0.06	31	2 (6.5)	551–738
Textile	0.08	33	0 (0)	–

From Oppenheimer *et al*. (1955)

4B.10 Poly(glycolic acid)

4B.10.1 *Subcutaneous administration*

Rat: A group of 50 male Wistar rats [age unspecified] was given subcutaneous implants of poly(glycolic acid) film (20 × 10 × 1 mm) that was completely absorbed in the animal body within two months. All animals survived to 24 months, and one developed a fibrosarcoma at the site of implantation with a latency period of 704 days. One fibroma developed among 50 sham-operated controls (Nakamura *et al*., 1997).

4B.11 Polylactide

4B.11.1 *Subcutaneous administration*

Rat: A group of 50 male Wistar rats, 11 weeks of age, was given subcutaneous implants of purified poly-L-lactide (PLLA) sheets (20 × 20 × 1 mm); 20/41 survivors developed malignant tumours at the site of implantation during the 24-month experimental period. Most of the tumours were diagnosed as fibrosarcomas, and the minimal latency period was 320 days. No such tumour occurred among 30 controls subjected to sham operations. The degradation of PLLA during implantation was slow, the sheets remaining at their initial size at 24 months. However, in a separate group of 15 rats, the average molecular weight of explanted PLLA sheets determined at six-month intervals decreased with time: 253 000 (initial), 49 700 (six months), 45 000 (12 months), 34 800 (18 months) and 21 200 (24 months) (Nakamura *et al*., 1994).

4B.12 ε-Caprolactone–L-lactide copolymer

4B.12.1 *Subcutaneous administration*

Rat: A group of 50 male Wistar rats, 11 weeks of age, was given subcutaneous implants of ε-caprolactone–L-lactide copolymer sheets (20 × 20 × 1 mm) and observed for two years. Twenty-five local tumours were found at the site of implantation during the experimental period, including 16 fibrosarcomas, seven osteosarcomas, and two malignant fibrous histiocytomas. One fibrosarcoma and one osteosarcoma were found at the site of implantation in a sham-operated control group. The in-vivo degradation of the polymer is discussed in Section 5B.1.2(*d*) of this monograph (Nakamura *et al.*, 1998).

4B.13 Polystyrene and related polymers

4B.13.1 *Subcutaneous administration*

Rat: A group of 30 Wistar rats [sex and age unspecified] was given subcutaneous implants of polystyrene film (15 × 15 mm, 0.01 mm thick). Twenty-seven animals were still alive at the time of appearance of the first tumour, among which seven sarcomas developed at the site of implantation (25.9%) within latent periods ranging from 359 to 556 days (Oppenheimer *et al*., 1955). The same authors studied the effect of continued presence or removal of the polystyrene implants on tumour formation (Oppenheimer *et al*., 1958) (see Section 5B.4.2).

Groups of Wistar rats [initial number, sex and age unspecified] were given subcutaneous implants of polystyrene of different physical forms. The incidence of sarcomas observed at the site of implantation is given in Table 49 (Nothdurft, 1956).

Table 49. Injection-site tumours in rats given implants of polystyrene

Form	Effective no. of rats	No. of tumour-bearing rats (%)
Smooth discs (17 mm diameter)	47	37 (78.7)
Perforated discs	51	25 (49.0)
Rods, spheres, fibres	40	15 (37.5)
Powder	Not reported	0 (0)

From Nothdurft (1956)

Groups of 25 Wistar rats from three different sources, 3–4 months of age, were given subcutaneous implants of discs (1.45 cm diameter, 0.026 mm thick) and perforated rings (central hole, 6 mm) of polystyrene. Differences were found in the incidence of local sarcomas (8–48%) according to the source of rats (Wistar E being the most sensitive), but no appreciable difference was found between rings and discs (Rivière *et al*., 1960).

Polystyrene materials having anionic, cationic and neutral properties were prepared by coprecipitation of two oppositely charged linear polyelectrolytes—a cationic polymer, poly(vinylbenzyltrimethylammonium) chloride, and sodium poly(styrene sulfonate). The anionic material (A) had an excess polyanion content of 0.5 meq/g of dry resin, the cationic material (B) had an excess polycation content of 0.5 meq/g of dry resin, and the neutral material (C) contained equivalent parts of polyanion and polycation. Three groups of 16 male CB Wistar rats, six to eight weeks of age, were given film implants of these materials (A, B and C; 20 × 20 mm) subcutaneously, while a further 16 rats (group D) were not given plastic implants but incisions were made, and these groups of rats were observed for 92 weeks, when only three rats remained alive. Three, nine and one local tumours occurred in groups

A, B, and C, respectively, while no local tumour was found in group D (Carter *et al*., 1971).

4B.14 Poly(vinyl alcohol)

4B.14.1 *Subcutaneous administration*

Rat: Male Wistar rats [number and age unspecified] were given subcutaneous implants of poly(vinyl alcohol) (Ivalon) sponge of unspecified size into the abdominal wall and were observed for lifespan. Three local sarcomas were found in 34 animals still alive at the appearance of the first local sarcoma at 567 days (Oppenheimer *et al*., 1955).

A group of 25 Bethesda black rats [sex and age unspecified] was given subcutaneous implants of single doses of 500 mg per animal of poly(vinyl alcohol) powder (molecular weight, 120 000) and was observed for up to two years. No local tumours were seen, but three benign and six malignant tumours at various sites were observed in treated rats, and three benign and 17 malignant tumours were found among 200 controls (Hueper, 1959).

A group of 25 male and female Wistar rats [age unspecified] was given subcutaneous implantations of poly(vinyl alcohol) sponges ($4 \times 5 \times 0.16$ mm) into the abdominal tissues; 21 animals survived 300 days. All animals had died or were killed within 800 days. Multiple sections were taken from each implantation site, but no local tumour was detected (Russell *et al*., 1959).

Groups of 20 Chester Beatty rats [sex unspecified], 70 days of age, were given subcutaneous implants of thick ($20 \times 20 \times 5$ mm) and thin ($20 \times 20 \times 2$ mm) poly(vinyl alcohol) (Ivalon) sponges into the right flank. Fourteen of the rats with implanted thick sponges lived 10 months or longer and developed local sarcomas, whereas only one of the rats bearing thin sponges had a local sarcoma among 18 rats that lived 12 months or longer (Dukes & Mitchley, 1962).

Groups of male Holtzman rats [number unspecified], 5–6 weeks of age, were given two subcutaneous implants of poly(vinyl alcohol) (Ivalon) sponges (20 mm diameter, 3–4 mm thick). Local sarcomas were found in 9/12 rats (75%) that lived for at least 18 months (only one animal had tumours at both implanted sites) (Dasler & Milliser, 1963).

A group of 39 albino rats [sex and age unspecified] was given subcutaneous implants of poly(vinyl alcohol) (Ivalon) sponges ($20 \times 20 \times 5$ mm) into the tissue of the back. Twenty rats were killed at intervals from two days to one year; the remaining 19 were kept until they died or were killed at 29 months. Local tumours developed in three rats (two sarcomas and one fibroma or low-grade fibrosarcoma) (Walter & Chiaramonte, 1965).

The possible role of the thickness of sponge implants was investigated in groups of male Chester Beatty rats, eight weeks of age, that were given subcutaneous implants of poly(vinyl alcohol) (Prosthex) ($20 \times 20 \times 5$ mm (2 cm^3) or $33 \times 33 \times 2$ mm (2 cm^3)) into the right flank. Of those given the thicker implant, 9/24 developed local

sarcomas, whereas only 1/24 with the thinner implants developed a local sarcoma. In addition, five sarcomas arose in 24 rats with 12.6 × 12.6 × 5 mm (800 mm^3) implants, and only 1/24 in animals with 20 × 20 × 2 (800 mm^3) implants and 1/24 with 8 × 8 × 5 mm (320 mm^3) implants. The incidence of local sarcomas in inbred Woodruff hooded rats given 20 × 20 × 5 mm (2 cm^3) implants of Prosthex was similar to that in the Chester Beatty rats (12/24). The experiment lasted 800 days (Roe *et al*., 1967).

A group of 50 male Wistar rats [age unspecified] was given subcutaneous implants of poly(vinyl alcohol) hydrogel (water content, 80%) film (20 × 10 × 1 mm); 22/50 survivors developed malignant tumours at the site of implantation during the 24-month experimental period. Most of the tumours that developed were diagnosed as malignant fibrous histiocytomas and the latency period was 568 ± 89 days. One fibroma developed among 50 controls subjected to sham operations (Nakamura *et al*., 1997).

4B.15 Poly(vinyl chloride)

4B.15.1 *Subcutaneous administration*

Rat: A group of 45 Wistar rats [sex and age unspecified] was given subcutaneous implants in the abdominal wall of squares or discs (0.04 mm thick and 15 mm wide) of a commercial poly(vinyl chloride) (PVC) sheet known to contain some additives. At the appearance of the first tumour, 44 animals were still alive. In 17 (38.6%), malignant tumours (fibrosarcomas and one liposarcoma) developed at the site of film implantation, with a latent period of 189–727 days; a similar but perforated film did not produce local tumours in 27 rats at risk. No local tumour was found in a group of 50 rats given a subcutaneous implant of cotton (Oppenheimer *et al*., 1952, 1955). In a similar group of rats, subcutaneous implants of a pure PVC film (0.03 mm thick) produced four malignant tumours at the implantation site after 533 days (Oppenheimer *et al*., 1955). [The Working Group noted that the reporting of this experiment was preliminary and that final results were never published.]

Three groups of Wistar rats [initial number, sex and age unspecified] were given subcutaneous implants of a PVC disc (17 mm diameter [thickness unspecified]), perforated discs of the same diameter or a powder form [particle size unspecified] and observed for 23 months. The total number of sarcomas at the site of implantation was 75/95 (79%) surviving rats given unperforated discs and 33/76 (43%) rats given perforated discs, whereas no tumour was found in rats given powder (Nothdurft, 1956).

A group of 35 male and female Wistar rats, weighing 60 g, was given a subcutaneous implant of PVC film (4 × 5 × 0.16 mm) into the abdomen. A group of 25 control rats received an implant of glass of similar size. After 300 days, 30 and 20 animals were still alive in the two groups, respectively; all surviving rats were killed 800 days after implantation. One sarcoma and one fibroma were found after 580 days in the PVC-treated rats, whereas no local tumour developed in the control group (Russell *et al*., 1959). [The Working Group noted the small size of the film.]

Groups of 20 male and 20 female Wistar rats [age unspecified] were given subcutaneous implants of three kinds of plasticized polyvinyl chloride film from

different suppliers (PVC-1, PVC-2 and PVC-3; $10 \times 20 \times < 1$ mm). Tumour incidence at the site of implantation during the two-year test period was 3/17 males and 5/20 females for PVC-1, 5/15 males and 6/20 females for PVC-2 and 8/18 males and 13/20 females for PVC-3. All tumours were diagnosed as malignant fibrous histiocytomas. No local tumours occurred in 12 male and 12 female untreated controls (Maekawa *et al*., 1984).

4B.15.2 *Other routes of administration*

In 37 male and female albino rats, weighing 120–150 g at the beginning of the study, the right kidney was wrapped in PVC film, following a method developed to induce renal hypertension. Five of 16 rats that survived more than seven months developed sarcomas at the site, four within 7–11.5 months and one after 19 months. Unperforated PVC sheets, 1 mm thick, were implanted near the kidney in 20 other rats; sarcomas developed in 2/5 rats that survived 16–18 months. Perforated PVC sheets were implanted near the kidney in 15 rats; a sarcoma developed in 1/4 rats that survived to 17–18 months after implantation (Kogan & Tugarinova, 1959).

A group of 80 outbred albino rats [sex and age unspecified] was given implants of PVC film [size unspecified] by laparotomy to surround the kidney. The animals were killed at 3, 10, 15, 30, 90, 195, 285, 300 and 380 days after implantation. Of rats that survived 285–375 days, 6/16 developed fibrosarcomas at the site of implantation (Raikhlin & Kogan, 1961).

4B.16 Vinyl chloride–vinyl acetate copolymer

4B.16.1 *Subcutaneous administration*

Mouse: A group of CBA/H-T6 mice including males and females, 1.5–2 months of age, was given subcutaneous implants into each flank of vinyl chloride–vinyl acetate copolymer coverslips ($15 \times 22 \times 0.2$ mm). Sarcomas at the site of implantation developed in 65% of the males within 9–12 months and in almost all of the females after 7–12 months. A control group of 80 mice with no implant developed no subcutaneous tumours (Brand *et al*., 1967a). [The Working Group noted the limited reporting.]

Groups of CBA mice [initial number, sex and age unspecified] were given subcutaneous implants of smooth or roughened films of unplasticized vinyl chloride–vinyl acetate copolymer ($15 \times 22 \times 0.2$ mm). When film with a smooth surface was implanted, the first tumour was seen after nine months and the total number of tumour-bearing animals at the site of implantation was 52/53; with the roughened surface, 8/26 mice developed tumours after 16 months (Brand *et al*., 1975b).

A group of 30 male and 46 female CBA mice, six weeks of age, were given subcutaneous implants of vinyl chloride–vinyl acetate copolymer powder (particle size, 50–100 μm; corresponding by weight to two films of $15 \times 22 \times 0.2$ mm) and were observed until death. No treatment-related tumour was reported; however, one sarcoma found in a female was attributed by the authors to clumping of the powder (Brand *et al*., 1975c).

Groups of 9–124 male and female mice of 18 strains [age unspecified] were given subcutaneous implants of vinyl chloride–vinyl acetate copolymer films (15 × 22 × 0.2 mm or 7 × 15 × 0.2 mm) to test strain differences in response. The incidence of tumours was 90–100% in CBA/H and CBA/H-T6 female mice, AKR/J males, BALB/cJ and BALB/c Wat females, C57BL/10ScSn females and (C57BL/10ScSc × CBA/H)F_1 males and females. No tumour was induced in males of strain I/LnJ or strain SJL/J. The tumour incidence in other strains was intermediate, the males being less sensitive than females, except for AKR mice (Brand *et al*., 1977).

Further extensive experiments on factors affecting tumour formation after implantation of vinyl chloride–vinyl acetate copolymer films are described in Sections 5B.4.3 and 5B.4.4.

4B.17 Cellophane

4B.17.1 *Subcutaneous administration*

Mouse: Two groups of male albino [Longacre] and C57BL mice [age unspecified] were given subcutaneous implants of a commercial cellophane film (15 mm diameter and 0.04 mm thick); 8/35 and 1/22 survivors developed local sarcomas at the site of implantation within 245–498 and 369 days, respectively (Oppenheimer *et al*., 1952, 1955).

Rat: A group of 55 male Sherman and/or Wistar rats, 8–10 months of age, was given subcutaneous implants in the abdominal wall of cellophane films (20–30 mm^2). The shortest latent period for development of a local tumour was 471 days, and 42 animals survived beyond this period; among these, 15 (35.7%) developed tumours at the site of implantation (Oppenheimer *et al*., 1948).

Groups of male Wistar rats [initial number and age unspecified] were given subcutaneous implants of cellophane films (15 mm in diameter) of various qualities and physical states. The incidences of malignant tumours found at the site of implantation and the ranges of latent periods are summarized in Table 50 (Oppenheimer *et al*., 1955). The same authors studied the effect of continued presence or removal of the cellophane implants on tumour formation (Oppenheimer *et al*., 1964) (see section 5B.4.2).

A group of 35 male and female Wistar rats (weighing 60 g) [sex unspecified] was given a subcutaneous implant of a square sheet of cellophane film measuring 4 × 5 × 0.16 mm and was observed for two years. At 300 days, 30 rats were still alive. No malignant tumour was found at the site of implantation within two years (Russell *et al*., 1959). [The Working Group noted the small size of the film.]

Four groups of rats [initial numbers, strain, sex and age unspecified] were given subcutaneous implants of ground cellophane (< 0.1 cm) and a cellophane film of different sizes (10 × 30 mm, 20 × 30 mm and 70 × 25 mm) and were observed for one year. No tumours associated with the implant were found among 144 rats treated with ground cellophane, whereas the incidences of tumours at the implantation site were 6/184 (3.2%), 6/36 (16.6%) and 5/30 (16.6%) for the 10 × 30 mm, 20 × 30 mm and 70 × 25 mm films, respectively. Among the 17 tumours that appeared, nine were

Table 50. Injection-site tumours in rats given cellulose films

Type of cellophane	Thickness (mm)	Effective no. of rats	No. (%) of local tumours	Latent period (days)
A. Commercial sausage casing	0.04	42	15 (35.7)	495–779
B. Type A after extraction with alcohol for 3 days	0.04	44	20 (45.4)	322–665
C. Type B after additional extraction with benzene	0.04	39	18 (46.1)	390–706
D. A special form employed for tissue culture	0.01	19	3 (15.8)	423–521
E. Type D perforated	0.01	22	4 (18.2)	504–594

From Oppenheimer *et al*. (1955)

polymorphocellular sarcomas, four were spindle-cell sarcomas, one was a fibrosarcoma, one a giant-cell sarcoma and one an osteoblastic tumour (Ol'shevskaya, 1962). [The Working Group noted the short period of observation.]

Groups of 60–290 male rats, weighing 100–120 g, [strain and age unspecified] were given subcutaneous implants of a commercial cellophane film (Cellophane N55; 1 mm thick) of different sizes or 50–100 cut pieces of about 1–2 mm in diameter. The incidence of local tumours is summarized in Table 51. The first tumour appeared 10 months after implantation (Vasiliev *et al*., 1962).

Table 51. Injection-site tumours in rats given cellulose films

Film size (mm)	No. of rats per group	Effective no. of rats	No. of local tumours	%
Cut pieces	200	180	0	0
10 × 30	290	184	56	30
20 × 30	67	48	29	60
70 × 20[a]	60	24	11	46

[a] Before implantation, each film was folded in half
From Vasiliev *et al*. (1962)

4B.17.2 *Other experimental systems*

Rat: The left kidney of a group of 55 male Sherman and/or Wistar rats, 8–10 months of age, was wrapped loosely with cellophane film and animals were observed. The shortest time for appearance of a tumour was 362 days from the date of wrapping, and the total number of rats that developed local tumours was 8/23 that survived over 11 months (Oppenheimer *et al*., 1948).

4B.18 Millipore filters

4B.18.1 *Subcutaneous administration*

Mouse: In a study reported as an abstract, groups of Swiss albino mice [initial numbers, sex and age unspecified] were given subcutaneous implants of Millipore filters [diameter unspecified] of different pore sizes and were observed for 18 months. The total incidence of tumours was 21/35 (60%) for the group given implants of 0.05 μm pore size, 18/34 (53%) for 0.10 μm pore size and 2/39 (5%) for 0.45 μm pore size. One year after implantation of a solid Millipore filter without any pores, tumours were found in 11/33 (33%) animals, while with a solid Plexiglas (poly(methyl methacrylate)) disc and with a Millipore filter of the same diameter with 0.05 μm pores, tumours were found in 14/41 (34.1%) and 18/39 (46.1%) of the animals, respectively (Goldhaber, 1962).

A group of female 93 CBA mice [age unspecified] was given subcutaneous implants of hydrophilic Millipore filter discs (20 mm diameter; eight different pore sizes ranging from 0.025 to 8.0 μm) and the animals were observed until death. The incidence of sarcomas is summarized in Table 52. The latency of the tumours was 7–27 months (Karp *et al*., 1973).

[The Working Group noted that the exact chemical compositions of the various Millipore filters were not specified.]

Table 52. Tumour incidence in mice given implants of Millipore filters with a range of pore sizes

Pore size (μm)	No. of tumours/no. of implanted animals
0.025	11/11
0.05	6/10
0.10	8/10
0.22	0/9
0.45	0/9
0.45[a]	0/9
0.80	0/9
3.0	0/9
3.0[a]	1/8
8.0	0/9

[a] Millipore filter reinforced with nylon microweb material

From Karp *et al*. (1973)

4B.18.2 *Intraperitoneal administration*

Mouse: A group of male and female BALB/c AnN mice, 4–8 weeks of age, was given intraperitoneal implants of two Millipore filter discs (14 and 17.5 mm diameter) [pore size unspecified]. Four of 30 mice developed sarcomas at the site of implantation (Merwin & Redmon, 1963).

4B.19 Epoxy resins

4B.19.1 *Subcutaneous administration*

Rat: A group of 22 male Wistar rats (weighing 175–200 g) was given subcutaneous implants of an epoxy resin disc (prepared from triglycidyl *para*-aminophenol and a curing agent, nonylphenol and aminoethylpiperazine; 18 mm diameter and 0.14 mm thick) bilaterally on both sides of the abdomen, while another group of 24 rats received the epoxy resin disc and a glass coverslip of the same size on each side of the abdomen. After 39 months, the survivors were killed and examined. None of the effective number of 27 rats developed tumours (Lavorgna *et al*., 1972).

4B.20 Aluminium oxide ceramics

4B.20.1 *Subcutaneous administration*

Rat: Five groups of male Sprague-Dawley rats, weighing 220 g at the start of treatment, received subcutaneous implants of various forms of an aluminium oxide ceramic (99.6% pure). Group 1 (33 rats) each received eight discs (20 mm diameter, 3 mm thick) implanted subcutaneously; Group 2 (27 rats) each received eight discs of the same size but perforated with 13 1-mm holes; Group 3 (21 rats) each received four porous discs of the same size (pores, 200–400 μm); Group 4 (47 rats) each received aluminium oxide powder [amount and particle size unspecified]; and Group 5 (22 rats) served as sham-operated controls. Sarcomas occurred between nine and 21 months, as shown in Table 53 (Griss *et al*., 1977).

4B.21 Glass sheet

4B.21.1 *Subcutaneous administration*

In some experiments investigating the carcinogenicity of plastic films by subcutaneous administration, glass sheet was also investigated, often as a control.

Mouse: In Swiss mice, 6/42 effective animals implanted with glass sheet (12 × 12 × 1.2 mm) developed local sarcomas within 90 weeks (Tomatis, 1963). [The Working Group noted that there was no control group of untreated animals.]

Rat: In three experiments using 50 albino, 25 Wistar and 22 Wistar rats given implants of glass discs (18 × 0.2 mm), glass sheets (4 × 5 × 0.16 mm) or glass discs (18 mm diameter, 0.4 mm thick), 0/23, 0/20 and 0/22 surviving rats developed local sarcomas. Observation times were 12–14 months, 300 days and 39 months, respectively (Oppenheimer *et al*., 1952; Russell *et al*., 1959; Lavorgna *et al*., 1972).

Table 53. Injection-site tumours in rats treated with aluminium oxide ceramics

Material	No. of rats	No. of implants	Sarcomas/ no. of animals with sarcoma	Discs with sarcoma (%)
Solid disc	33	264	46/32	17.4
Perforated disc	27	216	55/27	25.4
Porous disc	21	84	16/16	17
Powder	47		0/0	0
Control	22		0/0	0

From Griss *et al*. (1977)

4B.22 Major factors that affect tumour incidence

4B.22.1 *Physical factors*

(*a*) *Size (surface area) of the implant*

Based upon observations from several studies reported above, it is evident that, following implantation into the tissues of rodents, large films induced more sarcomas than small ones.

Rats that received subcutaneous implants of cellophane films of different sizes developed local tumours (6/184 (3.2%) for 10 × 30 mm film, 6/36 (16.6%) for 20 × 30 mm film and 5/30 (16.6%) for 70 × 25 mm film), while cellophane powder did not produce local tumours (Ol'shevskaya, 1962). Similar results were obtained in another study in rats with cellophane film (56/184 (30%) for 10 × 30 mm film, 29/48 (60%) for 20 × 30 mm film and 11/24 (46%) for doubly folded 70 × 20 mm film), while no local tumour was found for cut pieces (Vasiliev *et al*., 1962). Following intramuscular implantation of poly(methyl methacrylate) discs of various sizes into rats, the incidences of local tumours were 0/142, 17/142 (12%) and 34/142 (24%) for discs of 4, 12 and 18 mm diameter, respectively (Stinson, 1964). Vinyl chloride–vinyl acetate copolymer films, 7 × 15 or 15 × 22 mm, were implanted subcutaneously into female CBA/H or CBA/H-T6 mice. Local tumour incidences over a 30-month observation period were 63.5 and 95%, respectively (Brand *et al*., 1973). In another experiment designed to determine dose (surface area)-related tumour incidences, different numbers of polyurethane discs of 3.1 mm in diameter were implanted intraperitoneally into rats to give doses of 93.8, 187.5, 375, 750 and 1500 mg per rat. The local tumour incidences were 0, 1, 2, 8 and 24 for the five groups, respectively (Autian *et al*., 1976).

(*b*) *Continuity*

The following incidences of tumours were found in rats at the site of subcutaneous implantation with plain, perforated and textile films of four polymeric materials of 15 mm diameter: polyester (Dacron): 8/41 (19.5%), 2/42 (4.8%) and 0%, respectively;

polyethylene: 11/55 (20%), 6/41 (14.6%) and 1/40 (2.5%); polyamide (Nylon): 7/26 (27.0%), 2/31 (6.5%) and 0%; and polytetrafluoroethylene: 8/34 (23.5%), 6/32 (18.7%) and no data, respectively; a polyethylene powder of the corresponding weight produced no local tumour (Oppenheimer *et al*., 1955). Another study of subcutaneous implantation of polyethylene film and mesh into rats gave incidences of 4/45 (8.9%) and 1/52 (1.9%), respectively (Shulman *et al*., 1963). In the case of polystyrene, the following incidences were observed: 37/47 (78.7%) for smooth discs (17 mm in diameter), 25/51 (49.0%) for perforated discs, 15/40 (37.5%) for rods, spheres, fibres and 0% for powder (Nothdurft, 1956). In contrast, no appreciable difference in tumour incidence was found between the polystyrene discs of 14.5 mm in diameter and rings with a central hole of 6 mm diameter (Rivière *et al*., 1960).

Following subcutaneous implantation of poly(vinyl chloride) discs of 17 mm diameter into rats, the following incidences of local tumours were observed: 75/95 (79%) for plain film, 33/76 (43%) for perforated film, and 0% for powder, respectively (Nothdurft, 1956). Subcutaneous implantation of 15 × 22 mm films of vinyl chloride–vinyl acetate copolymer into mice induced tumours in almost 100%, while no tumours developed with powdered copolymer of the same weight (Brand *et al*., 1975b,c). Subcutaneous implantation of rectangular smooth-surfaced poly(vinyl chloride) films (22 × 15 × 0.2 mm) into mice induced local sarcomas in 17/30 (56.6%), whereas the corresponding perforated films with 50–60 holes (0.3 mm wide)/cm^2 induced sarcomas in only 3/29 (10.3%) (Moizhess & Vasiliev, 1989).

A decrease in local tumour incidence was observed on changing the implant from film to powder for other materials: powdered silicone (25 mg) produced no tumours among 30 rats at the subcutaneous implantation site, while 3/30 tumours were produced by a 300 mg Silastic cube (Hueper, 1961).

(*c*) *Pore size*

The effect of pore size on tumour development after subcutaneous implantation of Millipore filters was studied in mice: during the 18 months of study, the local tumour incidences were 21/35 (60%), 18/34 (52.9%) and 2/39 (5%) for the groups given implants of 0.05, 0.10 and 0.45 μm pore size, respectively (Goldhaber, 1962). In another lifetime study of subcutaneous implantation in mice using Millipore filter discs of 20 mm diameter with eight different pore sizes, tumours did not develop with the filters with pore size larger than 0.22 μm (Karp *et al*., 1973). Greater pore surface also led to decreasing local tumour incidence following subcutaneous implantation of polyurethane in rats, with a significant delay in the development of the first tumour (Nakamura *et al*., 1995).

(*d*) *Surface roughening*

Subcutaneous implantation of polyethylene discs (20 mm diameter) with a smooth surface into rats produced local sarcomas in 35/71 rats compared with 7/60 rats for roughened discs (Bates & Klein, 1966). In CBA mice that received subcutaneous

implants of vinyl chloride–vinyl acetate copolymer films (15 × 22 mm) with smooth or rough surfaces. A marked delay in tumour incidence was seen, with 98% of the animals in the smooth-implant group having tumours at the end of their lifetime versus 31% in the rough-implant group (Brand *et al*., 1975c).

(*e*) *Thickness*

Two studies measured the effects of thickness of poly(vinyl alcohol) implants on local tumour incidence. In one, thick (20 × 20 × 5 mm) and thin (20 × 20 × 2 mm) poly(vinyl alcohol) sponges of the same surface area but with different volume induced incidences of 14/20 and 1/18, respectively, of local tumours after subcutaneous implantation into rats (Dukes & Mitchley, 1962). In the other study, poly(vinyl alcohol) implants of the same volume but of different thickness (thus with different surface area) were implanted subcutaneously into rats. Nine of 24 rats developed local sarcomas with the 20 × 20 × 5 mm (2000 mm^3) implants, whereas only 1/24 rats developed a sarcoma with the 33 × 33 × 2 mm (2000 mm^3) implants; the same trend was observed with 12.6 × 12.6 × 5 mm (800 mm^3) and 20 × 20 × 2 (800 mm^3) implants: 5/24 and 1/24 (Roe *et al*., 1967).

4B.22.2 *Chemical factors*

(*a*) *Composition*

Different materials of the same shape and size induced different incidences of local tumour development in the same experimental protocol using the same animal species and strain (see Table 54). Materials included in Table 54 are listed in the order from hydrophilic to hydrophobic and there is no apparent correlation between hydrophilicity/hydrophobicity and tumour development.

Table 54. Subcutaneous implantation studies with various materials in male Wistar rats

Film (10 × 20 × 1 mm)	Tumour incidence (%)	Reference
Poly(vinyl alcohol) hydrogel	22/50 (44)	Nakamura *et al*. (1997)
Poly(2-hydroxyethyl methacrylate)	7/19 (37)	Maekawa *et al*. (1984)
Poly-L-lactide	20/50 (40)	Nakamura *et al*. (1994)
Poly(vinyl chloride)		Oppenheimer *et al*.
plain film	17/44 (39)	(1955)
perforated film	0/27	
Polyurethane	11/30 (37)	Nakamura *et al*. (1992)
Polyethylene	21/50 (42)	Nakamura *et al*. (1994)
Polypropylene	17/50 (34)	Imai & Watanabe (1987)
Silicone	2/30 (6.7)	Nakamura *et al*. (1992)

Tissue responses, including tumour development, to a 1:1 blended film of silicone and polyurethane were intermediate between those of pure silicone and polyurethane of the same shape and size (Nakamura *et al*., 1992). This suggests that chemical characteristics of the material surface may to some extent determine long-term local tissue effects, including tumorigenesis.

(*b*) *Effects of purification and leachable oligomers*

Either purification of material by organic solvent extraction or deletion/addition of leachable oligomers from/to the material did not have significant effects on tumour incidence: the incidences with commercial cellophane film, with the same film after alcohol extraction for three days, and after additional extraction with benzene were 15/42 (35.7%), 20/44 (45.4%) and 18/39 (46.1%), respectively (Oppenheimer *et al*., 1955).

The incidences of tumours with polyurethane TM-3 with and without methanol extraction were 1/11 (9.1%) and 6/18 (33.3%), respectively, but this difference was not statistically significant (Imai & Watanabe, 1987).

Changing the oligomer content in the polyurethane by deletion or addition of oligomers did not lead to a change in the tumour incidence: neat polyurethane produced tumours in 8/30 (26.7%) rats; oligomer-deleted polyurethane in 6/30 (20%) rats; and oligomer-added polyurethane in 8/30 (26.7%) rats (Nakamura *et al*., 1995).

(*c*) *Miscellaneous (surface coating, electric charge)*

A marked effect of collagen-immobilization of porous polyethylene blocks in decreasing tumour incidence was found in a one-year subcutaneous implantation study in rats: neat polyethylene produced tumours in 11/24 (45.8%) rats, while collagen-immobilized polyethylene produced tumours in 1/24 (4.2%) rats (Kinoshita *et al*., 1993).

Polystyrene films having anionic, cationic and neutral electric properties were tested in rats: the tumour incidences were 3/16 (18.8%), 9/16 (56.3%), and 1/16 (6.3%), respectively (Carter *et al*., 1971).

These studies suggest that surface chemistry may play a more important role in tumorigenesis than bulk chemistry.

4C. Composite Medical and Dental Implants

Rabbit: A total of 40 male and female adult New Zealand White rabbits received subcutaneous implants of eight types of miniature silicone breast prosthesis (21 × 10 mm) into pockets of both flanks. Groups of 10 animals were evaluated at one, six, 12 and 18 months after implantation. The shell of the prostheses was made of polysulfane-based silicone elastomer. This silicone shell was either bare, backed with a piece of perforated silicone, backed with a patch of Dacron mesh or completely covered with polyurethane foam (3 mm thick, pore sizes of approximately

250–800 μm). Four types were silicone gel-filled and another four types were saline-filled. Survivors after one, six, 12, and 18 months were 10, 10, 10 and four, respectively; no local tumour was found in any group (Lilla & Vistnes, 1976).

4D. Other Foreign Bodies

Experimental data on the carcinogenicity of lead and lead compounds were reviewed by IARC (1980, 1987c).

No data on carcinogenic effects of depleted uranium were available to the Working Group.