3. Studies of Cancer in Experimental Animals

3.1 Inhalation exposure: simulated environmental tobacco smoke

Since the previous *IARC Monograph* on tobacco smoking (IARC, 1986), studies that include exposure to sidestream cigarette smoke or to simulated environmental tobacco smoke from cigarettes have been conducted. For experimental purposes, many of the studies employed a mixture of 89% sidestream and 11% mainstream tobacco smoke prepared by smoking machines from standard reference cigarettes, referred to in the published literature and in this section as simulated environmental tobacco smoke (Teague *et al*., 1994). Although this experimental exposure system was designed to mimic human exposure, it provides an exposure pattern that differs from that encountered by humans exposed to secondhand smoke. No studies were available on sidestream smoke or simulated environmental smoke from other tobacco products.

The mice used in the studies described below were of the specially inbred strain A/J and outbred strain Swiss, both of which are highly susceptible to lung tumour development (Shimkin & Stoner, 1975). Both strains carry the pulmonary adenoma susceptibility-1 genetic locus (*Pas1*), a locus affecting genetic predisposition to lung tumours in mice (Manenti *et al.*, 1997). Strain A/J mice carry the *Eco*RI-generated 0.55 Kb DNA fragment of the K-*ras* oncogene which is associated with high susceptibility to lung tumour development (Malkinson, 1992). Both strains are highly susceptible to chemical induction of peripheral lung tumours that originate primarily from type II pneumocytes. It should be noted that type II pneumocytes are precursors for a relatively small fraction (~5–10%) of human adenocarcinomas (i.e. bronchiolo-alveolar carcinomas). Most adenocarcinoma cells are derived from bronchiolar cells and not from type II pneumocytes.

Mouse

Male strain A/J mice (6–8 weeks old) were exposed in chambers to sidestream smoke generated from Kentucky 1R4F reference cigarettes. Mice were exposed for 6 h/day, 5 days/week at chamber concentrations of 4 mg/m^3 total suspended respirable particulate matter. The experiment was terminated after 6 months. The fraction of animals bearing lung tumours was the same in those exposed to smoke (33%; 12/36) as in those exposed to filtered air (33%; 12/36). The average number of tumours per lung (0.42 tumours/smoke-exposed mouse; 0.39 tumours/control mouse) was also similar (Witschi *et al.*,

1995). [The Working Group noted the low concentration of tobacco smoke used and the short duration of the study.]

Male strain A/J mice (6–8 weeks old) were exposed to simulated environmental tobacco smoke that consisted of a mixture of 89% sidestream and 11% mainstream smoke from Kentucky 1R4F reference cigarettes, at a chamber concentration of 87 mg/m^3 total suspended particulate matter. Mice were exposed in 0.44 m^3 stainless steel inhalation chambers for 6 h/day, 5 days/week for 5 months and then killed for assessment of lung tumour incidence and multiplicity (see Table 3.1). The incidence of lung tumours in mice exposed to simulated environmental tobacco smoke (25%; 6/24) was not significantly different from that in controls (8.3%; 2/24). There was no significant difference between lung tumour multiplicities (total number of lung tumours per total number of animals) in exposed and control animals (0.3 ± 0.1 and 0.1 ± 0.1 tumour/mouse, respectively [mean ± SE]). A second group of mice exposed for 5 months to simulated environmental tobacco smoke was allowed to recover for a further 4 months in filtered air before being killed for analysis of lung tumour incidence and multiplicity. Tumour incidence was significantly greater in mice exposed to smoke (83.3%; 20/24) than in controls kept in air (37.5%; 9/24; $p < 0.05$, Fisher's

Table 3.1. Lung tumours in strain A/J mice exposed to filtered and unfiltered simulated environmental tobacco smoke

Exposure conditions	Parameter	Filtered air controls	Animals exposed to ETS
5 months in simulated ETS (87 mg TSP/m^3), 6 h/day, 5 days/week	Tumour incidence[a] Tumour multiplicity[b]	8.3% (2/24) 0.1 ± 0.1	25.0% (6/24) 0.3 ± 0.1
5 months in simulated ETS (87 mg TSP/m^3), 6 h/day, 5 days/week, then 4 months recovery in air	Tumour incidence Tumour multiplicity	37.5% (9/24) 0.5 ± 0.2	83.3% (20/24)[c] 1.4 ± 0.2[d]
5 months in unfiltered simulated ETS (78.5 mg TSP/m^3) and 4 months recovery in air	Tumour incidence Tumour multiplicity	41.6% (10/24) 0.5 ± 0.1	57.7% (15/26) 1.3 ± 0.3[d]
5 months in filtered simulated ETS (0.1 mg TSP/m^3) and 4 months recovery in air	Tumour incidence Tumour multiplicity	37.5% (9/24) 0.5 ± 0.1	66.7% (16/24) 1.2 ± 0.3[d]
5 months in filtered simulated ETS (0.1 mg TSP/m^3)	Tumour incidence Tumour multiplicity	20% (4/20) 0.3 ± 0.1	50% (12/24) 0.7 ± 0.2

Modified from Witschi *et al*. (1997a,b)
ETS, simulated environmental tobacco smoke; TSP, total suspended particulate matter
[a] Percentage of animals with lung tumours (incidence)
[b] Total number of lung tumours/total number of mice in the group (mean ± SE)
[c] $p < 0.05$, Fisher's exact test
[d] $p < 0.05$, Welch's alternate *t*-test

exact test) and tumour multiplicities were significantly higher in the group exposed to smoke (1.4 ± 0.2 versus 0.5 ± 0.2, $p < 0.05$, Welch's alternate *t*-test). More than 80% of all tumours were adenomas and the remainder were adenocarcinomas (Witschi *et al*., 1997a).

Female strain A/J mice (10 weeks old) were exposed to unfiltered (one group of 26 animals) or high efficiency particulate air (HEPA)-filtered simulated environmental tobacco smoke (two groups of 24 animals) which consisted of a mixture of 89% sidestream and 11% mainstream smoke from Kentucky 1R4F reference cigarettes. The concentration of total suspended particulates was 78.5 mg/m^3 in the unfiltered smoke exposure chamber and 0.1 mg/m^3 in the filtered smoke chamber (see Table 3.1). In addition, three groups of 24 control animals were exposed to filtered air. Lung tumour incidence and multiplicity in animals exposed to filtered smoke for 6 h/day, 5 days/week, and killed after 5 months were not significantly greater than those in controls kept in filtered air. Mice exposed as above to filtered tobacco smoke and then allowed to recover in air for 4 months had a lung tumour incidence of 16/24 (67%) and an average lung tumour multiplicity of 1.2 ± 0.3, compared with an incidence of 9/24 (37.5%) and a lung tumour multiplicity of 0.5 ± 0.1 in control mice breathing filtered air. Lung tumour multiplicity was significantly higher in mice exposed to filtered smoke than in controls ($p < 0.05$). Mice exposed to unfiltered smoke had a lung tumour incidence of 15/26 (57.5%) and a lung tumour multiplicity of 1.3 ± 0.3, whereas controls kept in filtered air had a tumour incidence of 10/24 (41.6%) and a lung tumour multiplicity of 0.5 ± 0.1 (multiplicity greater in treated mice, $p < 0.05$ than in controls kept in filtered air, Welch's alternate *t*-test). The authors concluded that the gas phase of simulated environmental tobacco smoke is as carcinogenic as unfiltered environmental tobacco smoke (Witschi *et al*., 1997b).

In a study of the effects of the experimental chemopreventive agents, phenethyl isothiocyanate and *N*-acetylcysteine, on the occurrence of lung tumours, male and female strain A/J mice (6–8 weeks old) were exposed to simulated environmental tobacco smoke that consisted of a mixture of 89% sidestream and 11% mainstream smoke from Kentucky 1R4F reference cigarettes. Mice were exposed for 6 h/day, 5 days/week for 5 months in 0.4 m^3 stainless steel inhalation chambers in which the concentration of total airborne suspended particulates was 82.5 mg/m^3. Controls were placed, within their cages, into chambers of the same size as the inhalation chambers. At the conclusion of the exposure period, the mice were transferred to a conventional animal holding facility. Nine months after the beginning of the experiment, the animals were killed and the lungs prepared for tumour analysis and histopathological examination. Lung tumour multiplicity, but not incidence, was increased in mice exposed to simulated environmental tobacco smoke. Lung tumours occurred in 20/29 (69%) of the controls with a multiplicity of 0.9 ± 0.2, and in 24/33 (73%) of the mice exposed to smoke with a multiplicity of 1.3 ± 0.2 (mean ± SEM, $p < 0.05$ by two-way ANOVA) (Witschi *et al*., 1998).

As part of a study on chemoprevention of tobacco smoke-induced lung tumours by dietary supplements of *myo*-inositol/dexamethasone, male strain A/J mice (8–10 weeks old) were exposed for 5 months to a mixture of 89% sidestream and 11% mainstream cigarette smoke. The animals were placed, within their cages, in stainless steel inhalation

chambers ventilated with tobacco smoke or filtered air (controls). Exposure to simulated environmental tobacco smoke took place for 6 h/day, 5 days/week. Exposure during the first 2 weeks was to an average of 71 mg total suspended particles/m^3; this was followed by exposure for 3 weeks to 86 mg/m^3 and finally to an average of 132 mg/m^3 for the remainder of the exposure period. After 5 months, all mice were removed from the inhalation chambers and transferred to a conventional animal holding facility with controlled temperature and humidity. Mice were killed 9 months after the beginning of the experiment. The incidence of lung tumours in control mice was 15/30 (50%) and the lung tumour multiplicity was 0.6 ± 0.1; the incidence of tumours in mice exposed to simulated environmental tobacco smoke was 30/35 (86%) and the multiplicity was 2.1 ± 0.3. The difference in lung tumour multiplicity between exposed and control mice was statistically significant ($p < 0.05$) (Witschi *et al.*, 1999).

As part of a study on chemoprevention of lung tumours induced by exposure to tobacco smoke, male strain A/J mice (10 weeks old) were exposed in stainless steel inhalation chambers for 6 h/day, 5 days/week to a mixture of 89% sidestream cigarette smoke and 11% mainstream smoke prepared from Kentucky 1R4F reference cigarettes. The total suspended particulate concentration was 137 mg/m^3. Inhalation exposure took place for 5 months and was followed by a recovery period of 4 months in filtered air in a conventional animal facility. Control mice were kept in chambers of the same size as the inhalation chambers, but ventilated with filtered air, for the first 5 months of the study. Mice were killed 9 months after the beginning of exposure. In the first of two studies, the lung tumour incidence in control mice was 35/54 (65%) and lung tumour multiplicity was 1.0 ± 0.1. In mice exposed to smoke, the tumour incidence was 25/28 (89%; i.e. significantly different from controls, $p < 0.05$, Fisher's exact test) and tumour multiplicity was 2.4 ± 0.3 (i.e. significantly different from controls, $p < 0.01$ by parametric or non-parametric ANOVA). In the second experiment, conducted under the same conditions of exposure, lung tumour incidence in control mice was 18/30 mice and the incidence in mice exposed to smoke was 38/38 ($p < 0.01$, Fisher's exact test). Lung tumour multiplicity was 0.9 ± 0.2 in control mice and 2.8 ± 0.2 in animals exposed to smoke ($p < 0.01$, ANOVA) (Witschi *et al*., 2000).

In a third study conducted using the same experimental design, strain A/J mice [sex not specified] were exposed continuously to simulated environmental tobacco smoke for 9 months. There was no statistically significant increase in lung tumour incidence (85% [23/27] versus 63% [53/84]) or lung tumour multiplicity (1.5 ± 0.2 versus 1.0 ± 0.1) (Witschi, 2000).

Female strain A/J mice (4 weeks of age) were exposed to simulated environmental tobacco smoke (89% sidestream and 11% mainstream smoke) from Kentucky 2R1 reference cigarettes. Exposure continued for 5 months for 6 h/day, 5 days/week. The concentration of total suspended particulates was 120 mg/m^3 air. Control mice were kept in chambers ventilated with filtered air. Mice were then kept for a 4-month recovery period in filtered air, after which they were killed and lungs tumours were counted. The lung tumour incidence in mice exposed to smoke was 15/20 (75%); the incidence in sham-exposed controls was 5/20 (25%; $p < 0.01$). Lung tumour multiplicity in mice exposed to

smoke was 1.05 ± 0.17 and that in control mice was 0.25 ± 0.10 ($p < 0.01$). In a third group of mice exposed to simulated environmental tobacco smoke under the same conditions for 9 months and killed immediately at the end of the exposure period, the lung tumour incidence (6/20; 30%) and multiplicity (0.4 ± 0.15) were not significantly different from the tumour incidence and multiplicity in control mice. In a fourth group of mice exposed to simulated tobacco smoke under the same conditions for 2 months, followed by a recovery period of 7 months, lung tumour incidence (8/20; 40%) and multiplicity (0.50 ± 0.15) were also not significantly greater than in control mice. These data are in agreement with the results of Witschi *et al*. (1997a,b, 1998 and 1999) which indicate that strain A/J mice require a 4-month recovery period following a smoke exposure for 5 months to demonstrate a positive carcinogenic effect of environmental tobacco smoke (D'Agostini *et al*., 2001).

Witschi *et al*. (2002) exposed male Swiss albino mice to simulated environmental tobacco smoke for 5 months, followed by 4 months of recovery in air. The lung tumour incidence was 1/26 (4%) in sham-exposed mice and 6/31 (20%) in mice exposed to simulated environmental tobacco smoke, with a fivefold increase ($p = 0.075$). Lung tumour multiplicity was 0.04 ± 0.04 in sham-exposed mice and 0.35 ± 0.14 in mice exposed to environmental tobacco smoke ($p < 0.05$). When BALB/c mice were exposed to simulated environmental tobacco smoke under identical conditions, the incidence of lung tumours was increased (33%, 9/27 versus 20%, 6/30), but the multiplicity was not (0.4 versus 0.2).

As part of a series of pilot experiments on chemoprevention of cancer induced by environmental tobacco smoke, De Flora *et al*. (2003) reported studies of the effects of environmental tobacco smoke in Swiss albino mice. However, these studies were published in a review, and the reporting of study details was incomplete.

Groups of gestating female Swiss albino mice were exposed for 20 days to simulated environmental tobacco smoke. The exposure conditions were similar to those described by D'Agostini *et al*. (2001). The exposure of gestating mice to environmental tobacco smoke decreased the body weights of dams during the 3 months following delivery [details not given]. Similarly, in the female progeny of dams exposed to smoke, the body weight 10 days after birth was slightly, but significantly lower than that of female progeny from sham-exposed dams [details not given]. Dams exposed to tobacco smoke during gestation had significantly higher yields of lung tumours than sham-exposed dams. The lung tumour incidence at 8.5 months of age was increased from 1/22 (4.5%) in sham-exposed dams to 4/14 (28.6%) in dams exposed to tobacco smoke. The lung tumour multiplicity at 8.5 months of age was increased from 0.05 ± 0.5 in sham-exposed dams to 0.36 ± 0.17 (mean ± SE; $p < 0.05$) in dams exposed to tobacco smoke. The progeny of sham-exposed dams and dams exposed to environmental tobacco smoke, kept either 8.5 or 15 months after birth in filtered air, had identical yields of lung tumours. The incidence of lung tumours in the progeny at 8.5 months was 10% (1/10) and the lung tumour multiplicity was 0.1 ± 0.1. At 15 months, the lung tumour incidence in the progeny was 20% (2/10) and the lung tumour multiplicity was 0.3 ± 0.21 (De Flora *et al*., 2003).

In a second experiment (see Table 3.2), De Flora *et al*. (2003) investigated the effects of gestation and length of the exposure period on lung tumours induced by environmental tobacco smoke in Swiss mice. The exposure to environmental tobacco smoke during gestation (for 20 days) increased the tumour incidence from 4.4% (1/23) in sham-exposed dams to 23.8% (10/42; $p < 0.05$) in dams exposed to smoke. The lung tumour multiplicity in sham-exposed dams (0.09 ± 0.09) was significantly lower than that in the mice exposed to smoke (0.38 ± 0.13; $p < 0.05$). A similar trend was seen in non-gestating Swiss albino mice exposed for an equivalent period (20 days), but the increases in tumour incidence and lung tumour multiplicity were not significant. When non-gestating mice were exposed to environmental tobacco smoke for 5 months, followed by 4 months of recovery in filtered air, there was an increase in lung tumour incidence from 9.1% (2/22) in sham-exposed mice to 42.9% (9/21; $p < 0.01$) in mice exposed to tobacco smoke and in lung tumour multiplicity from 0.14 to 0.57 ($p < 0.01$) in sham-exposed compared to smoke-exposed mice. The increases were more pronounced if the animals were exposed to environmental tobacco smoke for 9 consecutive months.

In summary, when strain A/J mice of either sex are exposed to sufficiently high concentrations of simulated environmental tobacco smoke for a period of 5 months and are then kept in filtered air for a further 4 months, lung tumour multiplicities are consistently and significantly higher in mice exposed to tobacco smoke than in concomitant controls.

Table 3.2. Lung tumour yield in female Swiss albino mice, either gestating or non-gestating, exposed to simulated environmental tobacco smoke for varying time periods

Exposure to simulated ETS (time)	Gestating	Percentage of animals with lung tumour (incidence)	Lung tumour multiplicity[a]
0[b]	–	9.1% (2/22)	0.14 ± 0.10
0[b]	+	4.4% (1/23)	0.09 ± 0.09
20 days[c]	–	20.9% (9/43)	0.28 ± 0.09
20 days[c]	+	23.8% (10/42)[e]	0.38 ± 0.13[e]
5 months[d]	–	42.9% (9/21)[f]	0.57 ± 0.16[f]
9 months	–	50.0% (11/22)[f]	0.68 ± 0.17[f]

From De Flora *et al*. (2003)
ETS, environmental tobacco smoke
[a] Total number of lung tumours/total number of mice in the group (mean ± SE)
[b] Sham-exposed mice kept in filtered air for 9 months
[c] Exposed to ETS throughout gestation, or for an equivalent period in non-gestating mice, followed by 8 months and 10 days of recovery in filtered air
[d] Followed by 4 months of recovery in filtered air
[e] $p < 0.05$
[f] $p < 0.01$, compared with the corresponding sham-exposed mice, assessed by χ^2 analysis (incidence data) or Student's *t* test for unpaired data (multiplicity data)

In one experiment, filtered simulated environmental tobacco smoke induced lung tumours as effectively as whole simulated environmental tobacco smoke. At the higher levels of exposure, the incidences of lung tumour were also significantly higher in mice exposed to simulated environmental tobacco smoke than in controls. Similarly, the exposure of Swiss mice to environmental tobacco smoke for 5 months followed by a 4-month recovery period resulted in a significant increase in lung tumour response. In contrast to the findings in A/J mice, however, treatment of Swiss mice with environmental tobacco smoke for 9 consecutive months also resulted in a significant increase in the lung tumour response. Moreover, the short-term exposure of Swiss mice to environmental tobacco smoke led to an increased occurrence of lung tumours after 9 months.

3.2 Administration of condensates of sidestream smoke

3.2.1 *Mouse*

The comparative carcinogenicity of cigarette sidestream and mainstream smoke condensates was tested on the skin of female NMRI mice. Commercial brand German blond tobacco cigarettes were smoked to a defined butt length on a smoking machine using a puff duration of 2 s/min. Sidestream and mainstream smoke condensates were collected separately, dissolved in acetone, and administered on the shaved skin of the animal's lower back. Mice received half a dose twice a week for 3 months to give total weekly doses of 5, 10 and 15 mg. The animals were kept until natural death. No cutaneous or subcutaneous tumours developed in any of three control groups (42, 44 and 43 mice). In animals given mainstream smoke condensate, there were four malignant and three benign tumours in seven of 177 treated mice: two mammary adenocarcinomas, one haemangiosarcoma and one schwannoma in 58 mice that received the 5-mg dose; no tumours in any of the 61 mice that received the 10-mg dose, and three squamous-cell papillomas of the skin in 58 mice that received the 15-mg weekly dose. In the mice given sidestream smoke condensate, there were 16 malignant and 14 benign tumours in 30 of 182 treated mice: one mammary adenocarcinoma, three squamous-cell carcinomas and one squamous-cell papilloma of the skin in 60 mice that received the 5-mg dose; two mammary adenocarcinomas, one squamous-cell carcinoma and two squamous-cell papillomas of the skin in 61 mice that received the 10-mg dose; and two mammary adenocarcinomas, one mixed mammary tumour, six squamous-cell carcinomas and 11 squamous-cell papillomas in 61 mice that received the 15-mg dose. The overall carcinogenic effect of sidestream smoke condensate was significantly higher than that of mainstream smoke condensate ($p < 0.001$) (Mohtashamipur *et al*., 1990).

3.2.2 *Rat*

The carcinogenicity of sidestream cigarette smoke condensate was studied by collecting particles and semivolatiles from commercial German cigarettes smoked on a smoking machine and implanting the condensed material in a mixture of trioctanoin and

beeswax into the lungs of female Osborne-Mendel rats at a dose corresponding to the products of a single cigarette. The fraction containing PAHs with four and more rings (dose, 1.06 mg/rat) induced five lung carcinomas in 35 treated rats. A sixfold higher dose (6.4 mg/rat) induced two lung carcinomas in five treated rats. The combined fractions containing no PAHs and PAHs of two and three rings (16 mg/rat) caused one lung carcinoma in 35 treated rats, and the semivolatiles (11.8 mg/rat) gave rise to no carcinoma in 35 treated rats (Grimmer *et al*., 1988).

3.3 Observational studies of cancer in companion animals

Many species of animals are kept as pets, or companion animals, and these animals commonly share the environments of their owners. In consequence they are also exposed to toxic agents that may be present in the shared environment. The use of epidemiological methods to investigate environmental carcinogens through analysis of the occurrence of tumours in companion animals has been reviewed by Bukowski and Wartenberg (1997). Such data have been used in previous *IARC Monographs*, notably in the evaluation of carcinogenic risks associated with surgical implants and other foreign bodies (IARC, 1999).

3.3.1 *Case reports*

Case reports of lung cancer in the household pets of smokers are useful for generating hypotheses, but usually contain insufficient details to allow useful analysis (Cummins, 1994).

3.3.2 *Case–control studies*

(*a*) *Dog*

Lung: A case–control study was conducted using 51 pet dogs with confirmed primary lung cancer from two veterinary teaching hospitals in the USA during 1985–87. Dogs with cancers at sites other than the lung (i.e. breast, soft connective tissues, skin, gastrointestinal tract, thyroid, bone, lymphoid and others) and not suspected of being related to cigarette smoking were chosen as controls (n = 83). Types of exposure to secondhand smoke that were assessed for both case and control dogs included the number of smokers who resided in the household, the number of packs of cigarettes smoked per day by the heaviest smoker and the time per day spent by the dog inside the home. Age, sex, body size and skull shape were included in a stratified analysis. A weak, statistically non-significant association was found between exposure to secondhand tobacco smoke and the risk of canine lung cancer. The crude odds ratio for exposure to environmental tobacco smoke was 1.5 (95% CI, 0.7–3.0). After adjustment for age, sex, skull shape, time spent indoors, and hospital of origin, the odds ratio rose slightly to 1.6 (95% CI, 0.7–3.7). The risk estimate for dogs aged 10 years or less was 2.7 (95% CI, 1.0–7.2); that for older dogs

was 0.8 (95% CI, 0.3–2.2). A suggestion that skull shape exerted a modifying effect on risk for lung cancer was noted: the odds ratio was non-significantly increased in dogs of breeds with short (brachycephalic) and medium length (mesocephalic) noses (odds ratio, 2.4; 95% CI, 0.7–7.8), but not in dogs with long noses. It was noted that primary canine lung cancer is rare (approximately 4 cases per 100 000 hospitalizations) (Reif *et al*., 1992).

Nasal cavity and paranasal sinuses: Sinonasal cancer is estimated to be tenfold more prevalent in dogs than lung cancer (Bukowski *et al.*, 1998).

A case–control study of nasal cancer in pet dogs treated at the veterinary teaching hospital at Colorado State University, USA, included 103 dogs with cancer of the nasal cavity and paranasal sinuses. Dogs with cancers at other sites (chiefly lymphoma, melanoma, haemangiosarcoma, and breast, bone and oral cavity) served as controls. The controls were similar to cases with respect to age, sex, breed and time spent outdoors. Telephone interviews were conducted with the owners of the pets to obtain data on exposure to environmental tobacco smoke. These data included the number of smokers in the household, the number of packs of cigarettes smoked per day at home by each smoker, the number of years that each person had smoked during the dog's lifetime and the time spent by the dog inside the home. The crude odds ratio for the presence of a smoker in the home and risk of nasal cancer was 1.1 (95% CI, 0.7–1.8). After stratification by anatomical features, the risk appeared to be restricted to long-nosed (dolichocephalic) dogs (odds ratio, 2.0; 95% CI, 1.0–4.1) (Reif *et al.*, 1998).

A case–control study was conducted to investigate the environmental causes of sinonasal cancers among pet dogs. Data on indoor environmental exposure including the presence of smokers in the household were collected for 129 dogs with histologically confirmed sinonasal cancer diagnosed during 1989–93 at the University of Pennsylvania School of Veterinary Medicine, USA. These were compared with 176 control dogs diagnosed with primary stomach, bowel, omental or liver cancers during the same period. Long-nosed dogs were significantly more likely to present with sinonasal cancer than dogs with short or medium-length noses (odds ratio, 3.2; 95% CI, 1.1–10). Elevated odds ratios were reported for dogs living in households that used coal fires or kerosene heaters for indoor heating (2.7; 95% CI, 1.4–5.4) and in which household chemicals were stored in the living area (5.5; 95% CI, 1.2–29). There was no excess risk associated with smokers living in the home (odds ratio, 0.70; 95% CI, 0.41–1.2) (Bukowski *et al.*, 1998).

Urinary bladder: A case–control study of household dogs was conducted to determine whether exposure to sidestream cigarette smoke, chemicals in the home, use of topical insecticides or obesity are associated with the occurrence of bladder cancer in canines. Information was obtained by interviewing the owners of 59 dogs with transitional cell carcinoma of the urinary bladder, diagnosed histologically at the University of Pennsylvania School of Veterinary Medicine, USA, between January 1982 and June 1985. Dogs matched on age and size of breed (n = 71) with other chronic diseases or neoplasms, excluding diseases of the urinary tract, served as controls. The risk of bladder cancer was correlated with use of topical insecticide and was enhanced in overweight dogs. The risk of bladder

cancer was not found to be related to exposure to household chemicals or to sidestream cigarette smoke at the levels of 1–3000 lifetime pack–years (odds ratio, 1.3; 95% CI, 0.5–3.1) or > 3000 lifetime pack–years (odds ratio, 0.8; 95% CI, 0.3–2.0) (Glickman *et al*., 1989). [The Working Group noted that the exposure is most likely expressed as lifetime number of packs.]

(*b*) *Cat*

Malignant lymphoma

A case–control study of domestic cats was conducted to determine whether exposure to household environmental tobacco smoke is associated with the occurrence of feline malignant lymphoma. Information on the level of smoking in the household two years prior to diagnosis was obtained from questionnaires sent to the owners of 80 cats with malignant lymphoma diagnosed during 1993–2000 at the Foster Small Animal Hospital, MA, USA. These cases were compared with 114 control cats diagnosed with renal disease during the same period. The relative risk of malignant lymphoma for cats exposed to any household tobacco smoke was 2.4 (95% CI, 1.2–4.5). The risk increased with both duration and level of exposure, with evidence of a linear trend. Cats exposed to tobacco smoke for five or more years had a relative risk of 3.2 (95% CI, 1.5–6.9; p for trend = 0.003) when compared with cats in nonsmoking households (Bertone *et al.*, 2002).

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