INVOLUNTARY SMOKING

1. Composition, Exposure and Regulations

1.1 Composition

1.1.1 *Secondhand smoke*

During smoking of cigarettes, cigars, pipes and other tobacco products, in addition to the mainstream smoke drawn and inhaled by smokers, a stream of smoke is released between puffs into the air from the burning cone. Once released, this stream (also known as the sidestream smoke) is mixed with exhaled mainstream smoke as well as the air in an indoor environment to form the secondhand smoke to which both smokers and nonsmokers are exposed. A small additional contribution to the smoke issues from the tip of the cigarette and through the cigarette paper during puffing and through the paper and from the mouth end of the cigarette between puffs (IARC, 1986; NRC, 1986; US EPA, 1992). Thus, secondhand tobacco smoke is composed of aged exhaled mainstream smoke and diluted sidestream smoke.

Secondhand tobacco smoke contains a variable proportion of exhaled mainstream smoke ranging from 1 to 43% (Baker & Proctor, 1990). Because of its rapid dilution and dispersion into the indoor environment, secondhand tobacco smoke acquires different physicochemical properties to those of mainstream smoke and sidestream smoke and the concentrations of the individual constituents are decreased. The principal physical change is a decrease in the proportion of smoke constituents found in the particulate phase as opposed to the vapour phase of the smoke. The median particle size of secondhand tobacco smoke is subsequently smaller than that of the particles of mainstream smoke. The principal chemical change is in the composition (i.e. in the relative quantities of the individual constituents present); this is caused by differences in the ways in which individual constituents respond to ventilation and to contact with indoor surfaces. There is some indication that chemical transformation of reactive species also occurs.

The effects of exposure to secondhand tobacco smoke, or involuntary (passive) smoking, cannot be estimated from any individual constituents. Secondhand tobacco smoke is actually a complex mixture, containing many compounds for which concentrations can vary with time and environmental conditions. Cigarette smoking is the main source for involuntary exposure because it is by far the most prevalent form of tobacco smoking although specific patterns may differ between countries. Emissions of sidestream smoke in indoor environments with low ventilation rates can result in concentrations of

toxic and carcinogenic agents above those generally encountered in ambient air in urban areas (IARC, 1986; Jenkins *et al.*, 2000).

Studies on the complex composition of secondhand tobacco smoke in 'real world' conditions have been limited partly because of the presence of additional sources of secondhand smoke constituents. Therefore compositional and physical studies of secondhand tobacco smoke have often been performed in environmental chambers (also known as a 'controlled experimental atmosphere'). The disadvantage of the controlled experimental atmosphere is that it does not reflect real life situations. The studies of the chemical composition of secondhand tobacco smoke, either in a controlled experimental atmosphere or in the field, have been limited. This is mainly because there are still no standardized criteria for the development of experimental atmospheres that represent secondhand tobacco smoke (Jenkins *et al.*, 2000).

Respirable suspended particles (only those particles that are small enough to reach the lower airways of the human lung) can exist in many forms in indoor air: those resulting from secondhand tobacco smoke are present in the form of liquid or waxy droplets. They are smaller than the particles in mainstream smoke. The mass median diameter of mainstream smoke particles averages 0.35–0.40 μm. Gravimetric determination indicates that the respirable suspended particles of secondhand tobacco smoke in typically encountered environments may comprise one-third of the respirable suspended particles in indoor air. However, in some environments, this fraction may be as much as two-thirds (Jenkins *et al*., 2000).

Respirable suspended particle concentrations of 4091 $\mu g/m^3$ were measured in an experimental room in which 120 cigarettes were smoked during 9 hours in 1 day for the evaluation of exposure to benzene and other toxic compounds (Adlkofer *et al*., 1990).

Worldwide in indoor environments where people smoke, the mean levels of respirable suspended particles ranged from 24 to 1947 $\mu g/m^3$. Background levels of respirable suspended particles depend on many factors including local vehicular traffic patterns, quality of ventilation systems and the presence of other sources (e.g. cooking and wood-burning stoves). Comparisons between smoking and nonsmoking locations revealed up to threefold higher concentrations of respirable suspended particles in smoking areas. The US EPA-proposed maximal level for fine particles in outdoor ambient air (65 $\mu g/m^3$ particulate matter, that is 2.5 μm or smaller in size, for 24 h) is frequently exceeded in indoor situations where people are smoking (Jenkins *et al*., 2000).

Besides respirable suspended particles and nicotine (see Section 1.2), carbon monoxide (CO) has been the most extensively studied constituent of secondhand tobacco smoke. The contemporary commercial cigarettes in the USA deliver approximately 15 mg CO in mainstream smoke and an additional 50 mg in sidestream smoke (Jenkins *et al*., 2000). In an indoor environment, CO concentrations are rapidly diluted. The measured mean concentrations reported for CO in offices, other workplaces, functions and public gatherings, transportation, restaurants and cafeterias, bars and taverns where people smoke ranged from 0.2 to 33 ppm. The American Society of Heating, Refrigerating and

Air-Conditioning Engineers (ASHRAE) standard for CO concentration in indoor air is 9 ppm (Jenkins *et al*., 2000).

The mean levels of nitric oxide (NO) in indoor areas were reported from not detected to 500 ppb and those of nitrogen dioxide (NO_2) from not detected to 76 ppb (Jenkins *et al*., 2000).

There are a number of studies that have addressed the composition of secondhand tobacco smoke beyond the 'common' constituents such as nicotine, CO and respirable suspended particles. A few of these are shown in Table 1.1 (Eatough *et al*., 1989; Löfroth *et al*. 1989; Higgins *et al.*, 1990; Löfroth, 1993; Martin *et al*., 1997). The focus of these studies was primarily on vapour-phase constituents. Vapour phase represents the bulk of the mass of secondhand tobacco smoke whereas the respirable suspended particle-related constituents are present at very low concentrations that are very difficult to quantify. For example, if the levels of respirable suspended particles are in the range of 20 to 1000 $\mu g/m^3$, constituents of the particulate phase present at concentrations of 1–100 ppm in the particles themselves will be present at airborne concentrations from 20 pg/m^3 to 100 ng/m^3. These are very low concentrations for detection by any sampling and analysis method (Jenkins *et al*., 2000).

As can be seen from the data in Table 1.1, the field studies show considerable variation in the measured levels of constituents of secondhand tobacco smoke. Similar concentrations of benzene and isoprene to those shown in Table 1.1 were reported in a smoke-filled bar (from 26 to 36 $\mu g/m^3$ and 80–106 $\mu g/m^3$, respectively), although the nicotine levels were much lower (22 $\mu g/m^3$). The concentration of 1,3-butadiene measured in the smoke-filled bar was from 2.7 to 4.5 $\mu g/m^3$ (Brunnemann *et al*., 1990). In a field study of 25 homes of smokers, Heavner *et al*. (1995) estimated that the median fraction of benzene contributed by secondhand tobacco smoke was 13% (ranging from 0 to 63%).

In a study of six homes of smokers, secondhand tobacco smoke was found to make a substantial contribution to the concentrations of 1,3-butadiene (Kim *et al*., 2001).

The levels of carbonyl compounds measured in an experimental room under extremely high concentrations of secondhand tobacco smoke (Adlkofer *et al*., 1990) were: formaldehyde, 49 $\mu g/m^3$; acetaldehyde, 1390 $\mu g/m^3$ and propionaldehyde, 120 $\mu g/m^3$. The concentrations of other constituents of secondhand tobacco smoke were: nicotine, 71 $\mu g/m^3$; benzene, 206 $\mu g/m^3$; benzo[*a*]pyrene, 26.7 ng/m^3; pyrene, 25 ng/m^3 and chrysene, 70.5 ng/m^3.

Benzo[*a*]pyrene was also detected in natural environments containing secondhand tobacco smoke, with concentrations ranging from not detected to 3.6 ng/m^3 (or up to 3.35 ng/m^3 when the background concentration was subtracted) (Jenkins *et al*., 2000). Trace levels of some other polycyclic aromatic hydrocarbons (PAHs; such as naphthalene, chrysene, anthracene, phenanthrene and benzofluoranthenes) were also reported. The vapour-phase 2- to 3-ring PAHs predominate quantitatively over the higher-ring system PAHs.

Table 1.1. Concentrations (in μg/m^3) of selected constituents of secondhand tobacco smoke in some experimental and real-life situations[a]

Constituent	18-m^3 chamber: mean for 50 best-selling US cigarettes (Martin *et al.*, 1997)	Living quarters (Löfroth, 1993)	Tavern (Löfroth *et al.*, 1989)	Discothèque (Eatough *et al.*, 1989)	Home (Higgins *et al.*, 1990)
Respirable suspended particles	1440	240–480	420	801[b]	–
Nicotine	90.8	8–87	71	120	51.8
CO (ppm)	5.09	–	4.8	22.1	–
Benzene	30	–	27	–	17.6
Formaldehyde	143	–	104	–	–
1,3-Butadiene	40	–	19	–	–
Acetaldehyde	268	–	204	–	–
Isoprene	657	50–200	150	–	83.3
Styrene	10	–	–	–	7.3
Catechol	1.24	–	–	–	–
3-Ethenyl pyridine	37.1	–	–	18.2	–
Ethylbenzene	8.5	–	–	–	8.0
Pyridine	23.8	–	–	17.6	6.5
Toluene	54.5	–	–	–	51.2
Limonene	29.1	–	–	–	22.0

Modified from Jenkins *et al*. (2000)

–, not reported

[a] These are not typical average concentrations, but represent the higher end of the exposure scale.

[b] Fine particles (< 2 μm size)

The levels of *N*-nitrosodimethylamine (NDMA) measured in the field (e.g. in workrooms, conference rooms, restaurants and bars where people smoked) ranged from less than 10 ng/m^3 to 240 ng/m^3 (Jenkins *et al*., 2000). In unventilated offices in which 11–18 cigarettes were smoked during a 2-h period, up to 8.6 ng/m^3 *N*-nitrosodiethylamine (NDEA) and up to 13 ng/m^3 *N*-nitrosopyrrolidine (NPYR) were measured.

The *N*′-nitrosonornicotine (NNN) concentrations measured in a poorly ventilated office where heavy smoking of cigarettes, cigars and pipes took place ranged from not detected to 6 ng/m^3 and those of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) from not detected to 13.5 ng/m^3 (Klus *et al*., 1992). The upper levels reported by Klus *et al*. (1992) and by Adlkofer *et al*. (1990) for the 'heavily smoked rooms' (11 cigarettes smoked in 2 h in a 84 m^2 office) were somewhat lower than those measured by Brunnemann *et al.* (1992): NNN concentrations ranged from not detected to 22.8 ng/m^3 and NNK concentrations between 1.4 and 29.3 ng/m^3, measured inside bars, restaurants, trains, and a car, an office and a smoker's home (Brunnemann *et al*., 1992).

The effects of cigar smoking on indoor levels of CO, respirable suspended particles and particle-bound PAH particles were investigated in an office where several brands of cigar were machine smoked, in a residence where two cigars were smoked by a person and at cigar social events where up to 18 cigars were smoked at a time. The average concentrations of CO at cigar social events were comparable with, or larger than, those measured on a main road during rush-hour traffic. A mass balance model developed for predicting secondhand tobacco smoke was used in this study to obtain CO, respirable suspended particle and PAH emission. These factors show that cigars can be a stronger source of CO than cigarettes. In contrast, cigars may have lower emissions of respirable suspended particles and PAHs per gram of tobacco consumed than cigarettes, but the greater size and longer smoking time of a single cigar results in greater total respirable suspended particle and PAH emission than from a single cigarette (Klepeis *et al.*, 1999). Nelson *et al*. (1997) tested six brands of cigar and the yields of respirable suspended particles averaged 52 mg/cigar. Yields of CO, nitric oxide (NO) and nitrogen dioxide (NO_2) averaged 32, 10.5 and 2.1 mg/cigar, respectively, and that of volatile organic compounds (VOC) (analysed with gas chromatograph-flame ionization detection (FID)) was estimated to be 340 mg/cigar (propane equivalent). Ratios of secondhand tobacco smoke respirable suspended particles to the surrogate standards for the particulate markers ultraviolet particulate matter (UVPM) and fluorescent particulate matter (FPM) were 6.5 and 27.8, respectively. Another particulate marker, solanesol, made up 2.1% of the particles from cigars. For the two gas-phase markers, the ratio of 3-ethenyl pyridine to other gas-phase species was more consistent than ratios involving nicotine.

The comparative analysis of the composition of secondhand tobacco smoke from Eclipse (a cigarette that primarily heats tobacco rather than burning it) and from four commercial cigarettes with a wide range of Federal Trade Commission (FTC) yields is shown in Table 1.2 (Bombick *et al*., 1998). Eclipse contributed similar amounts of CO to secondhand tobacco smoke to those contributed by burning-tobacco cigarettes but contributed 86–90% less respirable suspended particles. Commercial cigarettes, however,

Table 1.2. Mean concentrations (in μg/m^3) of selected components of secondhand smoke of four commercial cigarette brands and Eclipse[a] measured in a chamber with a controlled experimental atmosphere

Constituent	Full-flavour brand	Full-flavour light	100-mm brand	Ultra-light	Eclipse
Respirable suspended particles	1458	1345	1706	1184	181
Nicotine	54	63	58	51	4.3
CO (ppm)	6.5	6.2	7.9	6.6	5.2
3-Ethenylpyridine	25	28	28	34	0.56
Acetaldehyde	313	301	384	312	46
Phenol	17.4	16.7	20.0	16.8	4
NO_x (ppb)	241	233	268	250	24
Total hydrocarbons[b]	2.6	2.6	3.0	2.8	0.47

From Bombick *et al*. (1998)

[a] A cigarette that primarily heats (rather than burns) tobacco

[b] Analysed with gas chromatograph–flame ionizing detector (ppm)

contributed a similar amount of constituents to secondhand tobacco smoke, regardless of their ranking on the FTC scale.

1.1.2 *Exhaled mainstream smoke*

Baker and Proctor (1990) estimated that exhaled mainstream smoke contributes 3–11% of CO, 15–43% of particles and 1–9% of nicotine to secondhand tobacco smoke. Non-inhaling smokers can contribute larger amounts. There is little information on how much exhaled mainstream smoke contributes to the overall composition of secondhand tobacco smoke except that the contribution to the particulate phase is more significant than that to the vapour phase (see monograph on tobacco smoke/Section 4 — breath compounds).

1.1.3 *Sidestream smoke*

The composition of cigarette sidestream smoke is similar to that of mainstream smoke. However, the relative quantities of many of the individual constituents of sidestream smoke are different from those found in mainstream smoke. Also, the absolute quantities of most of the constituents released in sidestream smoke differ from those delivered in mainstream smoke (Jenkins *et al.*, 2000).

Like mainstream cigarette smoke, sidestream smoke contains many compounds that are emitted as gases and particles. The distinction between particle and vapour-phase constituents is appropriate for those constituents that are non-volatile (e.g. high-mole-

cular-weight organic compounds and most metals) and those that are clearly gases (e.g. CO). Constituents with appreciable vapour pressure (i.e. most of the constituents of tobacco smoke) can be found in both the particulate phase and the vapour phase of cigarette smoke. The term 'semivolatiles' has been used to describe such constituents. The degree to which these compounds are distributed between the particle and vapour phases is determined by their volatility (and stability) and the characteristics of their environment. These constituents are distributed preferentially in the particulate phase in highly concentrated smokes, such as those inhaled by smokers, and preferentially in the particle and vapour phases in highly diluted smokes, such as those encountered by involuntary smokers. The phase distribution and the ultimate fate of any given constituent released into the ambient environment is likely to differ depending upon ambient conditions and upon the chemical or physical properties of that constituent.

The manner in which cigarettes are smoked greatly influences their mainstream delivery and sidestream emissions. For the different machine-smoking protocols referred to in this monograph, see Table 1.9 in the monograph on tobacco smoke. Particulate matter that is released in mainstream smoke during active smoking enters the respiratory tract largely intact, whereas the particulate matter in sidestream smoke is available for inhalation only after dilution in ambient air and after the physical and chemical changes that occurred during that dilution. However, conventional analysis of sidestream smoke provides only information on the quantities of individual smoke constituents released into the air. Moreover, the methods for analysis of sidestream smoke are not as well defined as those for mainstream smoke (Jenkins *et al.*, 2000).

As they leave the cigarette, sidestream smoke particles are initially slightly smaller than mainstream smoke particles (geometric mean diameter, 0.1 μm versus 0.18 μm; Guerin *et al*., 1987). The natural dissipation rates of sidestream smoke particles dispersed in an experimental chamber were studied from the standpoint of a static atmosphere and were expressed as half-lives of residence in the air. The half-lives for particles with diameters less than 0.3 μm, 0.3–0.5 μm and 0.5–1 μm were found to be 25.5, 12.8 and 4.9 h, respectively. Total particulate matter decreased by half over 6.2 h (Vu Duc & Huynh, 1987). However in real-life situations the ageing of sidestream smoke over several minutes may lead to an increase in particle size of secondhand tobacco smoke due to the coagulation of particles and the removal of smaller particles that attach to surfaces in the environment. Sidestream smoke is produced at generally lower temperatures and with a very different oxygen flux to that of mainstream smoke.

The ratio of sidestream smoke to mainstream smoke is customarily used to express the distribution of individual constituents between the two smoke matrices. The distribution of specific components is dependent on their mechanism of formation. Higher ratios of sidestream smoke to mainstream smoke between cigarettes or smoking conditions generally reflect a lower mainstream smoke delivery with no significant change in sidestream smoke delivery. Under similar smoking conditions, filter-tipped cigarettes will have lower mainstream smoke yields than their untipped analogues. Sidestream smoke yields will not vary greatly, because they reflect the weight of tobacco burned during

smouldering. In general, more tobacco is burned during smouldering than during puffing (Guerin *et al.*, 1987).

Adams *et al.* (1987) reported that sidestream smoke contains more alkaline and neutral compounds than mainstream smoke (the pH of the sidestream smoke of cigarettes with a wide range of FTC yields averaged 7.5 [7.2–7.7], whereas the pH of mainstream smoke averaged 6.1 [6.0–6.3]). The differences are due to temperature during burning and mechanisms of chemical transfer (release) from unburned tobacco.

Many constituents of sidestream smoke belong to chemical classes known to be genotoxic and carcinogenic. These include the IARC group 1 carcinogens benzene, cadmium, 2-aminonaphthalene, nickel, chromium, arsenic and 4-aminobiphenyl; the IARC group 2A carcinogens formaldehyde, 1,3-butadiene and benzo[*a*]pyrene; and the IARC group 2B carcinogens acetaldehyde, isoprene, catechol, acrylonitrile, styrene, NNK, NNN and lead among others.

Adams *et al*. (1987) determined the levels of selected toxic and carcinogenic agents in the mainstream and sidestream smoke of four different types of US commercial cigarette brands — untipped and filter-tipped — with a wide range of FTC yields. In this study, smoke was generated by a machine using the standard FTC method. The concentrations of all agents except NNN were higher in the sidestream than in the mainstream smoke of both untipped and filter-tipped brands. The tar yields in sidestream smoke ranged from 14 to 24 mg per cigarette (similar to the range reported by Ramsey *et al*., 1990) and were, on average, 5.3 times higher than those in mainstream smoke. The highest sidestream smoke/mainstream smoke ratio for tar was calculated for ultra low-yield cigarettes (ratio, 15.7) and the lowest for untipped cigarettes (ratio, 1.12). The mainstream smoke yields are strongly affected by variables that only slightly affect sidestream smoke yields (Guerin *et al*., 1987). The ratios of sidestream smoke to mainstream smoke for nicotine, CO and NNK for the ultra low-yield brand were 21.1, 14.9 and 22.3, respectively. The highest emissions of nicotine, NNK and NNN were measured in the sidestream smoke of untipped cigarettes (4.62 mg, 1444 ng and 857 ng, respectively). In mainstream smoke, these values were 2.04 mg, 425 ng and 1007 ng, respectively. The levels of volatile *N*-nitrosamines in sidestream smoke greatly exceeded those measured in mainstream smoke (e.g. 735 ng versus 31.1 ng NDMA per untipped cigarette and 685 ng versus 4.1 ng NDMA for ventilated filter-tipped cigarettes; average ratio, 95). The average ratio of sidestream smoke to mainstream smoke for the carcinogen NPYR was 10. The authors concluded that the availability of cigarettes with greatly reduced amounts of carcinogens in mainstream smoke had little bearing on the emissions of carcinogens in sidestream smoke.

Chortyk and Schlotzhauer (1989) compared the emissions of various smoke components for 19 low-yield brands of filter-tipped cigarettes with those measured for a reference high-yield untipped brand. It was found that low-yield cigarettes produced large quantities of tar in sidestream smoke, about equal to that of the high-yield cigarette. On an equal weight basis, the low-tar cigarettes emitted more of these hazardous compounds into sidestream and secondhand smoke than did the high-tar cigarette.

The yields of various constituents of sidestream smoke of 15 Canadian cigarette brands measured using the FTC machine-smoking protocol with the exception that cigarettes were smoked to a butt length of 30 mm, ranged as follows: tar, from 15.8 to 29.3 mg per cigarette in non-ventilated brands and from 24.2 mg to 36.0 mg in ventilated brands; nicotine, from 2.7 mg to 4.6 mg in non-ventilated brands and 3.0 mg to 6.1 mg in ventilated brands, and CO, from 40.5 mg to 67.3 mg in non-ventilated brands and 46.5 mg to 63.1 mg in ventilated brands. Yields in sidestream smoke were much higher than those in mainstream smoke for all brands tested. The average ratios for sidestream smoke to mainstream smoke were 3.5, 6.6 and 6.8 for tar, nicotine and CO, respectively. The highest yields from sidestream smoke were obtained from the brands with the lowest mainstream smoke yields (Rickert *et al*., 1984). The concentrations of carbon monoxide in the sidestream smoke in the Canadian cigarettes were higher than those reported for four different types of American blend cigarettes smoked according to the FTC protocol (Adams *et al*., 1987). Differences in the tobacco blend may be one explanation for this discrepancy and Canadian cigarettes are made predominantly from flue-cured tobacco.

The average yields of total particulate matter and nicotine in sidestream smoke generated by the machine-smoking of two cigarette brands that are popular among smokers in India (one filter-tipped and one untipped) were 16.51 and 0.9 mg per cigarette, respectively (Pakhale & Maru, 1998). In the sidestream smoke from bidis, these concentrations were 5.5 mg total particulate matter and 0.25 mg nicotine. The sidestream smoke released from chuttas contained 19.8 mg total particulate matter and 2.07 mg nicotine per unit. In all Indian products, the emissions of total particulate matter were much higher in mainstream smoke than in sidestream smoke, which is demonstrated clearly by the ratio of sidestream smoke to mainstream smoke which ranged from 0.13 to 0.49 (see also the monograph on tobacco smoke, Section 1.2.7). This is a modified, more intensive smoking standard (two puffs per minute instead of one) used because of the poor burning properties of the tobacco in Indian products.

In the 1999 Massachusetts Benchmark Study (Borgerding *et al.*, 2000), a subset of 12 brands was analysed for the chemical composition of the sidestream smoke that was generated by machine-smoking using the 'more intense' Massachusetts method. The data obtained are summarized in Table 1.3. The concentrations of the constituents of the sidestream smoke determined in this study differed significantly from those obtained using the standard FTC method that had been reported by Adams *et al*. (1987): the yields of CO, ammonia and benzo[*a*]pyrene were higher, those of tar and catechol were of the same order of magnitude and those of NNN and NNK were significantly lower. NNN and NNK levels were even lower than those measured in the mainstream smoke generated by the same intense machine-smoking method. The values obtained by the Massachusetts Study for some gaseous compounds such as 1,3-butadiene, acrolein, isoprene, benzene and toluene were also far below those obtained by machine-smoking using the FTC method (Brunnemann *et al*., 1990; Table 1.4). For the 12 commercial cigarette brands tested by the Massachusetts puffing parameters, the highest median sidestream smoke/mainstream smoke ratios in the Massachusetts study were obtained for ammonia (ratio, 147),

Table 1.3. Average values of 44 smoke constituents in the sidestream smoke of 12 commercial cigarette brands assayed in the 1999 Massachusetts Benchmark Study using Massachusetts smoking parameters

Constituent	Unit	Range	SS/MS ratio[a]
Ammonia	mg/cig.	4.0–6.6	147
1-Aminonaphthalene	ng/cig.	165.8–273.9	7.10
2-Aminonaphthalene	ng/cig.	113.5–171.6	8.83
3-Aminobiphenyl	ng/cig.	28.0–42.2	10.83
4-Aminobiphenyl	ng/cig.	20.8–31.8	5.41
Benzo[*a*]pyrene	ng/cig.	51.8–94.5	3.22
Formaldehyde	µg/cig.	540.4–967.5	14.78
Acetaldehyde	µg/cig.	1683.7–2586.8	1.31
Acetone	µg/cig.	811.3–1204.8	1.52
Acrolein	µg/cig.	342.1–522.7	2.53
Propionaldehyde	µg/cig.	151.8–267.6	1.06
Crotonaldehyde	µg/cig.	62.2–121.8	1.95
Methyl ethyl ketone	µg/cig.	184.5–332.6	1.49
Butyraldehyde	µg/cig.	138.0–244.9	2.68
Hydrogen cyanide	mg/cig.	0.19–0.35	0.77
Mercury	ng/cig.	5.2–13.7	1.09
Nickel	ng/cig.	ND–NQ	
Chromium	ng/cig.	ND–ND	
Cadmium	ng/cig.	122–265	1.47
Arsenic	ng/cig.	3.5–26.5	1.51
Selenium	ng/cig.	ND–ND	
Lead	ng/cig.	2.7–6.6	0.09
Nitric oxide	mg/cig.	1.0–1.6	2.79
Carbon monoxide	mg/cig.	31.5–54.1	1.87
'Tar'	mg/cig.	10.5–34.4	0.91
Nicotine	mg/cig.	1.9–5.3	2.31
Pyridine	µg/cig.	195.7–320.7	16.08
Quinoline	µg/cig.	9.0–20.5	12.09
Phenol	µg/cig.	121.3–323.8	9.01
Catechol	µg/cig.	64.5–107.0	0.85
Hydroquinone	µg/cig.	49.8–134.1	0.94
Resorcinol	µg/cig.	ND–5.1	
meta-Cresol + *para*-Cresol[b]	µg/cig.	40.9–113.2	4.36
ortho-Cresol	µg/cig.	12.4–45.9	4.15[c]
NNN	ng/cig.	69.8–115.2	0.43
NNK	ng/cig.	50.7–95.7	0.40
NAT	ng/cig.	38.4–73.4	0.26
NAB	ng/cig.	11.9–17.8	0.55
1,3-Butadiene	µg/cig.	81.3–134.7	1.30

Table 1.3 (contd)

Constituent	Unit	Range	SS/MS ratio[a]
Isoprene	µg/cig.	743.2–1162.8	1.33
Acrylonitrile	µg/cig.	24.1–43.9	1.27
Benzene	µg/cig.	70.7–134.3	1.07
Toluene	µg/cig.	134.9–238.6	1.27
Styrene	µg/cig.	23.2–46.1	2.60

From Borgerding *et al*. (2000)
SS, sidestream smoke; MS, mainstream smoke; NNN, *N*′-nitrosonornicotine; NNK, 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone; NAT, *N*′-nitrosoanatabine; NAB, *N*′-nitrosoanabasine; ND, not detected; limit of detection for chromium, 8 ng/cigarette; for selenium, 5 ng/cigarette; for resorcinol, 0.6 µg/cigarette; for nickel, 6.8 ng/cigarette; NQ, not quantifiable; limit of quantification for nickel, 10 ng/cigarette
[a] Median value for the sidestream/mainstream smoke ratios for the 12 commercial cigarette brands
[b] Reported together

Table 1.4. Concentrations of selected gas-phase compounds in sidestream smoke of commercial cigarettes

Compound	Federal Trade Commission method (Adams *et al*., 1987; Brunnemann *et al*., 1990)	1999 Massachusetts Benchmark Study (Borgerding *et al.*, 2000)
NNN (ng/cig.)	185–857	70–115
NNK (ng/cig.)	386–1444	51–96
1,3-Butadiene (µg/cig.)	205–250[a]	81–135
Acrolein (µg/cig.)	723–1000	342–523
Isoprene (µg/cig.)	4380–6450	743–1163
Benzene (µg/cig.)	345–529	71–134
Toluene (µg/cig.)	758–1060	135–239

NNN, *N*′-nitrosonornicotine; NNK, 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone)
[a] 400 µg 1,3-butadiene measured in the sidestream smoke collected after emission into an environmental chamber (Löfroth, 1989)

Table 1.5. Yields of IARC carcinogens in regular-sized Canadian cigarettes. Comparison of International Organization for Standardization (ISO)[a] and Health Canada (HC)[b] machine-smoking parameters[c]

Compound	ISO smoking parameters						
	Regular (full flavour)	Light	Extra light	Ultra light	ISO/ISO regular/ light	ISO/ISO regular/ extra light	ISO/ISO regular/ ultra light
IARC Group 1 carcinogens							
Benzene (µg/cig.)	222.0	250.0	260.0	296.0*	0.9	0.9	0.8*
Cadmium (ng/cig.)	438.0	484.0	502.0*	627.0*	0.9	0.9*	0.7*
2-Aminonaptthtalene (ng/cig.)	157.0	147.0	175.0	186.0	1.1	0.9	0.8
Nickel (ng/cig.)	34.3	45.1	74.4*	73.0*	0.8	0.5*	0.5*
Chromium (ng/cig.)	61.0	62.0	121*	82.9*	1.0	0.5*	0.7*
Arsenic (ng/cig.)	ND	NQ	ND	ND			
4-Aminobiphenyl (ng/cig.)	22.1	19.5	21.0	21.2	1.1	1.1	1.0
IARC Group 2A carcinogens							
Formaldehyde (µg/cig.)	378.0	326.0	414.0	431.0	1.2	0.9	0.9
1,3-Butadiene (µg/cig.)	196.0	185.0	264.0	299.0	1.1	0.7	0.7
Benzo[*a*]pyrene (ng/cig.)	48.8	98.3	92.2	113.0	0.5	0.5	0.4
IARC Group 2B carcinogens							
Acetaldehyde (µg/cig.)	1416.0	1454.0	1449.0	1492.0	1.0	1.0	0.9
Isoprene (µg/cig.)	1043.0	1164.0	1060.0	1172.0	0.9	1.0	0.9
Catechol (µg/cig.)	130.0	117.0	149.0	148.0	1.1	0.9	0.9
Acrylonitrile (µg/cig.)	78.6	85.6	74.1	81.8	0.9	1.1	1.0
Styrene (µg/cig.)	74.0	84.7	87.5	108.0*	0.9	0.8	0.7*
NNK (ng/cig.)	95.2	153.4	38.3	34.7	0.6	2.5	2.7
NNN (ng/cig.)	23.3	53.9	43.7	45.2	0.4	0.5	0.5
Lead (ng/cig.)	54.8	39.4	22.3	18.5	1.4	2.5	3.0

Source: Government of British Columbia (2003)

NNN, *N*′-nitrosonornicotine; NNK, 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone; ND, not detectable; NQ, not quantifiable

[a] ISO smoking parameters: 35 mL puff in 2 sec, interval 60 sec, ventilation holes not blocked

[b] HC: Health Canada smoking parameters: 56 mL puff in 2 sec, interval 26 sec, ventilation holes fully blocked

[c] Reporting period: year 1999

* Changed according to personal communication with B. Beech, Health Canada

3-aminobiphenyl (ratio, 10.8), formaldehyde (ratio, 14.8), pyridine (ratio, 16.1) and quinoline (ratio, 12.1).

Often, conflicting results concerning the phase distribution of individual constituents and poor agreement between laboratories for quantitation of sidestream emissions are attributed to different methods used for smoke generation and collection.

Table 1.5 shows the yields of IARC carcinogens in sidestream smoke generated under standard International Organization for Standardization (ISO) and the more intense Health Canada methods, of four popular regular-size Canadian cigarette brands.

On the basis of their mainstream smoke tar yields as measured by the ISO/FTC machine-smoking method, the four cigarette brands may be classified as ‘full flavour’, ‘light’, ‘extra light’ and ‘ultra light’. British Columbia has established the Tobacco Testing and Disclosure Regulation and became the first jurisdiction in the world to require Canadian tobacco manufacturers to disclose on a brand-by-brand basis the contents of cigarettes and tobacco and the levels of potentially toxic chemicals in tobacco smoke.

Table 1.5. (contd)

HC smoking parameters										
Regular (full flavour)	Light	Extra light	Ultra light	HC/HC regular/ light	HC/HC regular/ extra light	HC/HC regular/ ultra light	HC/ISO Regular	HC/ISO Light	HC/ISO Extra light	HC/ISO Ultra light
98.1	140.0	141.0	158.0	0.7	0.7	0.6	0.4	0.6	0.5	0.5*
256.0	276.0	282.0	355.0	0.9	0.9	0.7	0.6	0.6	0.5*	0.5*
113.0	71.1	112.0	102.0	1.6	1.0	1.1	0.7	0.5	0.6	0.5
17.6	49.3	35.5	34.8	0.4	0.5	0.5	0.5	1.1	0.5*	0.5*
47.1	57.2	54.6	69.4	0.8	0.9	0.7	0.8	0.9	0.5*	0.8*
ND	ND	ND	ND							
16.3	12.5	17.2	15.1	1.3	0.9	1.1	0.7	0.6	0.8	0.7
311.0	208.0	256.0	327.0	1.5	1.2	1.0	0.8	0.6	0.6	0.8
120.0	109.0	168.0	175.0	1.1	0.7	0.7	0.6	0.6	0.6	0.6
31.9	39.5	41.2	44.0	0.8	0.8	0.7	0.7	0.4	0.4	0.4
1174.0	969.0	1079.0	1277.0	1.2	1.1	0.9	0.8	0.7	0.7	0.9
525.0	818.0	763.0	858.0	0.6	0.7	0.6	0.5	0.7	0.7	0.7
104.0	82.0	96.1	109.0	1.3	1.1	1.0	0.8	0.7	0.6	0.7
41.1	50.1	47.6	51.9	0.8	0.9	0.8	0.5	0.6	0.6	0.6
38.7	61.6	50.8	55.6	0.6	0.8	0.7	0.5	0.7	0.6	0.5*
69.8	116.5	65.6	89.9	0.6	1.1	0.8	0.7	0.8	1.7	2.6
19.3	37.8	24.3	30.1	0.5	0.8	0.6	0.8	0.7	0.6	0.7
40.0	30.1	27.0	24.3	1.3	1.5	1.6	0.7	0.8	1.2	1.3

Among the 44 smoke components reported by the manufacturers on a yearly basis, there are seven IARC group 1 carcinogens (benzene, cadmium, 2-aminonaphthalene, nickel, chromium, arsenic and 4-aminobiphenyl), three IARC group 2A carcinogens (formaldehyde, 1,3-butadiene and benzo[*a*]pyrene) and eight IARC group 2B carcinogens (acetaldehyde, isoprene, catechol, acrylonitrile, styrene, NNK, NNN and lead).

Of the seven IARC group 1 carcinogens, arsenic yields in sidestream smoke were below the detection limits of both the ISO and Health Canada smoking methods. In general, yields of the six other IARC group 1 carcinogens in sidestream smoke were higher when measured by the ISO than by the Health Canada smoking method. The ISO and Health Canada methods gave similar yields for nickel and chromium in the 'light' cigarette and for chromium in the 'ultra light' cigarette.

For most IARC group 2A and 2B carcinogens, the yields in sidestream smoke measured by the Health Canada method were 40–80% of corresponding yields measured by the ISO method. Exceptionally, for NNK and lead the yields measured by the Health Canada method were higher than the yields measured by the ISO method, but only for the 'extra light' and 'ultra light' brands. The yields of NNK measured by the Health Canada method were up to 2.6-fold higher than the yields measured by the ISO method (Government of British Columbia, 2003).

Table 1.5 also allows comparisons of sidestream smoke yields between the brands. There is no significant difference between the total sidestream smoke yields of IARC group 1 carcinogens of 'full flavour' and 'light', extra light and ultra light cigarettes when measured by either the ISO or Health Canada methods.

The data in Tables 1.3 and 1.5 suggest that during more intense smoking (as employed by the Massachusetts and Health Canada methods: i.e. larger puffs, shorter interval between puffs and partial or complete blockage of ventilation holes), smaller quantities of tobacco are burned during the smouldering of the cigarette, thus affecting the emissions of toxins in sidestream smoke. Therefore, the real-life contribution of sidestream smoke to the overall concentrations of selected components of secondhand tobacco smoke may have been overestimated in the past because most smokers draw smoke from their cigarettes with an intensity more similar to that of the Massachusetts or Health Canada methods than the FTC machine-smoking method (Djordjevic *et al*., 2000). This concept needs to be investigated more thoroughly, especially in view of the finding that an increase in puff volume from 17.5 mL to 50 mL and in filter ventilation from 0 to 83% failed to reduce the levels of tar, CO and nicotine in the sidestream smoke, whereas the yields in mainstream smoke and subsequently the ratios of sidestream smoke to mainstream smoke changed significantly (Guerin *et al*., 1987).

In addition to the constituents listed in Table 1.3, some further constituents have been quantified in sidestream smoke since the publication of the 1986 *IARC Monograph*. These are NDMA (up to 735 ng per cigarette), *N*-nitrosopiperidine (NPIP, 19.8 ng) and NPYR (up to 234 ng) (Adams *et al*., 1987); and volatile hydrocarbons, e.g. ethene up to 1200 μg, propene up to 1300 μg, butenes up to 900 μg and pentenes up to 2100 μg. The sidestream smoke emissions of various unsaturated gaseous hydrocarbons were 3–30 times those reported for the mainstream smoke emissions. These compounds constitute a potential health risk as they are metabolized *in vivo* to reactive genotoxic epoxides (Löfroth *et al*., 1987; Löfroth, 1989). High-molecular-weight *n*-alkanes (C_{27} [66–86.5 μg per cigarette], C_{29} [28–39 μg per cigarette] C_{31} [148–197 μg per cigarette], C_{33} [43.5–62 μg per cigarette]) were also quantified in the sidestream smoke of commercial cigarettes (Ramsey *et al.*, 1990).

The co-mutagenic beta-carbolines, norharman and harman, were quantified in the sidestream smoke condensates of some Japanese cigarette brands. The concentrations per cigarette were 4.1–9.0 μg for norharman and 2.1–3.0 μg for harman (Totsuka *et al.*, 1999).

1.2 Exposure

Exposure to secondhand smoke can take place in any of the environments where people spend time. A useful conceptual framework for considering exposure to secondhand smoke is offered by the microenvironmental model that describes personal exposure to secondhand smoke as the weighted sum of the concentrations of secondhand smoke in the microenvironments where time is spent and the weights supplied by the time spent in each (Jaakkola & Jaakkola, 1997). A microenvironment is a space, e.g. a room in a

dwelling or an office area, with a relatively uniform concentration of secondhand smoke during the time that is spent in that particular microenvironment. For research purposes and for considering health risks, personal exposure is the most relevant measure for evaluating and projecting risk (Samet & Yang, 2001).

Within the framework of the microenvironmental model, there are several useful indicators of exposure to secondhand smoke, ranging from surrogate indicators to direct measurements of exposure and of biomarkers that reflect dose (Table 1.6). One useful surrogate, and the only indicator available for many countries, is the prevalence rate of smoking among men and women. It provides at least a measure of likelihood of exposure. For the countries of Asia, for example, where smoking rates among men are very high and those among women are low, the prevalence data for men imply that most women are exposed to tobacco smoke at home (Samet & Yang, 2001).

The components of secondhand smoke include a number of irritating and odiferous gaseous components, such as aldehydes. Nonsmokers typically identify the odour of secondhand smoke as annoying, and the odour detection thresholds determined for secondhand smoke is at concentrations that are three or more orders of magnitude lower

Table 1.6. Indicators of exposure to secondhand tobacco smoke

Measure	Indicator
Surrogate measures	Prevalence of smoking in men and women
Indirect measures	Report of secondhand tobacco smoke exposure in the home and in the workplace
	Smoking in the household Number of smokers Smoking by parent(s) Number of cigarettes smoked
	Smoking in the workplace Presence of secondhand tobacco smoke Number of smokers
Direct measures	Concentration of secondhand tobacco smoke components Nicotine Respirable particles Other markers
	Biomarker concentrations Cotinine Carboxyhaemoglobin

From Samet & Yang (2001)

than the secondhand smoke concentrations measured in field settings and correspond to a fresh air dilution volume > 19 000 m^3 per cigarette (Junker *et al.*, 2001).

The indirect measures listed in Table 1.6 are generally obtained by questionnaires. These measures include self-reported exposure and descriptions of the source of secondhand smoke (e.g. smoking), in relevant microenvironments, most often the home and workplace. Self-reported exposure to secondhand smoke is a useful indicator of being exposed, although questionnaire-based reports of intensity of exposure are of uncertain validity. Questionnaires have been used to ascertain the prevalence of passive smoking; some of these have included questions directly related to the WHO definition of passive smoking: i.e. exposure for at least 15 minutes per day on more than 1 day per week (Samet & Yang, 2001).

Questionnaires have been used widely for research purposes to characterize smoking (the source of secondhand smoke) in the home and work environments. A simple mass-balance model gives the concentration of secondhand smoke as reflecting the rate of its generation, i.e., the number of smokers and of cigarettes smoked, the volume of the space into which the smoke is released, and the rate of smoke removal by either air exchange or air cleaning (Ott, 1999). Information on smoking can be collected readily by adults within the household (the source term), although reports of numbers of cigarettes smoked in the home are probably less valid than exposure predicted using the mass balance model. For workplace environments, smoking can be reported by co-workers, although the complexity of some workplace environments may preclude the determination of the numbers of smokers in the work area or the numbers of cigarettes smoked. The other determinants of secondhand smoke concentration, namely, room volume and air exchange are not readily determined by questionnaire and are assessed only for specific research purposes (Samet & Yang, 2001).

The direct measures of exposure to secondhand smoke include measurement of the concentrations of components of secondhand smoke in the air and of the levels of secondhand smoke biomarker in biological specimens. Using the microenvironmental model, researchers can estimate exposure to secondhand smoke by measuring the concentration of secondhand smoke in the home, workplace, or other environments and then combining the data on concentrations with information on the time spent in the microenvironments where exposure took place. For example, to estimate exposure to secondhand smoke in the home, the concentration of a marker in the air, e.g. nicotine, would be measured and the time spent in the home would be assessed, possibly using a time–activity diary in which information on all locations where time is spent is collected (Samet & Yang, 2001).

Because cigarette smoke is a complex mixture, exposure assessment depends on the choice of a suitable marker compound that is found in both mainstream smoke and secondhand tobacco smoke. No compound has a consistent ratio with all other components. Therefore, the choice of marker can affect the estimate of exposure.

The selection of a particular secondhand smoke component for monitoring is largely based on technological feasibility. Air can be sampled either actively, using a pump that passes air through a filter or a sorbent, or passively, using a badge that operates on the

principle of diffusion. A number of secondhand smoke components have been proposed as potential indicators; these include small particles in the respirable size range and the gases, nicotine, which is present in the vapour phase in secondhand smoke, and carbon monoxide. Other proposed indicators include more specific measures of particles and other gaseous components (Guerin et al., 1992; Jenkins & Counts, 1999). The most widely studied components have been respirable particles, which are sampled actively with a pump and filter, and nicotine, which can be collected using either active or passive sampling methods. The respirable particles in indoor air have sources other than active smoking and are nonspecific indicators of secondhand smoke; nicotine in air, by contrast, is highly specific because smoking is its only source (Jenkins *et al.*, 2000). Nicotine concentration can be measured readily using a passive filter badge, which is sufficiently small to be worn by a child or an adult or to be placed in a room (Hammond, 1999).

Biomarkers of exposure are compounds that can be measured in biological materials such as blood, urine or saliva. Cotinine, a metabolite of nicotine, is a highly specific indicator of exposure to secondhand smoke in nonsmokers (Benowitz, 1999). Some foods contain small amounts of nicotine, but for most persons cotinine level offers a highly specific and sensitive indicator of exposure to secondhand smoke (Benowitz, 1999). In nonsmokers, the half-life of cotinine is about 20 h; it therefore provides a measure of exposure to secondhand smoke over several days. It is an integrative measure that reflects exposure to secondhand smoke in all environments where time has been spent. Cotinine can be readily measured in blood, urine and even saliva with either radioimmunoassay or chromatography. New methods for analysis extend the sensitivity to extremely low levels (Benowitz, 1996; Benowitz, 1999). Alternatives to nicotine as a tobacco-specific marker substance are few. One such compound is 3-ethenylpyridine (also called 3-vinyl pyridine); it is a pyrolisis product of nicotine degradation during smoking present almost exclusively in the vapour phase of tobacco smoke. It has been employed to a small extent for measuring the concentrations of secondhand tobacco smoke in air (Heavner *et al.*, 1995; Hodgson *et al.*, 1996; Scherer *et al.*, 2000; Vainiotalo *et al.*, 2001), and a correlation between nicotine and 3-ethenylpyridine has been reported in some studies (Jenkins *et al.*, 1996; Moschandreas & Vuilleumier, 1999; Hyvärinen *et al.*, 2000). 3-Ethenylpyridine, solanesol and ultraviolet-absorbing particulate matter as markers of secondhand smoke have been suggested as being potentially better correlated with other constituents of secondhand smoke than nicotine and respirable particles (Hodgson *et al.*, 1996; Jenkins *et al.*, 1996). There are however many fewer data available on measurements using other tobacco-specific marker compounds than those based on air nicotine.

1.2.1 *Measurements of nicotine and particulate matter in indoor air*

The report of the US Environmental Protection Agency (US EPA, 1992) summarizes over 25 separate studies that reported concentrations of nicotine in air measured in more than 100 different indoor microenvironments. Hammond (1999) also reported an extensive survey of the concentrations of nicotine in air. Based on the large numbers of

measurements made in various indoor environments in the USA between 1957 and 1991, the average concentrations of nicotine in air showed about 100-fold variation, i.e. from 0.3–30 μg/m^3 (US EPA, 1992). The average concentrations in homes with one or more smokers typically ranged from 2 to 10 μg/m^3, with the highest averages being up to 14 μg/m^3. Data from the mid 1970s until 1991 indicate that the nicotine concentrations in offices were similar to those measured in homes, with a large overlap in the range of air concentrations for the two types of environment. The maximum levels of nicotine, however, were considerably higher in offices than in domestic environments (US EPA, 1992; California EPA, 1997). In studies using controlled and field conditions, the concentrations of nicotine in air were found to increase as a function of the number of smokers present and the number of cigarettes consumed (US EPA, 1992).

Jenkins *et al*. (1996) studied exposure to secondhand tobacco smoke in 16 cities in the USA by sampling personal breathing zone air from about 100 nonsmokers in each city. The demographics of the study subjects were comparable with the population of the USA in general, although more women than men participated in the study. The mean 24-h time-weighted average concentration of nicotine was 3.27 μg/m^3 for those exposed to secondhand tobacco smoke both at work and away from work, 1.41 μg/m^3 for those only exposed away from work and 0.69 μg/m^3 for those who were exposed only at work. The mean 24-h time-weighted average concentration of nicotine in air measured by personal monitoring, for those who were not exposed to secondhand tobacco smoke was 0.05 μg/m^3 (Jenkins *et al*., 1996).

Personal exposure to particulate matter associated with secondhand tobacco smoke was determined using the set of specific markers such as respirable suspended particles, fluorescent particulate matter and solanesol-particulate matter. The ranges of mean concentrations of these particles for workers exposed to secondhand smoke in 11 countries were: respirable suspended particles, from 24 to 112 μg/m^3; fluorescent particulate matter, from 5.7 to 57 μg/m^3; and solanesol-particulate matter, from 3.6 to 64 μg/m^3 (Jenkins *et al.*, 2000). By measuring the levels of solanesol-particulate matter and nicotine, the exposure to secondhand tobacco smoke of office workers living and working with smokers was determined to be higher in winter than in summer (median 24-h time-weighted average concentrations, 25 μg versus 2.4 μg solanesol-particulate matter and 1.3 μg versus 0.26 μg nicotine, respectively) (Phillips & Bentley, 2001).

1.2.2 *Population-based measurements of exposure*

Most population-based estimates of exposure to secondhand tobacco smoke have been obtained from self-reports. When measuring exposure to secondhand smoke in indoor areas, nicotine or respirable suspended particles can be measured in air sampled using personal monitors. In a few studies, biomarkers such as cotinine have been measured in physiological fluids.

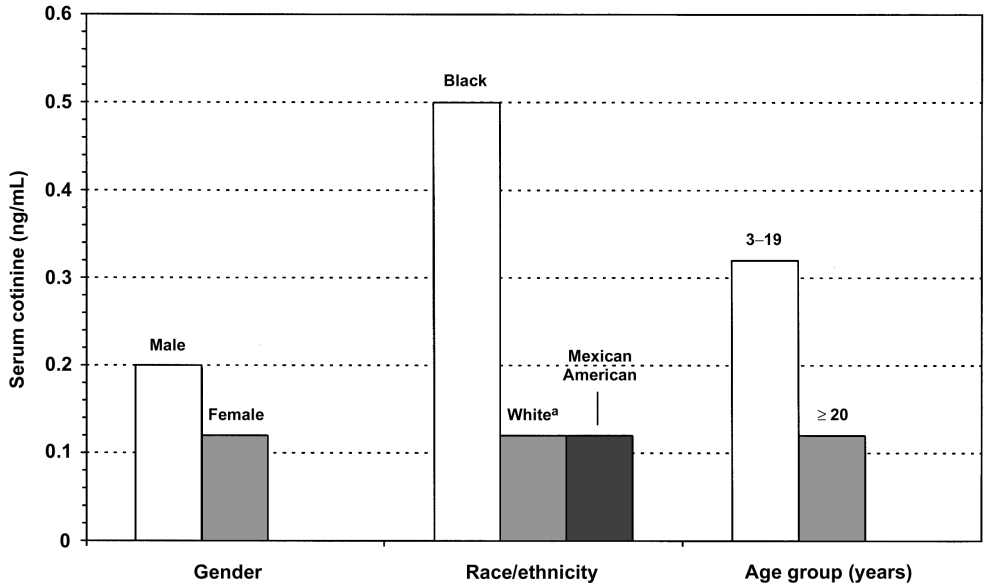
(*a*) *Adults*

Some studies suggest that exposure to secondhand tobacco smoke is related to occupation and socioeconomic status, and that higher exposure is more common among adults employed in blue-collar jobs, service occupations and poorly paid jobs and among the less well educated (Gerlach *et al*., 1997; Curtin *et al*., 1998; Whitlock *et al*., 1998). Exposure to secondhand tobacco smoke may also be higher among racial and ethnic minority groups in areas of the USA, although it is unclear if this is due to different socioeconomic status (Gerlach *et al.*, 1997).

Relatively few data are available on the prevalence of nonsmokers' exposure to secondhand tobacco smoke on a population basis, using biomarkers. Survey data from a study in the USA in 1988–91 showed that 37% of adult non-tobacco users lived in a home with at least one smoker or reported exposure to secondhand tobacco smoke at work, whereas serum cotinine levels indicated more widespread exposure to nicotine. Of all the non-tobacco users surveyed including children, 88% had detectable serum cotinine levels, indicating widespread exposure to secondhand tobacco smoke in residents of the USA (Pirkle *et al.*, 1996). Data were recently published on the serum cotinine levels measured in 2263 nonsmokers in 12 locations across the USA (Figure 1.1) (CDC, 2001). As reported previously (Pirkle *et al.*, 1996), exposure to secondhand tobacco smoke tended to be higher among men than among women. Among racial/ethnic groups, blacks had the highest cotinine levels. People younger than 20 years of age had higher cotinine levels than those aged 20 years and older.

Table 1.7 summarizes the data obtained from a number of recent population-based studies that used questionnaires to characterize exposure. Some of these studies were national in scope, e.g. the national samples in Australia, China and the USA, whereas others were from single states or specific localities. Several of the studies incorporated cotinine as a biomarker. Unfortunately, few data are available from developing countries (Samet & Yang, 2001). In a case–control study of lung cancer and exposure to secondhand smoke in 12 centres from seven European countries, 1542 control subjects up to 74 years of age were interviewed between 1988 and 1994 about their exposure to secondhand smoke. Exposure of adults to secondhand smoke from a spouse who smoked was reported by 45% of the subjects (including 2% who were exposed to smoke from cigars or pipes only); an additional 8% were not exposed to spousal smoke, but reported exposure to secondhand smoke produced by cohabitants other than spouses. Exposure to secondhand smoke in the workplace was reported by 71% of men and 46% of women. Combined exposure to secondhand smoke both from the spouse and at the workplace was reported by 78%. Exposure to secondhand smoke in vehicles was reported by 20% and exposure in public indoor settings such as restaurants was reported by 29% (Boffetta *et al.*, 1998). Recent data from Finland illustrate trends in self-reported exposure to secondhand tobacco smoke at work and at home over a 15-year period. In 1985, 25% of employed nonsmoking men and 15% of employed nonsmoking women were exposed to

Figure 1.1. 75th percentile of serum cotinine concentrations for the US nonsmoking population aged 3 years and older, National Health and Nutrition Examination Survey, 1999



From CDC (2001)
[a] Includes other racial/ethnic groups

secondhand tobacco smoke at work. In contrast, the figures for exposure to secondhand smoke in 2000 were 8% of men and 4% of women (Jousilahti & Helakorpi, 2002).

In a 1993 review of existing studies, Siegel (1993) noted wide variation in the concentrations of secondhand tobacco smoke by location when measured by weighted mean levels of nicotine in the ambient air of offices (4.1 μg/m^3), restaurants (6.5 μg/m^3), bars (19.7 μg/m^3) and dwellings with at least one smoker (4.3 μg/m^3).

The recently published study in the USA of the median serum cotinine concentration measured in nonsmokers aged 3 years and older found a 75% decrease over the period 1991–99 (CDC, 2001), suggesting positive effects of policies for cleaner indoor air.

(*b*) *Children*

Because the home is a predominant location for smoking, children are exposed to tobacco smoke as they go about their daily lives, i.e. while eating, playing and even sleeping. The exposure at home may be added to exposure at school and in vehicles. Consequently, in many countries, children cannot avoid inhaling tobacco smoke (Samet & Yang, 2001).

Table 1.7. Prevalence of exposure to secondhand tobacco smoke — population-based studies

Reference	Study design and population	Results
Europe		
Somerville *et al.* (1988)	Cross-sectional study; 4337 children aged 5–11 years in England and 766 in Scotland, from the 1982 National Health Interview Survey on Child Health in the United Kingdom	Prevalence = 42% in England and 60% in Scotland
Dijkstra *et al.* (1990)	Cohort study; nonsmoking children aged 6–12 years over a 2-year period, in the Netherlands	Prevalence = 66%
Jaakkola *et al.* (1994)	Population-based cross-sectional study; random sample of 1003 children aged 1–6 years in Espoo, Finland	25.2% reported exposure to secondhand tobacco smoke at home; 74.8% of children did not, assessed by parent-completed questionnaire.
Brenner *et al.* (1997)	Cross-sectional study; survey of 974 predominantly blue-collar employees of a south German metal company	> 60% of nonsmoking blue collar workers reported being exposed to secondhand smoke at work; 52% of nonsmoking white collar workers exposed if smoking allowed in immediate work area, and 18% if smoking not allowed
Boffetta *et al.* (1998)	Case–control study of lung cancer and exposure to secondhand tobacco smoke in 12 centres from seven European countries, 1542 control subjects up to 74 years of age were interviewed between 1988 and 1994 about exposure to secondhand tobacco smoke	Prevalence during childhood was 66%. Prevalence in adulthood (spousal smoke) was 45% (including 2% with exposure to cigar or pipe smoke only). In addition, 8% who were not exposed to spousal smoke were exposed to secondhand tobacco smoke produced by cohabitants other than spouse. Prevalence in the workplace was 71% among men and 46% among women. Combined prevalence from the spouse and at the workplace was 78%. Prevalence of exposure to secondhand tobacco smoke in vehicles was 20% and in public indoor settings such as restaurants, it was 29%.

Table 1.7 (contd)

Reference	Study design and population	Results
Lund *et al.* (1998)	Children born in 1992; descriptive study of exposure to secondhand tobacco smoke at home in 3547 households in Denmark, Finland, Iceland, Norway and Sweden in 1995–96	Prevalence of weekly exposure was 47% in Denmark, 7% in Finland, 46% in Iceland, 32% in Norway and 15% in Sweden.
Jousilahti & Helakorpi (2002)	A cohort of 58 721 men and women aged 15 to 64 years was followed-up by annual questionnaires on exposure to secondhand smoke at work and at home between 1985 and 2000 in Finland.	In the middle of the 1980s, about a quarter of employed nonsmoking men and 15% of nonsmoking women were exposed for at least 1 hour daily to environmental tobacco smoke at work. In 2000, the proportions were 7.9% and 4.4%, respectively. Exposure to environmental tobacco smoke at home also decreased slightly. In 2000, 14.3% of the nonsmoking men and 13% of the nonsmoking women aged 15 to 64 years were exposed to secondhand smoke either at work or at home.
America		
Coultas *et al.* (1987)	Cross-sectional study; 2029 Hispanic children and adults in New Mexico (1360 nonsmokers and ex-smokers also had salivary cotinine measured)	Prevalence = 39% ≥ 18 years; 48%, 13–17 years; 45%, 6–12 years, and 54% < 5 years. Mean salivary cotinine concentrations = 0 to 6 ng/mL; 35% of members of nonsmoking households had detectable levels of cotinine.
Greenberg *et al.* (1989)	Questionnaire-based cross-sectional study; mothers of 433 infants from a representative population of healthy neonates from 1986–87 in North Carolina	55% lived in a household with at least one smoker; 42% of infants had been exposed during the week preceding data collection; cotinine was detected in 60% of urine samples (median = 121 ng/mg creatinine).
Chilmonczyk *et al.* (1990)	Cross-sectional study; 518 infants aged 6–8 weeks receiving well-child care in the offices of private physicians in greater Portland, Maine	91% of infants living in households where only the mother smoked (43 households) had urinary cotinine levels ≥ 10 µg/L; 8% of infants living in households where no smoking was reported (305 households) had urinary cotinine levels ≥ 10 µg/L.

Table 1.7 (contd)

Reference	Study design and population	Results
Overpeck & Moss (1991)	Cross-sectional study; sample of 5356 children ≤ 5 years of age from the National Health Interview Survey in 1988	Approximately 50% of all US children ≤ 5 years of age exposed to prenatal maternal smoking and/or secondhand smoke from household members after birth; 28% were exposed both prenatally and postnatally, 21% only after birth and 1.2% only prenatally.
Borland *et al.* (1992)	Cross-sectional study; sample of 7301 nonsmokers from the larger study of Burns & Pierce (1992)	31.3% of nonsmoking workers reported exposure at work ≥ 1 time in the preceding 2 weeks; 35.8% males vs 22.9% females; 41.9% < 25 years vs 26.4% for older workers; 43.1% with < 12 years of education vs 18.6% with ≥ 16 years of college education
Burns & Pierce (1992)	Cross-sectional study; head of household in 32 135 homes in California, contacted by stratified random-digit dialling from June 1990 to July 1991	32.2% of children aged 5–11 years and 36.5% of adolescents aged 12–17 years were exposed at home.
Jenkins *et al.* (1992)	Cross-sectional study; telephone interviews with 1579 English-speaking adults and 183 adolescents (12–17 years of age) from October 1987 to September 1988 in California	46% of nonsmokers were exposed during the day: 43% of adult nonsmokers and 64% of adolescent nonsmokers. Exposure most frequently occurred at home, in restaurants or in cars. The average duration of exposure was longest in workplaces.
Jenkins *et al.* (1992); Lum (1994)	Cross-sectional study; same population as described above and additional 1200 children aged ≤ 11 years (< 8 years old with a parent or guardian) from April 1989 to February 1990 in California	Prevalence of exposure among smokers and nonsmokers = 61% for adults and 70% for adolescents during the day; 35% to 45% of children, infants, and preschoolers were reported to be exposed to secondhand smoke; average duration = 3.5 h.
Pierce *et al.* (1994)	Cross-sectional study; using the California Adult Tobacco Surveys in 1990, 1992 and 1993 with 8224 to 30 716 adults 18 years and older and 1789 to 5531 teenagers 12–17 years of age interviewed	15.1% smoked prior to pregnancy and of these, 37.5% quit after the pregnancy (between 1988 and 1992, 9.4% of women smoked during pregnancy).

Table 1.7 (contd)

Reference	Study design and population	Results
Pletsch (1994)	Cross-sectional study; 4256 Hispanic women aged 12–49 years who participated in the Hispanic Health and Nutrition Examination Survey (HHANES) from 1982 to 1984	Age-specific household exposure for nonsmokers was 31%–62% for Mexican-Americans, 22%–59% for Puerto Ricans and 40%–53% for Cuban-Americans; 59% of Puerto Rican and 62% of Cuban-American adolescents had high levels of exposure.
Thompson *et al.* (1995)	Cross-sectional study; 20 801 US employees from 114 work sites	52.4% of respondents reported being exposed to secondhand tobacco smoke at work
Kurtz *et al.* (1996)	Questionnaire-based cross-sectional survey; sample of 675 African-American students enrolled in grades 5–12 in an urban public school district in Detroit, Michigan	Smoking rates were higher among students with parents who smoked; 48% reported paternal smoking; 46% reported maternal smoking.
Mannino *et al.* (1996)	17 448 children aged 1–10 years from 1991 US National Health Interview Survey	41% of children with lower socioeconomic status experienced daily exposure at home; 21% of children with higher socioeconomic status experienced daily exposure at home.
Pirkle *et al.* (1996)	Cross-sectional study; 9744 adults aged 17 years or older from the NHANES III Study, 1988–91	Prevalence for males was 43.5% and for females, 32.9%; 87.9% had detectable serum cotinine levels.
Stamatakis *et al.* (2002)	Cross-sectional study of ethnically diverse non-smoking women, aged 40 years and older, across the United States (n = 2326)	Exposure to secondhand tobacco smoke at home was associated with being American Indian/Alaska Native (aOR, 1.5; 95% CI, 1.0–2.6). Compared with college graduates, exposure to secondhand tobacco smoke at work was higher among women with some high school education (aOR, 2.8; 95% CI, 1.5–5.3) and high school graduates (aOR, 3.1; 95% CI, 1.9–5.1) and substantially higher for women who worked where smoking was allowed in some (aOR, 15.1; 95% CI, 10.2–22.4) or all (aOR, 44.8; 95% CI, 19.6–102.4) work areas.

Table 1.7 (contd)

Reference	Study design and population	Results
Asia		
Lam *et al.* (1998)	Questionnaire-based cross-sectional study; sample of 6304 students aged 12–15 years, from 172 classes of 61 schools in Hong Kong	53.1% were living in a household with at least one smoker; 35.2% had only one smoker; 9.5% had two and 2.5% had three or more smokers in the household; 38% of fathers and 3.5% of mothers smoked.
Yang *et al.* (1999)	Cross-sectional study; 120 298 records (63 793 males and 56 020 females) of persons aged 15–69 years from the 1996 National Prevalence Survey of Smoking in China	Of the nonsmoking respondents, 53.5% reported passive exposure to smoke. Over 60% of female nonsmokers between ages 25 and 50 years were passively exposed to tobacco smoke; 71% of participants reported exposure to smoke at home, 32% in public places and 25% in their workplace.
Africa		
Steyn *et al.* (1997)	Questionnaire-based cross-sectional study; 394 pregnant women attending antenatal services in Johannesburg, Cape Town, Port Elizabeth and Durban in urban South Africa, 1992	Most women who smoked stopped or reduced tobacco use during their pregnancy; 70% lived with at least one smoker in the house.
Australia and New Zealand		
Sherrill *et al.* (1992)	Cohort study; 634 children aged 9–15 years; New Zealand	Overall prevalence = 40%
Lister & Jorm (1998)	Cross-sectional study; data from the Australian Bureau of Statistics 1989–90 National Health Survey of parents and their children (n = 4281) aged 0–4 years; Australia	45% of children lived in households with ≥ 1 current smoker; 29% had a mother who smoked.

Modified from Samet & Yang (2001)
aOR, adjusted odds ratio for sociodemographic characteristics (race, age, education, location and having children in the home), health risk behaviours, and the type of smoking policy in the workplace

Data on the exposure of children to secondhand tobacco smoke are limited. In perhaps the most comprehensive cross-sectional study to date, researchers examined exposure to secondhand tobacco smoke in 17 448 children aged 1–10 years in the USA. Exposure varied considerably according to socioeconomic status: 41% of children of lower socioeconomic status experienced daily exposure to secondhand tobacco smoke in their home, whereas only 21% of children of higher socioeconomic status were exposed daily. Exposure to secondhand tobacco smoke did not vary by race, family size, gender or season (Mannino *et al*., 1996). In a multicentre study conducted in 1988–94 in seven European countries, exposure to secondhand smoke in childhood was reported by 66% of respondents (Boffetta *et al*., 1998). Parent-reported exposure to secondhand tobacco smoke among children varied widely across the countries of Denmark, Finland, Iceland, Norway and Sweden (Lund *et al*., 1998). For example, Finnish parents were more likely than all other Nordic parents to protect their children from secondhand tobacco smoke. Exposure was highest in Denmark and Iceland, where children were exposed in almost half of all households and in nine of ten households with daily smokers. The lack of common metrics for measuring exposure to secondhand tobacco smoke in children is a significant challenge when comparing data between countries.

1.3 Regulations

1.3.1 *Policy options*

There are a range of options available for the regulation of secondhand tobacco smoke. Of these options, the least effective is designating smoking areas that have no separate ventilation. This option provides only minimal protection to nonsmokers; studies have shown that substantial exposure to secondhand tobacco smoke occurs in workplaces where there are smoking areas without separate ventilation (Repace, 1994). A more effective option is the use of separately ventilated smoking lounges; this protects non-smokers but is costly and may elevate lung cancer risk in smokers (Siegel *et al*., 1995). Separately ventilated smoking lounges also endanger workers (e.g. waiting staff) who must enter these areas as part of their job. Finally, the most effective alternative is a totally smoke-free workplace (Brownson *et al*., 2002).

1.3.2 *Prevalence of regulations*

In 1985, only about 38% of workers in the USA were employed by firms that had policies restricting smoking (Farrelly *et al*., 1999). Since that time, smoking restrictions have become increasingly common. According to the 1999 National Worksite Health Promotion Survey, 79% of workplaces with 50 or more employees had formal smoking policies that prohibited smoking or allowed it only in separately ventilated areas (US Department of Health and Human Services, 2000). Data showed that, from 1995–96, 64% of indoor workers in the USA were covered by a total ban on smoking in the workplace.

The proportion of workers in the USA who work in a smoke-free workplace varies considerably by state — from 84% in Maryland and Utah to 40% in Nevada (Burns *et al*., 2000). There are few systematic data available on the enforcement of existing policies to restrict smoking in the workplace, although existing studies suggest that compliance is likely to be high (Stillman *et al*., 1990; Wakefield *et al.*, 1996). National data from the USA also suggest that despite some protective laws, workers in blue-collar and service occupations remain much more likely to be exposed to secondhand tobacco smoke in the workplace than other categories of workers (Gerlach *et al*., 1997). In the USA, hospitals are the only sector that has voluntarily implemented a nationwide smoking ban. This ban was announced in November 1991 and full implementation was required by December 31, 1993. Two years after implementation, the policy was found to have been successful with 96% of hospitals complying with the smoking ban standard (Longo *et al.*, 1995; Brownson *et al.*, 2002).

A recent overview of the legislation restricting smoking at work in different countries has been provided by the American Cancer Society (Corrao *et al*., 2000) (Table 1.8). Despite using a wide range of already published sources together with Internet searches, no information could be found for many countries. Thus, absence of an entry in this Table does not imply certainty that no legislation exists in a particular country. Conversely, the existence of a law banning or restricting smoking implies nothing about its enforcement. In general, it appears that voluntary restrictions under control of the employer are more common in developing countries than in developed countries (Brownson *et al.*, 2002). A country that relies on voluntary action to ban or restrict smoking may have quite high rates of worker protection. For example, although Australia banned smoking in all federal government workplaces in 1988, it has been left to individual employers to determine their own policies. Yet, in 1999, 71% of indoor workers in the state of Victoria reported a total ban on smoking at their workplace, 21% reported some restrictions on smoking and 8% reported unrestricted smoking (Letcher & Borland, 2000). As in other countries, employees in small Australian workplaces are less likely to report protection, as are workers in particular types of employment (Wakefield *et al.*, 1996; McMaugh & Rissell, 2000). In a survey of indoor workers, 38% of those employed in a restaurant or hotel, 15% of warehouse/store workers and 17% of those working in a workshop or factory reported unrestricted smoking where they worked, compared with only 3% of workers in open-plan offices (Letcher & Borland, 2000). In the United Kingdom, workplace restrictions are also voluntary. In 1997, 40% of the workforce was estimated to be working in a totally smoke-free environment (Freeth, 1998). A survey of 1500 workplaces in Scotland found that 79% of them had designated nonsmoking areas, but only 22% had banned smoking completely (ASH, 2001). Despite the limitations of the data presented in Table 1.9, it is apparent that most countries have some laws that restrict smoking. However, it is very likely that there is considerable need for improvement in protection of workers from secondhand tobacco smoke in almost all countries (Brownson *et al.*, 2002).

A few researchers have begun to examine the prevalence of smoking restrictions in the home because such restrictions are likely to have beneficial effects on the health of

Table 1.8. Variations in workplace smoking policies in selected countries

Country	Type of policy[a]				Comments
	B	R	V	X	
Africa					
Benin	x				Certain workplaces only
Botswana	x				Areas accessible to public, common areas
Mali	x				Public service offices
Nigeria	x				Offices
South Africa	x				Designated smoking areas
Uganda			x		
Tanzania			x		
Zambia	x				
Americas					
Argentina		x			
Barbados			x		
Belize			x		Some private workplaces
Brazil			x		
Canada	x				
Chile	x				Areas accessible to public
Costa Rica	x				
Cuba			x		
Dominican Republic	x				Offices
Ecuador	x				Working areas
El Salvador		x			
Grenada			x		
Guatemala	x				Areas accessible to the public
Honduras	x				
Mexico	x				Working areas
Panama	x				Areas accessible to public
Peru	x				
Trinidad and Tobago			x		
United States				x	State and local levels
Venezuela		x			
Eastern Mediterranean					
Cyprus	x				Private and public
Egypt	x				Enclosed public places
Iran	x				Areas accessible to public
Iraq		x			Administrative measures
Kuwait			x		
Lebanon			x		Upon request by nonsmokers
Morocco	x				Public administration and service offices
Sudan	x				Areas accessible to public
Syria	x				

Table 1.8 (contd)

Country	Type of policy[a]				Comments
	B	R	V	X	
Tunisia			x		
Europe					
Austria	x				Unless appropriate ventilation exists
Belarus		x			
Belgium	x		x		Areas accessible to public and other areas
Bosnia & Herzegovina		x			
Bulgaria	x				Unless nonsmokers give written permission for smoking
Croatia	x				
Czech Republic	x				During work hours when nonsmokers are present
Denmark	x				Voluntary restrictions in private workplaces
Estonia	x				Labour environments
Finland	x				Designated smoking areas
France	x				Except individual offices
Germany			x		
Greece		x			
Hungary	x				Areas accessible to public
Iceland	x				Areas accessible to public
Ireland	x				Areas accessible to public
Israel	x				Except in designated areas
Krygyzstan			x		
Latvia		x			
Lithuania	x				Enclosed areas
Netherlands		x			Public and private
Norway	x				With 2 or more employees
Poland	x				
Portugal		x			
Moldova	x				
Romania			x		
Russia	x				
San Marino	x				
Slovakia		x			
Slovenia		x			
Spain		x			
Sweden		x			
Switzerland		x			
Turkey	x				With 5 or more employees
Ukraine	x				
United Kingdom			x		

Table 1.8 (contd)

Country	Type of policy[a]				Comments
	B	R	V	X	
South-East Asia					
Bangladesh			x		
India		x			
Nepal		x			
Sri Lanka			x		Administrative measures
Thailand	x				
Western Pacific					
Australia			x		
Cambodia	x				Partial ban
China	x				Administrative measures
Cook Islands		x			
Fiji			x		
Japan			x		Guideline, set by Ministry of Labour
Kiribati			x		
Lao People's Democratic Republic			x		
Malaysia	x				Areas accessible to the public
Micronesia		x			
Mongolia	x				Designated smoking areas
New Zealand	x				Common work areas and public areas
Niue			x		
Philippines	x				
Republic of Korea		x			
Samoa			x		
Solomon Islands		x			
Tokelau		x			
Tonga			x		

Brownson *et al.* (2002); adapted from Corrao *et al*. (2000); number of additional countries for which no information is available: Africa = 38; Americas = 15; Eastern Mediterranean = 13; Europe = 15; South-East Asia = 5; Western Pacific = 11.

[a] B, smoking is prohibited in workplaces according to national legislation and/or regulations; facilities with a designated smoking area are included in this category if nonsmoking areas must always remain uncontaminated by smoke; R, smoking is restricted, but not prohibited, in workplaces according to national legislation and/or regulations; V, employers voluntarily prohibit or restrict smoking in areas under their management; X, different state and county laws apply.

Table 1.9. Summary of selected studies on the effects of workplace smoking bans and restrictions on exposure to secondhand tobacco smoke

Reference/location	Industry/setting	Sample size	Outcome(s) studied/size of effect[a]
Millar (1988)/ Ontario, Canada	Department of Health and Welfare	4200 (12 locations)	Change in mean respirable suspended particulates = –6 μg/m^3 to –22 μg/m^3 (depending on the storey of the building)
Becker *et al.* (1989)/ Maryland, USA	Children's hospital	951 (9 locations)	Change in average nicotine vapour concentrations = –12.53 μg/m^3 to + 0.08 μg/m^3 (depending on the location)
Biener *et al*. (1989)/ Rhode Island, USA	Hospital	535	Percentage of workers 'bothered' by secondhand smoke in various workplace locations: offices = –20%; lounges = –20%
Gottlieb *et al*. (1990)/Texas, USA	Government agency	1158	Percentage of workers 'never bothered' by secondhand smoke = + 38.8%
Mullooly *et al*. (1990)/Oregon, USA	Health maintenance organization	13 736 1985: pre-ban 764 post-ban 1027 1986: pre-ban 1352 post-ban 1219	Presence of smoke in workplace = –21% (1985 sites); –35% (1986 sites)
Stillman *et al*. (1990)/Maryland, USA	Medical centre	8742 (7 locations)	Change in average 7-day nicotine vapour concentrations = –7.71 μg/m^3 to –0.72 μg/m^3 (depending on the location)
Borland *et al*. (1992)/ California, USA	Indoor workers in California	7301	Percentage of employees exposed to secondhand smoke at work = –42.1% between no policy and smoke-free policy
Broder *et al*. (1993)/ Toronto, Canada	Public sector workplaces	179 (3 buildings; 8–12 samples per floor)	Change in the mean measurements (for several secondhand smoke components) Volatile organic compounds = –0.7 mg/m^3
Patten *et al*. (1995)/California, USA	Statewide workers	8580 (at baseline survey)	Percentage of employees exposed to secondhand smoke at work = –56.3% difference between work area ban and no ban

Table 1.9 (contd)

Reference/location	Industry/setting	Sample size	Outcome(s) studied/size of effect[a]
Etter *et al*. (1999)/ Geneva, Switzerland	University	2908	Exposure to secondhand smoke (score 0–100; 'not at all' (0) to 'very much' (100)) = –4% (follow-up compared to baseline)

Brownson *et al.* (2002); modified from Hopkins *et al.* (2001)
[a] Values noted are absolute differences from baseline.

children. In 1997, a population-based, cross-sectional telephone survey was conducted using random-digit-dialling asking 6199 adult Oregonians to provide baseline data on tobacco use in Oregon. Seventy per cent of the households were composed of nonsmokers only, and 85% of those had a full ban on smoking inside the home. Of the households containing one or more smokers, 38% had a full household ban on smoking. Fifty per cent of households with at least a smoker and a child present did not have a full ban on indoor smoking (Pizacani *et al.*, 2003). Face-to-face interviews were conducted with 380 rural, low-income Native American and white parents of children aged 1–6 years in Oklahoma. The prevalence of complete smoking bans was 49% in Native American homes and 43% in white homes. Bans on smoking in cars were less common, with 35% of Native American and 40% of white caregivers reporting complete bans (Kegler & Malcoe, 2002). In Victoria, Australia, the percentage of respondents who reported discouraging visitors from smoking in the home rose from 27% in 1989 to 53% in 1997 (Borland *et al*., 1999), and not smoking in the presence of children rose from 14% in 1989 to 33% in 1996. Similarly, attitudes toward smoking in the home have changed in Ontario, Canada. The percentage of respondents favouring not smoking in homes where there were children increased from 51% in 1992 to 70% in 1996 (Ashley *et al*., 1998).

Only minimal regulation applies to constituents of cigarettes and tobacco smoke. This covers only the content of tar, nicotine and carbon monoxide (cf. Section 1.4(*e*) of the monograph on tobacco smoke).

1.3.3 *Effectiveness of regulations*

Evaluations of the effects and effectiveness of workplace smoking policies have used a wide variety of study designs and measurements of exposure to secondhand tobacco smoke and tobacco use behaviours. Most of the published studies are simple assessments conducted before and after adoption of a workplace policy, although more recent (and more complex) investigations have employed cross-sectional surveys of workers in work-places operating different policies. Few studies have evaluated or controlled for potential bias and confounding of the observed differences or changes in exposure to secondhand smoke or in tobacco use behaviours (Brownson *et al.*, 2002).

The effectiveness of workplace smoking policies has been measured by differences or changes in perceived air quality in the workplace following a ban or restriction, and by differences or changes in active measurements of nicotine vapour concentrations, metabolites, or levels of particles. Overall, workplace smoking policies have been highly effective in reducing the exposure of nonsmokers to secondhand tobacco smoke. The 'best evidence subset' comprised ten studies, including cross-sectional surveys, before-and-after comparisons, different settings or locations (offices, public sector workplaces, medical centres, workplaces community-wide) and different outcome measurements (Table 1.9) (Briss *et al*., 2000; Hopkins *et al*., 2001). In nine of ten studies, workplace smoking policies had a significant impact on exposure to secondhand tobacco smoke. In assessments conducted between 4 and 18 months after implementation of the policy, the median relative percentage difference in self-reported exposure to secondhand tobacco smoke was –60%, range +4% to –97%. Workplaces with smoking bans tended to show greater reduction in exposure to secondhand tobacco smoke than did workplaces with smoking restrictions (Hopkins *et al*., 2001; Brownson *et al*., 2002).

Hammond (1999) summarized the existing literature on average indoor nicotine concentrations when various workplace smoking policies were enacted. In workplaces with policies that had banned smoking, nicotine concentrations were generally decreased to less than 1 $\mu g/m^3$. The mean concentrations of nicotine in workplaces that allowed smoking ranged from 2 to 6 $\mu g/m^3$ in offices, 3 to 8 $\mu g/m^3$ in restaurants and from 1 to 6 $\mu g/m^3$ in the workplaces of blue-collar workers. By comparison, studies of nicotine concentrations that included at least 10 homes of smokers and that were sampled for 14 h to 1 week found average nicotine concentrations of between 1 and 6 $\mu g/m^3$.

References

Adams, J.D., O'Mara-Adams, K.J. & Hoffmann, D. (1987) Toxic and carcinogenic agents in undiluted mainstream smoke and sidestream smoke of different types of cigarettes. *Carcinogenesis*, **8**, 729–731

Adlkofer, F., Scherer, G., Conze, C., Angerer, J. & Lehnert, G. (1990) Significance of exposure to benzene and other toxic compounds through environmental tobacco smoke. *J. Cancer Res. clin. Oncol*., **116**, 591–598

ASH (Action on Smoking and Health) (2001) Smoking in the workplace. ASH, National Asthma Campaign and Trade Union Congress. WHO-Europe Partnership Project, Copenhagen [http://www.ash.org.uk/html/workplace/html/workplace.html]

Ashley, M.J., Cohen, J., Ferrence, R., Bull, S., Bondy, S., Poland, B. & Pederson, L. (1998) Smoking in the home: Changing attitudes and current practices. *Am. J. public Health*, **88**, 797–800

Baker, R.R. & Proctor, C.J. (1990) The origins and properties of environmental tobacco smoke. *Environ. int.*, **16**, 231–245

Becker, D.M., Conner, H.F., Waranch, H.R., Stillman, F., Pennington, L., Lees, P.S. & Oski, F. (1989) The impact of a total ban on smoking in the Johns Hopkins Children's Center. *J. Am. med. Assoc*, **262**, 799–802

Benowitz, N.L. (1996) Cotinine as a biomarker of environmental tobacco smoke exposure. *Epidemiol. Rev.*, **18**, 188–204

Benowitz, N.L. (1999) Biomarkers of environmental tobacco smoke exposure. *Environ. Health Perspect.*, **107** (Suppl. 2), 349–355

Biener, L., Abrams, D.B., Follick, M.J. & Dean, L. (1989) A comparative evaluation of a restrictive smoking policy in a general hospital. *Am. J. public Health*, **79**, 192–195

Boffetta, P., Agudo, A., Ahrens, W., Benhamou, E., Benhamou, S., Darby, S.C., Ferro, G., Fortes, C., Gonzalez, C.A., Jöckel, K.H., Krauss, M., Kreienbrock, L., Kreuzer, M., Mendes, A., Merletti, F., Nyberg, F., Pershagen, G., Pohlabeln, H., Riboli, E., Schmid, G., Simonato, L., Trédaniel, J., Whitley, E., Wichmann, H.E., Winck, C., Zambon, P. & Saracci, R. (1998) Multicenter case–control study of exposure to environmental tobacco smoke and lung cancer in Europe. *J. natl Cancer Inst.*, **90**, 1440–1450

Bombick, B.R., Avalos, J.T., Nelson, P.R., Conrad, F.W. & Doolittle, D.J. (1998) Comparative studies of the mutagenicity of environmental tobacco smoke from cigarettes that burn or primarily heat tobacco. *Environ. Mol. Mutag*., **31**, 169–175

Borgerding, M.F., Bodnar, J.A. & Wingate, D.E. (2000) *The 1999 Massachusetts Benchmark Study. Final Report. A Research Study Conducted after Consultation with the Massachusetts Department of Public Health*, Department of Health, Massachusetts

Borland, R., Pierce, J.P., Burns, D.M., Gilpin, E., Johnson, M. & Bal, D. (1992) Protection from environmental tobacco smoke in California. The case for a smoke-free workplace. *J. Am. med. Assoc.*, **268**, 749–752

Borland, R., Mullins, R., Trotter, L. & White, V. (1999) Trends in environmental tobacco smoke restrictions in the home in Victoria, Australia. *Tob. Control*, **8**, 266–271

Brenner, H., Born, J., Novak, P. & Wanek, V. (1997) Smoking behavior and attitude toward smoking regulations and passive smoking in the workplace. A study among 974 employees in the German metal industry. *Prev. Med.*, **26**, 138–143

Briss, P.A., Zaza, S., Pappaioanou, M., Fielding, J., Wright-De Aguero, L., Truman, B.I., Hopkins, D.P., Mullen, P.D., Thompson, R.S., Woolf, S.H., Carande-Kulis, V.G., Anderson, L., Hinman, A.R., McQueen, D.V., Teutsch, S.M., Harris, J.R. & The Task Force on Community Preventive Services (2000) Developing an evidence-based Guide to Community Preventive Services — Methods. *Am. J. prev. Med.*, **18**, 35–43

Broder, I., Pilger, C. & Corey, P. (1993) Environment and well-being before and following smoking ban in office buildings. *Can. J. public Health*, **84**, 254–258

Brownson, R.C., Hopkins, D.P. & Wakefield, M.A. (2002) Effects of smoking restrictions in the workplace. *Ann. Rev. public Health*, **23**, 333–348

Brunnemann, K.D., Kagan, M.R., Cox, J.E. & Hoffmann, D. (1990) Analysis of 1,3-butadiene and other selected gas-phase components in cigarette mainstream and sidestream smoke by gas chromatography–mass selective detection. *Carcinogenesis*, **11**, 1863–1868

Brunnemann, K.D., Cox, J.E. & Hoffmann, D. (1992) Analysis of tobacco-specific N-nitrosamines in indoor air. *Carcinogenesis*, **13**, 2415–2418

Burns, D. & Pierce, J.P. (1992) *Tobacco Use in California 1990–1991*, Sacramento, CA, California Department of Health Services

Burns, D.M., Shanks, T.G., Major, J.M., Gower, K.B. & Shopland, D.R. (2000) Restrictions on smoking in the workplace. In: *Population Based Smoking Cessation, Proceedings of a Conference on what Works to Influence Cessation in the General Population. Smoking and Tobacco*

Control Monograph No. 12, Bethesda, MD, US Department of Health and Human Services, National Institutes of Health, National Cancer Institute (NIH Pub. No. 00-4892), pp. 99–128

CDC (Centers for Disease Control and Prevention) (2001) *National Report on Human Exposure to Environmental Chemicals*, Atlanta, GA

California EPA (California Environmental Protection Agency) (1997) *Health Effects of Exposure to Environmental Tobacco Smoke, Final Report,* California Environmental Protection Agency, Office of Environmental Health Hazard Assessment

Chilmonczyk, B.A., Knight, G.J., Palomaki, G.E., Pulkkinen, A.J., Williams, J. & Haddow, J.E. (1990) Environmental tobacco smoke exposure during infancy. *Am. J. Public Health*, **80**, 1205–1208

Chortyk, O.T. & Schlotzhauer, W.W. (1989) The contribution of low-tar cigarettes to environmental tobacco smoke. *J. anal. Toxicol.*, **13**, 129–134

Corrao, M.A., Guindon, G.E., Sharma, N. & Shokoohi, D.F., eds (2000) *Tobacco Control Country Profiles*, Atlanta, GA, American Cancer Society [http://www.cancer.org/eprise/main/docroot/res/content/res_6_4x_other_publications]

Coultas, D.B., Howard, C.A., Peake, G.T., Skipper, B.J. & Samet, J.M. (1987) Salivary cotinine levels and involuntary tobacco smoke exposure in children and adults in New Mexico. *Am. Rev. Respir. Dis.*, **136**, 305–309

Curtin, F., Morabia, A. & Bernstein, M. (1998) Lifetime exposure to environmental tobacco smoke among urban women: Differences by socioeconomic class. *Am. J. Epidemiol.*, **148**, 1040–1047

Dijkstra, L., Houthuijs, D., Brunekreef, B., Akkerman, I. & Boleij, J.S. (1990) Respiratory health effects of the indoor environment in a population of Dutch children. *Am. Rev. Respir. Dis.*, **142**, 1172–1178

Djordjevic, M.V., Stellman, S.D. & Zang, E. (2000) Doses of nicotine and lung carcinogens delivered to cigarette smokers. *J. natl Cancer Inst.*, **92**, 106–111

Eatough, D.J., Benner, C.L., Tang, H., Landon, V., Richards, G., Caka, F.M., Crawford, J., Lewis, E.A., Hansen, L.D. & Eatough, N.L. (1989) The chemical composition of environmental tobacco smoke. III. Identification of conservative tracers of environmental tobacco smoke. *Environ. int.*, **15**, 19–28

Etter, J.-F., Ronchi, A. & Perneger, T.V. (1999) Short-term impact of a university based smoke free campaign. *J. Epidemiol. Community Health*, **53**, 710–715

Farrelly, M.C., Evans, W.N. & Sfekas, A.E. (1999) The impact of workplace smoking bans: Results from a national survey. *Tob. Control*, **8**, 272–277

Freeth, S. (1998) *Smoking-related Behaviour and Attitudes, 1997. A Report on Research using the Omnibus Survey produced on behalf of the Department of Health*, London, Office for National Statistics, p. 13

Gerlach, K.K., Shopland, D.R., Hartman, A.M., Gibson, J.T. & Pechacek, T.F. (1997) Workplace smoking policies in the United States: Results from a national survey of more than 100 000 workers. *Tob. Control*, **6**, 199–206

Gottlieb, N.H., Eriksen, M.P., Lovato, C.Y., Weinstein, R.P. & Green, L.W. (1990) Impact of a restrictive work site smoking policy on smoking behavior, attitudes, and norms. *J. occup. Med.*, **32**, 16–23

Government of British Columbia (2003) What is in cigarettes? Mainstream smoke and sidestream smoke chemical constituents by cigarette brand. [http://www.healthplanning.gov.bc.ca/ttdr/index.html Accessed 07.03.2003]

Greenberg, R.A., Bauman, K.E., Glover, L.H., Strecher, V.J., Kleinbaum, D.G., Haley, N.J., Stedman, H.C., Fowler, M.G. & Loda, F.A. (1989) Ecology of passive smoking by young infants. *J. Pediatr.*, **114**, 774–780

Guerin, M.R., Higgins, C.E. & Jenkins, R.A. (1987) Measuring environmental emissions from tobacco combustion: Sidestream cigarette smoke literature review. *Atmos. Environ.*, **21**, 291–297

Guerin M.R., Jenkins, R.A. & Tomkins, B.A., eds (1992) *The Chemistry of Environmental Tobacco Smoke: Composition and Measurement*. Center for Indoor Air Research, Chelsea, MI, Lewis Publishers

Hammond, S.K. (1999) Exposure of U.S. workers to environmental tobacco smoke. *Environ. Health Perspect.*, **107** (Suppl. 2), 329–340

Heavner, D.L., Morgan, W.T. & Ogden, M.W. (1995) Determination of volatile organic compounds and ETS apportionment in 49 homes. *Environ. int.*, **21**, 3–21

Higgins, C.E., Thompson, C.V., Ilgner, L.H., Jenkins, R.A. & Guerin, M.R. (1990) *Determination of Vapor Phase Hydrocarbons and Nitrogen-containing Constituents in Environmental Tobacco Smoke. Internal Progress Report*, Analytical Chemistry Division, Oak Ridge National Laboratory, Oak Ridge, TN 37831-6120

Hodgson, A.T., Daisey, J.M., Mahanama, K.R.R., Brinke, T. & Alevantis, L.E. (1996) Use of volatile tracers to determine the contribution of environmental tobacco smoke to concentrations of volatile organic compounds in smoking environments. *Environ. Int.*, **22**, 295–307

Hopkins, D.P., Briss, P.A., Ricard, C.J., Husten, C.G., Carande-Kulis, V.G., Fielding, J.E., Alao, M.O., McKenna, J.W., Sharp, D.J., Harris, J.R., Woollery, T.A., Harris, K.W. & The Task Force on Community Preventive Services (2001) Reviews of evidence regarding interventions to reduce tobacco use and exposure to environmental tobacco smoke. *Am. J. prev. Med.*, **20**, 16–66

Hyvärinen, M.J., Rothberg, M., Kähkönen, E., Mielo, T. & Reijula, K. (2000) Nicotine and 3-ethenylpyridine concentrations as markers for environmental tobacco smoke in restaurants. *Indoor Air*, **10**, 121–125

IARC (1986) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 38, *Tobacco Smoking*, Lyon, IARC*Press*

IARC (1999) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 71, *Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide*, Lyon, IARC*Press*

Jaakkola, M.S. & Jaakkola, J.J.K. (1997) Assessment of exposure to environmental tobacco smoke. *Eur. Respir. J.*, **10**, 2384–2397

Jaakkola, N., Ruotsalainen, R. & Jaakkola, J.J.K. (1994) What are the determinants of children's exposure to environmental tobacco smoke at home? *Scand. J. Soc. Med.*, **22**, 107–112

Jenkins, R.A. & Counts, R.W. (1999) Occupational exposure to environmental tobacco smoke: Results of two personal exposure studies. *Environ. Health Perspect.*, **107** (Suppl. 2), 341–348

Jenkins, P.L., Phillips, T.J., Mulberg, E.J. & Hui, S.P. (1992) Activity patterns of Californians: Use of and proximity to indoor pollutant sources. *Atmos. Environ.*, **26A**, 2141–2148

Jenkins, R.A., Palausky, A., Counts, R.W., Bayne, C.K., Dindal, A.B. & Guerin, M.R. (1996) Exposure to environmental tobacco smoke in sixteen cities in the United States as determined by personal breathing zone air sampling. *J. Expo. anal. environ. Epidemiol*., **6**, 473–502

Jenkins, R.A., Guerin, M.R. & Tomkins, B.A. (2000) Properties and measure of environmental tobacco smoke. In: *The Chemistry of Environmental Tobacco Smoke. Composition and Measurement*, 2nd Ed., Boca Raton, FL, Lewis Publishers, CRC Press

Jousilahti, P. & Helakorpi, S. (2002) Prevalence of exposure to environmental tobacco smoke at work and at home — 15-year trends in Finland. *Scand. J. Work Environ. Health*, **28** (Suppl. 2), 16–20

Junker, M.H., Danuser, B., Monn, C. & Koller, T. (2001) Acute sensory responses of nonsmokers at very low environmental tobacco smoke concentrations in controlled laboratory settings. *Environ. Health Perspect.*, **109**, 1045–1052

Kegler, M.C. & Malcoe, L.H. (2002) Smoking restrictions in the home and car among rural Native American and white families with young children. *Prev. Med*, **35**, 334–342

Kim, Y.M., Harrad, S. & Harrison, R.M. (2001) Concentrations and sources of VOCs in urban domestic and public microenvironments. *Environ. Sci. Technol.*, **35**, 997–1004

Klepeis, N.E., Ott, W.R. & Repace, J.L. (1999) The effect of cigar smoking on indoor levels of carbon monoxide and particles. *J. exp. anal. environ. Epidemiol.*, **9**, 622–635

Klus, H., Begutter, H., Scherer, G., Tricker, A.R. & Adlkofer, F. (1992) Tobacco-specific and volatile *N*-nitrosamines in environmental tobacco smoke of offices. *Indoor Environ*., **1**, 348–350

Kurtz, M.E., Kurtz, J.C., Johnson, S.M. & Beverly, E.E. (1996) Exposure to environmental tobacco smoke — Perceptions of African American children and adolescents. *Prev. Med.*, **25**, 286–292

Lam, T.H., Chung, S.F., Betson, C.L., Wong, C.M. & Hedley, A.J. (1998) Respiratory symptoms due to active and passive smoking in junior secondary school students in Hong Kong. *Int. J. Epidemiol.*, **27**, 41–48

Letcher, T. & Borland, R. (2000) Smoking bans in Victorian workplaces: 1999 update. In: Trotter, L. & Letcher, T., eds, *Quit Evaluation Studies*, Vol. 10, pp. 49–57, Centre for Behavioural Research on Cancer [http://www.quit.org.au/quit/qe10/10home.html], Melbourne, Australia. Victorian Smoking and Health Program, The Anti-Cancer Council of Victoria

Lister, S.M. & Jorm, L.R. (1998) Parental smoking and respiratory illnesses in Australian children aged 0–4 years: ABS 1989–1990 National Health Survey results. *Australian and New Zealand J. Public Health*, **22**, 781–786

Löfroth, G. (1989) Environmental tobacco smoke: Overview of chemical composition and genotoxic components. *Mutat. Res.*, **222**, 73–80

Löfroth, G. (1993) Environmental tobacco smoke. Multicomponent analysis and room to room distribution in homes. *Tob. Control*, **2**, 222–225

Löfroth, G., Burton, R., Goldstein, G., Forehand, L., Hammond, K., Mumford, J., Seila, R. & Lewtas, J. (1987) Genotoxic emission factors for sidestream cigarette smoke components (Abstract). *Environ. Mutag*., **9** (Suppl. 8), 61

Löfroth, G., Burton, R.M., Forehand, L., Hammond, S.K., Seila, R.L., Zweidinger, R.B. & Lewtas, J. (1989) Characterization of environmental tobacco smoke. *Environ. Sci. Technol*., **23**, 610–614

Longo, D.R., Brownson, R.C. & Kruse, R.L. (1995) Smoking bans in US hospitals. Results of a national survey. *J. Am. med. Assoc.*, **274**, 488–491

Lum, S. (1994) Duration and location of ETS exposure for the California population. Memorandum from S. Lum, Indoor Exposure Assessment Section, Research Division, California Air Resources Board, to L. Haroun, Reproductive and Cancer Hazard Assessment Section, Office of Environmental Health Hazard Assessment, 3 February (cited according to Samet and Yang, 2001)

Lund, K.E., Skrondal, A., Vertio, H. & Helgason, A.R. (1998) Children's residential exposure to environmental tobacco smoke varies greatly between the Nordic countries. *Scand. J. soc. Med.*, **26**, 115–120

Mannino, D.M., Siegel, M., Husten, C., Rose, D. & Etzel, R. (1996) Environmental tobacco smoke exposure and health effects in children: Results from the 1991 National Health Interview Survey. *Tob. Control*, **5**, 13–18

Martin, P., Heavner, D.L., Nelson, P.R., Maiolo, K.C., Risner, C.H., Simmons, P.S., Morgan, W.T. & Ogden, M.W. (1997) Environmental tobacco smoke (ETS): A market cigarette study. *Environ. int.*, **23**, 75–90

McMaugh, K. & Rissell, C. (2000) Smoking restrictions in small businesses of inner West Sydney: A management perspective. *J. occup. Health Saf.-Aust. NZ*, **16**, 37–45

Millar, W.J. (1988) Evaluation of the impact of smoking restrictions in a government work setting. *Can. J. public Health*, **79**, 379–382

Moschandreas, D.J. & Vuilleumier, K.L. (1999) ETS levels in hospitality environments satisfying ASHRAE standard 62-1989: 'Ventilation for acceptable indoor air quality'. *Atmos. Env*., **33,** 4327–4340

Mullooly, J.P., Schuman, K.L., Stevens, V.J., Glasgow, R.E. & Vogt, T.M. (1990) Smoking behavior and attitudes of employees of a large HMO before and after a work site ban on cigarette smoking. *Public Health Rep.*, **105**, 623–628

Nelson, P.R., Kelly, S.P. & Conrad, F.W. (1997) Generation of environmental tobacco smoke by cigars (Abstract No. 46). In: *Proceedings of the 51st Tobacco Chemist's Research Conference, Winston-Salem, NC, September 14–17, 1997*

NRC (National Research Council) (1986) *Environmental Tobacco Smoke. Measuring Exposures and Assessing Health Effects*, Washington DC, National Academy Press

Ott, W.R. (1999) Mathematical models for predicting indoor air quality from smoking activity. *Environ. Health Perspect.*, **107** (Suppl. 2), 375–381

Overpeck, M.D. & Moss, A.J. (1991) Children's exposure to environmental cigarette smoke before and after birth. Health of our nation's children, United States, 1988. *Adv. Data*, **202**, 1–11

Pakhale, S.S. & Maru, G.B. (1998) Distribution of major and minor alkaloids in tobacco, mainstream and sidestream smoke of popular Indian smoking products. *Food Chem. Toxicol.*, **36**, 1131–1138

Patten, C.A., Pierce, J.P., Cavin, S.W., Berry, C.C. & Kaplan, R.M. (1995) Progress in protecting non-smokers from environmental tobacco smoke in California workplaces. *Tob. Control*, **4**, 139–144

Phillips, K. & Bentley, M.C. (2001) Seasonal assessment of environmental tobacco smoke and respirable suspended particle exposures for nonsmokers in Bremen using personal monitoring. *Environ. int.*, **27**, 69–85

Pierce, J.P., Evans, N., Farkas, S.J., Cavin, S.W., Berry, C., Kramer, M., Kealey, S., Rosbrook, B., Choi, W. & Kaplan, R.M. (1994) *Tobacco Use in California: An Evaluation of the Tobacco Control Program, 1989–1993*. La Jolla, CA. Cancer Prevention and Control, University of California, San Diego

Pirkle, J., Flegal, K., Bernert, J., Brody, D., Etzel, R. & Maurer, K. (1996) Exposure of the US population to environmental tobacco smoke. The Third National Health and Nutrition Examination Survey,1988 to 1991. *J. Am. med. Assoc.*, **275**, 1233–1240

Pizacani, B.A., Martin, D.P., Stark, M.J., Koepsell, T.D., Thompson, B. & Diehr, P. (2003) Household smoking bans: Which households have them and do they work? *Prev. Med.*, **36**, 99–107

Pletsch, P.K. (1994) Environmental tobacco smoke exposure among Hispanic women of reproductive age. *Public Health Nursing*, **11**, 229–235

Ramsey, R.S., Moneyhun, J.H. & Jenkins, R.A. (1990) Generation, sampling and chromatographic analysis of particulate matter in dilute sidestream tobacco smoke. *Anal. chem. Acta*, **236**, 213–220

Repace, J.L. (1994) Risk management of passive smoking at work and at home. *Saint Louis University Public Law Review*, **13**, 763–785

Rickert, W.S., Robinson, J.C. & Collishaw, N. (1984) Yields of tar, nicotine, and carbon monoxide in the sidestream smoke from 15 brands of Canadian cigarettes. *Am. J. public Health*, **74**, 228–231

Samet, J. & Yang, G. (2001) Passive smoking, women and children. In: Samet, J. & Yoon, S.-Y., eds, *Women and the Tobacco Epidemic, Challenges for the 21st Century* (WHO/NMH/TF1/01.1), Geneva, World Health Organization

Scherer, G., Frank, S., Riedel, K., Meger-Kossien, I. & Renner, T. (2000) Biomonitoring of exposure to polycyclic aromatic hydrocarbons of nonoccupationally exposed persons. *Cancer Epidemiol. Biomarkers Prev.*, **9**, 373–380

Sherrill, D.L., Martinez, F.D., Lebowitz, M.D., Holdaway, M.D., Flannery, E.M., Herbison, G.P., Stanton, W.R., Silva, P.A. & Sears, M.R. (1992) Longitudinal effects of passive smoking on pulmonary function in New Zealand children. *Am. Rev. Respir. Dis.*, **145**, 1136–1141

Siegel, M. (1993) Involuntary smoking in the restaurant workplace. A review of employee exposure and health effects. *J. Am. med. Assoc.*, **270**, 490–493

Siegel, M., Husten, C., Merritt, R.K., Giovino, G.A. & Eriksen, M.P. (1995) Effects of separately ventilated smoking lounges on the health of smokers: Is this an appropriate public health policy ? *Tob. Control*, **4**, 22–29

Somerville, S.M., Rona, R.J. & Chinn, S. (1988) Passive smoking and respiratory conditions in primary school children. *J. Epidemiol. Community Health*, **42**, 105–110

Stamatakis, K.A., Brownson, R.C. & Luke, D.A. (2002) Risk factors for exposure to environmental tobacco smoke among ethnically diverse women in the United States. *J. Women's Health Gend. Based Med.*, **11**, 45–51

Steyn, K., Yach, D., Stander, I. & Fourie, J.M. (1997) Smoking in urban pregnant women in South Africa. *S. Afr. Med. J.*, **87**, 460–463

Stillman, F.A., Becker, D.M., Swank, R.T., Hantula, D., Moses, H., Glantz, S. & Waranch, H.R. (1990) Ending smoking at the Johns Hopkins Medical Institutions. An evaluation of smoking prevalence and indoor air pollution. *J. Am. med. Assoc.*, **264**, 1565–1569

Thompson, B., Emmons, K., Abrams, D., Ockene, J.K. & Feng, Z. (1995) ETS exposure in the workplace. Perceptions and reactions by employees in 114 work sites. Working Well Research Group [corrected]. *J. Occup. environ. Med.*, **37**, 1086–1092

Totsuka, Y., Ushiyama, H., Ishihara, J., Sinha, R., Goto, S., Sugimura, T. & Wakabayashi, K. (1999) Quantification of the co-mutagenic beta-carbolines, norharman and harman, in cigarette smoke condensates and cooked foods. *Cancer Lett.*, **143**, 139–143

US Department of Health and Human Services (2000) *National Worksite Health Promotion Survey*. Available at: http://www.cdc.gov/nchs/data/hp2000/safety/sumtable.pdf (accessed 24 January 2003), Washington DC, Office of Disease Prevention and Health Promotion

US EPA (US Environmental Protection Agency) (1992) *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders* (EPA/600/6-90/006F), Washington DC, United States Environmental Protection Agency

Vainiotalo, S., Vaaranrinta, R., Tornaeus, J., Aremo, N., Hase, T. & Peltonen, K. (2001) Passive monitoring method for 3-ethenylpyridine: A marker for environmental tobacco smoke. *Environ. Sci. Technol.,* **35**, 1818–1822

Vu Duc, T. & Huynh, C.K. (1987) Deposition rates of sidestream tobacco smoke particles in an experimental chamber. *Toxicol. Lett.*, **35**, 59–65

Wakefield, M., Roberts, L. & Owen, N. (1996) Trends in prevalence and acceptance of workplace smoking bans among indoor workers in South Australia. *Tob. Control*, **5**, 205–208

Whitlock, G., MacMahon, S., Vander Hoorn, S., Davis, P., Jackson, R. & Norton, R. (1998) Association of environmental tobacco smoke exposure with socioeconomic status in a population of 7725 New Zealanders. *Tob. Control*, **7**, 276–280

Yang, G., Fan, L., Tan, J., Qi, G., Zhang, Y., Samet, J.M., Taylor, C.E., Becker, K. & Xu, J. (1999) Smoking in China. Findings of the 1996 National Prevalence Survey. *JAMA*, **282**, 1247–1253

2. Studies of Cancer in Humans

2.1 Lung cancer

The section summarizes the results of the relevant cohort studies and case–control studies of the association between lung cancer and exposure to secondhand smoke. They are ordered by source of exposure, i.e. secondhand smoke from partners at home, at the workplace, during childhood and from other sources. For each type of study, the results are presented first without differentiation according to the levels of exposure and then the exposure–response relationship is described.

The most commonly used measure of exposure to secondhand smoke has been from the spouse. This is because it is well defined and has been validated using cotinine studies of never-smokers who do or do not live with smokers. Spousal exposure is also a marker of exposure to tobacco smoke in general because people who live with smokers tend to mix with smokers outside the home. Other measures of exposure, at the workplace or during childhood, are not so well validated. It is more difficult to quantify exposure at the workplace than spousal exposure; the extent of exposure may vary considerably between different working environments (exposure from the spouse is clearly defined and fairly consistent); people are more likely to change jobs than to remarry or divorce and, in studies based on people who have died from lung cancer, it may be more difficult for the next of kin or other respondent to know whether or not the subject had been exposed to secondhand smoke at work. Exposure during childhood has not been validated and, in studies of exposure to secondhand smoke, the relative risk for lung cancer associated with exposure during childhood should be stratified according to spousal exposure. Few studies have done this, and, even when they have, the number of lung cancer cases has been too small to enable robust conclusions to be drawn.

2.1.1 *Cohort studies*

There have been eight cohort studies of nonsmokers who were followed for several years to determine the risk for lung cancer (these are described in Table 2.1). Six of these studies (Garfinkel, 1981; Hirayama, 1984; Butler, 1988; Cardenas *et al.*, 1997; Jee *et al*., 1999; Nishino *et al*., 2001) reported the risk of lung cancer associated with exposure to secondhand smoke from the spouse. All six studies found that the risk for nonsmoking women with partners who smoked was higher than that for those whose partner did not

Table 2.1. Cohort studies of secondhand smoke and lung cancer

Reference (country, years of study)	Cohort sample	Cohort eligibility; follow-up	Source of exposure	Incidence/death; covariates adjusted for; comments
Garfinkel (1981) (USA, 1960–72)	176 739 married nonsmoking women	ACS Study: friends, neighbours and relatives of American Cancer Society volunteers; deaths reported by volunteers; death certificates obtained from state health departments; 93% follow-up Veterans Study: questionnaire mailed to veterans holding a US Government life insurance; 85% response; death certificates supplied to the Veterans' Administration or through field work at health departments	Active smoking by current spouse	Deaths 1) Crude death rates; 2) analysis with women matched by age, race, highest educational status of husband or wife, residence and occupational exposure of husband
Hirayama (1984) (Japan, 1965–81)	91 540 married nonsmoking women	95% of the census population in the study area in 29 health centre districts; follow-up consisted of special annual census and special death registry system.	Active smoking by current spouse	Deaths SMRs
Butler (1988) (USA, 1974–82)	Spouse pairs: 9378 subjects; AHSMOG cohort: 6467 subjects (66% overlap)	Non-Hispanic white Adventists; spouse pairs with a non-smoking wife; AHSMOG cohort enrolled for air pollution study; deaths ascertained by linkage to California death certificate file, national death index and notification of death by church clerks; cases ascertained with hospital history forms and review of hospital and tumour registry records; 99% histologically confirmed	Spouse pair cohort: active smoking by current spouse; AHSMOG cohort: exposure at work	Cases/deaths Adjusted for age
DeWaard *et al.* (1995) (the Netherlands, 1977–91)	23 cases and 191 controls	Nested case–control study among women enrolled in breast cancer screening projects (DOM project, enrolment 1975–77, aged 50–64 years and Lutine Study, enrolment 1982–83, aged 40–49 years)	Exposure assessed by measurement of urinary cotinine levels in declared nonsmokers	Cases/deaths Cotinine excretion adjusted for creatinine resulted in higher odds ratios.

Table 2.1 (contd)

Reference (country, years of study)	Cohort sample	Cohort eligibility; follow-up	Source of exposure	Incidence/death; covariates adjusted for; comments
Cardenas *et al.* (1997) (USA, 1982–89)	288 776 (96 542 men, 192 234 women) nonsmoking subjects	Friends, neighbours and relatives of American Cancer Society volunteers in all 50 States; aged > 30 years; death monitored by volunteers and through national death index; cause of death classified according to ICD-9.	Active smoking by current spouse; self-reported exposure at home, at work or in other areas	Deaths Adjusted for age, race, education, blue-collar employment, asbestos exposure, consumption of vegetables, citrus fruits and fat, history of chronic lung disease
Jee *et al.* (1999) (Republic of Korea, 1992–97)	157 436 married nonsmoking women	Both spouses had to have completed the Korean Medical Insurance Corporation medical examination; aged > 40 years; cases ascertained from diagnosis on discharge summary	Active smoking by current husband	Cases Univariate analysis; multivariate analysis adjusted for age of husband and wife, socioeconomic status, residence, husband's vegetable consumption and occupation
Speizer *et al.* (1999) (USA, 1976–92)	121 700 women, US registered nurses in 1976; unknown subcohort of nonsmokers	Female nurses aged 30–55 years, Nurses' Health Study; deaths ascertained by family members, postal service or through national death index; cases confirmed by pathology reports	Information on exposure to second-hand smoke during childhood and adulthood ascertained in 1982	Cases Adjusted for age
Nishino *et al.* (2001) (Japan, 1984–92)	31 345 (13 992 men, 17 353 women) non-smokers	Residents of six primary school sectors in a city and the whole area of two towns in north-eastern Honshu, aged > 40 years; cases ascertained by linkage to the prefectural cancer registry; cancer sites coded according to ICD-9	Any smoker in the household	Cases 1) Crude relative risk; 2) stratification by smoking status of husband and other household members; 3) multivariate relative risk adjusted for age, study area, alcohol intake, green and yellow vegetable intake, fruit intake, meat intake and past history of lung disease

SMR, standardized mortality ratio

smoke (see Table 2.2). In both cohort studies that reported on the effect in nonsmoking men whose wives smoked, the relative risk was increased (Hirayama 1984; Cardenas *et al.*, 1997). The two other cohort studies, which were based on general exposure to secondhand smoke (deWaard *et al*., 1995; Speizer *et al*., 1999), obtained similar results.

Table 2.2. Epidemiological studies[a] of the risk for lung cancer in lifelong non-smokers whose spouses smoked relative to the risk in those whose spouses did not smoke[b]

Reference (country)	No. of cases of lung cancer	Crude relative risk (95% CI)	Adjusted relative risk (95% CI)[c]
Women			
Case–control studies (n = 40)			
Chan & Fung (1982) (Hong Kong, SAR)	84	0.8 [0.4–1.3]	NR[d]
Correa *et al*. (1983) (USA)	22	2.1 [0.8–5.3]	NR
Trichopoulos *et al*. (1983) (Greece)	62	2.1 [1.2–3.8]	NR
Buffler *et al*. (1984) (USA)	41	0.8 [0.3–1.9]	0.8 (0.3–1.8)
Kabat & Wynder (1984) (USA)	24	0.8 [0.3–2.5]	NR
Lam (1985) (Hong Kong, SAR)	60	2.0 [1.1–3.7][e]	NR
Garfinkel *et al*. (1985) (USA)	134	1.2 [0.8–1.9]	1.2 (0.9–1.6)
Wu *et al*. (1985) (USA)	29	NR	1.2 (0.5–3.3)
Akiba *et al*. (1986) (Japan)	94	1.5 [0.9–2.6]	1.5 [0.8–2.8][f]
Lee *et al*. (1986) (United Kingdom)	32	1.0 [0.4–2.6]	1.0 (0.4–2.7)
Brownson *et al*. (1987) (USA)[g]	19	1.5 (0.4–6.0)	
Gao *et al*. (1987) (China)	246	1.2 (0.8–1.7)	1.3 (1.0–1.8)
Humble *et al*. (1987) (USA)	20	2.3 [0.8–6.8]	2.2 (0.7–6.6)
Koo *et al*. (1987) (Hong Kong, SAR)	86	1.6 [0.9–2.7]	1.6 (0.9–3.1)
Lam *et al*. (1987) (Hong Kong, SAR)	199	1.7 [1.2–2.4]	NR
Pershagen *et al*. (1987) (Sweden)	70	1.0 [0.6–1.7]	1.2 (0.7–2.1)
Geng *et al*. (1988) (China)	54	2.2 [1.1–4.3]	NR
Inoue & Hirayama (1988) (Japan)	22	2.6 (0.7–8.8)[h]	NR
Shimizu *et al*. (1988) (Japan)	90	1.1 [0.6–1.8]	1.1 (NR)
Choi *et al.* (1989) (Republic of Korea)	75	1.6 (0.9–2.9)	1.6 (NR)
Kalandidi *et al*. (1990) (Greece)	90	1.6 [0.9–2.9]	2.1 (1.1–4.1)
Sobue (1990) (Japan)	144	1.1 [0.7–1.5]	1.1 (0.8–1.6)
Wu-Williams *et al*. (1990) (China)	417	0.8 [0.6–1.0]	0.7 (0.6–0.9)
Liu & Chapman (1991)[i] (China)	54	0.7 [0.3–1.7]	0.8 (0.3–2.0)
Brownson *et al*. (1992) (USA)	431	1.0 [0.8–1.2]	1.0 (0.8–1.2)
Stockwell *et al*. (1992) (USA)	210	NR	1.6 (0.8–3.0)
Du *et al*. (1993) (China)	75	1.2 (0.7–2.1)	NR
Liu *et al*. (1993) (China)	38	1.7 (0.7–3.8)	NR
Fontham *et al*. (1994) (USA)	651	1.3 (1.0–1.5)	1.3 (1.0–1.6)
Kabat *et al*. (1995) (USA)	67	1.1 [0.6–2.0]	1.1 (0.6–1.9)
Sun *et al*. (1996) (China)	230	NR	1.2 (0.8–1.7)

Table 2.2 (contd)

Reference (country)	No. of cases of lung cancer	Crude relative risk (95% CI)	Adjusted relative risk (95% CI)[c]
Wang *et al*. (1996) (China)	135	1.1 [0.7–1.8]	NR
Boffetta *et al*. (1998) (Europe)	508	1.0 [0.8–1.3]	1.1 (0.9–1.4)
Shen *et al*. (1998) (China)	70	[1.5 (0.7–3.3)]	1.6 (0.7–3.9)
Zaridze *et al*. (1998) (Russia)	189	1.6 [1.1–2.3]	1.5 (1.1–2.2)
Rapiti *et al*. (1999) (India)	41	1.0 [0.4–2.4]	1.2 (0.5–2.9)
Zhong *et al*. (1999) (China)	407	1.2 [0.8–1.6]	1.1 (0.8–1.5)
Kreuzer *et al*. (2000)[j] (Germany)	100	0.9 [0.6–1.4]	0.8 (0.5–1.3)
Lee *et al*. (2000)[k] (Taiwan, China)	268	1.7 [1.3–2.4]	1.8 (1.3–2.5)
Johnson *et al*. (2001) (Canada)	71	NR	1.2 (0.6–4.0)
Cohort studies (n = 6)			
Garfinkel (1981) (USA)	153	NR	1.2 [0.9–1.4]
Hirayama (1984) (Japan)	200	NR	1.5 [1.0–2.1][l]
Butler (1988) (USA)	8	NR	2.0 (0.5–8.6)
Cardenas *et al*. (1997) (USA)	150	NR	1.2 (0.8–1.6)
Jee *et al*. (1999) (Republic of Korea)	63	NR	1.9 (1.0–3.5)
Nishino *et al*. (2001) (Japan)	24	NR	1.9 (0.8–4.4)
Men			
Case–control studies (n = 9)			
Correa *et al*. (1983) (USA)	8	2.0 [0.2–11.8][m]	NR
Buffler *et al*. (1984) (USA)	11	0.5 (0.1–2.2)[m]	0.5 (0.2–1.7)
Kabat & Wynder (1984) (USA)	12	1.0 [0.2–6.7][m]	NR
Akiba *et al*. (1986) (Japan)	19	2.1 (0.5–8.6)	1.8 (0.5–7.0)[f]
Lee *et al*. (1986) (United Kingdom)	15	1.3 (0.3–5.4)[m]	1.3 (0.4–4.4)
Choi *et al.* (1989) (Republic of Korea)	13	2.7 (0.5–15.2)[m]	2.7 (NR)
Kabat *et al*. (1995) (USA)	39	1.6 [0.7–3.9]	1.6 (0.7–3.8)
Boffetta *et al*. (1998) (Europe)	141	1.3 [0.8–2.2]	NR
Kreuzer *et al.* (2000)[j] (Germany)	23	0.4 (0.1–3.0)	NR
Cohort studies (n = 2)			
Hirayama (1984) (Japan)	64	NR	2.3 [1.1–4.8]
Cardenas *et al*. (1997) (USA	97	NR	1.1 (0.6–1.8)

CI, confidence interval

[a] Only the most recent publication is used for studies that have been updated from previously published reports. Also, studies based on subjects who are included in a larger series are not listed here.

[b] In addition, there are four studies that gave results for men and women combined: Hole *et al*. (1989) (7 cases), relative risk, 2.1 (95% CI, 0.5–12.8); Janerich *et al*. (1990) (188 cases), relative risk, 0.9 (95% CI, 0.6–1.6) for analysis based on subjects interviewed directly and 0.4 (0.2–1.0) for analysis based on interviews with surrogate respondents; Schwartz *et al*. (1996) (257 cases), relative risk, 1.1 (95% CI, 0.8–1.6); Boffetta *et al*. (1999a) (69 cases), relative risk 1.22 (95% CI, 0.7–2.1).

[c] Adjusted for at least age (other factors included dietary habits, education and social class)

Table 2.2 (contd)

[d] Not reported or estimatable from the reported results
[e] Results for adenocarcinoma only
[f] The original report presented 90% confidence intervals that were converted to 95% confidence intervals for this table.
[g] The raw data came from the US Environmental Protection Agency (1992).
[h] Results reported in the US Environmental Protection Agency report (1992), which also noted that the results reported in this article (odds ratio, 2.3) were erroneous
[i] One of the 202 controls was a smoker, but this would have a negligible effect on the result, so this study was included.
[j] Results from analysis excluding cases and controls already included in the study by Boffetta *et al*. (1998) [personal communication M. Kreuzer]
[k] Crude results are for comparisons between women married to smokers and those married to non-smokers. The adjusted result was obtained by pooling the odds ratio corresponding to women married to smokers who smoked in their presence with the odds ratio corresponding to women married to smokers who did not smoke in their presence.
[l] Authors reported a 90% confidence interval that was adjusted to a 95% confidence interval for this table. It should also be noted that this result was for a comparison of women whose husbands smoked 1–19 cigarettes/day with women whose husbands were nonsmokers, and did not include the highest exposure group (≥ 20 cigarettes/day).
[m] Fisher's exact 95% confidence intervals were estimated.

Exposure–response relationships

The analysis of exposure–response relationships provides critical evidence for or against a causal relationship between exposure to secondhand smoke and the development of lung cancer.

In the study by Garfinkel (1981), the relative risk did not increase with increasing exposure levels.

In the study by Hirayama (1984), the relative risks for women were 1.4, 1.4, 1.6 and 1.9 when their husbands were ex-smokers, and when they smoked 1–14, 15–19 or ≥ 20 cigarettes/day, respectively (p value for trend test, 0.002). Similarly the relative risk for nonsmoking men increased with exposure level: it was 2.1 when the wives smoked 1–19 cigarettes/day and 2.3 when they smoked ≥ 20 cigarettes/day (p value for trend test, 0.02).

The study by Cardenas *et al.* (1997) also found a significant exposure–response relationship. When the husbands smoked 1–19, 20–39 and ≥ 40 cigarettes/day, the relative risks for women exposed to secondhand smoke were 1.1, 1.2 and 1.9 respectively (p value for trend test, 0.03). There was no evidence of an association between risk and the length of time the couples had been married. A similar analysis for nonsmoking men exposed to secondhand smoke would not be robust because the number of cases was too small. The particular strengths of this study were the near complete data on cause of death (97%), direct questioning of both partners about their smoking habits, and the taking into account of numerous potential confounders such as previous lung disease, occupational exposure to asbestos, dietary habits and education.

Taken together, the three large cohort studies demonstrate an increased incidence of deaths from lung cancer associated with exposure to secondhand smoke from the spouse. The increase in deaths from lung cancer in the study by Hirayama (1984) is significant, and this study and that by Cardenas *et al.* (1997) also reported a significant exposure–response relationship.

2.1.2 *Case–control studies*

Many case–control studies have been undertaken in several countries (mostly China and the USA) (described in Table 2.3). In these studies lung cancer cases were ascertained and matched with controls (usually for age and other factors). The controls were selected from either the general population or the hospital in which the patients with lung cancer were diagnosed. Details of the smoking habits of the partners of both cases and controls were obtained either by interview or questionnaire. In some instances the next of kin provided the relevant information. These studies were based on various measures of exposure to secondhand smoke, including exposure from the partner, at the workplace, during childhood or exposure from other sources. The following section describes only large, relevant studies in which all cases and controls were interviewed in person and no information from the next of kin was used to reconstruct exposure.

(*a*) *Description of studies*

The study of Lam *et al.* (1987) included 199 cases and 335 controls from Hong Kong, Special Administrative Region of China. The study is characterized by good data on exposure (from various sources) to secondhand smoke, valid classification of the smoking habits of the husband and a consideration of potential confounders (including education, place of birth, duration of residence and marital status).

The study from China by Gao *et al*. (1987) included 246 cases and 375 controls. The cases were identified using a system built upon the Shanghai Cancer Registry. The analyses were controlled for age and education.

The study of Wu-Williams *et al.* (1990), also from China, included 417 cases and 602 controls. A limitation of this study is that it was not able to control for important indoor sources of exposure to potential lung carcinogens such as those produced during burning of coal and frying in oil.

The study of Brownson *et al.* (1992) in the USA included 431 cases and 1166 controls. It is characterized by good documentation of data on exposure in the home and the workplace, and took into account potential confounders (age, sex and socioeconomic status).

In the study of Fontham *et al*. (1994) in the USA, 651 cases and 1253 controls were interviewed. Possible misclassification of smokers and potential confounding by age, occupational exposure to known carcinogens, eating habits, familial history of lung cancer and education were taken into account. The smoking status was verified by means of cotinine determination to minimize the misclassification of smokers as nonsmokers.

Table 2.3. Main study design characteristics of case–control studies on exposure to secondhand smoke and lung cancer

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Chan & Fung (1982) (Hong Kong, SAR, 1976–77)	Women: 84 cases, 139 controls	Histologically confirmed cases of bronchial cancer were identified in five hospitals in Hong Kong. Controls were identified from patients in the orthopaedic ward at the same hospitals and were selected from the 'same general age group' as the cases.	None	Patients were interviewed using a questionnaire that included a question on exposure to passive smoke at home.
Correa *et al*. (1983) (USA, not reported)	Men: 8 cases, 178 controls Women: 22 cases, 133 controls	Cases of primary lung cancer identified from admission and pathology records at 29 hospitals. Patients with bronchioalveolar cancer were excluded. Controls were randomly selected from patients attending the same hospital and matched for race, sex and age. Patients with smoking-related diseases were excluded from the controls.	None	Study subjects were interviewed with a questionnaire including questions on history of exposure from smoking spouses and parental smoking.
Trichopoulos *et al*. (1983) (Greece, 1978–82)	Men and women: 77 cases, 225 controls	Cases of lung cancer other than adenocarcinoma of the terminal bronchi were identified from three hospitals in Athens. Controls were drawn from an orthopaedic hospital in the same area as the cases. The cases and controls had 'similar demographic and socioeconomic profiles'.	None	Physicians interviewed subjects concerning smoking habits of their spouses.
Buffler *et al*. (1984) (USA, 1976–80)	Men: 11 cases, 90 controls Women: 41 cases, 196 controls	Patients aged 30–79 years with histologically confirmed lung cancer were identified from hospital and state records in six counties in Texas. Population-based and deceased controls were selected from state and federal records that were matched to cases on age, race, sex, region of residence and vital status.	Age, race, sex, region of residence and vital status	Questionnaires were administered to study subjects or next of kin, which included questions on household members who smoked regularly.
Kabat & Wynder (1984) (USA, 1971–80)	Men: 25 cases, 25 controls Women: 53 cases, 53 controls	Cases of primary cancer of the lung were selected from hospitals. One control was matched to each case on age, sex, race, hospital and date of interview. Controls were selected from other hospitalized patients who had diseases that were not tobacco related.	None	Study subjects were interviewed in hospital using a standardized questionnaire that included questions on spousal and workplace exposure.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Lam (1985) (Hong Kong, SAR, 1981–84)	Women: 60 cases, 144 controls	Cases of primary lung cancer were identified from a hospital in Hong Kong. Controls were selected from patients in the orthopaedic wards of the same hospital and were reported to be comparable in age and social class to the cases. Sufficient numbers of cases were available to permit a meaningful analysis only for adenocarcinoma.	Although age and social class appear to have been matched for, they were not controlled for in the analysis.	Exposure assessment used interviews of study subjects or next of kin, which included questions on exposure to secondhand smoke from parents, spouse or other family members.
Garfinkel *et al*. (1985) (USA, 1971–81)	Women: 134 cases, 402 controls	Cases and controls were identified from three hospitals in New Jersey and one in Ohio. Controls were colon and rectum cancers matched to the cases on age and hospital. Both cases and controls were histologically confirmed.	Age and hospital in all analyses. Logistic regression also controlled for socioeconomic status and year of diagnosis	Study subjects or next of kin were interviewed using a questionnaire designed to elicit information on exposure to secondhand smoke from the spouse or other household member(s).
Wu *et al*. (1985) (USA, 1981–82)	Women: 29 patients with adenocarcinomas and 62 controls; 2 with squamous-cell carcinomas and 30 controls[a]	Cases diagnosed by microscopy were identified from a population-based tumour registry in Los Angeles County. Cases were white residents, under 76 years of age who had no prior history of cancer (except melanoma). Neighbourhood controls met the same criteria and were matched to cases on date of birth.	Age. Active smoking was included in analyses that were not restricted to nonsmokers.	A structured telephone questionnaire was used to elicit information on exposure to secondhand smoke from spouse or other household members, and during childhood from household members.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Akiba *et al*. (1986) (Japan, 1971–80)	Women: 94 cases, 270 controls Men: 19 cases, 241 controls	Cases and controls were identified from a cohort of atomic bomb survivors in Hiroshima and Nagasaki. Cases were identified from tumour, mortality and other medical registries. Controls were matched to cases by birth, sex, city of residence, vital status and whether they participated in an annual medical programme. For deceased cases, the corresponding controls were required to have died from a disease other than cancer or chronic respiratory diseases, and were matched to cases on year of death.	Age, sex, city, and year of death	Subjects or next of kin were interviewed using a structured questionnaire to elicit information on exposure to secondhand smoke from a spouse or parent.
Lee *et al*. (1986) (United Kingdom, 1979–82)	Women: 32 cases, 66 controls Men: 15 cases, 30 controls	Cases and controls were nonsmokers identified from several hospitals in England. Controls were patients who did not have lung cancer, chronic bronchitis, ischaemic heart disease or stroke. Two controls for each case were selected and matched on sex, age, marital status, and as far as possible, hospital.	Age, sex, hospital and marital status	The patients and their spouses were interviewed to obtain a history of spousal smoking.
Schwartz (1996) (USA, 1984–87)	Men and women: 401 cases, 398 controls	Cases between the ages of 40 and 84 years were identified in Detroit from an Occupational Cancer Incidence Surveillance Study (OCISS) in conjunction with the Metropolitan Detroit Cancer Surveillance System. Population-based controls were randomly selected from the controls who took part in the OCISS study. Controls were frequency-matched to cases on age, sex, race and county of residence.	Age, sex and race	Telephone interviews were conducted with cases (17%) or controls (78%) or their proxies. The questionnaire included information on exposure to secondhand smoke at work or at home.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Brownson *et al*. (1987) (USA, 1979–82)	Women: 19 cases, 47 controls Men: 4 cases, 19 controls	Cases of adenocarcinoma and controls were identified from the Colorado Central Cancer Registry. All cases were confirmed by microscopy. Controls were patients with colon and bone marrow cancer and were group-matched to cases on age and sex. Cases and controls were required to have resided for a minimum of 6 months in the Denver metropolitan area prior to diagnosis.	Age, sex and socioeconomic status	Cases and controls or next of kin were interviewed and information collected on the smoking status of the spouse and the number of hours per day exposed to secondhand smoke.
Gao *et al*. (1987) (China, 1984–86)	Women: 246 cases, 375 controls	Cases of lung cancer were identified among female residents of Shanghai aged 35–69 from a system built upon the Shanghai Cancer Registry. Female controls were randomly selected from the Shanghai area and approximately frequency-matched on age.	Age and education	Cases and controls were interviewed to obtain information on exposure in childhood and adulthood.
Geng *et al*. (1988) (China, not stated)	Women: 54 cases, 93 controls	Cases were identified among females who had lived for more than 10 years in Tianjin, China. Controls were matched to the cases on sex, race, age and marital status. The precise source of the cases or controls is not stated.	None[b]	The methods used to collect information on exposure to secondhand smoke are not described.
Humble *et al*. (1987) (USA, 1980–82)	Men: 8 cases, 130 controls Women: 20 cases, 162 controls	Cases were identified from the New Mexican Tumor Registry. An initial series was selected between 1980 and 1982 that included all individuals less than 50 years of age, Hispanics aged over 50 years, and a random sample of male (40%) and female (50%) non-Hispanics over 50 years.	Ethnicity and age	Interviews of study subjects (48% cases) or their next of kin (52% cases) were conducted to collect information on spousal smoking habits.
Koo *et al*. (1987) (Hong Kong, SAR, 1981–83)	Women: 86 cases, 136 controls	Cases were identified as part of a larger study on female lung cancer in Hong Kong from the wards and outpatient departments of eight hospitals. An equal number of 'healthy' controls were selected and matched to cases on age, district and socioeconomic status (housing type).	Age, district and housing type, formal schooling and number of live births	Cases and controls were interviewed to elicit information on exposure to secondhand smoke from spouses and other relatives at home.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Lam *et al*. (1987) (Hong Kong SAR, 1983–86)	Women: 199 cases, 35 controls	Pathologically confirmed cases of lung cancer were identified from eight hospitals. Controls were matched to the cases on age and drawn from the same neighbourhood as the corresponding case.	None	Study subjects were interviewed using a questionnaire that included questions concerning the husband's smoking habits.
Pershagen *et al*. (1987) (Sweden, 1963–80)	Women: 70 cases[c]	Cases and controls were selected from two cohort studies in Sweden. The first was a sample of men and women aged 15–65 years in the 1960 National Census who were mailed a questionnaire on smoking habits in 1963. The second was from a study of Swedish twins born between 1886 and 1925. Lung cancer cases were identified until 1980 by links with the Swedish Cancer Registry and the National Register on Causes of Death. Two control series were selected at random from the cohort. One was based on matching controls to cases based on year of birth, and the other on vital status at the end of follow-up as well as year of birth.	Age and vital status	A questionnaire was mailed in 1984 to each study subject, or if they were dead, to their next of kin (excluding the husband). The questionnaire included questions on exposure to secondhand smoke from husbands and parents.
Inoue & Hirayama (1988) (Japan, 1972–83)	Women: 22 cases[d], 62 controls	Cases and controls are from Kamakure and Miura, Japan. The methods used to identify the cases and controls were not clearly stated. Controls were individuals with cerebrovascular disease who were matched to the cases on age, year of death and district.	Age, year of death and district	Interviews were conducted using 'standard questionnaires'.
Shimizu *et al*. (1988) (Japan, 1982–85)	Women: 90 cases, 163 controls	Cases of primary lung cancer were identified from 4 hospitals in Nagoya, Japan. Controls were patients from adjacent wards with diseases other than lung cancer who were matched to the cases on age and date of admission.	Age, hospital and date of admission	Participants answered a questionnaire on the first or second day of admission that included questions on exposure to secondhand smoke from the spouse and other family members, and at the workplace.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Choi *et al.* (1989) (Republic of Korea, 1985–88)	Women: 75 cases, 144 controls	375 patients with lung cancer admitted to Korean Cancer Centre Hospital with histopathologically confirmed diagnosis. Two controls were selected per case matched by age (± 5 years), gender, admission date and area (urban/rural); patients with smoking-related diseases were excluded.	Unmatched analysis of subgroup of non-smoking study subjects	A questionnaire was administered face-to-face including questions on smoking.
Janerich *et al*. (1990) (USA, 1982–85)	Men and women: 191 cases, 191 controls	Cases were identified from 125 diagnostic or treatment facilities covering 23 counties in New York State, and from the New York State cancer registry. Cases were between 20 and 80 years of age, and had to have been resident of one of the 23 counties. Controls were identified from records of the New York Department of Motor Vehicles, and matched to the cases on age, county of residence and smoking history (i.e. nonsmokers).	Age and county of residence	Face-to-face interviews were conducted with cases or controls or their next of kin. When a next-of-kin interview was required, the next of kin of the matching controls were also interviewed. The questionnaire included questions on exposure to smoke from the spouse, at the workplace and during childhood.
Kalandidi *et al*. (1990) (Greece, 1987–89)	Women: 90 cases, 120 controls	Cases with a 'definite' diagnosis of lung cancer were identified from 7 hospitals in the greater Athens area. Controls were women hospitalized in the orthopaedic department of the same or a nearby hospital, and were randomly selected from those who entered within a week of a corresponding case. Controls had to be 35 years or older.	Age, years of schooling, interviewer and total energy consumption	A questionnaire was administered face-to-face to the cases and controls that included questions on exposure to secondhand smoke from the spouse, other household members and at the workplace.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Sobue (1990) (Japan, 1986–88)	Women: 144 cases, 731 controls	Cases of lung cancer and controls aged 40–79 years were identified from eight hospitals in Osaka, Japan. Controls were individuals with diseases other than lung cancer.	Age and education	A self-administered questionnaire was given to cases and controls at the time of admission which included questions on exposure to secondhand smoke.
Wu-Williams *et al*. (1990) (China, 1985–87)	Women: 417 cases, 602 controls	Patients under the age of 70 years with primary lung cancers were identified in the cancer registries of Shenyang and Harbin, China and of major hospitals serving these areas. Controls were randomly selected from the populations of Shenyang and Harbin, and were frequency-matched to the cases by age.	Age, education and centre	Cases and controls were interviewed using a questionnaire that included questions concerning exposure to secondhand smoke from the spouse and other co-habitants, and at the workplace.
Liu *et al*. (1991) (China, 1985–86)	Men and women: 4 cases, 19 controls	Cases of lung cancer were identified from hospitals and clinics in Xuanwei. Controls were matched to the cases on age, sex and village of residence.	Age, sex, village of residence and cooking history	Cases and controls were personally interviewed using a questionnaire that included a question on exposure to second-hand smoke at home (primarily from the spouse)
Brownson *et al*. (1992) (USA, 1986–91)	Women: 431 cases, 1166 controls	Cases of primary lung cancer among white females were identified from the Missouri cancer registry; 76% of the cases were histologically verified. Controls were selected for women under 65 years from the state driver's license files, and for women 65 years or over from the Health Care Finance Administration's roster of Medicare recipients. Controls were frequency-matched to cases on age.	Age, previous lung disease and dietary β-carotene and fat	Telephone interviews were conducted that included questions concerning exposure to secondhand smoke during childhood and adulthood.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Stockwell *et al*. (1992) (USA, 1987–91)	Women: 210 cases, 301 controls	Cases of histologically confirmed primary lung cancer were identified from hospital tumour registries, and a state-wide cancer registry in 28 counties in central Florida. Population-based controls were selected using random digit dialling.	Age, race and education	Interviews of patients or next of kin were conducted in person, by telephone or occasionally by post. The questionnaire included questions on exposure to secondhand smoke at home, at work or in social settings.
Du *et al*. (1993) (China, 1985–86)	**1985 analysis** Men and women: 120 cases, 120 controls with non-respiratory disease, 120 controls with non-respiratory cancer **1986 analysis** Women: 75 cases, 128 non-cancer patients as controls plus 126 controls with tumours other than of the lung	Cases in this study were apparently identified from deaths reported to the local police stations in Guanghzo. Two separate analyses are presented (1) for nonsmokers in 1985 and (2) for female nonsmokers in 1986. Two control groups were selected for each analysis, but it is not clear how these controls were selected. The control groups for the first analysis consisted of (1) non-respiratory system diseases and (2) non-respiratory cancers. The control groups for the second analysis consisted of (1) non-tumour disease and (2) tumours other than of the lung. In the first analysis, controls were matched to cases on sex and age, and were matched on residence in both analyses.	First analysis sex, age and residence Second analysis did not adjust for covariates.	A questionnaire was used by trained personnel to obtain information from family members; it included questions on spousal smoking habits.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Liu *et al*. (1993) (China, 1983–84)	Women: 38 cases, 69 controls	Cases of primary lung cancer were identified from eight major hospitals covering most of Guangzhou. Controls were selected from inpatients at six of these hospitals and patients with chronic obstructive lung diseases, pulmonary tuberculosis, cancers and coronary heart disease were excluded. Controls were matched to cases on age, sex, residential district and date of diagnosis or admission to hospital.	Age, sex, residential area, calendar time, education and occupation	Interviews were carried out in the homes of the subjects using a questionnaire that included questions on spousal smoking habits.
Fontham *et al*. (1994) (USA, 1986–90)	Women: 651 cases, 1253 controls	Cases of primary lung cancer confirmed by microscopy were identified between 1986 and 1988 among residents of Atlanta, and Houston; and between 1989 and 1990 among residents of New Orleans, Los Angeles and San Francisco. Population-based controls were chosen using random digit dialling and random sampling from the Health Care Financing Administration's files. Controls were frequency-matched to cases on race, study centre and age. Cases and controls were required to be between 20 and 79 years of age, to speak English, Spanish or Chinese, and to have no prior history of cancer.	Age, race, study centre, education, family history of cancer, occupational and dietary factors	In-person interviews were conducted with cases and controls or with next of kin. The questionnaire included questions on exposure to secondhand smoke during adulthood (from spouse and at work), and during childhood (from parents or other household members). Urine cotinine measurements were made and used to eliminate individuals who may have been smokers.
Kabat *et al*. (1995) (USA, 1983–90)	Women: 69 cases, 187 controls Men: 100 cases, 117 controls	Histologically confirmed cases were identified in hospitals in New York City, Chicago, Detroit and Philadelphia. Controls were patients admitted to the same hospitals with diseases thought to be unrelated to tobacco smoke. Cases were matched to controls on age, sex, race, hospital and date of interview.	Age, sex, race, education and type of hospital (cancer centre versus other)	In-person interviews were conducted that included questions on exposure to secondhand smoke in childhood and adulthood (at home and in the workplace)

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
de Waard *et al*. (1995) (the Netherlands, 1989, 1991, 1992)	Women: 23 cases, 305 controls	Cases and controls were identified from two cohorts of women screened for breast cancer in Utrecht. The first cohort included women aged 50–64 years who were screened in 1975 and 1977, and re-examined 1 year later. The second cohort included women aged 40–49 years who were screened between 1982 and 1983. Lung cancer cases were identified from mortality and cancer incidence registries. Cancer cases and controls were identified for the first cohort in 1989, 1991 and 1992, whereas cases and controls for the second cohort were identified only in 1992. Four controls were selected for each case identified in 1989 and 1991, and two controls per case in 1992 from the cohort files. Controls were matched to cases on 'about the same age and day of urine collection' for the 1989 cases, and it is unclear whether this matching criterion was also applied to cases and controls from the other years.	Possibly age and calendar time, but it is not clear if these were matched for in all cases or adjusted for in the analyses.	Urinary cotinine concentrations measured in samples collected during the screenings. Non-smokers were defined as subjects with creatinine adjusted cotinine levels of < 9.2 ng/mg creatinine
Sun *et al*. (1996) (China, not reported)	Women: 230 cases, 230 controls	This was a population based case–control study in Harbin. Only an abstract was available, and the source of the cases and controls was not described in it.	Age and education	In-person interviews of cases and controls included questions on exposure to secondhand smoke during childhood, adolescence and adulthood.
Wang *et al*. (1996) (China, 1992–94)	Women: 135 cases, 135 controls	Cases of primary lung cancer who were between 35 and 69 years of age were identified in 18 hospitals in Shenyang. Controls were randomly selected from the urban population in Shenyang, and matched to cases on age.	Cases and controls were matched for age, but it is unclear whether an unmatched analysis was performed.	Cases and controls were interviewed face-to-face using a questionnaire that included questions on exposure to secondhand smoke in childhood and adulthood.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Boffetta *et al*. (1998) (Europe, 1988–94)	Men: 141 cases, 531 controls Women: 508 cases, 1011 controls	Cases and controls were ≤ 74 years of age and had smoked < 400 cigarettes in their lifetimes. Cases were identified from 12 centres in seven European countries and 96.5% were confirmed by microscopy. Controls were hospital-based in some centres and community-based in others. Hospital-based controls were chosen to exclude those with other diseases related to smoking. Community-based controls were drawn from population registries. Controls were matched to cases on age and sex using individual matching in some centres and frequency matching in others. Questionnaire response rates ranged from 53 to > 95% except for 3 centres who had response rates < 50% among controls.	Sex, age and centre	Questionnaire on exposure to secondhand smoke from spouse, during childhood, in the workplace and from other sources was developed based on a previous study of urine cotinine levels and exposure to secondhand smoke including smoke from cigarillos, cigars and pipes as well as cigarettes.
Jöckel *et al*. (1998b) (Germany, 1988–93)	Men and women: 71 cases, 236 controls	Cases and controls were also a part of the study by Boffetta *et al.* (1998). Nonsmokers were identified from a larger case–control study from Bremen, Frankfurt and the surrounding areas. Controls were population based and matched to the cases on sex, age and region.	Sex, age, region, exposure to asbestos, social class, and intake of vegetables and fruits	Compatible with questionnaire used in study by Boffetta 1998. Individuals who had never smoked regularly for more than 6 months were classified as 'never-smokers', and were combined with workers exposed to low levels of secondhand smoke (< 75th percentile) to form the referent group.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Shen *et al*. (1998) (China, 1993)	Women: 70 cases, 70 controls	Cases of primary lung cancer (adenocarcinoma) living ≥ 20 years in Nanjing; healthy controls came from the same neighbourhood, 1:1 matched by sex and age (± 5 years); response rate was 100%.	Chronic lung disease, cooking conditions, family history of lung cancer	Standardized questionnaire administered by trained staff covered exposure to secondhand smoke for the 20 years preceding diagnosis: no. of cigarettes smoked/day, no. of years of exposure to secondhand smoke.
Zaridze *et al*. (1998) (Russia, not reported)	Women: 189 cases, 358 controls	Histologically confirmed cases of primary lung cancer were identified in two cancer treatment hospitals in Moscow. Controls were female oncology patients from the same hospitals who did not have lung or upper respiratory cancers. Cases and controls were required to be nonsmokers who lived in Moscow.	Age and education	In-person interviews were conducted within 2–3 days of hospital admission; they included questions on exposure to secondhand smoke in adulthood and childhood.
Boffetta *et al*. (1999a) (Europe, 1988–94)	Women: 208 cases, 361 controls	Same as Boffetta *et al*. (1998) except that results are stratified by type of exposure to secondhand smoke (cigarettes or cigars, cigarillos and pipes)	Age and centre	Same as Boffetta *et al*. (1998)
Boffetta *et al*. (1999b) (Europe, 1994–96)	Men: 4 cases, 41 controls Women: 66 cases, 137 controls	Histologically confirmed lung adenocarcinomas were identified from 9 centres in 7 countries from a larger study designed to assess the role of biomarkers of susceptibility in lung cancer among nonsmokers. Controls were selected from nonsmokers in the source populations or in hospital patients. Controls were frequency-matched to cases on age and gender.	Age, gender, and centre. Some models also included urban residence, education and occupational exposure.	Exposure to secondhand smoke was assessed using the same questionnaire as in Boffetta *et al*. (1998).

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Rapiti *et al*. (1999) (India, 1991–92)	Men: 17 cases, 56 controls Women: 41 cases, 67 controls	Histologically or cytologically confirmed cases of primary lung cancer were identified in a hospital in Chandigarh, Northern India. Two controls were selected for each case. One control was a patient at the same hospital who was not hospitalized for more than a month and did not have a disease related to active or passive smoking, alcohol or diet. The other control was a visitor of the patient. No matching of cases and controls was performed.	Sex, age, religion and residence	Interviews of subjects were conducted that included questions on exposure to secondhand smoke from the spouse, at the workplace and during childhood.
Zhong *et al*. (1999) (China, 1992–94)	Women: 504 cases, 601 controls	Cases of primary lung cancer aged 35–69 years were identified from the Shanghai cancer registry. Controls were randomly selected from a Shanghai residential registry and frequency-matched to the age distribution of female lung cancer patients in Shanghai in 1987–89.	Age, income, vitamin C intake, kitchen smokiness, family history of lung cancer, and potentially high risk occupations, and respondent status	Personal interviews with study subjects or their next of kin (2.3% for controls, and 20.2% for cases). The interview included questions on exposure to secondhand smoke from the spouse, at the workplace and during childhood.
Brennan *et al*. (2000) (Europe, 1994–96)	Subset of cases and controls from centres included in Boffetta *et al*. (1998) for whom dietary information was available	Same as Boffetta *et al*. (1998), but analyses were restricted to centres that had information on subjects' consumption of fruit, lettuce, tomato, carrot, cheese, carotenoids, β-carotene or retinol. Analyses were stratified by high and low consumption of these dietary variables, and high and low exposure to secondhand smoke.	Age, gender and centre	Same as Boffetta *et al*. (1998). High exposure to secondhand smoke was defined as being in the upper quartile from combined spousal and workplace exposures.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Kreuzer *et al*. (2000) (Germany, 1990–96)	Men and women: 292 cases, 1338 controls	An extension of the German part of the European multicentre study (Boffetta *et al*., 1998). The cases and controls were a subset of nonsmokers from a larger study of radon exposure in Germany. Cases were identified from 15 hospitals in the study area and were restricted to those who were < 75 years of age; resident in the study area; had lived for > 25 years in Germany; interviewed within 3 months of diagnosis, and not too ill. Controls satisfying the first three criteria listed above were identified from mandatory registries or by modified random digit dialling and were frequency-matched to the cases on sex, age and region. The response rate in the cases was 76%, but that of the controls was only 41%.	Age, region, gender; some models included occupational exposure, exposure to radon, diet, family history of cancer, previous non-malignant respiratory disease and social class.	Same as Boffetta *et al*. (1998)
Lee *et al*. (2000) (China (Province of Taiwan), 1992–98)	Women: 268 cases, 445 controls	Histologically verified cases were identified from Kaohsiung Medical University Hospital in Taiwan. Controls were patients with conditions unrelated to tobacco smoking who were selected within 3 weeks of the case admission from the same hospital, and matched on age.	Age, date of hospital admission, residential area, education, occupation, tuber-culosis, cooking fuels and presence of a fume extractor	Interviews were conducted using a structured questionnaire designed to elicit information on exposure to secondhand smoke.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Wang *et al*. (2000) (China, 1994–98)	Men: 33 cases, 1214 controls Women: 200 cases, 407 controls	Cases of lung cancer who were aged 30–75 years and residents of Pingliang or Qingyang prefectures were identified from hospitals and clinics in these and neighbouring regions. Controls were randomly selected from 1990 census lists for the 2 prefectures and frequency matched to cases on age, sex and prefecture.	Age, sex and prefecture	In person interviews were conducted with cases and controls or with their next of kin when necessary. The questionnaire included questions on exposure to secondhand smoke during adulthood, childhood and in the workplace.
Johnson *et al*. (2001) (Canada, 1994–97)	Women: 71 cases, 761 controls	Cases of histologically confirmed primary lung cancer were identified from a national cancer surveillance system that covers 8 of Canada's 10 provinces. In five provinces controls were identified from health insurance plans, in one from property assessment databases, and in two using random digit dialling. Controls were frequency-matched to the expected distribution of cancer cases by age and province.	Age, province, education and fruit and vegetable consumption	Mailed questionnaires were completed by cases and controls except in one province where next of kin completed them. The questionnaires included questions on exposure to secondhand smoke at work, at home and during childhood.
Kreuzer *et al*. (2001) (Germany, 1990–96)	Men: 58 cases, 803 controls	Same as Kreuzer *et al*. (2000) except that analyses were restricted to men.	Same as Kreuzer *et al*. (2000)	Same as Boffetta *et al*. (1998). Results only presented for low and high exposure to secondhand smoke where high was defined as having greater than the 75th percentile of cumulative duration of exposure weighted by a subjective index of intensity.

Table 2.3 (contd)

Reference (country, years of study)	No. of non-smoking cases and controls	Eligibility criteria and comments	Covariates adjusted for	Source of exposure data
Kreuzer *et al*. (2002) (Germany, 1990–96)	Women: 234 cases, 535 controls	Same as Kreuzer *et al*. (2000) except that analyses were restricted to women	Same as Kreuzer *et al*. (2000)	Same as Boffetta *et al*. (1998). Results only presented for high and medium exposure to secondhand smoke versus low or non-exposed. High was defined as having greater than the 90th percentile of cumulative duration of exposure, and low was defined as having less than the 75th percentile.

[a] This study presented results separately for patients with adenocarcinoma and for patients with squamous-cell carcinoma. However, the numbers for the squamous-cell carcinomas were too few to present meaningful results for secondhand smoke in nonsmokers.
[b] Although this study did match cases to controls on several potential confounders, an unmatched analysis was published.
[c] The study had a total of 184 controls in each of the control groups. However, it is unclear how many controls were used in the analysis of exposure to secondhand smoke because several cases (and presumably their matched controls) were dropped from these analyses.
[d] Information on spousal smoking habits was available for only some of the cases and controls. The actual number of cases and controls included in the analysis was not reported, but was smaller than the given numbers.

The study from China by Sun *et al*. (1996) included 230 cases and 230 controls. The study controlled for age and education, but not for burning of coal and frying in oil.

The study of Lee *et al*. (2000) from China (Province of Taiwan) included 268 cases and 445 controls and was an extension of the study of Ko *et al*. (1997). Detailed information on exposure to secondhand smoke was collected, and nonsmoking status was verified by household members. Potential confounding by age, education, occupation, cooking fuels and other factors was allowed for.

The participants in a European multicentre study included 650 cases and 1542 controls from 12 centres in seven countries. Potential confounders such as occupational exposure, socioeconomic status and intake of fruits and vegetables were taken into account. The main publication was by Boffetta *et al.* (1998), but additional analyses were made of effects of secondhand smoke from cigars, cigarillos and pipes (Boffetta *et al*., 1999b) and of exposure to secondhand smoke and diet (Brennan *et al.*, 2000). In addition, the data from some centres on specific aspects have been published separately and in some cases with additional data (Germany: Jöckel *et al.*, 1998a,b; Kreuzer *et al.*, 2000, 2001, 2002; Sweden: Nyberg *et al.*, 1998).

The study of Zaridze *et al*. (1998) from Russia included 189 cases and 358 controls. Information on exposure to secondhand smoke in the family and from colleagues at work was obtained, and potential confounders (age and education) were considered.

(*b*) *Exposure to secondhand smoke from the partner*

Table 2.2 shows the relative risk for lung cancer associated with exposure to secondhand smoke from the spouse. Taking the crude relative risks, or the adjusted estimates when the crude ones are not available (in any event, the crude and adjusted estimates are similar) 25 of the 40 case–control studies of nonsmoking women showed an increased risk; the results of seven of the 25 studies were statistically significant (Trichopolous *et al.*, 1983; Lam, 1985; Lam *et al.*, 1987; Geng *et al.*, 1988; Fontham *et al.*, 1994; Zaridze *et al.*, 1998; Lee *et al.*, 2000). In studies of nonsmoking men, five of the nine studies showed an increased risk, although none were statistically significant.

Exposure–response relationships

Several studies reported the risk of lung cancer associated with increasing levels of exposure, in particular, the number of cigarettes smoked by the spouse per day, the number of years of living with a smoker and pack–years; these studies are listed in Table 2.4. Because most of these studies were relatively small, they would not have had sufficient statistical power to find an exposure–response relationship. Eight studies found a statistically significant trend (p value < 0.05) between lung cancer risk and the number of cigarettes smoked by the spouse (Trichopolous *et al.*, 1983; Hirayama, 1984; Garfinkel *et al.*, 1985; Lam *et al.*, 1987; Geng *et al.*, 1988; Inoue & Hirayama, 1988; Liu *et al.*, 1993; Cardenas *et al.*, 1997) and one other found an almost statistically significant trend (Akiba *et al.*, 1986; $p = 0.06$). Six studies found a statistically significant trend (p value < 0.05) for lung cancer risk and the number of years of marriage to a smoker (Gao *et al.*,

Table 2.4. Relative risk of lung cancer in lifelong nonsmoking women comparing those with the highest exposure to secondhand smoke from a smoking partner to women with nonsmoking partners (the relative risks are ranked in ascending order for each type of exposure)

Reference	Exposure level	Relative risk[a] (95% CI)	
	No. of cigarettes smoked per day by the spouse		
Garfinkel (1981)	≥ 20	1.1	(0.8–1.6)
Kabat *et al.* (1995)	> 10	1.1	(0.5–2.3)
Humble *et al.* (1987)	≥ 21	1.2	(0.3–5.2)
Koo *et al.* (1987)	≥ 21	1.2	(0.5–3.0)
Boffetta *et al.* (1998)	> 18.1	1.3	(0.8–2.2)
Wang *et al*. (1996)	≥ 20	1.4	(0.8–2.6)
Zhong *et al*. (1999)	> 20	1.4	(0.7–2.6)
Jee *et al*. (1999)	≥ 20	1.5	(0.7–3.3)
Du *et al.* (1993)	> 20	1.6[b]	(0.8–3.2)
Kalandidi *et al.* (1990)	≥ 41	1.6	(0.5–4.6)
Hirayama (1984)[c,d]	≥ 20	1.7	(1.1–2.7)
Cardenas *et al.* (1997)	≥ 40	1.9	(1.0–3.6)
Trichopoulos *et al.* (1983)	≥ 31	1.9	(0.7–5.0)
Akiba *et al.* (1986)[d]	≥ 30	2.1	(1.7–2.6)
Garfinkel *et al.* (1985)	≥ 20	2.1	(1.1–4.0)
Lam *et al.* (1987)	≥ 21	2.1	(1.1–4.0)
Geng *et al.* (1988)	≥ 20	2.8	(1.9–4.1)
Liu *et al.* (1993)	≥ 20	2.9	(1.2–7.3)
Pershagen *et al.* (1987)	≥ 16[e]	3.2	(1.0–9.5)
Inoue & Hirayama (1988)	≥ 20	3.4	(1.2–9.7)
	No. of years of marriage to a smoker		
Buffler *et al*. (1984)	≥ 33	0.9	(0.4–2.3)
Sun *et al*. (1996)	≥ 35	0.9	(0.5–1.7)
Boffetta *et al.* (1998)	≥ 43	1.0	(0.7–1.7)
Cardenas *et al.* (1997)	≥ 30	1.1	(0.6–2.1)
Wang *et al*. (1996)	≥ 41	1.1	(0.4–3.1)
Zhong *et al*. (1999)	≥ 36	1.1	(0.7–1.8)
Du *et al.* (1993)	≥ 30	1.2	(0.6–2.3)
Fontham *et al.* (1994)	≥ 31	1.2	(0.9–1.7)
Akiba *et al.* (1986)[d]	≥ 40	1.3	(0.6–2.8)
Zaridze *et al.* (1998)	> 15	1.4	(1.0–2.1)
Gao *et al.* (1987)	≥ 40	1.7	(1.0–2.9)
Kalandidi *et al.* (1990)	≥ 40	1.9	(0.8–4.3)
Wu *et al.* (1985)	≥ 31[f]	2.0	NA[g]
Humble *et al.* (1987)	≥ 27	2.1	(0.7–6.9)

Table 2.4 (contd)

Reference	Exposure level	Relative risk[a] (95% CI)	
Choi *et al.* (1989)	≥ 41	2.3	(1.0–5.6)
Stockwell *et al.* (1992)	≥ 40	2.4	(1.1–5.3)
Jee *et al*. (1999)	≥ 30	3.1	(1.4–6.6)
Geng *et al.* (1988)	≥ 40	3.3	(2.1–5.2)
	No. of pack–years of exposure[h]		
Rapiti *et al*. (1999)	> 128	0.4	(0.1–1.8)
Kreuzer *et al*. (2000)[i]	> 23	0.8	(0.2–3.1)
Brownson *et al.* (1992)	≥ 40	1.3	(1.0–1.7)
Boffetta *et al.* (1998)	≥ 23	1.5	(1.0–2.4)
Cardenas *et al.* (1997)	≥ 36	1.5	(0.8–2.6)
Fontham *et al.* (1994)	≥ 80	1.8	(1.0–3.3)
Lee *et al*. (2000)	> 40	3.3	(1.7–6.2)
Correa *et al.* (1983)	≥ 41	3.5	[1.2–10.2][j]

[a] Rate ratios for cohort studies (Garfinkel (1981), Hirayama (1984), Cardenas (1997) & Jee (1999)); odds ratios for case–control studies (all the other studies); adjusted relative risk, where not available crude relative risk

[b] Results are from an analysis using non-tumour controls. The paper also presents results using controls with tumours of sites other than lung (odds ratio, 1.4; 95% CI, 0.7–2.5).

[c] The results are from Table 2 of Hirayama (1984), which were adjusted by the wife's age.

[d] The report presented 90% CIs; 95% CIs were estimated for this table.

[e] For ≥ 30 years of marriage

[f] Years of exposure for adults (from partner and at workplace)

[g] Not available or estimatable from data presented in the paper

[h] Pack–years = number of packs of cigarettes smoked daily by the partner × years of smoking

[i] Some of the cases and controls reported on in Kreuzer *et al*. (2000) were part of another study included in this table (Boffetta *et al*., 1998). The results given here for the study by Kreuzer are based on those cases and controls that were not part of the study by Boffetta (personal communication M. Kreuzer).

[j] Confidence intervals in brackets were not given in the original report and were estimated for this table using an approximate method.

1987; Geng *et al.*, 1988; Stockwell *et al.*, 1992; Fontham *et al.*, 1994; Cardenas *et al.*, 1997; Jee *et al.*, 1999) and the results of two others were almost significant (Kalandidi *et al.*, 1990; Zaridze *et al.*, 1998; p value = 0.07 in both).

Table 2.4 shows the increase in risk in nonsmoking women who have the highest level of exposure according to each measure. All 20 of the studies that reported on the number of cigarettes smoked showed an increased risk in the highest exposure group, and seven of the studies reported a doubling of risk or more. Similarly, of the 18 studies that looked

at the number of years of marriage to a smoker, all but three showed an increased risk in the highest exposure group; six reported a relative risk of at least 2.0.

In summary, there is evidence of an exposure–response relationship, thus providing further support for a causal relationship between the development of lung cancer and exposure to secondhand smoke from partners.

(*c*) *Exposure to secondhand smoke at the workplace*

In total, 23 studies have been published on exposure to secondhand smoke at the workplace (Table 2.5). The results from these studies are mixed with some showing a positive association and others not. Only one study reported a statistically significant association between exposure to secondhand smoke at the workplace and risk for lung cancer (Reynolds *et al*., 1996). Many of the studies assessed only recent workplace exposure to secondhand smoke; this is likely to result in a serious misclassification of exposure because past exposure is more likely to be etiologically relevant.

Exposure–response relationships

Two studies found no statistically significant exposure–response relationship (Kalandidi *et al.*, 1990; Kabat *et al.*, 1995).

In the study by Reynolds *et al*. (1996) in the USA, the risk for lung cancer in women who were exposed to secondhand smoke at work was significantly increased to 1.6 (95% CI, 1.2–2.0). For women who had been exposed to secondhand smoke for 1–15, 16–30 or > 30 years, the relative risk for developing lung cancer increased significantly ($p < 0.001$) with the length of the exposure period: 1.5 (95% CI, 1.1–1.9), 1.6 (95% CI, 1.1–2.2) and 2.1 (95% CI, 1.4–3.2), respectively.

In the European multicentre study (Boffetta *et al.* 1998), the relative risk for lung cancer after exposure to secondhand smoke at work was 1.2 (95% CI, 0.9–1.5). No exposure–response relationship was seen when the data were analysed according to duration of exposure but a significant trend was observed after analysis of weighted exposure, which is most likely a better index of exposure than duration. A significant relative risk of 2.1 (95% CI, 1.3–3.2) was observed in the group with the highest weighted exposure.

Two studies from Germany which are included in part in Boffetta *et al.* (1998) also showed an increased risk in the highest exposure group of 1.9 (95% CI, 1.1–3.6) and 2.5 (women only, 95% CI, 1.1–5.7) (Jöckel *et al*., 1998b; Kreuzer *et al*., 2000).

The study of Rapiti *et al*. (1999) reported increasing relative risks with increasing duration of exposure, but the trend did not reach statistical significance.

In the study of Zhong *et al*. (1999), women ever exposed to secondhand smoke at work showed an odds ratio of 1.7 (95% CI, 1.3–2.3). There was a statistically significant ($p < 0.001$) increase in risk associated with the number of hours of exposure per day at work with odds ratios of 1.0 (95% CI, 0.6–1.7), 1.6 (95% CI, 1.0–2.5) and 2.9 (95% CI, 1.8–4.7) for 1–2, 3–4 and > 4 h per day. When the number of co-workers who smoked was considered there was again a statistically significant trend ($p < 0.001$) with odds ratios of 1.0 (95% CI, 0.6–1.6), 1.7 (95% CI, 1.1–2.8) and 3.0 (95% CI, 1.8–4.9) for 1–2,

Table 2.5. The relative risk for lung cancer in nonsmokers exposed to secondhand smoke at the workplace compared with nonsmokers who were not

Reference	Sex of subjects	No. of cases of lung cancer	Relative risk for lung cancer (95% CI) if exposed at the workplace	
			Crude analysis	Adjusted analysis
Kabat *et al*. (1984)	Men	25	3.3 [1.0–10.6]	NR
	Women	53	0.7 [0.3–1.5]	NR
Koo *et al*. (1984)	Women	88	1.2 [0.5–3.0]	NR
Garfinkel *et al*. (1985)	Women	76	NR	0.9 (0.7–1.2)[a]
Wu *et al*. (1985)	Women	29	NR	1.3 (0.5–3.3)[b]
Lee *et al*. (1986)	Men	10	1.6 [0.4–6.6]	NR
	Women	15	0.6 [0.2–2.3]	NR
Butler (1988)	Men	6	NR	1.0 [0.2–5.4]
	Women	7	NR	0.98 [0.2–5.4]
Shimizu *et al*. (1988)	Women	90	1.2 [0.6–2.6][c]	NR
Kalandidi *et al*. (1990)	Women	89	1.4 [0.8–2.5]	NR
Wu-Williams *et al*. (1990)	Women	415	1.2 [1.0–1.6]	1.2 (0.9–1.6)
Kabat *et al*. (1995)	Men	41	NR	1.0 (0.5–2.1)
	Women	58	NR	1.2 (0.6–2.1)
Reynolds *et al.* (1996)	Women	528	1.4 [1.1–1.7]	1.6 (1.2–2.0)
Schwartz *et al*. (1996)	Men + women	257	NR	1.5 (1.0–2.2)
Sun *et al*. (1996)	Women	230	NR	1.4 (0.9–2.0)
Wang *et al*. (1996)	Women	135	0.9 (0.5–1.8)	NR
Boffetta *et al*. (1998)	Men + women	650	1.1 [0.9–1.3]	1.2 (0.9–1.5)
	Men	141	1.2 [0.8–1.8]	NR
	Women	509	1.3 [1.0–1.6]	1.2 (0.9–1.5)
Zaridze *et al*. (1998)	Women	189	1.0 [0.7–1.6]	0.9 (0.6–1.4)
Boffetta *et al.* (1999a)	Men + women	70	1.2 (0.7–2.1)	1.0 (0.5–1.8)
Rapiti *et al*. (1999)	Men + women	58	NR	1.1 (0.3–4.1)[d]
Zhong *et al*. (1999)	Women	504	1.4 [1.0–1.8]	1.7 (1.3–2.3)
Kreuzer *et al*. (2000)[e]	Men + women	123	0.7 [0.5–1.0]	1.1 (0.7–1.7)
	Men	23	0.5 [0.2–1.3]	NR
	Women	100	1.1 [0.7–1.7]	1.4 (0.8–2.2)
Lee *et al*. (2000)	Women	268	1.2 [0.7–1.9]	0.9 [0.5–1.7]
Wang *et al*. (2000)	Men + women	233	NR	1.6 (0.7–3.3)
Johnson *et al*. (2001)	Women	71	1.2 [0.7–2.0]	NR

NR, not reported

[a] Results shown are for exposure over the preceding 25 years

[b] Results are for adenocarcinoma. There were too few cases in this study to permit an analysis for squamous-cell carcinoma or other histological types.

[c] The 95% CI was not reported. It was estimated using the average standard error taken from Kalandidi *et al*. (1990) and Nyberg *et al*. (1998), because all three studies included similar numbers of cases of lung cancer.

[d] The reported result was 1.1 (95% CI, 0.9–1.6); the authors reported the correct estimates in Wells *et al*. (1998).

[e] Some of the cases and controls in the study by Kreuzer *et al*. (2000) were also part of another study included in this table (Boffetta *et al*., 1998). The results given here are based on those cases and controls that were not part of the study by Boffetta *et al.* [personal communication M. Kreuzer].

3–4 and > 4 co-workers who smoked, whereas there was no increase in relative risk with increasing numbers of years of exposure to secondhand smoke. Risk estimates were not affected when analyses were restricted to personal interviews excluding proxy interviews.

In summary, the studies in which exposure–response relationships were analysed generally revealed an increase in the relative risk for lung cancer associated with exposure to secondhand smoke at work and statistically significant increases in relative risk in those groups with the highest level of exposure. The associations are stronger in studies with better assessment of exposure and other aspects of study design.

(*d*) *Exposure during childhood*

The studies on exposure to secondhand smoke during childhood are summarized in Table 2.6. The results of these studies have been somewhat contradictory. Out of 23 studies, only three studies of exposure from the mother reported a significantly increased relative risk (Brownson *et al*., 1992; Sun *et al*., 1996; Rapiti *et al*., 1999) and two studies reported a significant increase in relative risk related to exposure from the father or either parent (Sun *et al*., 1996; Rapiti *et al*., 1999). One study found a significant inverse association with exposure from the father or either parent (Boffetta *et al*., 1998).

Exposure–response relationships

The study of Wang *et al*. (2000) observed a significant trend ($p < 0.01$) with increasing pack–years of childhood exposure to secondhand smoke with odds ratios for men and women combined of 1.0, 1.4 (95% CI, 1.0–2.1), 1.8 (95% CI, 1.0–3.3) and 3.0 (95% CI, 1.0–8.9) for < 1, 1–9, 10–19 and ≥ 20 pack–years. In contrast, the study of Boffetta *et al*. (1998) suggested a negative trend for cumulative exposure, which was statitistically significant for all subjects combined ($p = 0.02$).

In summary, there is no clear indication that lung cancer risk in later life is associated with exposure to secondhand smoke in childhood. However, an important problem in interpreting these studies is the very poor quality of the assessment of exposure that occurred 50 or more years in the past.

(*e*) *Exposure from other sources*

Few studies have addressed exposure to secondhand smoke from other sources. Kreuzer *et al*. (2000) reported a significantly increased relative risk of 2.6 (95% CI, 1.3–5.4) for exposure in vehicles in the highest category of weighted duration of exposure.

Other studies have either not addressed these other sources of exposure or have considered them only as part of a cumulative exposure from all sources.

In summary, insufficient data are available to evaluate the risk from exposure to secondhand smoke from other sources.

Table 2.6. The relative risk[a] for lung cancer in nonsmokers exposed to second-hand smoke during childhood compared with that in nonsmokers who were not

Reference	Sex of subjects	No. of cases of lung cancer	Relative risk (95% CI) for lung cancer according to exposure during childhood		
			Mother	Father	Either parent
Garfinkel *et al*. (1985)	Women	134	NR	NR	0.9 (0.7–1.1)
Wu *et al*. (1985)	Women	29	NR	NR	0.6 (0.2–1.7)
Koo *et al*. (1987)	Women	88	NR	NR	0.6 [0.2–1.8]
Pershagen *et al*. (1987)	Women	47	NR	NR	1.0 (0.4–2.3)
Shimizu *et al*. (1988)	Women	90	4.0 [1.0–15.7][b]	1.1 [0.6–2.0][b]	NR
Svensson *et al*. (1989)	Women	34	3.1 [0.7–14.0]	0.9 [0.4–1.9]	NR
Janerich *et al*. (1990)	Men + women	191	NR	NR	1.3 [0.9–2.0]
Sobue (1990)	Women	144	1.4 [0.8–2.5]	0.8 [0.5–1.2]	NR
Wu-Williams *et al*. (1990)	Women	417	0.9 (0.7–1.1)	1.1 (0.8–1.4)	NR
Brownson *et al*. (1992)	Women	431	NR	NR	0.6 [0.5–0.8]
Stockwell *et al*. (1992)	Women	210	1.6 (0.6–4.3)	1.2 (0.6–2.3)	NR
Fontham *et al*. (1994)	Women	651	0.9 (0.7–1.2)	0.9 (0.7–1.0)	NR
Kabat *et al*. (1995)	Men	40	NR	NR	0.9 (0.4–1.9)
	Women	69	NR	NR	1.6 (0.95–2.8)
Sun *et al*. (1996)	Women	230	2.1 (1.3–3.3)	2.4 (1.6–3.5)	2.3 (1.6–3.4)
Wang *et al*. (1996)	Women	135	NR	NR	0.9 (0.6–1.5)
Zaridze *et al*. (1998)	Women	189	NR	1.0 [0.7–1.4]	NR
Boffetta *et al*. (1998)	Men + women	641	0.9 (0.6–1.5)	0.8 (0.6–0.9)	0.8 [0.6–0.9]
	Men	140	NR	NR	0.7 [0.5–1.1]
	Women	501	NR	NR	0.7 [0.6–0.9]

Table 2.6 (contd)

Reference	Sex of subjects	No. of cases of lung cancer	Relative risk (95% CI) for lung cancer according to exposure during childhood		
			Mother	Father	Either parent
Boffetta *et al.* (1999a)	Men + women	67	0.3 (0.1–1.1)	0.6 (0.3–1.0)	0.5 (0.3–0.9)
Rapiti *et al.* (1999)	Men + women	58	5.7 [1.3–25.6]	4.5 [2.3–8.8]	3.6 [1.8–6.9]
	Men	17	–[c]	0.2 [0.0–1.7]	0.2 [0.0–1.5]
	Women	41	7.7 [1.6–37.2]	12.6 [4.9–32.7]	8.7 [3.6–21.2]
Zhong *et al.* (1999)	Women	504	NR	NR	1.0 [0.8–1.3]
Kreuzer *et al.* (2000)[d]	Men + women	123	NR	NR	1.0 [0.7–1.5]
	Men	23	NR	NR	0.97 [0.4–2.3]
	Women	100	NR	NR	0.9 [0.5–1.4]
Lee *et al.* (2000)[e]	Women	268	1.5 [0.6–3.9]	1.2 [0.9–1.6]	NR
Wang *et al.* (2000)	Men + women	228	NR	NR	1.4 [1.0–2.0]
	Men	32	NR	NR	1.7 [0.8–3.9]
	Women	196	NR	NR	1.3 [0.9–1.9]
Johnson *et al.* (2001)	Women	71	NR	NR	1.3 [0.8–2.2]

NR, not reported

[a] The crude results are given in the table and where these were not available, the adjusted ones are given.

[b] Only the p value was reported ($p < 0.05$ mother; $p > 0.05$ father); the standard error used to estimate the 95% CI was taken to be the same as in Nyberg *et al*. (1998) because both studies have a similar number of cases.

[c] There were no exposed cases and controls, and thus the odds ratio is undefined.

[d] Results from an analysis that excluded cases and controls that were included in Boffetta *et al*. (1998)

[e] The adjusted results are for children whose parents smoked in their presence whereas the crude results are for having a parent who was a smoker which is consistent with the definition used in the other studies.

(*f*) *Bias and confounding*

There are two sources of bias (misclassification bias and bias resulting from exposure to secondhand smoke in the reference group) and several potential confounders (e.g. dietary confounding) that can result in the relative risk being overestimated or underestimated in the studies of the association between lung cancer and exposure to secondhand smoke described above.

(i) *Misclassification bias*

Misclassification bias occurs when some of the subjects recorded as never-smokers who are included in the studies are in fact current or former smokers who have misreported their smoking status. Their true smoking status makes these subjects more likely to develop lung cancer and because smokers tend to live with smokers, this bias will overestimate the true risk for lung cancer from exposure to secondhand smoke from the spouse. There has been much discussion in the literature on this bias, and it is the main factor proposed as partly or fully explaining the increased risk for lung cancer observed in epidemiological studies. The bias has four determinants:

- *The prevalence of smoking in a particular population*. This can be obtained directly from some of the studies or from national statistics.
- *The aggregation ratio (the extent to which a smoker is more likely to live with another smoker rather than a nonsmoker)*. It is generally accepted to be between 2 and 4 (Wald *et al*., 1986; US Environmental Protection Agency, 1992; Lee, 1992; Hackshaw *et al*., 1997).
- *The relative risk for lung cancer in current and former smokers misclassified as never-smokers*. Some meta-analyses have assumed that the risk for lung cancer in misclassified smokers is the same as that in all reported smokers (US Environmental Protection Agency, 1992; Lee, 1992, 1998). However, misclassified current smokers tend to be light smokers and misclassified former smokers have usually given up smoking many years before the study, so the risk in both groups will be less than the average risk in all current or former smokers. The overall relative risk for lung cancer in misclassified ever smokers has been estimated to be about 3 (Hackshaw *et al*., 1997).
- *The percentage of current and former smokers misclassified as never-smokers*. The percentage of misclassified current smokers can be estimated by comparing self-reported smoking status with serum, urine or salivary cotinine levels; current smokers who report themselves to be never-smokers would tend to have high concentrations (for example, a urinary cotinine concentration > 50 ng/mg creatinine). Wells *et al*. (1998) combined the results of 13 studies, seven of which were used in the US Environmental Protection Agency (1992) report, and concluded that the rates of misclassification of smokers are low; 1.6% of Caucasian women who were current smokers reported themselves as never-smokers. The estimate was higher, though still low, for women from a minority background (4.9%). Similar conclusions had been drawn from a review of six studies on cotinine and nicotine (two of which were included in the review by Wells *et al*., 1998) in which it was estimated that 3.1% of ever smokers were current smokers who reported themselves as never-smokers (Hackshaw *et al*., 1997). Two of the case–control studies on secondhand smoke and risk of lung cancer in female never-smokers (Table 2.2) measured urinary cotinine in the subjects and compared this with their reported smoking status. The percentage of reported never-smoking women with urinary cotinine concentrations > 50 ng/mg creatinine was 3.5% in the study by

Riboli *et al*. (1995) (included in Boffetta *et al.*, 1998 in Table 2.2) and 3.1% of patients with lung cancer and 5.0% of controls in the study by Fontham *et al*. (1994).

(ii) *Bias resulting from exposure to secondhand smoke in the reference group*

Studies of the risk for lung cancer and exposure to secondhand smoke have defined the reference group as never-smoking women with husbands who are nonsmokers. However, these women, although not exposed at home, may be exposed to secondhand smoke outside the home. This bias will tend to underestimate the true relative risk.

(iii) *Dietary confounding*

Several potential confounders have been proposed that may partly or fully explain the increased risk of lung cancer associated with exposure to secondhand smoke from the spouse. None of these potential confounders have been established as having a causal link with lung cancer. For example, dietary confounding (perhaps the main potential confounder) may arise because (i) nonsmokers who live with smokers tend to have similar diets, (ii) the diets of smokers tend to be poorer than those of nonsmokers (i.e. lower consumption of fruits and vegetables) and (iii) people who consume less fruits and vegetables may be more likely to develop lung cancer. Several of the observational studies listed in Table 2.2 had attempted to adjust for consumption of fruits and vegetables or other dietary factors (Dalager *et al.*, 1986 [used data from Correa *et al.* (1983) and Buffler *et al.* (1984) in Table 2.2]; Hirayama, 1989 [used data from Hirayama (1984)]; Kalandidi *et al.*, 1990; Alavanja *et al*., 1993 [used data from Brownson *et al.* (1992)]; Fontham *et al*., 1994; Mayne *et al.*, 1994 [used data from Janerich *et al.* (1990)]; Cardenas *et al.*, 1997; Boffetta *et al.*, 1998; Zhong *et al.*, 1999; Brennan *et al*., 2000; Johnson *et al.*, 2001); they showed that the effect of dietary confounding was negligible.

2.1.3 *Meta-analyses of observational studies of exposure to secondhand smoke and lung cancer in adults*

(*a*) *Introduction*

Since the publication of the first epidemiological studies that reported directly on the association between exposure to secondhand smoke and the risk of lung cancer in nonsmokers (Garfinkel, 1981; Hirayama, 1981), there have been several other cohort studies and case–control studies. Most of these studies were based on a relatively small number of lung cancer cases and did not, therefore, have enough power to show a statistically significant association on their own. Meta-analyses have therefore been performed with the aim of pooling the available data and thus providing a more precise estimate of the risk. A meta-analysis is a formal statistical technique used to combine the estimates of relative risk across studies into a single estimate. Originally developed for clinical trials, it has also been applied to observational studies (see Peto, 1992, for a brief

discussion of some aspects of meta-analyses of case–control and cohort studies on cancer). In spite of some concerns over the application of meta-analysis to studies of secondhand smoke and lung cancer, it is an appropriate approach for interpreting the published data collectively.

(*b*) *Published meta-analyses*

This section presents the results of selected published reports.

(i) *Exposure to secondhand smoke from the spouse*

Table 2.7 shows the main results of published meta-analyses on the risk for lung cancer in never-smokers associated with exposure to secondhand smoke from the spouse, including an indication of whether any adjustment was made for bias and confounding. All the pooled estimates show an increased risk (relative risks of 1.1–1.6), despite using different combinations of studies and methodology.

Some meta-analyses adjusted for the misclassification of ever-smokers as never-smokers (which will tend to overestimate risk). For example, in the analysis by Hackshaw *et al.* (1997) the relative risk was reduced from 1.24 to 1.18 after allowing for misclassification bias in 37 studies of nonsmoking women. In the analysis by Lee *et al.* (2001), which was based on 47 studies and used a different methodology, after allowing for misclassification bias the relative risk was reduced from 1.23 to 1.17. The effect is small.

Few meta-analyses have adjusted for background exposure to secondhand smoke from sources other than the spouse in the reference group (which will tend to underestimate risk). Hackshaw *et al.* (1997) reported that the effect of such an adjustment was to increase the observed relative risk from 1.24 to 1.42.

Few reviews have attempted to adjust for diet as a potential confounder. Hackshaw *et al*. (1997) used pooled data from nine studies of the risk of lung cancer associated with fruit and vegetable consumption in nonsmokers and pooled data from three studies on the difference in diet between nonsmokers who did and did not live with a smoker; the relative risk for lung cancer due to exposure to secondhand smoke from the spouse was reduced from 1.24 (as observed) to 1.21 after adjusting for fruit and vegetable consumption. A similarly small effect was reported by Lee *et al.* (2001), after adjusting for consumption of dietary fat and education as well as consumption of fruits and vegetables, and using different methodology and a larger set of studies (for the risk of lung cancer associated with each confounder: 17 studies on consumption of fruits and vegetables, seven on dietary fat and 12 on education; for the difference between nonsmokers who do and do not live with a smoker: nine studies on consumption of fruits and vegetables, seven on dietary fat and nine on education). The relative risk for lung cancer when the husband smoked 10 cigarettes/day was reduced from 1.10 (observed) to 1.09, after allowing for these three confounders (Lee *et al.*, 2001). In both analyses the effect of allowing for confounding was small.

Table 2.7. Summary results of selected published meta-analyses of the risk for lung cancer in never-smokers exposed to secondhand smoke from the spouse

Reference	No. of studies	Sex of subjects	Pooled relative risk (95% CI)	Pooled estimate adjusted for			Adjusted pooled relative risk
				Misclassification bias	Exposure to secondhand smoke other than from the spouse	Dietary confounding	
National Research Council (1986)	13	Men and women	1.34 (1.18–1.53)	Yes	Yes	No	1.42
	13	Women	1.32 (1.16–1.53)	No	No	No	
Wald *et al*. (1986)	13	Men and women	1.35 (1.19–1.54)	Yes	Yes	No	1.53
Fleiss & Gross (1991)	9 (USA only)	Women	1.12 (0.95–1.30)	No	No	No	
Lee (1992)	28	Men and women	1.20 (1.09–1.31)	No	No	No	
	28	Women	1.18 (1.07–1.30)	No	No	No	
	11	Men	1.39 (0.97–1.99)	No	No	No	
Tweedie & Mengersen (1992)	26	Women	1.17 (1.06–1.28)	Yes	Yes	No	1.08
US Environmental Protection Agency (1992)	11 (USA only)	Women	1.19 (1.04–1.35)	Yes	Yes	No	1.59
Hackshaw (1998)	37	Women	1.24 (1.13–1.36)	Yes	Yes	Yes	1.26
	9	Men	1.34 (0.97–1.84)	No	No	No	
Zhong *et al*. (2000)	40	Women	1.20 (1.12–1.29)	No	No	No	
Lee *et al.* (2001)	47	Women	1.23 (1.12–1.36)	Yes	No	No	1.17
Boffetta *et al*. (2002)	45	Women	1.25 (1.14–1.38)	No	No	No	
	9	Men	1.25 (0.95–1.65)				

Generally, the overestimation due to misclassification bias and potential confounding seems to be balanced by the underestimation due to exposure to secondhand smoke in the reference group (Hackshaw *et al.*, 1997).

(ii) *Exposure at the workplace*

Interest in the risk of lung cancer associated with exposure to secondhand smoke at work has increased over the years and several meta-analyses have been published. These are listed in Table 2.8; some report no association, for example, Lee (1992) and Levois and Layard (1994), whereas others do report an association (Biggerstaff *et al.*, 1994; Wells, 1998; Zhong *et al*., 2000). However, the results of some of the studies may be unreliable because they used levels of exposure reported by next of kin (who may not know the true exposure status of the case or control), and because some studies evaluated only recent exposure to secondhand smoke in the workplace. Wells *et al*. (1998) excluded studies that documented only recent exposure and also studies that (i) included more than 50% surrogate responses for cases, (ii) had only minimal exposure, (iii) included exposure to other respiratory carcinogens, (iv) included subjects who had smoked, and (v) did not report appropriate data to allow the confidence intervals to be checked. Based on these criteria, Wells *et al*. (1998) identified the following studies for inclusion in their meta-analysis: Wu *et al*. (1985), Shimizu *et al*. (1988), Kalandidi *et al*. (1990), Kabat *et al*. (1995) and Reynolds *et al*. (1996); the pooled risk estimate was 1.4 (1.2–1.7). Overall, there seems to be an increased risk of lung cancer in subjects exposed to secondhand smoke at the workplace.

Table 2.8. Summary of results from published meta-analyses of exposure to secondhand smoke and lung cancer in never-smokers exposed at the workplace

Reference	No. of studies included	Sex	Pooled relative risk (95% CI)
Lee (1992)	9	Men and women	0.98 (0.84–1.08)
Biggerstaff *et al*. (1994)	8	Women	1.12 (0.93–1.34)
Levois & Layard (1994)	14	Men and women	1.01 (0.92–1.11)
Chappell & Gratt (1996)	8	Men and women	0.99 (0.91–1.08)
Wells *et al*. (1998)	5[a]	Men and women	1.39 (1.15–1.68)
Zhong *et al*. (2000)	14	Men and women	1.16 (1.05–1.28)

[a] Restricted to studies that were based on self-reported exposure

(iii) *Exposure during childhood*

There have been few meta-analyses on the risk of lung cancer in adulthood following exposure to secondhand smoke during childhood; the results of three of these meta-analyses are given in Table 2.9. None suggested an association, although no stratification

Table 2.9. Results from published meta-analyses of exposure to secondhand smoke and lung cancer in adult never-smokers exposed during childhood

Reference	No. of studies included	Sex	Pooled relative risk (95% CI)
Lee *et al*. (1992)	10	Men and women	0.98 (0.86–1.12)
Boffetta *et al*. (2000)	11	Men and women	
		Men and women	0.91 (0.80–1.05)
		From father	0.83 (0.72–0.95)
		From mother	0.99 (0.78–1.26)
Zhong *et al*. (2000)	18	Men and women	0.91 (0.83–1.00)

according to gender or exposure from the mother or father was carried out. Overall, published meta-analyses have found no evidence for an increased risk for lung cancer associated with childhood exposure to secondhand smoke.

(iv) *Statistical methods and other considerations*

Pooling relative risks

Different methods of combining relative risk estimates from individual studies have generally tended to give similar results. For example, in 37 studies of the risk for lung cancer of never-smoking women exposed or unexposed to secondhand smoke from the spouse, the relative risks (95% CI) using the fixed or random effects model were 1.21 (1.12–1.30) and 1.24 (1.13–1.36), respectively (Hackshaw *et al*., 1997) (the random effects model allows for heterogeneity between the risk estimates).

More complex approaches, such as Bayesian analysis, also do not yield materially different results. The difference between the pooled estimates obtained using a Bayesian model and those obtained using a simpler random effects model was small. Tweedie *et al.* (1996) pooled 40 studies of male or female never-smokers exposed to secondhand smoke from the spouse, the pooled relative risk for lung cancer was 1.20 (95% CI, 1.07–1.34) using the random effects model and 1.22 (95% CI, 1.08–1.37) using a Bayesian model (Tweedie *et al*., 1996).

Pooling results relating to exposure–response relationships

Several studies on the effects of exposure to secondhand smoke in never-smokers have reported the relative risk for lung cancer according to the number of cigarettes smoked by the spouse or the number of years that the nonsmoker has lived with a spouse who smokes. A few researchers, using various combinations of studies and methodology, have attempted to pool the results of epidemiological studies of exposure–response in never-smoking women. For an increase of 10 cigarettes per day smoked by the husband, the excess relative risk for lung cancer compared with never-smoking husbands was esti-

mated to be 23% (95% CI, 14–32) by Hackshaw *et al*. (1997), 17% (95% CI, 12–22) by Brown (1999) and 10% (95% CI, 5–15) by Lee *et al.* (2000). The excess relative risk that resulted from living for 10 years with a husband who smokes compared with one who does not was estimated to be 11% (95% CI, 4–17) by Hackshaw *et al*. (1997) and 7% (95% CI, 4–11) by Lee *et al.* (2000). The estimates are reasonably consistent between different reports and all found a statistically significant increase in risk associated with increasing exposure.

Heterogeneity between the estimates of relative risk

Performing a meta-analysis when there are statistically significant differences between the estimates of relative risk may yield an incorrect pooled estimate. If heterogeneity exists, an attempt should be made to explain it. If it can be explained by a single factor (or factors), then estimates should be stratified according to that factor. The authors of several reviews of the association between exposure to secondhand smoke and lung cancer have allowed for the existence of heterogeneity between geographical regions or found evidence of it and therefore stratified the relative risk estimates according to region (for example, US Environmental Protection Agency, 1992; Lee, 1998). Lee (1998) assessed heterogeneity related to several factors including geographical region, study publication date, study type and study size and concluded that there were statistically significant differences between the relative risk estimates by almost all factors. However, this was shown to be due to a single large discrepant study that unduly influenced the assessment of heterogeneity; this may be a problem especially when there are relatively few studies in the meta-analysis. In the meta-analysis by Hackshaw *et al*. (1997), the test for heterogeneity based on 37 studies on nonsmoking women was almost significant (p = 0.10), although when one study was excluded the p value became 0.46. The discrepant study, from China, was large (417 cases of lung cancer) and reported an almost statistically significant *reduction* in the risk of lung cancer associated with exposure to secondhand smoke from the spouse (relative risk, 0.8; 95% CI, 0.6–1.0), making its results inconsistent with those of the other studies. When this study was excluded, no evidence of heterogeneity was found for several factors (Hackshaw *et al*., 1997; Hackshaw, 1998; Zhong *et al*., 2000).

Publication bias

In meta-analyses of studies of the relationship between secondhand smoke and lung cancer there is a possibility of publication bias if studies with positive results (those that show an increased risk of lung cancer) are more likely to be published than studies with negative ones (those that show a decreased risk or no difference in risk). The pooled estimate of risk would then be biased upwards. Simple methods to ascertain whether much publication bias exists suggest that there is little evidence of this, for example funnel plots (Lubin, 1999) or estimating the number of negative unpublished studies that would be required to explain the increased risk observed from epidemiological studies — about 300 (Hackshaw *et al*., 1997; Lee, 1998); it is implausible that there would be so many

unpublished negative studies. Copas and Shi (2000) used a complex method to adjust the observed relative risk for lung cancer (reported in Hackshaw *et al*., 1997) for publication bias; the pooled estimate was reduced from 1.24 to 1.15, but Copas and Shi assumed that 40% of all studies are unpublished. Even with such an extreme assumption, the adjusted estimate is consistent with the reported relative risk adjusted for bias and confounding (1.26; 95% CI, 1.06–1.47). The problem with assessing publication bias is that it is difficult to determine empirically how many studies are unpublished (Bero *et al*., 1994).

(*c*) *Updated meta-analyses*

Several individual studies on secondhand smoke and the risk of lung cancer in nonsmokers have been published since one of the last detailed meta-analyses on the subject (Hackshaw *et al*., 1997). This section presents updated meta-analyses using currently available results. The selection of studies to be included is as described by Hackshaw *et al*. (1997), and the method of pooling the relative risk estimates is that described by Dersimonian and Laird (1986), which allows for any heterogeneity between the estimates. Some case–control studies reported only crude estimates of relative risk, some reported only adjusted estimates (adjusted for various factors such as age and diet) and others reported both crude and adjusted estimates. Consideration therefore needed to be given to which should be used in the meta-analyses. Pooled estimates were obtained based on the crude relative risks and, where these were not available, the adjusted relative risks. This reduces the effect of those studies that adjusted for factors that are not established confounders. The pooled estimate was also obtained based on the adjusted relative risks, and where these were not available, the crude relative risks to show that the two approaches yielded similar results.

Table 2.10 shows the results of the updated meta-analyses according to type of exposure to secondhand smoke and gender of the subject (for the estimates from the individual studies, see Tables 2.2, 2.5 and 2.6).

(i) *Exposure from the spouse*

Among nonsmoking women who lived with a spouse who smoked, the risk of lung cancer was increased by 24% (relative risk, 1.24; 95% CI, 1.14–1.3; Table 2.10). This estimate was based on the crude estimates of relative risk found in the studies and, where these were not available, the adjusted estimates. Use of the adjusted estimates and, where these were not available, the crude estimates yielded a similar relative risk of 1.27 (95% CI, 1.15–1.41). The studies came from several countries, and the test for heterogeneity between the relative risk estimates across all 46 studies just misses statistical significance (p value = 0.08). However, if the discrepant study from China by Wu-Williams *et al*. (1990) that reported an almost statistically significant decrease in risk due to exposure to secondhand smoke is excluded, the pooled relative risk is not materially changed (1.25; 95% CI, 1.17–1.33), but the test for heterogeneity yields a p value of 0.34. Among nonsmoking men who lived with a smoker, the risk of lung cancer was increased by 37%. The risk estimates for both nonsmoking men and women are statistically significant.

Table 2.10. Summary of the updated meta-analyses of the relative risk for lung cancer in never-smokers exposed to specified sources of secondhand smoke

Source of exposure	No. of studies (total no. of lung cancer cases)	Sex of subject	Pooled relative risk (95% CI)[a]	*p* value	Evidence of significant heterogeneity between the studies
Spouse	46 (6257)	Women	1.24 (1.14–1.34)	< 0.001	No, $p = 0.08$[b]
	11 (442)	Men	1.37 (1.02–1.83)	0.03	No, $p = 0.80$
Workplace	19 (3588)	Women	1.19 (1.09–1.30)	< 0.001	No, $p = 0.87$
	6 (246)	Men	1.12 (0.80–1.56)	0.51	No, $p = 0.38$
	7 (1582)	Women and men combined	1.03 (0.86–1.23)	0.74	No, $p = 0.10$
Childhood					
Mother	9 (2085)	Women	1.50 (1.04–2.14)	0.03	Yes, $p = 0.004$
Father	10 (2274)		1.25 (0.94–1.68)	0.13	Yes, $p < 0.001$
Either parent	14 (2576)		1.11 (0.87–1.42)	0.41	Yes, $p < 0.001$
Either parent	5 (252)	Men	0.86 (0.62–1.20)	0.38	No, $p = 0.35$
Either parent	6 (1306)	Women and men combined	1.14 (0.77–1.70)	0.51	Yes, $p < 0.001$

[a] Based on the crude relative risks from the individual reports and where these were not available, the adjusted estimates

[b] When the study by Wu-Williams *et al*. (1990) from China is excluded (it reported an almost statistically significant decrease in risk for lung cancer associated with exposure to secondhand smoke), the pooled relative risk is similar 1.25 (1.17–1.33), but the test for heterogeneity yields a *p* value of 0.34.

(ii) *Exposure at the workplace*

The increase in risk for lung cancer in nonsmoking women is about 20% (relative risk, 1.19; 95% CI, 1.09–1.30; Table 2.10). If the pooled estimate was based on the adjusted relative risks reported in the studies and, where these were not available, the crude estimates, the result was similar (relative risk, 1.21; 95% CI, 1.09–1.35). There was also an increase in risk in men (12%) though this result was not statistically significant (probably because of the smaller number of studies and fewer cases of lung cancer in the meta-analysis). There was no evidence of heterogeneity between the individual risk estimates.

(iii) *Exposure during childhood*

There is a statistically significant increase in risk among women exposed to secondhand smoke from the mother during childhood (50% increase in risk, but the confidence interval is wide, 4–114%). There is a lower, and non-significant increase in risk for exposure to secondhand smoke from the father (25%). However, there is significant heterogeneity between the estimates of relative risk. The results on exposure during childhood are less clear than those on exposure from the spouse or at the workplace.

Overall, the evidence from the meta-analyses is clear; adult nonsmokers exposed to secondhand smoke have a higher risk for lung cancer. Although the precise quantitative estimate of risk may vary between different measures of exposure, it is consistently raised. The data on exposure to secondhand smoke from the spouse also show that risk increases with increasing exposure. The evidence for an association between lung cancer and childhood exposure to secondhand smoke is less consistent than that for exposure in adulthood.

2.2 Breast cancer

Five prospective cohort studies (Hirayama, 1984; Jee *et al*., 1999; Wartenberg *et al*., 2000; Nishino *et al*., 2001; Egan *et al*., 2002) and 12 reports of 10 case–control studies (Sandler *et al*., 1985a,b; Smith *et al*., 1994; Morabia *et al*., 1996; Millikan *et al*., 1998; Lash & Aschengrau, 1999; Delfino *et al*., 2000; Johnson *et al*., 2000; Marcus *et al*., 2000; Morabia *et al*., 2000; Chang-Claude *et al.*, 2002; Kropp & Chang-Claude, 2002) have examined the role of secondhand smoke in breast cancer. The cohort studies are summarized in Table 2.11 and the reports from the case–control studies are summarized in Table 2.12.

2.2.1 *Cohort studies*

The first cohort study that suggested a possible association of exposure to secondhand smoke with breast cancer was reported by Hirayama in 1984. Specific details of how risk estimates for breast cancer were calculated were provided by Wells (1991). A total of 115 deaths from breast cancer were identified after 15 years of follow-up (1966–81) of over

Table 2.11. Cohort studies of breast cancer and involuntary exposure to tobacco smoke

Reference	Country	Sample	Source of information on exposure	Duration and completeness of follow-up	Relative risk (95% CI)	
Hirayama (1984)	Japan	115 breast cancer deaths among 91 540 nonsmoking married women	In-person interview (baseline)	15 years of follow-up. Completeness not reported	*Husband ever smoked* 1.26 (0.8–2.0)	
Jee *et al.* (1999)	Republic of Korea	138 breast cancer cases among 157 436 non-smoking married women	Self-administered questionnaire: husband's active smoking in 1992 and 1994; wife's involuntary smoking in 1993	3.5 years of follow-up of breast cancer cases. Completeness not reported	*Husband's smoking status* Former smoker Current smoker Current smoker for > 30 years	 1.2 (0.8–1.8) 1.3 (0.9–1.8) 1.7 (1.0–2.8)
Wartenberg *et al*. (2000)	USA	669 breast cancer deaths among 146 488 never-smoking single-marriage women	Postal questionnaire to both husband and wife	12 years of follow-up. 98% completeness	*Husband's smoking status* Former smoker Current smoker (baseline) *Years husband smoked* 1–10 11–20 21–30 ≥ 31 *p* trend = 0.9	 1.0 (0.8–1.2) 1.0 (0.8–1.2) 0.9 (0.6–1.3) 0.7 (0.5–1.0) 1.0 (0.7–1.3) 1.1 (0.8–1.3)

Table 2.11 (contd)

Reference	Country	Sample	Source of information on exposure	Duration and completeness of follow-up	Relative risk (95% CI)
Nishino *et al*. (2001)	Japan	67 incident cases of breast cancer among 9675 never-smoking women aged ≥ 40	Self-administered questionnaires	9 years of follow-up. Completeness not reported	*Husband smoked* 0.6 (0.3–1.1) *Other household member smoked* 0.8 (0.4–1.5)
Egan *et al*. (2002)	USA	1359 breast cancer cases among 35 193 never-smoking women	Postal questionnaire	14 years of follow-up of invasive breast cancer. 96% completeness	*Parental smoking* Mother only 1.0 (0.7–1.4) Father only 1.1 (1.0–1.3) Both parents 0.9 (0.8–1.1) *Current exposure to secondhand smoke* Occasional 1.2 (1.0–1.4) Regular at home or at work 1.0 (0.8–1.2) Regular at home and at work 0.9 (0.7–1.2)

Table 2.12. Case–control studies of breast cancer and involuntary exposure to tobacco smoke

Reference	Country	Sample	Source of information on exposure	Duration and completeness of follow-up	Relative risk (95% CI)	
Sandler *et al*. (1985a)	USA	29 nonsmoking incident cases; 223 nonsmoking controls	Postal question-naire	22 months; cases diagnosed in women aged 15–59 years. 70% case response rate; 57% control response rate	Maternal smoking Paternal smoking	0.9 0.9
Sandler *et al*. (1985b)	USA	32 nonsmoking incident cases; 247 nonsmoking controls	Postal question-naire	22 months; cases diagnosed in women aged 15–59 years. 70% case response rate; 75% response rate for telephone controls; 60% response rate for friend controls	Husband's smoking	2.0 (0.9–4.3)
Smith *et al*. (1994)	United Kingdom	94 nonsmoking incident cases; 99 nonsmoking controls	In-person inter-view with postal questionnaire on exposure to secondhand smoke	3 years; cases diagnosed in women aged < 36 years. 72% case response rate; 89% control response rate. Data on exposure to secondhand smoke available on 65% of matched pairs	*Childhood exposure in cigarette–years* 1–200 > 200 *Adult exposure* *From partner in cigarette–years* ≥ 1 *From other household smokers (years)* 1–5 ≥ 6 *At work (years)* 1–5 ≥ 6 *Period of exposure* Child only Adult only Both	 1.2 (0.5–2.9) 1.1 (0.5–2.7) 1.6 (0.8–3.1) 1.5 (0.7–3.2) 1.1 (0.5–2.8) 1.7 (0.7–3.8) 1.4 (0.6–3.1) 1.3 (0.2–10.8) 3.1 (0.7–13.3) 2.6 (0.7–9.4)

Table 2.12 (contd)

Reference	Country	Sample	Source of information on exposure	Duration and completeness of follow-up	Relative risk (95% CI)	
Morabia *et al*. (1996)	Switzerland	126 never-smoking incident cases; 620 never-smoking controls	In-person interview	22 months for cases diagnosed in women < 75 years of age. 71% case response rate; 70% control response rate	Ever exposed to second-hand smoke	3.2 (1.7–5.9)
					(Hours/day) × year	
					1–50	3.1 (1.5–6.2)
					> 50	3.2 (1.6–6.3)
					Ever exposed to second-hand smoke from spouse	3.1 (1.6–6.1)
					From spouse (hours/day) × year	
					1–50	3.1 (1.3–7.5)
					> 50	3.2 (1.5–6.5)
Millikan *et al*. (1998)	USA	248 never-smoking incident cases; 253 never-smoking controls	In-person interview plus 30-mL blood sample	3.5 years for cases diagnosed in women 20–74 years of age. 77% case response rate; 68% control response rate; 98% of study subjects provided blood samples	*Exposed to secondhand smoke after age 18 years*	
					All-nonsmokers	1.3 (0.9–1.9)
					Premenopausal	1.5 (0.8–2.8)
					NAT1*10	1.7 (0.7–4.3)
					NAT1non*10	1.3 (0.5–3.2)
					NAT2rapid	2.3 (0.9–6.2)
					NAT2slow	1.2 (0.5–2.8)
					Postmenopausal	1.2 (0.7–2.2)
					NAT1*10	1.2 (0.6–2.6)
					NAT1non*10	1.3 (0.5–3.6)
					NAT2rapid	0.8 (0.4–1.8)
					NATslow	1.9 (0.7–5.2)

Table 2.12 (contd)

Reference	Country	Sample	Source of information on exposure	Duration and completeness of follow-up	Relative risk (95% CI)	
Lash & Aschengrau (1999)	USA	120 never-smoking cases, 406 never-smoking controls	Proxy interview; 33% of cases and 45% of controls	3 years for cases diagnosed in women. 79% case response rate; 75% control response rate	Passive smoking	2.0 (1.1–3.7)
					By years of exposure to secondhand smoke	
					≤ 20	3.2 (1.5–7.1)
					> 20	2.1 (1.0–4.1)
Delfino *et al*. (2000)	USA	64 never-smoking cases; 149 never-smoking controls (benign breast disease)	Self-administered questionnaire	Cases diagnosed in women 40 years of age and above (duration not reported). 82% case response rate; 85% control response rate	Any exposure to second-hand smoke	1.3 (0.7–2.5)
					High versus low exposure to secondhand smoke	1.5 (0.8–2.9)
					Premenopausal cases	2.7 (0.9–8.0)
					Postmenopausal cases	1.0 (0.5–2.3)
Johnson *et al*. (2000)	Canada	378 premenopausal and 700 post-menopausal never-smoking cases; 369 pre- and 845 post-menopausal never-smoking controls	Postal question-naire	≥ 3 years for cases diagnosed in women 20–74 years of age. 72% case response rate; 64% control response rate	*Premenopausal*	
					Any exposure to second-hand smoke	2.3 (1.2–4.6)
					Childhood exposure only	1.6 (0.6–4.4)
					Adult exposure only	2.6 (1.1–6.0)
					Exposure during childhood and adulthood	2.6 (1.2–5.5)
					Postmenopausal	
					Any exposure to second-hand smoke	1.2 (0.8–1.8)
					Childhood exposure only	0.9 (0.4–2.0)
					Adult exposure only	1.1 (0.6–1.8)
					Exposure during childhood and adulthood	1.3 (0.8–2.0)

Table 2.12 (contd)

Reference	Country	Sample	Source of information on exposure	Duration and completeness of follow-up	Relative risk (95% CI)	
Marcus *et al*. (2000)	USA	445 never-smoking cases; 423 never-smoking controls	In-person interview	3.5 years for cases diagnosed in women 20–74 years of age. 77% case response rate; 68% control response rate	Never-smokers exposed to secondhand smoke before age 18 years	0.8 (0.6–1.1)
Morabia *et al*. (2000)	Switzerland	84 never-smoking cases; 99 never-smoking controls	In-person interview and buccal swab	1 year for incident cases diagnosed in women < 75 years of age. 71% case response rate; 70% control response rate in original study; 83% response rate in substudy	Any exposure to secondhand smoke *NAT2 acetylation genotype* Slow Fast	3.1 (1.5–6.0) 1.9 (0.7–4.6) 5.9 (2.0–17.4)
Chang-Claude *et al.* (2002)	Germany	174 never-smoking cases; 365 never-smoking controls	Self-administered questionnaire and for passive smoking questions by telephone interview	4 years for cases; passive smoking response rates: ~46% of total eligible and 48% of eligible controls	*Ever exposed by NAT2 acetylator status* Rapid Slow	 2.0 (1.0–4.1) 1.2 (0.7–2.0)
Kropp & Chang-Claude (2002)	Germany	197 never-smoking cases; 459 never-smoking controls	Self-administered questionnaire and for passive smoking questions by telephone interview	4 years for cases; passive smoking response rates: ~46% of total eligible and 48% of eligible controls	*Exposure to secondhand smoke* As a child only As an adult only Both *Lifetime in (hours/day) × years* 1–50 ≥ 51 $p = 0.009$	 1.1 (0.6–2.3) 1.9 (1.2–3.0) 1.6 (1.0–2.6) 1.4 (0.9–2.3) 1.8 (1.2–2.9)

91 000 married nonsmoking Japanese women. Women whose husbands had ever smoked had a small non-significantly increased risk of breast cancer (relative risk, 1.26; 95% CI, 0.8–2.0*)*. [The Working Group noted this was a first prospective report with a number of limitations. For example, it reported mortality rather than incidence; there was limited assessment of risk specific to breast cancer (spouse only); there was no adjustment for potential confounders; exposure was assessed at only one time-point.]

In a study in the Republic of Korea, Jee *et al*. (1999) also found small non-significantly increased risks of breast cancer associated with husbands' smoking status: for former smokers the relative risk was 1.2 (95% CI, 0.8–1.8) and for current smokers the relative risk was 1.3 (95% CI, 0.9–1.8). Relative risks were adjusted for age of husbands and wives, socioeconomic status, residence, vegetable consumption and occupation of the husband. These findings were based on 138 incident and prevalent breast cancer cases in 3.5 years of follow-up (July 1994–December 1997) of a cohort of 157 436 nonsmoking Korean women. A higher risk, of borderline significance, was observed for women married to current smokers who had smoked for more than 30 years (relative risk, 1.7; 95% CI, 1.0–2.8). [The Working Group noted that this study had several limitations, i.e. prevalent cases were not excluded; limited adjustment was made for potential confounders, and the adjustment did not include reproductive or hormonal factors; assessment of exposure included only secondhand smoke from the spouse.]

Wartenberg *et al*. (2000) reported findings from the large American Cancer Society Cancer Prevention Study II cohort based on 12 years of follow-up (1982–94) of never-smoking women who had been married once. A total of 669 deaths from breast cancer were included and risk estimates were adjusted for year of age at baseline, race, number of years of education, history of breast cancer in mother or sister, personal history of breast cysts, age at first live birth, age at menopause, number of spontaneous abortions, use of oral contraceptives, use of estrogen replacement therapy, body mass index, alcohol intake, fat consumption, vegetable consumption, occupation and occupation of spouse. No increased risks were found for women married to current smokers (relative risk, 1.0; 95% CI, 0.8–1.2) or former smokers (relative risk, 1.0; 95% CI, 0.8–1.2) when compared with never-smokers married to nonsmoking husbands. No association was found by type of tobacco. No trend in risk was observed by years, packs per day or pack–years of spousal smoking. No significant associations were noted between breast cancer and all exposures at home (relative risk, 1.1; 95% CI, 0.9–1.3), at work (relative risk, 0.8; 95% CI; 0.6–1.0), or in other places (relative risk, 0.9; 95% CI, 0.7–1.2). When reported exposures from all sources were combined and examined according to daily hours of exposure using no exposure from any source as referent (0 hour), no trend was observed. [The Working Group considered that the strengths of this study included the large number of cases, the excellent follow-up, the thorough statistical adjustment for potential confounders and that the spouse directly reported his own tobacco use. The limitations include the use of mortality rather than incidence as the outcome and that the assessment of spousal smoking was made at only one time-point.]

A smaller cohort study that included 9675 Japanese female never-smokers over the age of 40 years accrued 67 incident cases over a 9-year follow-up period (1984–92) (Nishino *et al*., 2001). Relative risks were adjusted for age, study area, alcohol consumption, intake of green and yellow vegetables, intake of fruit, age at first birth, number of live births, age at menarche and body mass index. The age-adjusted relative risk for breast cancer was 0.6 (95% CI, 0.3–1.0) among women whose husbands smoked when compared to that in women married to nonsmokers. The age-adjusted risk associated with living in a household with other smokers was also below unity (relative risk, 0.4; 95% CI, 0.2–0.8) when compared with women living in households where there were no smokers. Further adjustment of these relative risks for the potential confounders listed above did not appreciably change the risk estimates, but the relative risks were no longer statistically significant after full adjustment: exposure from spouse, 0.6 (95% CI, 0.3–1.1), and other household members, 0.8 (95% CI, 0.4–1.5*)*. [The Working Group considered that the strengths of this study include adjustment for some reproductive or hormonal and dietary factors; its limitations include the very small sample size, lack of information on marital status at baseline and inclusion of unmarried women at high risk of breast cancer as unexposed which may have reduced point estimates of relative risk.]

The Nurses' Health Study in the USA has provided the largest number of prospectively accrued breast cancer cases in never-smoking women (Egan *et al*., 2002). After 14 years of follow-up (1982–96), 1359 cases of invasive breast cancer were diagnosed among 35 193 never-smokers. Exposure to secondhand smoke was assessed as exposure during childhood as well as during adult life at home, at work and in other settings. Relative risks were adjusted for many variables including age, parity, age at first birth, menopausal status, age at menopause, change in weight (i.e. weight at age 18 years compared to the most recent reported weight), age at menarche, history of benign breast disease, family history of breast cancer, post-menopausal hormone treatment, alcohol intake and carotenoid intake. No statistically significant associations were found for exposure between breast cancer and exposure to secondhand smoke in adult life or in childhood, and most relative risks were near unity. No trends were apparent either for number of years lived with a smoker as an adult (p for trend = 0.87) or for a categorized index of adult exposures (p for trend = 0.97). Women who reported the highest levels of exposure to secondhand smoke during adulthood had a rate of breast cancer similar to that of women who reported no current exposure to secondhand smoke (relative risk, 1.0; 95% CI, 0.8–1.3). The findings were similar for pre- and postmenopausal women. [The Working Group noted that this study's main strength is that it is the largest and most methodologically rigorous prospective study to date. Other strengths were that exposure assessments were updated over time, incident cases rather than mortality were studied and comprehensive adjustment was made for potential confounders.]

2.2.2 *Case–control studies*

The first two reports (Sandler *et al*., 1985a,b) on involuntary smoking and breast cancer were based on a case–control study conducted in North Carolina, USA. Cases were selected from a single hospital tumour registry and included patients diagnosed between 1 July 1979 and 31 March 1981, who were between the ages of 15 and 59 years at the time of diagnosis. Approximately 60% of the controls were friends or acquaintances identified by cases and the remaining 40% were selected by systematic telephone sampling. The two control groups were combined after separate analyses of the two groups indicated similar results. The risk for breast cancer in nonsmoking women was not associated with exposure to secondhand smoke during childhood from either mother (relative risk, 0.9) or father (relative risk, 0.9) (Sandler *et al*., 1985a). Exposure to secondhand smoke in nonsmoking women based on husband's smoking was associated with a two-fold, nonsignificant increase in risk (relative risk, 2.0; 95% CI, 0.9–4.3) (Sandler *et al*., 1985b). Risk estimates of childhood exposure were adjusted for age and education, and risk estimates of exposure during adulthood were adjusted for age, race and education. Both reports included only a few lifetime nonsmokers with breast cancer (29 and 32 cases, respectively). [The Working Group noted that the limitations of this study include small sample size, lack of adjustment for reproductive factors and the potentially inappropriate control group (i.e. friends and neighbours of cases supplemented with controls selected by random digit dialling.]

Smith *et al*. (1994) investigated the relationship between exposure to secondhand smoke and risk for breast cancer in a sample of nonsmokers including 94 incident cases and 99 controls drawn from a larger study of breast cancer diagnosed in young women below the age of 36 years between 1982 and 1985. This study was conducted in the United Kingdom and information on exposure to secondhand smoke was collected by postal questionnaire in a sample of participants from the main study. Controls were selected randomly from the list of the case's general practitioner and matched to the case on age. Risk estimates were adjusted for age, residence, age at menarche, family history of breast cancer, history of biopsy for benign breast disease, oral contraceptive use and history of breastfeeding. Although most of the risk estimates exceeded unity as shown in Table 2.12, none were statistically significant and there was no evidence of a positive trend in risk associated with increasing exposure. When total lifetime exposure as measured in cigarette–years was considered, elevations in risk were found for all levels above zero (referent). However, the trend was not statistically significant. No effect of active smoking was found in this study. [The Working Group considered this study to have limited generalizability (cases < 36 years of age) and noted that no exposure–response relationship was observed despite comparatively high point estimates of risk.]

A population-based case–control study conducted in Switzerland by Morabia *et al*. (1996) was designed specifically to evaluate the role of exposure to secondhand smoke in risk of breast cancer. It included 126 cases and 620 controls who were lifetime never-smokers. Never-smokers were defined as having smoked fewer than 100 cigarettes in a

lifetime. Eligible cases were women less than 75 years of age who had been diagnosed with invasive breast cancer between 1 January 1992 and 31 October 1993. Population controls were selected from the official registers of residents of Geneva and were 30–74 years of age. This study included a detailed assessment of exposure to secondhand smoke and risk estimates were adjusted for the following potential confounders: age, education, body mass index, age at menarche, age at first live birth, oral contraceptive use, breast cancer in mother or sister, history of breast biopsy, alcohol intake and saturated fat intake. The referent unexposed group in this study included women who were never regularly exposed (< 1 (h/day) × years) to either active or passive smoking (28/244 cases and 241/1032 controls). Estimates of relative risk associated with any exposure to secondhand smoke, duration of exposure to secondhand smoke, exposure to spousal secondhand smoke only and duration of spousal smoking were all approximately three and were statistically significant; however, risk estimates stratified by duration (1–50 or > 50 (h/day) × years) were virtually identical and there was no suggestion of an exposure–response relationship. [The Working Group considered that the strengths of the study were its comprehensive assessment of exposure, being population-based and the large number of potential confounders included in the analysis. Concerns included the following: magnitude of the association between cancer and passive smoking is the same as that for active smoking in same study, no exposure–response relationship was found for secondhand smoke and the very restrictive reference category used may have biased the results.]

Morabia *et al*. (2000) next conducted a sub-study from the above-mentioned case–control study. It was designed to evaluate the role of *N*-acetyltransferase 2 (NAT2) in the relationship between breast cancer and active and passive smoking. Cases believed to be alive and living in Geneva in 1996–97 were re-contacted, as were a subset of controls, and asked to provide a buccal swab for DNA extraction and NAT2 genotyping for subsequent classification as slow or fast acetylators. This sub-study included 84 cases who were never-smokers and 99 controls who were never-smokers. As in the parent study, a three-fold increase in risk of breast cancer was associated with any reported exposure to secondhand smoke (relative risk, 3.1; 95% CI, 1.5–6.0). The association between exposure to secondhand smoke and breast cancer appeared to be modified by acetylation status; breast cancer risk was higher in persons with the fast acetylation genotype (relative risk, 5.9; 95% CI, 2.0–17.4) than in slow acetylators (relative risk, 1.9; 95% CI, 0.7–4.6). [The Working Group's comments on the parent study also applied to this sub-study.]

Millikan *et al*. (1998) conducted a population-based case–control study in North Carolina, USA, that also examined the effect of *N*-acetylation genotypes (NAT1 and NAT2), exposure to secondhand smoke and breast cancer risk. Cases included women between 20 and 74 years of age who were diagnosed with invasive primary breast cancer between May 1993 and December 1996. Controls less than 65 years of age were selected from files of the North Carolina Division of Motor Vehicles and those from 65 to 74 years of age from the United States Health Care Financing Administration (HCFA) files. All African–American cases and a sample of white cases were selected. This report was based

on cases and controls who provided a blood sample. Cases and controls were broadly frequency-matched on race (African–American and white) and age (age less than 50 years and 50 years and above). Relative risk estimates were adjusted for age, race, age at menarche, age at first full-term pregnancy, parity, family history of breast cancer, breast biopsies showing benign tumours and alcohol consumption. Statistically non-significant increases in risk were associated with exposure to secondhand smoke after the age of 18 years in never-smokers (relative risk, 1.3; 95% CI, 0.9–1.9). The point estimates for premenopausal (relative risk, 1.5; 95% CI, 0.8–2.8) and postmenopausal women (relative risk, 1.2; 95% CI, 0.7–2.2) were not substantially different. Stratification by menopausal status and NAT1 and NAT2 genotypes resulted in statistically non-significant relative risks for all subgroups. The point estimates for exposure to secondhand smoke after the age of 18 years were highest for pre-menopausal never-smoking women for NAT1*10 (relative risk, 1.7; 95% CI, 0.7–4.3) and NAT2rapid (relative risk, 2.3; 95% CI, 0.9–6.2).

Marcus *et al*. (2000) included additional cases from this North Carolina study without the requirement for a blood sample and addressed the issue of exposure to secondhand smoke before the age of 18 years. Exposure to secondhand smoke at home during childhood showed no statistically significant association with risk of breast cancer in this study (relative risk, 0.8; 95% CI, 0.6–1.1). [The Working Group considered that the strengths of this study included the large number of never-smoking cases and controls; the multiethnic study population (although no ethnicity-specific risk estimates for exposure to secondhand smoke were reported and that the study investigated possible high-risk subgroups.]

Lash and Aschengrau (1999) reported the findings of a case–control study conducted in five towns in Massachusetts, USA. The incident cases of breast cancer were diagnosed from 1983–1986. Population controls from these towns for living cases under 65 years of age were selected using random-digit dialling and for women 65 years and older from the US Health Care Financing Administration (HCFA) files. Because deceased cases were also eligible for this study, deceased controls were selected from Massachusetts Department of Vital Statistics and Research. A total of 120 cases and 406 controls were never-smokers. About one-third of the interviews relating to cases and 45% of the interviews relating to controls were with proxy respondents. Age, parity, history of breast cancer other than index diagnosis, family history of breast cancer, history of benign breast disease, and history of radiation therapy were adjusted for in the analyses. A twofold increase in risk (relative risk, 2.0; 95% CI, 1.1–3.7) was associated with any exposure to secondhand smoke; however, increasing duration was not associated with increasing risk. The relative risk estimates for exposure to secondhand smoke and for active smoking also determined in this study were similar. [The Working Group noted that the limitations of the study were that the original study was not designed to evaluate exposure to secondhand smoke; it was unclear whether controls from the parent study which included three types of cancer cases were matched to breast cancer cases in this substudy, and that this substudy included a large number of proxy respondents.]

Findings from a small clinic-based case–control study, conducted in Orange County, California, USA, were reported by Delfino *et al*. (2000). Three breast cancer centres were

included in the study. Subjects diagnosed with a suspicious breast mass detected either clinically or radiographically who were over the age of 39 years were considered to be eligible. Information on exposure was obtained from a self-administered questionnaire completed prior to biopsy in order to minimize recall bias and interviewer bias. Among women who were never-smokers, 64 were subsequently found to have malignant tumours and comprised the case series, and 149 never-smokers with benign breast disease were classified as controls. Risk estimates for exposure to secondhand smoke in the home were adjusted for age, menopausal status, age at menarche, age at first full-term pregnancy, total months of pregnancy, lactation history, education, race/ethnicity, body mass index and family history of breast cancer. NAT2 genotype was also determined, but was not associated with risk for breast cancer in this study. No statistically significant association was found between exposure to secondhand smoke and breast cancer risk in these never-smokers (relative risk, 1.3; 95% CI, 0.7–2.5) for any exposure to secondhand smoke in the home. [The Working Group considered that the strengths of this study included the fact that exposure data were collected prior to determination of case–control status. Its limitations were that it was a small study and that information on exposure to secondhand smoke was limited to exposure in the household.]

A large Canadian study (Johnson *et al*., 2000) identified population-based incident cases of breast cancer aged 25–74 years at diagnosis from the National Enhanced Cancer Surveillance System beginning in April 1994 in some provinces (later in others) and continuing until July 1997. The study included 378 premenopausal and 700 postmenopausal never-smoking cases and 369 pre- and 845 postmenopausal population-based never-smoking controls. Exposure to secondhand smoke in the household during childhood and adult life as well as in the workplace were assessed. Relative risk estimates were adjusted for age, province, education, body mass index, alcohol use, physical activity, age at menarche, age at the end of first pregnancy lasting 5 months or longer, number of live births, months of breastfeeding and height. There was no evidence of an association between breast cancer and exposure to secondhand smoke during childhood or adulthood in postmenopausal women (relative risk estimates ranged from 0.9 to 1.3, none were statistically significant). However, premenopausal women had significantly elevated risks for breast cancer associated with any exposure to secondhand smoke (relative risk, 2.3; 95% CI, 1.2–4.6), exposure to secondhand smoke during adulthood (relative risk, 2.6; 95% CI, 1.1–6.0), and exposure to secondhand smoke during both childhood and adulthood (relative risk, 2.6; 95% CI, 1.2–5.5). There was evidence of a strong dose–response relationship in premenopausal women associated with duration of residential and occupational exposure (p for trend = 0.0007). [The Working Group noted that the risk associated with passive smoking was similar in magnitude to that in former active smokers (relative risk, 2.6) and was higher than that for current active smokers (relative risk, 1.9) in the same study. The limitations of the study were that information was missing on a large number of cases and controls who were excluded from this study and information on exposure to secondhand smoke was available for only 59% of never-smokers.]

Two recent reports from a case–control study of breast cancer in German women aged 50 years and younger have used as the referent for assessing the risks of both active and involuntary smoking those women who have experienced no active and no passive exposure to tobacco smoke (lifetime non-exposed: < 1 (h/day) × year) (Kropp & Chang-Claude, 2002; Chang-Claude *et al.*, 2002). The study included 706 cases (response rate, 70.1%) and 1381 controls (response rate, 61.2%). Data were initially collected by self-administered questionnaires for active smoking, and later, living cases and controls were re-contacted for information on involuntary exposure to tobacco smoke. Of the original participants, approximately 66% of the cases and 79% of the controls completed this part of the study. Risk estimates were adjusted for daily alcohol intake, total number of months of breastfeeding, education, first-degree family history of breast cancer, menopausal status and body mass index. For active smoking, a relative risk of 1.1 (95% CI, 0.6–2.0) was recorded, whereas never-smokers exposed to involuntary smoking had a statistically increased risk of about 60% (Kropp & Chang-Claude, 2002). In a subgroup analysis of 422 cases and 887 controls, the effect of NAT2 on the association between tobacco and breast cancer was considered (Chang-Claude *et al.*, 2002). When compared to women who had never been exposed to any tobacco smoke, no association with active smoking was seen in rapid acetylators and a modest statistically non-significant increase in risk was observed in slow acetylators. In contrast, passive smoking was associated with a statistically non-significant risk that was higher in rapid than in slow acetylators (relative risk, 2.0; 95% CI, 1.0–4.1; and 1.2; 95% CI, 0.7–2.0, respectively). [The Working Group noted that this study has included many subgroup analyses, had reported incongruent findings related to active and involuntary smoking in the same study AND had obtained passive smoking data for only about 50% of study subjects. However, the strength of this study was the inclusion of a referent group of subjects who had not been exposed to any tobacco smoke during their lifetimes by self-report.]

2.3 Childhood cancers

Many studies have evaluated the association of cancer risk in childhood with exposure to parental smoking since this issue was considered previously in the *IARC Monograph* Volume 38 (IARC, 1986). These associations will be evaluated below for all cancers combined and separately, for brain tumours, leukaemias and lymphomas, and other childhood cancers.

Few studies distinguish times of exposure to tobacco smoke from parents, i.e. whether the exposure was preconception, *in utero* or postnatal. Exposure may have occurred in all three periods even when a study reports on only one, or exposure may also be reported as ‘ever’. Involuntary smoking during each of these time periods tends to be correlated, in particular exposure to secondhand smoke from the father because father’s smoking habits are less likely to change.

2.3.1 *All sites combined*

Four cohort studies (Neutel & Buck, 1971; Golding *et al*., 1990; Pershagen *et al*., 1992; Klebanoff *et al*., 1996) and ten case–control studies (Buckley *et al*., 1986; McKinney *et al*., 1986; Stjernfeldt *et al*., 1986; Forsberg & Kallen, 1990; John *et al*., 1991; Golding *et al*., 1992; Sorahan *et al*., 1995; Ji *et al*., 1997; Sorahan *et al*., 1997a,b) (Table 2.13) have examined the role of involuntary exposure to tobacco smoke in risk for childhood cancers in general.

All four cohort studies specifically reported on the risk associated with cancer related to mothers' smoking during pregnancy. Neutel and Buck (1971) identified 97 deaths from childhood cancer in a cohort of 89 302 births from Ontario (Canada), and England and Wales followed from 7 to 10 years. Children with a mother who had smoked during pregnancy had a relative risk of 1.3 (95% CI, 0.8–2.2). No exposure–response relationship was apparent. [The Working Group noted several limitations of this study: no control for potential confounders; completeness of follow-up unknown, and limited assessment of exposure to secondhand smoke.]

Golding *et al*. (1990) followed a cohort of 16 193 births for 10 years (1970–80) and a total of 33 cancers were diagnosed. After adjustment for social class, exposure to X-rays during pregnancy, term delivery, administration of pethidine in labour and of drugs during infancy, a statistically significant increase in risk was found for children whose mothers smoked five or more cigarettes per day during the index pregnancy (relative risk, 2.5; 95% CI, 1.2–5.1). [The Working Group noted that the strength of this study was that the effect of exposure to secondhand smoke was independent of other risk factors found in this study. Its limitations were that the completeness of follow-up was unknown and that there was limited assessment of exposure to secondhand smoke.]

Pershagen *et al*. (1992), in Sweden, followed a large cohort of 497 051 births. In 5 years of follow-up, a total of 327 cancers that could be linked to data on maternal smoking were diagnosed. Relative risks were adjusted for year and county of birth, birth order and maternal age. No association was found for any maternal smoking during pregnancy (relative risk, 1.0; 95% CI, 0.8–1.3) and no exposure–response relationship was seen for number of cigarettes smoked during pregnancy (< 10 cigarettes per day, relative risk, 1.0; ≥ 10 cigarettes per day, relative risk, 0.9). No cancer at any of the sites evaluated individually was associated with maternal smoking. [The Working Group noted that the strengths of this study were that it was the largest cohort study, some statistical adjustment of risk estimates had been made and there was a high rate of follow-up. Its limitation was that there had been limited assessment of exposure to secondhand smoke.]

The most recent prospective study to evaluate the association between maternal smoking during pregnancy and childhood cancer is the US Collaborative Perinatal Project that included 54 795 children born from 1959–66 who were followed until the age of seven or eight years (Klebanoff *et al*., 1996). The hazard ratio for cancer in children whose mother smoked during pregnancy compared to those whose mother did not was 0.7 (95% CI, 0.4–1.2). Adjustment of the hazard ratio for maternal race, age, education,

Table 2.13. Childhood cancers, all sites combined, and involuntary exposure to parental smoking

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Relative risk (95% CI)
Cohort studies					
Neutel & Buck (1971) (Canada, United Kingdom)	72 952 births in Ontario; 16 350 births in England and Wales	Interview	7–10 years in Ontario; 7 years in England and Wales; completeness not reported	Maternal smoking during pregnancy	1.3 (0.8–2.2)
Golding *et al*. (1990) (United Kingdom)	16 193 births, 33 cases	Cancer registry, medical record	10 years diagnosis of children ≤ 10 years of age; completeness not reported	Maternal smoking ≥ 5 cigarettes/day during pregnancy	2.5 (1.2–5.1)
Pershagen *et al*. (1992) (Sweden)	497 051 births, 327 cases	Cancer registry	5 years follow-up; 327 of 422 cancers linked to births with smoking data; 99% complete follow-up	Maternal smoking during pregnancy *Cigarettes/day* < 10 ≥ 10	1.0 (0.8–1.3) 1.0 (0.8–1.4) 0.9 (0.6–1.3)
Klebanoff *et al*. (1996) (USA)	54 795 births, 51 cases		7–8 years follow-up of cancers diagnosed in children ≤ 8 years old; completeness of follow-up not reported	Maternal smoking during pregnancy *Incidence rate* Smoker Nonsmoker *Hazard ratio*	 0.9 per 1000 4 per 1000 $p < 0.15$ 0.7 (0.4–1.2)

Table 2.13 (contd)

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Relative risk (95% CI)
Case–control studies					
Buckley *et al*. (1986) (USA, Canada)	1814 cases, 720 controls	In-person interview	3 years diagnosis in children (age not reported); 100% response rate	Maternal smoking during pregnancy *Cigarettes/day* < 10 ≥ 10	 1.3 (0.9–1.9) 1.0 (0.8–1.2)
McKinney *et al*. (1986) (United Kingdom)	555 cases, 1110 controls	Not reported	Duration and response rate not reported; children < 15 years of age	Maternal smoking during pregnancy *Cigarettes/day* 1–10 ≥ 11	 1.1 (0.9–1.5) 0.8 (0.7–1.1)
Stjernfeldt *et al*. (1986) (Sweden)	305 cases, 340 controls	Physician-distributed questionnaire	3 years diagnosis of children < 17 years old; > 95% response rate	Maternal smoking during pregnancy *Cigarettes/day* 1–9 ≥ 10	 1.1 1.6, $p < 0.01$
Forsberg & Kallen (1990) (Sweden)	69 cases, 139 controls	Medical record	2 years diagnosis of children < 10 years of age; response rate not reported	Any maternal smoking	1.1 (0.6–2.0)
John *et al*. (1991) (USA)	223 cases, 196 controls	Telephone interview	7 years diagnosis of children < 15 years of age; 71% case response rate; 63% control response rate	Any maternal smoking in first trimester Paternal smoking in year prior to birth	1.3 (0.7–2.1) 1.2 (0.8–2.1)

Table 2.13 (contd)

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Relative risk (95% CI)
Golding *et al*. (1992) (United Kingdom)	195 cases, 558 controls	Medical record	20 years diagnosis of children (age not reported); response rate not reported	Maternal smoking in pregnancy	2.0 (1.3–3.2)
Sorahan *et al*. (1995) (United Kingdom)	1641 cases, 1641 controls	In-person interview	Deaths 1977–81 in children < 16 years of age; 61% case response rate; control response rate not reported	Maternal prenatal smoking *Cigarettes/day* 1–9 10–19 20–29 30–39 ≥ 40 Paternal prenatal smoking *Cigarettes/day* 1–9 10–19 20–29 30–39 ≥ 40	 1.0 (0.7–1.3) 1.2 (1.0–1.4) 1.0 (0.8–1.2) 0.9 (0.6–1.5) 1.6 (0.9–3.0) 1.2 (0.8–1.8) 1.2 (1.0–1.6) 1.3 (1.1–1.5) 1.4 (1.0–1.8) 1.5 (1.1–2.0)
Sorahan *et al*. (1997a) (United Kingdom)	1549 cases, 1549 controls	In-person interview	Deaths 1953–55 in children < 16 years of age; 88% case response rate; 94% control response rate	Maternal smoking *Cigarettes/day* 1–9 10–20 > 20	 1.0 (0.8–1.2) 1.2 (1.0–1.5) 1.2 (0.7–2.3) *p* for trend = 0.09

Table 2.13 (contd)

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Relative risk (95% CI)
Sorahan *et al*. (1997a) (contd)				Paternal smoking *Cigarettes/day* 1–9 10–20 > 20 *p* for trend < 0.001	 1.0 (0.8–1.3) 1.3 (1.1–1.6) 1.4 (1.1–1.9)
Sorahan *et al*. (1997b) (United Kingdom)	2587 cases, 2587 controls	In-person interview	Deaths 1971–76 in children < 16 years of age; 63% case response rate; control response rate not reported	Maternal smoking only Paternal smoking only Both parents smoking	1.0 (0.8–1.1) 1.3 (1.1–1.5) 1.3 (1.3–2.4)
Ji *et al*. (1997) (China)	642 cases, 642 controls	In-person interview	10 years diagnosis of children < 15 years of age; 83% case response rate; 100% control response rate	Paternal smoking *Cigarettes/day* < 10 10–14 ≥ 15 Paternal smoking (years) < 10 10–14 ≥ 15 *p* for trend = 0.007	 1.5 (1.1–2.3) 1.1 (0.8–1.6) 1.5 (1.0–2.3) 1.2 (0.7–1.8) 1.1 (0.8–1.7) 1.7 (1.2–2.5)

socioeconomic status, height and pre-pregnancy weight as well as previous pregnancies, exposure to diagnostic radiation during pregnancy, feeding of infant in hospital, sex of infant and date of delivery had only a minimal effect on the point estimates, all of which remained in the range of 0.6. [The Working Group noted that the limitations of this study were that the completeness of follow-up was unknown, but the estimates of expected incidence suggest that few cases were missed, and that assessment of exposure to secondhand smoke was limited.]

Buckley *et al*. (1986) conducted a case–control analysis using data from the US/Canada Children's Cancer Study Group. These investigators compared smoking by mothers and fathers of 1814 childhood cancer cases with that of parents of 720 controls selected at random from approximately the same geographical regions as cases. Smoking in the periods before and during pregnancy was assessed. No association was found between maternal smoking during pregnancy (< 10 cigarettes per day, relative risk, 1.3; 95% CI, 0.9–1.9; ≥ 10 cigarettes per day, relative risk, 1.0; 95% CI, 0.8–1.2) and no association with paternal smoking was found [relative risk not reported]. Adjustment for potential confounders such as year of birth, age of mother, illnesses during pregnancy and socioeconomic factors, did not alter findings. [The Working Group noted that the strength of this study was the large sample size and its limitations were that the report lacked details of the study and the control group was not well described.]

In a case–control study based on the Inter-Regional Epidemiological Study of Childhood Cancer in the United Kingdom, 555 cases of cancer in children < 15 years of age and 1110 controls matched for age and sex were compared for exposure to maternal smoking during pregnancy (McKinney *et al*., 1986). There was no evidence of an association between maternal smoking and risk for childhood cancer (1–10 cigarettes per day, relative risk, 1.1; 95% CI, 0.9–1.5; > 11 cigarettes per day, relative risk, 0.8; 95% CI, 0.7–1.1). [The Working Group noted that the strength of this study was the large sample size. The limitations were that the report provided few study details; other than matching for age and sex there was no adjustment for potential confounders, and there was limited assessment of exposure to secondhand smoke.] This dataset was recently re-evaluated (Sorahan *et al*., 2001). Microfilmed interview records of all study subjects were reviewed and information on parental cigarette smoking habits was re-abstracted. There was a statistically significant positive trend ($p = 0.02$) associated with daily paternal cigarette consumption before pregnancy for all cancers combined when cases were compared with controls selected from General Practitioners' (GPs') lists ($n = 555$), but no significant association was observed when cases were compared with hospital controls ($n = 555$). The opposite was seen for maternal smoking before pregnancy: an inverse trend ($p < 0.001$) was noted between daily cigarette consumption when cases were compared with hospital controls, but not when compared with GP controls. Risk estimates were adjusted for socioeconomic status, ethnicity, parental age at child's birth and other parent's smoking. [The Working Group noted that the two sets of controls produced very different results that are not easily explained.]

Stjernfeldt *et al*. (1986) reported the findings of a nationwide case–control study in Sweden that included 305 cases of cancer in children ≤ 16 years of age and 340 children with insulin-dependent diabetes mellitus who served as controls. Estimates of relative risk were adjusted for year of child's birth and maternal age, illness during pregnancy, occupation and place of residence. A 50% ($p < 0.01$) increase in risk for cancer was associated with in-utero exposure to maternal smoking. [The Working Group noted that the strengths of the study included the good response rate and the attempt to control for response bias by using children with diabetes mellitus as controls; its limitation was that the appropriateness of the control group was unknown.]

A case–control study from Sweden by Forsberg and Kallen (1990) found no association between childhood cancers and maternal smoking (relative risk, 1.1; 95% CI, 0.6–2.0) based on 69 cases and 139 controls for whom maternal smoking status was known. [The Working Group noted that the limitations of this study included the small sample size, uncertainty as to whether original case–control matching also applied to the substudy sample and the limited assessment of exposure.]

John *et al*. (1991) evaluated both maternal and paternal prenatal smoking histories in relation to risk for childhood cancer. The study included 223 incident cases < 15 years of age diagnosed from 1976 to 1983 in Denver, CO, USA. Controls were selected using random digit dialling and were matched to cases on age, sex and telephone exchange, and 196 controls were included in the analysis. Mothers' and fathers' smoking was highly correlated. Of the 109 children exposed to mother's smoking during the first trimester, 81% were also exposed to father's tobacco smoking while an additional 105 children were exposed to father's smoking alone. Mother's smoking during the first trimester was associated with a modest statistically nonsignificant increase in risk for childhood cancer after adjustment for father's education (relative risk, 1.3; 95% CI, 0.7–2.1). Children whose mothers did not smoke who were exposed to father's smoking also had a modest, statistically non-significant increase in risk (relative risk, 1.2; 95% CI, 0.8–2.1). [The Working Group noted that this study included a more detailed assessment of exposure to secondhand smoke than did earlier studies.]

Golding *et al*. (1992) conducted a case–control study in the United Kingdom to assess the association of childhood cancer with administration of intramuscular vitamin K and pethidine during labour. Data on mothers' smoking during pregnancy as a potential confounder were collected. A twofold increase in risk (relative risk, 2.0; 95% CI, 1.3–3.2) adjusted for year of delivery was found. [The Working Group noted that this study was not designed to investigate exposure to secondhand smoke, that only maternal smoking during pregnancy was recorded and that there was only minimal control for potential confounders.]

Three reports from the Oxford Survey of Childhood Cancer (OSCC) provided data from large case–control studies of childhood cancer deaths during different time periods: 1977–81 (Sorahan *et al*., 1995), 1953–55 (Sorahan *et al*., 1997a) and 1971–76 (Sorahan *et al*., 1997b). The first report in 1995 included 1641 cases and an equal number of controls. There was no association with prenatal maternal cigarette smoking; however,

paternal smoking was associated with a statistically significant positive trend (p for trend = 0.003). When cigarette use by one or both parents was adjusted for social class, maternal age at birth and use of alcohol, the relative risk was 1.4 (95% CI, 1.1–1.7) for father's use of cigarettes and 1.4 (95% CI, 1.1–1.7) for cigarette use by both parents, whereas cigarette use by mother was not statistically significantly associated with an increased risk (relative risk, 1.2; 95% CI, 1.0–1.6). A total of 1549 deaths from childhood cancer between 1953 and 1955 and 1549 matched healthy controls were used to further investigate the earlier findings from the OSCC (Sorahan *et al.*, 1997a). After adjustment for smoking by the spouse, social class, age of father, age of mother, birth order, and exposure to obstetric radiography, no statistically significant dose–response trend was found to be associated with maternal smoking, but maternal smoking only was associated with a 30% increased risk for childhood cancer (relative risk, 1.3; 95% CI, 1.1–1.5). At the highest level of paternal smoking (> 20 cigarettes per day), a clear trend was noted (p for trend < 0.001) with a relative risk of 1.4 (95% CI, 1.1–1.9); paternal smoking only was also associated with increased risk (relative risk, 1.7; 95% CI, 1.3–2.2). The third report (Sorahan *et al.*, 1997b) which examined deaths from 1971 to 1976 provided very similar results to those in the first two reports, i.e. no clear association with childhood cancer was evident for maternal smoking and there was a statistically significant positive trend for paternal smoking. [The Working Group noted the very large sample sizes, the consistent findings over time, the adjustment for potential confounders and the assessment of exposure from mothers and fathers with data for trends.]

A large case–control study in China by Ji *et al*. (1997) also examined paternal smoking and risk for cancer in children (< 15 years of age) of nonsmoking mothers. Relative risks were adjusted for birth weight, income, paternal age, education and alcohol drinking. For all sites combined, the relative risk for 'ever smoking' by the father was 1.3 (95% CI, 1.0–1.7). Statistically significant trends were found for duration of paternal smoking (p for trend = 0.007) and pack–years (p for trend = 0.01), but not age of starting smoking (p for trend = 0.28) or cigarettes per day (p for trend = 0.07). [The Working Group noted the large sample size, the minimization of exposure misclassification by including only children of nonsmoking mothers, the adjustment for potential confounders and the extensive exposure assessment for fathers.]

Boffetta *et al*. (2000) conducted a meta-analysis of childhood cancers associated with passive exposure to smoke based on the random effects model. The relative risk estimate for maternal smoking during pregnancy for all cancers combined included all cohort studies and eight of the ten case–control studies listed in Table 2.13 (Sorahan *et al*. 1997b; Ji *et al*. 1997; were not included). The results suggest a small increase in risk for all cancers for maternal smoking during pregnancy (relative risk, 1.1; 95% CI, 1.0–1.2), but not for specific cancer sites. Results on exposure before and after pregnancy were too sparse for any conclusion to be drawn. Studies of exposure to paternal tobacco smoke and risk for all cancers combined are fewer than those addressing maternal smoking and no relative risk was reported in this meta-analysis.

2.3.2 *Brain and central nervous system*

Table 2.14 lists one cohort study (Pershagen *et al*. 1992) and 15 case–control studies (Gold *et al*., 1979; Preston-Martin *et al*., 1982; Stjernfeldt *et al*., 1986; Howe *et al*., 1989; Kuijten *et al*., 1990; Gold *et al*., 1993; Bunin *et al*., 1994; Cordier *et al*., 1994; Filippini *et al*., 1994; McCredie *et al*., 1994; Norman *et al*., 1996; Ji *et al*., 1997; Sorahan *et al*., 1997a,b; Filippini *et al*., 2000) that have examined parental smoking and risk for brain tumours or for all tumours of the central nervous system combined.

Only the cohort study of Pershagen *et al*. (1992) (see section 2.3.1) has published a relative risk for tumours of the central nervous system. No association was found between maternal smoking in pregnancy and risk for tumours of the central nervous system.

The first case–control study to examine risk for brain tumour and maternal smoking was reported by Gold *et al*. (1979). This study was conducted in the USA and included 84 children with brain tumours and two control groups. One control group comprised 78 children with other malignancies matched on sex, race, date and age at diagnosis, and the other, 73 children selected from the state birth certificate file and matched on sex, date of birth and race. Risk associated with maternal smoking before and during pregnancy was associated with large non-statistically significant risks for childhood brain tumour that were based on a small sample size.

Preston-Martin *et al.* (1982) reported the findings from a larger case–control study in the USA designed to evaluate the risk for brain tumour associated with childhood exposure to *N*-nitroso compounds, including those from tobacco smoke. No increased risk was associated with maternal smoking, but a relative risk of 1.5 ($p = 0.03$) was found for children of mothers living with a smoker during pregnancy. The small Swedish case–control study by Stjernfeldt *et al*. (1986) (see section 2.3.1) found no increased risk for tumours of the central nervous system associated with maternal smoking in pregnancy.

An exploratory case–control study of brain tumours in Canadian children diagnosed in Ontario between 1977 and 1983 included 74 cases and 138 age- and sex-matched controls. The study found neither maternal nor paternal smoking during pregnancy to be statistically significantly associated with risk for brain tumours (Howe *et al*., 1989). Similarly, a population-based case–control study in the USA of childhood astrocytomas that included 163 case–control pairs found no increased risk associated with any smoking by either mother or father (Kuijten *et al.*, 1990).

A large population-based case–control study in the USA of childhood brain tumours examined smoking by both parents in some detail. The study included exposure assessments for the preconception period as well as the pre- and postnatal period (year of birth of child) and dose–response estimates (Gold *et al*., 1993). There was no statistically significant association between risk for brain tumours and any indicator of parental smoking. [The Working Group noted that this was a well-conducted study designed to examine parental smoking in detail, and having sufficient statistical power.]

Bunin *et al.* (1994) studied the two most common types of brain tumour, astrocytoma and primitive neuroectodermal tumour, in children less than six years of age. Controls,

Table 2.14. Tumours of the brain and central nervous system and involuntary exposure to parental smoking

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Results Relative risk (95% CI)
Cohort study					
Pershagen *et al*. (1992) (Sweden)	497 051 births, 81 CNS tumours	Cancer registry	Up to 5 years follow-up; 99% complete	Maternal smoking during pregnancy *Cigarettes/day* < 10 ≥ 10	 0.9 (0.5–1.6) 1.1 (0.6–2.1)
Case–control studies					
Gold *et al*. (1979) (USA)	84 brain tumours, 73 population controls, 78 cancer controls	In-person interview	10 years diagnosis of children < 20 years old; 66% case response rate; 20% population control response rate; 44% cancer control response rate	Maternal smoking during pregnancy With population controls With cancer controls	 5.0, $p < 0.22$ ∞
Preston-Martin *et al*. (1982) (USA)	209 brain tumours, 209 controls	Telephone interview	5 years diagnosis of cases < 25 years old; 66% case response rate; 78% control response rate	Maternal smoking during pregnancy Mother living with a smoker	1.1 (one-sided $p = 0.42$) 1.5 (one sided $p = 0.03$)
Stjernfeldt *et al*. (1986) (Sweden)	43 brain and CNS tumours, 332 controls	Physician-distributed questionnaire	3 years diagnosis in children < 17 years old; > 95% response rate	Maternal smoking during pregnancy *Cigarettes/day* 1–9 ≥ 10	 1.0 0.9

Table 2.14 (contd)

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Results Relative risk (95% CI)	
Howe *et al*. (1989) (Canada)	74 brain tumours, 138 controls	In-person interview	6 years diagnosis of children < 20 years of age; 60% case response rate; 86% control response rate	*Any smoking*	Mother 1.4 (0.7–3.0)	Father 1.1 (0.6–2.1)
Kuijten *et al*. (1990) (USA)	163 astrocytomas, 163 controls	In-person interview	6 years diagnosis of children < 15 years of age; 80% case response rate; 73% control response rate	*Any smoking*	Mother 1.0 (0.6–1.7)	Father 0.8 (0.5–1.3)
Gold *et al*. (1993) (USA)	361 brain tumours, 1083 controls	In-person interview	4 years diagnosis of children < 18 years of age; 85% case response rate; 85% control response rate	*Any smoking*	Mother 0.9 (0.7–1.2)	Father 1.1 (0.8–1.4)
				During year of birth (packs/day)		
				< 1	0.8 (0.6–1.3)	0.7 (0.4–1.2)
				≥ 1	1.0 (0.7–1.4)	1.1 (0.8–1.5)
				Two years before birth (packs/day)		
				< 1	0.8 (0.5–1.1)	0.9 (0.5–1.5)
				≥ 1	1.0 (0.7–1.4)	1.2 (0.9–1.6)

Table 2.14 (contd)

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Results Relative risk (95% CI)	
Bunin *et al*. (1994) (USA)	155 astrocytic gliomas, 166 primitive neuroectodermal tumours and 155 and 166 controls, respectively	Telephone interview	3 years diagnosis of children < 6 years of age; 65% case response rate; 83% control response rate	**Astrocytic glioma**	Mother	Father
				Ever smoked	1.1 (0.7–1.8)	1.1 (0.7–1.8)
				Smoked during pregnancy	1.0 (0.6–1.7)	1.0 (0.6–1.7)
				Primitive neuro-ectodermal tumour		
				Ever smoked	0.9 (0.6–1.5)	0.9 (0.6–1.5)
				Smoked during pregnancy	1.0 (0.6–1.7)	1.0 (0.6–1.7)
Cordier *et al*. (1994) (France)	75 brain tumours, 113 controls	In-person interview	2 years diagnosis of children < 15 years of age; 69% case response rate; 72% control response rate	Any smoking by mother	1.6 (0.7–3.5)	
Filippini *et al*. (1994) (Italy)	91 brain tumours, 321 controls	In-person interview	3 years diagnosis of children < 15 years of age; 88% case response rate; 75% control response rate	Maternal smoking during pregnancy	1.7 (0.8–3.8)	
				Maternal smoking		
				1–10 cigarettes/day	2.0 (1.0–4.0)	
				> 10 cigarettes/day	1.6 (0.5–4.8)	
				Paternal smoking before pregnancy	1.3 (0.8–2.4)	
McCredie *et al*. (1994) (Australia)	82 brain tumours, 164 controls	In-person interview	4 years diagnosis of children < 15 years of age; 85% case response rate; 60% control response rate	Questions related to sources of exposure to *N*-nitroso compounds including tobacco smoke	No association	

Table 2.14 (contd)

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Results Relative risk (95% CI)	
Norman *et al*. (1996) (USA)	540 brain tumours, 801 controls	In-person and telephone interviews	6 years diagnosis of children < 15 years of age; 71% case response rate; 74% control response rate	Any smoking	Mother 1.0 (0.7–1.3)	Father 1.2 (0.9–1.5)
Ji *et al*. (1997) (China)	107 brain tumours, 107 controls	In-person interview	10 years diagnosis of children < 15 years of age; 83% case response rate; 100% control response rate	Paternal smoking *Cigarettes/day* 1–9 10–14 ≥ 15 *Duration of exposure (years)* < 10 10–14 ≥ 15	 1.5 (0.5–4.5) 1.6 (0.6–4.7) 2.1 (0.6–8.1) 0.8 (0.2–3.8) 1.3 (0.4–4.1) 3.4 (0.9–12.5)	
Sorahan *et al*. (1997a) (United Kingdom)	229 CNS tumours, 229 controls	In-person interview	Deaths 1953–55 in children < 16 years of age; 88% case response rate; 94% control response rate	Parental smoking	Mother 1.0 (0.8–1.4)	Father 1.2 (1.0–1.5)
Sorahan *et al*. (1997b) (United Kingdom)	410 CNS tumours, 410 controls	In-person interview	Deaths 1971–76 in children < 16 years of age; 63% case response rate; control response rate not reported	Parental smoking	Mother 1.1 (1.0–1.2)	Father 1.0 (0.9–1.1)

Table 2.14 (contd)

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Results Relative risk (95% CI)
Filippini *et al*. (2000) (Italy)	244 CNS tumours, 502 controls	Telephone interview	5 years diagnosis of children < 16 years old; 85% case response rate; 88% control response rate	*Maternal smoking* Before pregnancy Before she knew she was pregnant *Maternal exposure to secondhand smoke* During early pregnancy During late pregnancy	 1.2 (0.9–1.7) 1.5 (1.0–2.3) 1.8 (1.2–2.6) 1.7 (1.2–2.5)

CNS, central nervous system

selected by random-digit dialling, were matched to cases on race, year of birth, and telephone area code and prefix. Estimates of relative risk for astrocytoma were adjusted for income level, but primitive neuroectodermal tumour estimates were unadjusted. No association was found between either of these types of tumour and maternal active (ever and/or during pregnancy) or passive smoking (during pregnancy) or paternal smoking (ever and/or during pregnancy).

A non-statistically significant increase in risk for brain tumours (relative risk, 1.6; 95% CI, 0.7–3.5) associated with any smoking by the mother was found in a small case–control study in France (Cordier *et al*. 1994). Filippini *et al.* (1994) in Italy assessed the risk associated with active and passive smoking by mothers during pregnancy in a case–control study with 91 cases. Active smoking by the mother during pregnancy was associated with a relative risk of 1.7 (95% CI, 0.8–3.8); no dose–response relationship was observed. Relative risks were adjusted for education level. Among nonsmoking mothers, the relative risks for light and heavy exposure to secondhand smoke were 1.7 (95% CI, 0.8–3.6) and 2.2 (95% CI, 1.1–4.5; p trend = 0.02). McCredie *et al*. (1994) conducted another small, population-based case–control study of brain tumours in Australia. Two controls were matched to each case by age and sex. No association was found with exposure to tobacco smoke from another member of the household, but no risk estimates were provided. [The Working Group noted that the limitations of these studies were that they lacked statistical power; there was limited adjustment for potential confounders and limited assessment of exposure.]

The findings from a large, population-based case–control study of brain tumours in children < 15 years of age diagnosed from 1984 to 1991 provided no support for an association between brain tumour risk and maternal or paternal smoking before pregnancy or maternal smoking during pregnancy (Norman *et al*. 1996). Risk estimates were at or below unity and there was no evidence of a relationship between risk for brain tumours and amount or timing of exposure. [The Working Group noted that the strengths of this study were that it was large and included a relatively detailed assessment of exposure.]

Three studies discussed previously (Ji *et al*. 1997; Sorahan *et al*. 1997a,b) found no increased risk for brain tumours associated with father's smoking (Ji *et al*., 1997) or of tumours of the central nervous system associated with maternal or paternal smoking (Sorahan *et al*., 1997a,b; 2001).

Filippini *et al*. (2000) in northern Italy, conducted a population-based case–control study of childhood tumours of the central nervous system with cases diagnosed from 1988 to 1993. Cases from their previous study (Filippini *et al*., 1994) were excluded. Active smoking by parents before pregnancy was not associated with increased risk. Active smoking by mothers in early pregnancy was associated with a small increase in risk (relative risk, 1.5; 95% CI, 1.0–2.3). An increase in risk was also associated with passive smoking by nonsmoking mothers in early pregnancy (relative risk, 1.8; 95% CI, 1.2–2.6) and late pregnancy (relative risk, 1.7; 95% CI, 1.2–2.5).

The results of the meta-analysis by Boffetta *et al*. (2000) indicated no significant increase in risk for tumours of the central nervous system associated with maternal

smoking during pregnancy (relative risk, 1.0; 95% CI, 0.9–1.2), but exposure to paternal smoking suggested an increased risk for brain tumours (relative risk, 1.1; 95% CI, 1.1–1.4). [The Working Group noted that this meta-analysis included two studies of neuroblastoma and one study of retinoblastoma with tumours of the central nervous system.]

2.3.3 *Leukaemias and lymphomas*

The only cohort study to report specifically on lymphatic and haematopoietic cancers (Pershagen *et al.*, 1992) and 16 case–control studies with data on one or more of these types of malignancy are included in Table 2.15 (Manning & Carroll, 1957; Stewart *et al*., 1958; Van Steensel-Moll *et al*., 1985; Buckley *et al*., 1986; McKinney *et al*., 1986; Stjernfeldt *et al*., 1986; Magnani *et al*., 1990; John *et al*., 1991; Roman *et al*., 1993; Severson *et al*., 1993; Shu *et al*., 1996; Ji *et al*., 1997; Sorahan *et al*., 1997a,b; Brondum *et al*., 1999; Infante-Rivard *et al*., 2000).

A total of 129 lymphatic and haematopoietic cancers were diagnosed during 5 years of follow-up in the Swedish cohort (Pershagen *et al*., 1992). No association was observed between the development of these cancers and smoking during pregnancy or any amount of smoking by the mother.

Manning and Carroll (1957) found no difference in the proportion of mothers of children with leukaemia who smoked 10 or more cigarettes per day at the time of interview when compared to control mothers (39% versus 38%) and a somewhat lower proportion of mothers of children with lymphoma (31%) who smoked at that level. A second early study (Stewart *et al.*, 1958) reported a very small but statistically significant increase in risk for death from leukaemia among children of mothers who had ever smoked (relative risk, 1.1; $p < 0.04$). [The Working Group noted that neither study was designed specifically to study the effects of involuntary smoking; only unadjusted proportions were reported.]

Van Steensel-Moll *et al*. (1985) found no association between maternal smoking in the year before pregnancy and risk for acute lymphocytic leukaemia in a study in the Netherlands designed to assess maternal fertility problems and this risk. [The Working Group noted that the strength of this study was the large number of cases. Its limitations are the limited assessment of exposure and the questionable time period.] The case–control study in Sweden by Stjernfeldt *et al*. (1986) included 157 cases of acute lymphoblastic leukaemia, 16 cases of non-Hodgkin lymphoma and 15 cases of Hodgkin disease. A statistically significant positive trend (p trend < 0.01) was found for number of cigarettes smoked per day by the mother during pregnancy and risk for acute lymphoblastic leukaemia. No statistically significant association with smoking was observed for either non-Hodgkin lymphoma or Hodgkin disease based on a very small number of cases.

McKinney *et al*. (1986) found no association between maternal smoking during pregnancy and risk for childhood leukaemia or lymphoma. Buckley *et al.* (1986) also failed to find an association between maternal smoking during pregnancy in their large

Table 2.15. Childhood leukaemias and lymphomas and involuntary exposure to parental smoking

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Results Relative risk (95% CI)		
Cohort study							
Pershagen *et al*. (1992) (Sweden)	497 051 births, 129 lymphatic and haematopoietic cancers	Cancer registry	5 years follow-up; 327 of 422 cancers linked to births with smoking data.	Maternal smoking during pregnancy *Cigarettes/day* < 10 ≥ 10	1.0 (0.7–1.5) 1.2 (0.8–1.9) 0.8 (0.4–1.5)		
Case–control studies							
Manning & Carroll (1957) (USA)	188 leukaemias, 42 lymphomas, 50 hospital controls	Interview	3 years diagnosis of children < 15 years of age	Proportion of mothers smoking ≥ 10 cigarettes/day at time of interview	Leukaemia 39%	Lymphoma 31%	Controls 38%
Stewart *et al*. (1958) (United Kingdom)	677 leukaemias, 739 other cancers, 1416 living controls	In-person interview	3 years diagnosis of children < 15 years of age	Mother ever smoked	1.1 ($p < 0.04$)		
Van Steensel-Moll *et al*. (1985) (the Netherlands)	519 ALL, 507 controls	Postal questionnaire	7 years diagnosis of children < 15 years of age; 90% case response rate; 69% control response rate	Maternal smoking during year before pregnancy	1.0 (0.8–1.3)		
Stjernfeldt *et al*. (1986) (Sweden)	157 ALL, 16 NHL, 15 HD, 340 controls	Physician-delivered questionnaire	3 years diagnosis of children < 17 years of age; 95% response rate for both cases and controls	*Maternal smoking during pregnancy* 1–9 cigarettes/day ≥ 10 cigarettes/day	ALL 1.3 2.1	NHL 2.0 2.1	HD 1.1 0.3
McKinney *et al*. (1986) (United Kingdom)	171 leukaemias, 74 lymphomas, 2 controls/case	Not reported	Response rate not reported	*Maternal smoking during pregnancy* 1–10 cigarettes/day > 10 cigarettes/day	Leukaemia 1.0 (0.6–1.7) 0.6 (0.4–1.0)	Lymphoma 1.9 (0.9–4.0) 1.0 (0.5–2.1)	
Buckley *et al*. (1986) (USA, Canada)	742 ALL, 169 NHL, 720 controls	Question-naire	3 years diagnosis of cancer in children (age not given). Response rate not reported	*Maternal smoking during pregnancy* 1–9 cigarettes/day ≥ 10 cigarettes/day	ALL 1.0 (0.6–1.0) 0.9 (0.7–1.1)	NHL 0.8 (0.3–1.8) 1.0 (0.7–1.4)	

Table 2.15 (contd)

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Results Relative risk (95% CI)		
Magnani *et al*. (1990) (Italy)	142 ALL, 22 other leukaemias (non-ALL), 19 NHL, 307 controls	In-person interview	10 years diagnosis in cases < 15 years of age. Response rate not reported		ALL	Non-ALL	NHL
				Maternal smoking up to child's birth	0.7 (0.5–1.1)	2.0 (0.8–4.8)	1.7 (0.7–4.5)
				Paternal smoking	0.9 (0.6–1.5)	0.9 (0.3–2.1)	6.7 (1.0–43.4)
John *et al*. (1991) (USA)	73 leukaemias, 26 lymphomas, 196 controls	Telephone interview	7 years diagnosis in children < 15 years of age; 71% case response rate; 63% control response rate	*Maternal smoking*	ALL	Non-ALL	Lymphoma
				3 months before conception	2.1 (1.0–4.3)	0.8 (0.2–2.7)	1.9 (0.7–5.2)
				First trimester	2.3 (1.1–5.0)	1.1 (0.3–4.0)	2.5 (0.9–7.0)
				All 3 trimesters	2.5 (1.2–5.4)	0.6 (0.1–3.0)	2.7 (1.0–7.6)
Severson *et al*. (1993) (USA, Canada)	187 acute myeloid leukaemias, 187 controls	Telephone interview	4 years diagnosis in children < 18 years of age; 78% case response rate; 79% control response rate	*Maternal smoking*			
				During pregnancy	1.2 (0.8–1.9)		
				Current smoker	0.9 (0.6–1.4)		
				Ever smoker	1.3 (0.9–2.1)		
Roman *et al*. (1993) (United Kingdom)	54 leukaemias and NHL, 324 controls	Interview, birth certificates, occupational and medical records	17 years diagnosis in cases < 5 years of age; 76% case response rate; 95% control response rate	*Smoking during pregnancy*			
				From obstetric records	0.9 (0.3–2.5)		
				From interview	0.5 (0.2–1.2)		
Shu *et al*. (1996) (USA, Canada, Australia)	302 leukaemias, 558 controls	Telephone interview	5 years diagnosis of children ≤ 18 months of age; 79% case response rate; 75% control response rate		Mother	Father	
				Smoking during pregnancy		1.2 (0.9–1.8)	
				Cigarettes/day			
				1–10	0.7 (0.4–1.0)		
				11–20	0.6 (0.4–1.1)		
				> 20	0.6 (0.2–1.8)		
					p for trend = 0.03		
Ji *et al*. (1997) (China)	166 acute leukaemias, 87 lymphomas, 166 and 87 controls, respectively	In-person interview	10 years diagnosis of children <15 years of age; 83% case response rate; 100% control response rate	Paternal smoking before conception	Acute leukaemia	Lymphoma	
				Cigarettes/day			
				< 10	1.6 (0.7–3.9)	3.4 (0.8–14.0)	
				10–14	0.9 (0.4–1.5)	1.1 (0.3–4.8)	
				≥ 15	1.9 (0.8–4.6)	3.8 (0.9–16.5)	
					p for trend = 0.27	*p* for trend = 0.09	

Table 2.15 (contd)

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Results Relative risk (95% CI)	
Ji *et al*. (1997) (contd)				*Pack–years*		
				≤ 5	0.9 (0.4–2.2)	2.8 (0.6–12.8)
				> 5–< 10	1.1 (0.5–2.6)	1.3 (0.3–5.5)
				≥ 10	1.9 (0.8–4.6)	5.7 (1.3–26.0)
					p for trend = 0.06	*p* for trend = 0.03
Sorahan *et al*. (1997a) (United Kingdom)	367 ALL, 115 myeloid leukaemias, 27 monocytic leukaemias, 216 other, unspecified leukaemias, 125 lymphomas, equal numbers of controls	In-person interview	2 years diagnosis of children < 16 years old; 88% case response rate; 60% control response rate	Parental smoking	Mother	Father
				Leukaemias		
				ALL	1.2 (1.0–1.5)	1.1 (0.9–1.3)
				Myeloid	1.2 (0.9–1.7)	1.0 (0.7–1.3)
				Monocytic	1.2 (0.6–2.5)	1.1 (0.6–2.0)
				Other	1.2 (0.9–1.6)	1.1 (0.9–1.4)
				Lymphomas	0.8 (0.6–1.1)	1.4 (1.0–1.8)
Sorahan *et al*. (1997b) (United Kingdom)	573 ALL, 190 myeloid leukaemias, 25 monocytic leukaemias, 47 other unspecified leukaemias, 165 lymphomas, equal numbers of controls	In-person interview	5 years diagnosis in children < 16 years of age; 57% case response rate; 52% control response rate	Parental smoking	Mother	Father
				Leukaemias		
				ALL	1.0 (0.9–1.1)	1.1 (1.0–1.2)
				Myeloid	1.0 (0.8–1.2)	1.3 (1.1–1.5)
				Monocytic	0.7 (0.4–1.2)	0.8 (0.6–1.3)
				Other	0.9 (0.7–1.2)	1.0 (0.8–1.3)
				Lymphomas	1.1 (0.9–1.2)	1.1 (0.9–1.2)
Brondum *et al*. (1999) (USA)	1842 ALL, 1987 controls, 517 AML, 612 controls	Telephone interview	3.5 years diagnosis of acute leukaemia < 5–18 years of age. Case response rates: 92% ALL, 83% AML; control response rates: 76.5% ALL controls, 79.4% AML controls		ALL	AML
				Father ever smoked	1.0 (0.9–1.2)	0.9 (0.7–1.2)
				Mother ever smoked	1.0 (0.9–1.2)	1.0 (0.7–1.2)

Table 2.15 (contd)

Reference (country)	Sample	Source of information on exposure	Duration (from birth) and completeness of follow-up	Exposure	Results Relative risk (95% CI)		
Infante-Rivard *et al*. (2000)	491 ALL, 491 controls	Telephone interview	13 years diagnosis of ALL in children < 10 yrs of age. 96.3% case response rate; 83.8% control response rate	Parental smoking during childhood	Mother 1.0 (0.7–1.4)	Father 1.0 (0.7–1.4)	
				Cigarettes/day 1–20 > 20	1.0 (0.6–1.3)	1.0 (0.7–1.3)	
				Maternal smoking *Cigarettes/day*	1st trimester	2nd trimester	3rd trimester
				1–20	1.1 (0.8–1.6)	1.2 (0.8–1.6)	1.2 (0.8–1.6)
				> 20	1.0 (0.7–1.6)	1.2 (0.7–1.9)	1.2 (0.8–2.0)
	158 cases, 491 controls (case–case substudy)			*At > 20 cigarettes/day* CYP1A1*2A allele CYP1A1*2B allele CYP1A1*4 allele	Moderate risk increases Reduced risk Lower increases associated with father's smoking; mother's smoking risks higher in 3rd trimester		

ALL, acute lymphocytic leukaemia; NHL, non-Hodgkin lymphoma; HD, Hodgkin disease; AML, acute myeloblastic leukaemia

study that included 742 cases of acute lymphocytic leukaemia and 169 cases of non-Hodgkin lymphoma.

Magnani *et al.* (1990) found no association between acute lymphocytic leukaemia, other leukaemias or non-Hodgkin lymphoma during childhood and the mother's smoking up to the time of the child's birth. The father's history of smoking was associated with a risk for non-Hodgkin lymphoma (relative risk, 6.7; 95% CI, 1.0–43.4), but not for acute lymphocytic leukaemia or other leukaemias. This Italian hospital-based case–control study included 142 cases of acute lymphocytic leukaemia, but only a small number of non-Hodgkin lymphoma (n = 19) and other types of leukaemia (n = 22). Risk estimates were adjusted for socioeconomic status only.

The case–control study in the USA reported by John *et al*. (1991) included 73 cases of leukaemia and 26 cases of lymphoma. Statistically significant increases in risk were associated with maternal smoking 3 months before conception for acute lymphocytic leukaemia; with smoking during the first trimester for acute lymphocytic leukaemia; and during all three trimesters for acute lymphocytic leukaemia (relative risk, 2.5; 95% CI, 1.2–5.4) and lymphoma (relative risk, 2.7; 95% CI, 1.0–7.6).

A US–Canadian case–control study of acute myeloid leukaemia found no association between risk for acute myeloid leukaemia and maternal smoking before, during or after pregnancy (Severson *et al*. 1993). No association was observed with smoking by the father, but this was not quantified. [The Working Group noted the reasonably detailed exposure assessment, but although relative risks were adjusted for potential confounders, the factors were not named.]

A small case–control study of leukaemia and non-Hodgkin lymphoma in the United Kingdom examined maternal smoking based on obstetric notes and by interview (Roman *et al*., 1993). Both relative risks were below unity. [The Working Group noted that very little information was provided, that no adjustment was made for confounders, and the small size of the sample.]

Shu *et al*. (1996) found that maternal smoking during pregnancy was negatively associated with risk for leukaemia (all leukaemias, acute lymphocytic leukaemia or acute myeloblastic leukaemia) in infants. Paternal smoking one month prior to pregnancy was related to an elevated risk for acute lymphocytic leukaemia (relative risk, 1.6; 95% CI, 1.0–2.4), but not acute myeloblastic leukaemia and smoking by the father during pregnancy did not lead to a statistically significant increase in risk for any type of leukaemia. [The Working Group noted that the strengths of this study included the relatively detailed exposure from mothers' and fathers' smoking, and the adjustment for some potential confounders (sex, parental age, education and alcohol consumption by the mother during pregnancy).]

The case–control study of paternal smoking and childhood cancer in China reported by Ji *et al*. (1997) included 166 cases of acute leukaemia and 87 of lymphoma. No statistically significant association with paternal smoking was found for leukaemia, although a borderline positive trend was found for the father's number of pack–years of smoking (trend, p = 0.06). The father's smoking was associated with a fourfold increase in risk for

lymphoma (relative risk, 4.0; 95% CI, 1.3–12.5) and statistically significant positive dose–response trends for lymphoma were observed for number of years smoked preconception and pack–year history, but not for number of cigarettes smoked per day.

Sorahan *et al.* (1997a) reported a modest association between risk for acute lymphocytic leukaemia and maternal smoking (relative risk, 1.2; 95% CI, 1.0–1.5), but no increased risk was found for myeloid, monocytic or other types of leukaemia or lymphoma. This study found no relationship between paternal smoking and any type of leukaemia, but the risk estimate for lymphoma was 1.4 (95% CI, 1.0–1.8). No increased risks associated with parental smoking were found when cases and controls from a later time period, 1971–76, were examined (Sorahan *et al*. 1997b).

A large case–control study in the USA of parental cigarette smoking and risk for acute leukaemia collected detailed information on exposure to smoke from the mothers and fathers of 1842 children with acute lymphocytic leukaemia and 517 with acute myeloblastic leukaemia and controls matched on age, race, and telephone area code/exchange (Brondum *et al*., 1999). There was no association between risk for acute lymphocytic leukaemia and ever smoking by the father (relative risk, 1.0; 95% CI, 0.9–1.2) or mother (relative risk, 1.0; 95% CI, 0.9–1.2); similarly, no associations were observed between acute myeloblastic leukaemia and ever smoking by the father (relative risk, 0.9; 95% CI, 0.7–1.2) or the mother (relative risk, 1.0; 95% CI, 0.7–1.2). Parental smoking during or around the time of the index pregnancy was not related to risk, nor were the number of cigarettes smoked, years of smoking or pack–years. Risk estimates were adjusted for household income, mother's race and education and father's race and education. [The Working Group noted the good statistical power and the detailed histories of both parents and also that some adjustment has been made for potential confounders.]

A case–control study in Canada of acute lymphocytic leukaemia assessed the role of parental smoking and *CYP1A1* genetic polymorphisms (Infante-Rivard *et al*., 2000). There was no statistically significant association between parents' smoking and leukaemia overall. However, a substudy that included 158 of the 491 cases suggested that the effect of parental smoking may be modified by variant alleles in the *CYP1A1*. *CYP1A1*2B* tended to decrease risks and *CYP1A1*2A* and *CYP1A1*4* increased the risks associated with smoking in the second and third trimesters. [The Working Group noted that this was the first study to look at the interaction between parental smoking, *CYP1A1* and leukaemia.]

Sorahan *et al*. (2001) (see Section 2.3.1) found a statistically non-significant positive association between risk for acute lymphocytic leukaemia and daily cigarette consumption by fathers before pregnancy and a statistically non-significant inverse association between risk for acute lymphocytic leukaemia and daily smoking by mothers before pregnancy.

The results of the meta-analysis for maternal smoking during pregnancy indicated that there were no statistically significant associations for all lymphatic and haematopoietic neoplasms (relative risk, 1.0; 95% CI, 0.9–1.2), for non-Hodgkin lymphoma or total lymphomas (relative risk, 1.1; 95% CI, 0.9–1.5) or for all leukaemias, acute leukaemia or

acute lymphocytic leukaemia (relative risk, 1.1; 95% CI, 0.8–1.3) (Boffetta *et al*., 2000). The authors found evidence of publication bias for the data available on lymphomas ($p = 0.04$). Published studies with a small number of cases reported positive associations between exposure to tobacco smoke and childhood leukaemia, whereas larger studies showed no association. This suggests that small studies that had found no association or a negative association failed to be published. The meta-analysis for paternal smoking indicated no statistically significant association with acute lymphocytic leukaemia, but a twofold increase in risk for non-Hodgkin lymphoma (relative risk, 2.1; 95% CI, 1.1–4.0).

2.3.4 *Other childhood cancers*

Several other types of childhood cancer have been studied in relation to parental smoking in epidemiological investigations.

The cohort study by Pershagen *et al*. (1992) reported no statistically significant associations between mother's smoking during pregnancy and kidney cancer (30 cases; relative risk, 0.6; 95% CI, 0.2–1.5), eye tumours (28 cases; relative risk, 1.4; 95% CI, 0.6–2.8), endocrine tumours (13 cases; relative risk, 1.9; 95% CI, 0.6–6.0) or tumours of the connective tissue and muscle (15 cases; relative risk, 1.2; 95% CI, 0.4–3.6).

Magnani *et al*. (1989) conducted a hospital-based case–control study of soft-tissue sarcomas in Italy during 1983–84. The cases included 36 children with rhabdomyosarcoma and 16 cases of other soft-tissue sarcomas who were compared with 326 controls from the same hospitals. No associations were found between soft-tissue sarcoma or rhabdomyosarcoma and either mother's or father's smoking (all point estimates of relative risks were below unity). Smoking during several time periods, before, during and after birth was then looked at separately and the results were the same as for any smoking by the parents. [The Working Group noted that this was a small study, but that the exposure assessment included different time periods.]

Two studies in the USA (Holly *et al*., 1992; Winn *et al*., 1992) examined risk factors for Ewing's sarcoma. In their population-based study, Holly *et al*. (1992) looked at 43 cases and 193 controls selected by random digit dialling and matched to cases by sex and age. This tumour was not associated with smoking by the mother during pregnancy (relative risk, 1.1; 95% CI, 0.5–2.4) or by the father (relative risk, 0.9; 95% CI, 0.4–1.9). Risk estimates were adjusted for agricultural occupation of the father, poison or overdose of medication, area of residence, year of child's birth and income. [The Working Group noted that this was a small study that had made a detailed assessment of many factors, but less for parental smoking.] Winn *et al*. (1992) reported the findings of a larger case–control study that included 208 cases throughout the USA and two control groups with equal numbers of controls (sibling controls and regional controls). When cases were compared to regional controls, no significant risk estimates were found for smoking by either parent; however, parents were more likely to have smoked during pregnancy with the child with Ewing's sarcoma than during the pregnancy with the unaffected sibling; if only the mother smoked, the relative risk was 1.5 (95% CI, 0.3–9.0); if only the father

smoked, the relative risk was 3.1 (95% CI, 0.7–14.0); if both parents smoked, the relative risk was 7.3 (95% CI, 1.3–41.6).

Two case–control studies in the USA evaluated prenatal drug consumption by the mother and risk for neuroblastoma (Kramer *et al*., 1987; Schwartzbaum, 1992). The first study was population-based and included 104 cases diagnosed from 1970 to 1979, a first group of 104 controls matched on date of birth, race and the first five digits of case's telephone number and a second group of controls comprising siblings of the index case. No significant increase in risk was associated with maternal smoking during pregnancy when cases were compared to either control group. The second study compared 101 newly diagnosed cases of neuroblastoma and 690 controls diagnosed with other types of childhood cancer at St Jude Children's Research Hospital. Cigarette smoking by the mother during pregnancy was found to increase the risk for neuroblastoma (relative risk, 1.9; 95% CI, 1.1–3.2). [The Working Group noted the questionable appropriateness of the control group in the study by Schwartzbaum and the limited exposure assessments in both studies.]

Olshan *et al*. (1993) reported findings from the National Wilms Tumour Study, a case–control study from a national collaborative clinical trial group in the USA. The study was conducted using interviews with 200 cases and 233 matched controls identified by random-digit dialling. No association was found for mother's smoking during pregnancy and risk for Wilms tumour (relative risk for smoking ten or more cigarettes per day, 0.7; 95% CI, 0.4–1.3).

2.4 Other cancers

2.4.1 *All cancer sites combined*

Hirayama (1984) reported a statistically significant association (p for trend < 0.001) between husband's smoking and cancer mortality in wives for all sites combined in the Japanese cohort (relative risk for former smoker: 1–19 cigarettes per day, 1.1; 95% CI, 1.0–1.2; relative risk for ≥ 20 cigarettes per day, 1.2; 95% CI, 1.1–1.4).

Sandler *et al*. (1985b), in their study previously described in detail (Section 2.2.2), found an increased risk of all cancers combined among nonsmokers passively exposed to cigarette smoke in adulthood (relative risk, 2.1; 95% CI, 1.4–3.0). Risk did not differ according to race (white or non-white), but was statistically significant only among women aged 30–49 years.

Miller (1990) reported the findings from a case–control study in the USA of cancer deaths among nonsmoking women in which next-of-kins were interviewed by telephone. Data on 906 nonsmoking wives were included in this report. The cases were women who had died of any type of cancer and the controls were nonsmoking wives who had died of cardiovascular, respiratory, kidney and other non-cancer diseases, excluding trauma. A nonsmoker was defined as a person who had smoked fewer than 20 packs of cigarettes during her lifetime. The percentage of deaths from cancer among non-exposed, non-

employed wives was 2.2%; for exposed, non-employed wives, 18.9%, and for employed wives, 34.3% ($p < 0.001$). [The Working Group noted that the study used a questionable comparison group and a non-standard definition of a nonsmoker.]

2.4.2 *Cervical cancer*

Three Asian cohort studies described in Section 2.1 also reported on involuntary smoking and risk for cancer of the cervix. Risk for cervical cancer associated with involuntary exposure to smoking in nonsmokers was examined in a Japanese cohort study that found no significant increase in risk associated with husbands' smoking (Hirayama, 1984). A second cohort study also considered exposure to husbands' smoking and risk for cervical cancer in nonsmoking Korean women (Jee *et al*., 1999). The relative risk based on 203 cases of cervical cancer in nonsmokers was 0.9 (95% CI, 0.6–1.3) for women married to former and 0.9 (95% CI, 0.6–1.2) for women married to current smokers when compared with women married to nonsmokers. The cohort study by Nishino *et al*. (2001) included 11 incident cases of cervical cancer. Again, no association with husband's smoking status was observed (relative risk, 1.1; 95% CI, 0.3–4.5). [The Working Group noted that these cohort studies consistently indicated no association between exposure to secondhand smoke and cervical cancer.]

The case–control study from the USA reported by Sandler *et al*. (1985b; see Section 2.2.2) found an increased risk of cervical cancer associated with spousal smoking (relative risk, 2.1; 95% CI, 1.2–3.9). A second case–control study in the USA was conducted from 1984 to 1987 in Utah where a large percentage of the population are members of the Church of Jesus Christ of the Latter-day Saints which proscribes tobacco smoking (Slattery *et al*., 1989). The cases were population-based and controls were selected by random-digit dialling and matched to cases on age and county of residence. The response rates for cases and controls were 66% and 76%, respectively. Nonsmokers involuntarily exposed for 3 hours or more per day to secondhand smoke were found to have an increased risk for cervical cancer (relative risk, 3.4; 95% CI, 1.2–9.5). Self-characterized exposure to 'a lot' of secondhand smoke was also associated with increased risk (in-home relative risk, 2.9; 95% CI, 1.1–7.9; outside the home relative risk, 1.6; 95% CI, 0.6–4.5). [The Working Group noted that a statistically non-significant increase in risk was also observed in active smokers exposed to smoking by others.]

Coker *et al*. (1992) examined the risk of exposure to secondhand smoke in a case–control study of cervical intraepithelial neoplasma (CIN) of grades II ($n = 40$) and III ($n = 63$) in the USA. No statistically significant association was found between exposure to secondhand smoke and CIN II/III in nonsmokers, after adjustment for age, race, education, number of partners, contraceptive use, history of sexually transmitted disease and history of Pap smear. Another case–control study conducted in the USA compared 582 women with abnormal Pap smears (class 2–4) with 1866 controls with normal cytology (Scholes *et al*., 1999). Nonsmokers exposed to secondhand smoke from spouses, partners or other household members were found to have a borderline increase in risk for abnormal

cervical cytology compared to nonsmokers who were not exposed to these sources of secondhand smoke (relative risk, 1.4; 95% CI, 1.0–2.0). Risk estimates were adjusted for age, age at first sexual intercourse, and number of sexual partners during lifetime.

2.4.3 *Gastrointestinal cancers*

The incidence of colorectal cancer in relation to passive exposure to smoke, which was defined as having lived with a person who smoked, was examined in a 12-year prospective cohort study in Washington County, MD, USA (Sandler *et al*., 1988). A statistically significant reduction in risk for colorectal cancer was observed for nonsmoking women who were involuntarily exposed to smoking (relative risk, 0.7; 95% CI, 0.6–1.0), but an increased risk for this cancer was found for nonsmoking men exposed to secondhand smoke in the household (relative risk, 3.0; 95% CI, 1.8–5.0).

In a Swedish population-based case–control study, Gerhardsson de Verdier *et al*. (1992) found an increased risk for colon cancer in women (relative risk, 1.8; 95% CI, 1.2–2.8) and rectal cancer in men (relative risk, 1.9; 95% CI, 1.0–3.6) in association with passive smoking after adjustment for numerous potential confounders. [The Working Group noted that it is unclear whether the analysis was restricted to never-smokers.]

A large Canadian case–control study of 1171 patients newly diagnosed with histologically confirmed stomach cancer and 2207 population controls evaluated the risk associated with active and passive smoking (Mao *et al*., 2002). Response rates of approximately 65% were obtained for both cases and controls. The analysis of passive smoking was conducted in male never-smokers (132 cases, 343 controls). Questionnaires were mailed to respondents and provided information on lifetime exposure to secondhand smoke through residential and occupational histories and also looked at source, intensity, and duration of exposure. Risk estimates for passive smoking were adjusted for 10-year age group, province of residence, education, social class, total consumption of meat and total consumption of vegetables, fruits and juices. A positive trend ($p = 0.03$) in risk for cancer of the gastric cardia was associated with lifetime exposure to secondhand smoke (sum of years of residential plus occupational exposure) in male never-smokers. At the highest level of exposure (≥ 43 years), the relative risk was 5.8 (95% CI, 1.2–27.5). No increased risks or trends were associated with risk for distal gastric cancer. Risks assessed by subsite (cardia and distal), were similar for active and passive smoking.

2.4.4 *Nasopharyngeal and nasal sinus cavity cancer*

The relationship between involuntary exposure of nonsmokers to secondhand smoke and risk for these rare cancers of the upper respiratory tract has been examined in one cohort study (Hirayama, 1984) and four case–controls studies (Fukuda & Shibata, 1990; Zheng *et al*., 1993; Cheng *et al*., 1999; Yuan *et al*., 2000). A positive association was found in most of these studies.

Hirayama (1984) found an increased risk of nasal sinus cancer in women (histology not noted) associated with increasing numbers of cigarettes smoked by husbands of non-smoking women. When compared with nonsmoking women married to nonsmokers, wives whose husbands smoked had a relative risk of 1.7 (95% CI, 0.7–4.2) for 1–14 cigarettes per day, 2.0 (95% CI, 0.6–6.3) for 15–19 cigarettes per day and 2.55 (95% CI, 1.0–6.3) for ≥ 20 cigarettes per day (p for trend = 0.03).

Fukuda and Shibata (1990) reported the results of the first Japanese case–control study based on 169 cases of squamous-cell carcinoma of the maxillary sinus and 338 controls matched on sex, age and residence in Hokkaido, Japan. Among nonsmoking women, a relative risk of 5.4 ($p < 0.05$) was associated with exposure in the household to secondhand smoke from one or more smokers. Active smoking was associated with an increased risk for squamous-cell carcinoma in men in the same study.

Zheng *et al*. (1993) used data from the 1986 US National Mortality Followback Survey to assess risk for cancer of the nasal cavity and sinuses in relation to exposure to secondhand smoke in white men. A total of 147 deaths from cancer of the nasal cavity and sinuses were compared to 449 controls who had died from one of a variety of causes (excluding any causes strongly linked to alcohol and/or tobacco use). Data were obtained from postal questionnaires completed by next-of-kins. Among nonsmokers, patients with nasal cancer were more likely to have a spouse who smoked cigarettes (relative risk, 3.0; 95% CI, 1.0–8.9) after adjustment for age and alcohol use. When the analysis of cases was restricted to those with cancer of the maxillary sinus, the risk was somewhat higher (relative risk, 4.8; 95% CI, 0.9–24.7). The risks reported for active and for involuntary smoking were of similar magnitude in this study.

Neither involuntary exposure to tobacco smoke during childhood nor exposure during adult life were positively associated with an increased risk for nasopharyngeal cancer in a study in China (Province of Taiwan) (Cheng *et al*., 1999). Although histological type was not specified, all cases were histologically confirmed. Among never-smokers, the risk estimates for cumulative exposure to passive smoking (pack–person–years) in childhood declined as exposure increased (p for trend = 0.05); a similar but non-significant inverse relationship was found for exposure during adulthood. Significant elevations in risk of nasopharyngeal cancer were observed for active smokers in this study. [The Working Group noted that the exposure assessment was relatively detailed and that the estimates of relative risk were adjusted for age, sex, education and family history of nasopharyngeal cancer.]

A large population-based case–control study conducted in Shanghai, China, included 935 cases of nasopharyngeal carcinoma and 1032 population controls randomly selected from a population-registry and frequency-matched by sex and 5-year age group (Yuan *et al*., 2000). All cases were histologically confirmed, but the cell type was not specified. The study subjects were interviewed face to face, and the response rates were 84% for cases and 99% for controls. In female never-smokers, a consistent increase in risk related to exposure to secondhand smoke during childhood was noted. If the mother smoked, the relative risk was 3.4 (95% CI, 1.4–8.1); if the father smoked, the relative risk was 3.0

(95% CI, 1.4–6.2); if another household member smoked, the relative risk was 2.7 (95% CI, 1.1–6.9), and if any household member smoked, the relative risk was 3.0 (95% CI, 1.4–6.2). Risks associated with exposure to secondhand smoke during adulthood in women were also statistically significantly increased. For male never-smokers, the associations were weaker and were not statistically significant for exposure during childhood and adulthood. Gender-specific risk estimates were adjusted for age, level of education, consumption of preserved foods, oranges and tangerines, exposure to rapeseed oil, exposure to burning coal during cooking, occupational exposure to chemical fumes, history of chronic ear and nose conditions and family history of nasopharyngeal cancer. [The Working Group noted that this was a large, well-conducted study that included a detailed exposure assessment and adjustment for numerous potential confounders.]

2.4.5 *Tumours of the brain and central nervous system*

A population-based case–control study of patients with incident primary brain tumours diagnosed from 1987 through 1990 in Adelaide, Australia, was reported by Ryan *et al.* (1992). Controls were selected from the Australian electoral rolls which cover 95% of the population. Response rates of 90% and 63% were obtained for cases and controls, respectively. The study included 110 histologically confirmed cases of glioma, 60 meningioma cases and 417 controls. An increased risk of meningioma was associated with involuntary exposure to tobacco from the spouse, particularly among women (relative risk, 2.7; 95% CI, 1.2–6.1). No statistically significant association was found between active smoking and either glioma or meningioma in this study.

References

Akiba, S., Kato, H. & Blot, W.J. (1986) Passive smoking and lung cancer among Japanese women. *Cancer Res*., **46**, 4804–4807

Alavanja, M.C.R., Brown, C.C., Swanson, C., Brownson, R.C. (1993) Saturated fat intake and lung cancer risk among non-smoking women in Missouri. *J. nat. Cancer Inst.*, **85,** 6–16

Bennett, W.P., Alavanja, M.C.R., Blomeke, B., Vähäkangas, K.H., Castren, K., Welsh, J.A., Bowman, E.D., Khan, M.A., Flieder, D.B. & Harris, C.C. (1999) Environmental tobacco smoke, genetic susceptibility, and risk of lung cancer in never-smoking women. *J. natl Cancer Inst*., **91**, 2009–2014

Berlin, J.A., Longnecker, M.P. & Greenland, S. (1993) Meta-analysis of epidemiologic dose-response data. *Epidemiology*, **4**, 218–228

Bero, L.A., Glantz, S.A. & Rennie D. (1994) Publication bias and public health policy on environmental tobacco smoke. *J. Am. med. Assoc*., **272**, 133–136

Biggerstaff, B.J., Tweedie, R.L. & Mengersen, K.L. (1994) Passive smoking in the workplace: Classical and Bayesian meta-analysis. *Int. Arch. occup. environ. Health*, **66**, 269–277

Boffetta, P. (2002) Involuntary smoking and lung cancer. *Scand. J. Work Environ. Health*, **28** (Suppl. 2), 30–40

Boffetta, P., Agudo, A., Ahrens, W., Benhamou, E., Benhamou, S., Darby, S.C., Ferro, G., Fortes, C., Gonzales, C.A., Jöckel, K.-H., Krauss, M., Kreienbrock, L., Kreuzer, M., Mendes, A., Merletti, F., Nyberg, F., Pershagen, G., Pohlabeln, H., Riboli, E., Schmid, G., Simonato, L., Tredaniel, J., Whitley, E., Wichmann, H.-E., Winck, C., Zambon, P. & Saracci, R. (1998) Multicenter case–control study of exposure to environmental tobacco smoke and lung cancer. *J. natl Cancer Inst*., **90**, 1440–1450

Boffetta, P., Ahrens, W., Nyberg, F., Mukeria, A., Brüske-Hohlfeld, I., Fortes, C., Constantinescu, V., Simonato, L., Batura-Gabryel, H., Lea, S., Gaborieau, V. & Benhamou, S. (1999a) Exposure to environmental tobacco smoke and risk of adenocarcinoma of the lung. *Int. J. Cancer*, **83**, 635–639

Boffetta, P., Nyberg, F., Agudo, A., Benhamou, E., Joeckel, K.H., Kreuzer, M., Merletti, F., Pershagen, G., Pohlabeln, H., Simonato, L., Wichmann, H.E. & Saracci, R. (1999b) Risk of lung cancer from exposure to environmental tobacco smoke from cigars, cigarillos and pipes. *Int. J. Cancer*, **83**, 805–806

Boffetta, P., Tredaniel, J. & Greco, A. (2000) Risk of childhood cancer and adult lung cancer after childhood exposure to passive smoke: A meta-analysis. *Environ. Health Perspect*., **108**, 73–82

Brennan, P., Butler, J., Agudo, A., Benhamou, S., Darby, S., Fortes, C., Joeckel, K.H., Kreuzer, M., Nyberg, F., Pohlabeln, H., Saracci, R., Wichmann, H.E. & Boffetta, P. (2000) Joint effect of diet and environmental tobacco smoke on risk of lung cancer among nonsmokers. *J. natl Cancer Inst*., **92**, 426–427

Brondum, J., Shu, X.-O., Steinbuch, M., Severson, R.K., Potter, J.D. & Robison, L.L. (1999) Parental cigarette smoking and the risk of acute leukemia in children. *Cancer*, **85**, 1380–1388

Brown, K.G. (1999) Lung cancer and environmental tobacco smoke: Occupational risk to nonsmokers. *Environ. Health Perspect*., **107** (Suppl. 6), 885–890

Brownson, R.C., Reif, J.S., Keefe, T.J., Ferguson, S.W. & Pritzl, J.A. (1987) Risk factors for adenocarcinoma of the lung. *Am. J. Epidemiol*., **125**, 25–34

Brownson, R.C., Alavanja, M.C., Hock, E.T. & Loy, T.S. (1992) Passive smoking and lung cancer in nonsmoking women. *Am. J. public Health*, **82**, 1525–1530

Buckley, J.D., Hobbie, W.L., Ruccione, K., Sather, H.N., Woods, W.G. & Hammond, G.D. (1986) Maternal smoking during pregnancy and risk of childhood cancer [Letter]. *Lancet*, **ii**, 519–520

Buffler, P.A., Pickle, L.W., Mason, T.J. & Contant, C. (1984) The causes of lung cancer in Texas. In: Mizell, M. & Corres, P., eds, *Lung Cancer: Causes and Prevention*, New York, Verlag Chemie International, pp. 83–99

Bunin, G.R., Buckley, J.D., Boesel, C.P., Rorke, L.B. & Meadows, A.T. (1994) Risk factors for astrocytic glioma and primitive neuroectodermal tumor of the brain in young children: A report from the Children's Cancer Group. *Cancer Epidemiol. Biomarkers Prev.*, **3**, 197–204

Butler, T.L. (1988) *The Relationship of Passive Smoking to Various Health Outcomes Among Seventh-day Adventists in California*, Los Angeles, University of California, Doctoral thesis

Cardenas, V.M., Thun, M.J., Austin, H., Lally, C.A., Clark, W.S., Greenberg, S. & Heath, C.W., Jr (1997) Environmental tobacco smoke and lung cancer mortality in the American Cancer Society's cancer prevention study II. *Cancer Causes Control*, **8**, 57–64

Chan, W.C. & Fung, S.C. (1982) Lung cancer in non-smokers in Hong Kong. In: Grundmann, E., ed., *Cancer Epidemiology* (Cancer Campaign 6), Stuttgart, Gustav Fischer Verlag, pp. 199–202

Chang-Claude, J., Krupp, S., Jager, B., Bartsch, H. & Risch, A. (2002) Differential effect of NAT2 on the association between active and passive smoke exposure and breast cancer risk. *Cancer Epidemiol. Biomarkers Prev.*, **8**, 698–704

Chappell, W.R. & Gratt, L.B. (1996) A graphical method for pooling epidemiological studies. *Am. J. public Health*, **88**, 1011–1012

Cheng, Y.-J., Hildesheim, A., Hsu, M.-M., Chen, I.-H., Brinton, L.A., Levine, P.H., Chen, C.-J. & Yang, C.-S. (1999) Cigarette smoking, alcohol consumption and risk of nasopharyngeal carcinoma in Taiwan. *Cancer Causes Control*, **10**, 201–207

Choi, S.-Y., Lee, K.-H. & Lee, T.-O. (1989) A case–control study on risk factors in lung cancer. *Korean J. Epidemiol.*, **11**, 66–80

Coker, A.L., Rosenberg, A.J., McCann, M.F. & Hulka, B.S. (1992) Active and passive cigarette smoke exposure and cervical intraepithelial neoplasia. *Cancer Epidemiol. Biomarkers Prev.*, **1**, 349–356

Copas, J.B. & Shi, J.Q. (2000) Reanalysis of epidemiological evidence on lung cancer and passive smoking. *Br. med. J.*, **320**, 417–418

Cordier, S., Iglesias, M.-J., LeGoaster, C., Guyot, M.-M., Mandereau, L. & Hemon, D. (1994) Incidence and risk factors for childhood brain tumors in the Ile de France. *Int. J. Cancer*, **59**, 776–782

Correa, P., Pickle, L.W., Fontham, E., Lin, Y. & Haenszel, W. (1983) Passive smoking and lung cancer. *Lancet*, **ii**, 595–597

Dalager, N.A., Pickle, L.W., Mason, T.J., Correa, P., Fontham, E.T.H., Stemhagen, A., Buffler, P.A., Ziegler, R.G. & Fraumeni, J.F., Jr (1986) The relation of passive smoking to lung cancer. *Cancer Res.*, **46**, 4808–4811

Delfino, R.J., Smith, C., West, J.G., Lin, H.J., White, E., Liao, S.-Y., Gim, J.S.Y., Ma, H.L., Butler, J. & Anton-Culver, H. (2000) Breast cancer, passive and active cigarette smoking and *N*-acetyltransferase 2 genotype. *Pharmacogenetics*, **10**, 461–469

Dersimonian, R. & Laird, N. (1986) Meta-analysis in clinical trials. *Controlled clin. Trials*, 177–188

Du, Y.X., Cha, Q., Chen, Y.Z. & Wu, J.M. (1993) Exposure to environmental tobacco smoke and female lung cancer in Guangzhou, China. *Proc. Indoor Air*, **1**, 511–516

Egan, K.M., Stampfer, M.J., Hunter, D., Hankinson, S., Rosner, B.A., Holmes, M., Willett, W.C. & Colditz, G.A. (2002) Active and passive smoking in breast cancer: Prospective results from the Nurses' Health Study. *Epidemiology*, **13**, 138–145

Filippini, G., Farinotti, M., Lovicu, G., Maisonneuve, P. & Boyle, P. (1994) Mothers' active and passive smoking during pregnancy and risk of brain tumors in children. *Int. J. Cancer*, **57**, 769–774

Filippini, G., Farinotti, M. & Ferrarini, M. (2000) Active and passive smoking during pregnancy and risk of central nervous system tumours in children. *Paediatr. perinatal Epidemiol.*, **14**, 78–84

Fleiss, J.L. & Gross, A.J. (1991) Meta-analysis in epidemiology, with special reference to studies of the association between exposure to environmental tobacco smoke and lung cancer: A critique. *J. clin. Epidemiol.*, **44**, 127–139

Fontham, E.T.H., Correa, P., Wu-Williams, A.H., Reynolds, P., Greenberg, R.S., Buffler, P.A., Chen, V.W., Boyd, P., Alterman, T., Austin, D.F., Liff, J. & Greenberg, S.D. (1991) Lung cancer in nonsmoking women: A multicenter case–control study. *Cancer Epidemiol. Biomarkers Prev.*, **1**, 35–43

Fontham, E.T.H., Correa, P., Reynolds, P., Wu-Williams, A., Buffler, P.A., Greenberg, R.S., Chen, V.W., Alterman, T., Boyd, P., Austin, D.F. & Liff, J. (1994) Environmental tobacco smoke and lung cancer in nonsmoking women. A multicenter study. *J. Am. med. Assoc*., **271**, 1752–1759

Forsberg, J.-G. & Kallen, B. (1990) Pregnancy and delivery characteristics of women whose infants develop child cancer. *APMIS*, **98**, 37–42

Fukuda, K. & Shibata, A. (1990) Exposure–response relationships between woodworking, smoking or passive smoking and squamous cell neoplasms of the maxillary sinus. *Cancer Causes Control*, **1**, 165–168

Gao, Y.-T., Blot, W.J., Zheng, W., Ershow, A.G., Hsu, C.W., Levin, L.I., Zhang, R. & Fraumeni, J.F., Jr (1987) Lung cancer among Chinese women. *Int. J. Cancer*, **40**, 604–609

Garfinkel, L. (1981) Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. *J. natl Cancer Inst*., **66**, 1061–1066

Garfinkel, L., Auerbach, O. & Joubert, L. (1985) Involuntary smoking and lung cancer: A case–control study. *J. natl Cancer Inst*., **75**, 463–469

Geng, G.Y., Liang, Z.H., Zhang, A.Y. & Wu, G.L. (1988) On the relationship between smoking and female lung cancer. In: Aoki, M., Hisamichi, S. & Tominaga, S., eds, *Smoking and Health*, Amsterdam, Elsevier, pp. 483–486

Gerhardsson de Verdier, M., Plato, N., Steineck, G. & Peters, J.M. (1992) Occupational exposures and cancer of the colon and rectum. *Am. J. ind. Med.*, **22**, 291–303

Gold, E., Gordis, L., Tonascia, J. & Szklo, M. (1979) Risk factors for brain tumors in children. *Am. J. Epidemiol*, **109**, 309–319

Gold, E.B., Leviton, A., Lopez, R., Gilles, F.H., Hedley-Whyte, E.T., Kolonel, L.N., Lyon, J.L., Swanson, G.M., Weiss, N.S., West, D., Aschenbrener, C. & Austin, D.F. (1993) Parental smoking and risk of childhood brain tumors. *Am. J. Epidemiol.*, **137**, 620–628

Golding, J., Paterson, M. & Kinlen, L.J. (1990) Factors associated with childhood cancer in a national cohort study. *Br. J. Cancer*, **62**, 3034–3038

Golding, J., Greenwood, R., Birmingham, K. & Mott, M. (1992) Childhood cancer, intramuscular vitamin K, and pethidine given during labor. *Br. med. J*., **305**, 341–346

Hackshaw, A.K. (1998) Lung cancer and passive smoking. *Stat. Meth. med. Res*., **7**, 119–136

Hackshaw, A.K., Law, M.R. & Wald, N.J. (1997) The accumulated evidence on lung cancer and environmental tobacco smoke. *Br. med. J*., **315**, 980–988

Hackshaw, A.K., Law, M.R. & Wald, N.J. (2000) Increased risk is not disputed. *Br. med. J*., **321**, 1221–1222

Heller, W.-D., Scherer, G., Sennewald, E. & Adlkofer, F. (1998) Misclassification of smoking in a follow-up population study in southern Germany. *Clin. Epidemiol*., **51**, 211–218

Hirayama, T. (1981) Nonsmoking wives of heavy smokers have a higher risk of lung cancer: A study from Japan. *Br. med. J*., **282**, 183–185

Hirayama, T. (1984) Cancer mortality in nonsmoking women with smoking husbands based on a large-scale cohort study in Japan. *Prev. Med*., **13**, 680–690

Hirayama, T. (1989) Dietary habits are of limited importance in influencing the lung cancer risk among Japanese females who never smoked. In: Bieva, C.J., Courtois, Y. & Govaerts, M., eds, *Present and Future Indoor Air Quality. Proceedings of the Brussels Conference*, Amsterdam, Elsevier Science

Hole, D.J., Gills, C.R., Chopra, C. & Hawthorne, V.M. (1989) Passive smoking and cardiorespiratory health in a general population in the west of Scotland. *Br. med. J*., **299**, 423–427

Holly, E.A., Aston, D.A., Ahn, D.K. & Kristiansen, J.J. (1992) Ewing's bone sarcoma, paternal occupational exposure, and other factors. *Am. J. Epidemiol.*, **135**, 122–129

Howe, G.R., Burch, J.D., Chiarelli, A.M., Risch, H. & Choi, B.C.K. (1989) An exploratory case–control study of brain tumors in children. *Cancer Res.*, **49**, 4349–4352

Humble, C.G., Samet, J.M. & Pathak, D.R. (1987) Marriage to a smoker and lung cancer risk. *Am. J. public Health*, **77**, 598–602

IARC (1986) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 38, *Tobacco Smoking*, Lyon, IARC*Press*

Infante-Rivard, C., Krajinovic, M., Labuda, D. & Sinnett, D. (2000) Parental smoking, *CYP1A1* genetic polymorphisms and childhood leukemia (Quebec, Canada). *Cancer Causes Control*, **11**, 547–553

Inoue, R. & Hirayama, T. (1988) Passive smoking and lung cancer in women. In: Aoki, M., Hisamichi, S. & Tominaga, S., eds, *Smoking and Health*, Amsterdam, Elsevier, pp. 283–285

Janerich, D.T., Thompson, W.D., Varela, L.R., Greenwald, P., Chorost, S., Tucci, C., Zaman, M.B., Melamed, M., Kiely, M. & McKneally, M.F. (1990) Lung cancer and exposure to tobacco smoke in the household. *New Engl. J. Med.*, **323**, 632–636

Jee, S.H., Ohrr, H. & Kim, I.-S. (1999) Effects of husbands' smoking on the incidence of lung cancer in Korean women. *Int. J. Epidemiol.*, **28**, 824–828

Ji, B.T., Shu, X.O., Linet, M.S., Zheng, W., Wacholder, S., Gao, Y.T., Ying, D.M. & Jin, F. (1997) Paternal cigarette smoking and the risk of childhood cancer among offspring of nonsmoking mothers. *J. natl Cancer Inst.*, **89**, 238–244

Jöckel, K.-H., Krauss, M., Pohlabeln, H., Ahrens, W., Kreuzer, M., Kreienbrock, L., Möhner, M. & Wichmann, H.E. (1998a) Lungenkrebsrisiko durch berufliche Exposition – Passivrauchen. In: Wichmann, H.E., Jöckel, K.-H. & Robra, B.P., eds, *Fortschritte in der Epidemiologie, Lungenkrebsrisiko durch berufliche Exposition*, Landsberg, Ecomed, pp. 227–236

Jöckel, K.-H., Pohlabeln, H., Ahrens, W. & Krauss, M. (1998b) Environmental tobacco smoke and lung cancer. *Epidemiology*, **9**, 672–675

John, E., Savitz, D.A. & Sandler, D.P. (1991) Prenatal exposure to parents smoking and childhood cancer. *Am. J. Epidemiol.*, **133**, 123–132

Johnson, K.C., Hu, J., Mao, Y. & The Canadian Cancer Registries Epidemiology Research Group. (2000) Passive and active smoking and breast cancer risk in Canada, 1994–97. *Cancer Causes Control*, **11**, 211–221

Johnson, K.C., Hu, J., Mao, Y. & Canadian Cancer Registries Epidemiology Research Group (2001) Lifetime residential and workplace exposure to environmental tobacco smoke and lung cancer in never-smoking women, Canada 1994–1997. *Int. J. Cancer*, **93**, 902–906

Kabat, G.C. (1990) Epidemiologic studies of the relationship between passive smoking and lung cancer. In: *Proceedings of the 1990 Annual Winter Meeting of the Toxicology Forum*, Washington DC

Kabat, G.C. & Wynder, E.L. (1984) Lung cancer in nonsmokers. *Cancer*, **53**, 1214–1221

Kabat, G.C., Stellman, S.D. & Wynder, E.L. (1995) Relation between exposure to environmental tobacco smoke and lung cancer in lifetime nonsmokers. *Am. J. Epidemiol.*, **142**, 141–148

Kalandidi, A., Trichopoulos, D., Hatzakis, A., Tzannes, S. & Saracci, R. (1987) Passive smoking and chronic obstructive lung disease. *Lancet*, **ii**, 1325–1326

Kalandidi, A., Katsouyanni, K., Voropoulou, N., Bastas, G., Saracci, R. & Trichopoulos, D. (1990) Passive smoking and diet in the etiology of lung cancer among non-smokers. *Cancer Causes Control*, **1**, 15–21

Katada, H., Mikami, R., Konishi, M., Koyama, Y. & Narita, N. (1988) Effect of passive smoking in lung cancer development in women in the Nara region. *Gan No Rinsho*, **34**, 21–27

Keil, U., Stieber, J., Filipiak, B., Löwel, H. & Wichmann, H.E. (1998) On misclassification of smoking (Letter to the Editor). *J. clin. Epidemiol*., **52**, 91–93

Klebanoff, M.A., Clemens, J.D. & Read, J.S. (1996) Maternal smoking during pregnancy and childhood cancer. *Am. J. Epidemiol.*, **144**, 1028–1033

Ko, Y.-C., Lee, C.-H., Chen, M.-J., Huang, C.-C., Chang, W.-Y., Lin, H.-J., Wang, H.-Z. & Chang, P.-Y. (1997) Risk factors for primary lung cancer among non-smoking women in Taiwan. *Int. J. Epidemiol*., **26**, 24–31

Koo, L.C., Ho, J.H.-C. & Saw, D. (1983) Active and passive smoking among female lung cancer patients in Hong Kong. *J. exp. clin. Cancer Res*., **4**, 367–375

Koo, L.C., Ho, J.H.-C. & Saw, D. (1984) Is passive smoking an added risk factor for lung cancer in Chinese women? *J. exp. clin. Cancer Res*., **3**, 277–283

Koo, L.C., Ho, J.H., Saw, D. & Ho, C.Y. (1987) Measurements of passive smoking and estimates of lung cancer risk among non-smoking Chinese females. *Int. J. Cancer*, **39**, 162–169

Koo, L.C., Ho, J.H.-C. & Rylander, R. (1988) Life-history correlates of environmental tobacco smoke: A study on nonsmoking Hong Kong Chinese wives with smoking versus nonsmoking husbands. *Soc. Sci. Med*., **26**, 751–760

Kramer, S., Ward, E., Meadows, A.T. & Malone, K.E. (1987) Medical and drug risk factors associated with neuroblastoma: A case–control study. *J. natl Cancer Inst*., **78**, 797–804

Kreuzer, M., Krauss, M., Kreienbrock, L., Jockel, K.-H. & Wichmann, H.-E. (2000) Environmental tobacco smoke and lung cancer: A case–control study in Germany. *Am. J. Epidemiol*., **151**, 241–250

Kreuzer, M., Gerken, M., Kreienbrock, L., Wellmann, J., Wichmann, H.E. (2001) Lung cancer in lifetime nonsmoking men – results of a case–control study in Germany. *Br. J. Cancer*, **84**, 134–140

Kreuzer, M., Heinrich, J., Kreienbrock, L., Rosario, A.S., Gerken, M. & Wichmann, H.E. (2002) Risk factors for lung cancer among nonsmoking women. *Int. J. Cancer*, **100**, 706–713

Kropp, S. & Chang-Claude, J. (2002) Active and passive smoking and risk of breast cancer by age 50 years among German women. *Am. J. Epidemiol*., **156**, 616–626

Kuijten, R.R., Bunin, G.R., Nass, C.C. & Meadows, A.T. (1990) Gestational and familial risk factors for childhood astrocytoma: Results of a case–control study. *Cancer Res.*, **50**, 2608–2612

Lam, W.K. (1985) *A Clinical and Epidemiological Study of Carcinoma of the Lung in Hong Kong*, Hong Kong, University of Hong Kong, Doctoral thesis

Lam, T.H., Kung, I.T., Wong, C.M., Lam, W.K., Kleevens, J.W., Saw, D., Hsu, C., Seneviratne, S., Lam, S.Y. & Lo, K.K. (1987) Smoking, passive smoking and histological types in lung cancer in Hong Kong Chinese women. *Br. J. Cancer*, **56**, 673–678

Lash, T.L. & Aschengrau, A. (1999) Active and passive cigarette smoking and the occurrence of breast cancer. *Am. J. Epidemiol.*, **149**, 5–12

Lee, P.N. (1987a) Lung cancer and passive smoking: Association of an artifact due to misclassification of smoking habits? *Toxicol. Lett*., **35**, 157–162

Lee, P.N. (1987b) Passive smoking and lung cancer association: A result of bias? *Hum. Toxicol*., **6**, 517–524

Lee, P.N. (1988) *Misclassification of Smoking Habits and Passive Smoking*, Berlin, Springer Verlag

Lee, P.N. (1991a) *Correcting Meta-analyses of the Association of Lung Cancer in Females with Spouse (or Household) Exposure for Bias due to Misclassification of Active Smoking Status* (Report submitted to US Environmental Protection Agency, dated 29 November 1991)

Lee, P.N. (1991b) An estimate of adult mortality in the United States from passive smoking. *Environ. int.*, **17**, 379–381

Lee, P.N. (1992) *Environmental Tobacco Smoke and Mortality*, Basel, Karger

Lee, P.N. (1998) Difficulties in assessing the relationship between passive smoking and lung cancer. *Stat. Meth. med. Res*., **7**, 137–163

Lee, P.N., Chamberlain, J. & Alderson, M.R. (1986) Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. *Br. J. Cancer*, **54**, 97–105

Lee, C.H., Ko, Y.C., Goggins, W., Huang, J.J., Huang, M.S., Kao, E.L. & Wang, H.Z. (2000) Lifetime environmental exposure to tobacco smoke and primary lung cancer of non-smoking Taiwanese women. *Int. J. Epidemiol*., **29**, 224–231

Lee, P.N., Forey, B. & Fry, J.S. (2001) Revisiting the association between environmental tobacco smoke and exposure to lung cancer risk. III. Adjustment for the biasing effect of misclassification of smoking habits. *Indoor Built Environ.*, **10**, 384–398

Levois, M.E. & Layard, M.W. (1994) Inconsistency between workplace and spousal studies of environmental tobacco smoke and lung cancer. *Regul. Toxic. Pharmacol*., **19**, 309–316

Liu, Z., He, X. & Chapman, R.S. (1991) Smoking and other risk factors for lung cancer in Xuanwei, China. *Int. J. Epidemiol*., **20**, 26–31

Liu, Q., Sasco, A.J., Riboli, E. & Hu, M.X. (1993) Indoor air pollution and lung cancer in Ghuangzhou, People's Republic of China. *Am. J. Epidemiol*., **137**, 145–154

Lubin, J.H. (1999) Estimating lung cancer risk with exposure to environmental tobacco smoke. *Environ. Health Perspect*., **107** (Suppl. 6), 879–883

McCredie, M., Maisonneuve, P. & Boyle, P. (1994) Perinatal and early postnatal risk factors for malignant brain tumours in New South Wales children. *Int. J. Cancer*, **56**, 11–15

McKinney, P.A., Stiller, C.A. (for the IRESCC group) (1986). Maternal smoking during pregnancy and the risk of childhood cancer [Letter]. *Lancet*, **ii**, 519

Magnani, C., Pastore, G., Luzzatto, L., Carli, M., Lubrano, P. & Terracini, B. (1989) Risk factors for soft tissue sarcomas in childhood: A case–control study. *Tumori*, **75**, 396–400

Magnani, C., Pastore, G., Luzzatto, L. & Terracini, B. (1990) Parental occupation and other environmental factors in the etiology of leukemias and non-Hodgkin's lymphomas in childhood: A case–control study. *Tumori*, **76**, 413–419

Manning, M.D. & Carroll, B.E. (1957) Some epidemiological aspects of leukemia in children. *J. natl Cancer Inst.*, **19**, 1087–1094

Mao, Y., Hu, J., Semenciw, R., White, K., and the Canadian Cancer Registries Epidemiology Research Group (2002) Active and passive smoking and the risk of stomach cancer, by subsite, in Canada. *Eur. J. Cancer Prev.*, **11**, 27–38

Marcus, P.M., Newman, B., Millikan, R.C., Moorman, P.G., Baird, D.D. & Qaqish, B. (2000) The associations of adolescent cigarette smoking, alcoholic beverage consumption, environmental tobacco smoke, and ionizing radiation with subsequent breast cancer risk (United States). *Cancer Causes Control*, **11**, 271–278

Mayne, S.T., Janerich, D.T., Greenwald, P., Chorost, S., Tucci, C., Zaman, M.B., Melamed, M.R., Kiely, M. & McKneally, M.F. (1994) Dietary beta carotene and lung cancer risk in US non-smokers. *J. natl Cancer Inst.*, **86**, 33–38

Miller, G.H. (1990) The impact of passive smoking: Cancer deaths among nonsmoking women. *Cancer Detect. Prev.*, **14**, 497–503

Millikan, R.C., Pittman, G.S., Newman, B., Tse, C.-K.J., Selmin, O., Rockhill, B., Savitz, D., Moorman, P.G. & Bell, D.A. (1998) Cigarette smoking, *N*-acetyltransferases 1 and 2, and breast cancer risk. *Cancer Epidemiol. Biomarkers Prev.*, **7**, 371–378

Morabia, A., Bernstein, M., Heritier, S. & Khatchatrian, N. (1996) Relation of breast cancer with passive and active exposure to tobacco smoke. *Am. J. Epidemiol.*, **143**, 918–928

Morabia, A., Bernstein, M.S., Bouchardy, I., Kurtz, J. & Morris, M.A. (2000) Breast cancer and active and passive smoking: The role of the *N*-acetyltransferase 2 genotype. *Am. J. Epidemiol.*, **152**, 226–232

National Research Council (1986) *Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects*, Washington DC, National Academy Press

Neutel, C.I. & Buck, C. (1971) Effect of smoking during pregnancy on the risk of cancer in children. *J. natl Cancer Inst.*, **47**, 59–63

Nishino, Y., Tsubono, Y., Tsuji, I., Komatsu, S., Kanemura, S., Nakatsuka, H., Fukao, A., Satoh, H. & Hisamichi, S. (2001) Passive smoking at home and cancer risk: A population-based prospective study in Japanese nonsmoking women. *Cancer Causes Control*, **12**, 797–802

Norman, M.A., Holly, E.A., Ahn, D.K., Preston-Martin, S., Mueller, B.A. & Bracci, P.M. (1996) Prenatal exposure to tobacco smoke and childhood brain tumors: Results from the United States West Coast Childhood Brain Tumor Study. *Cancer Epidemiol. Biomarkers Prev.*, **5**, 127–133

Nyberg, F., Isaksson, I., Harris, J.R. & Pershagen, G. (1997) Misclassification of smoking status and lung cancer risk from environmental tobacco smoke in never-smokers. *Epidemiology*, **8**, 304–309

Nyberg, F., Agrenius, V., Svartengren, K., Svensson, C. & Pershagen, G. (1998) Environmental tobacco smoke and lung cancer in nonsmokers: Does time since exposure play a role? *Epidemiology*, **9**, 301–308

Olshan, A.F., Breslow, N.E., Falletta, J.M., Grufferman, S., Pendergrass, T., Robison, L.L., Waskerwitz, M., Woods, W.G., Vietti, T.J. & Hammond, G.D. (1993) Risk factors for Wilms tumor: Report from the National Wilms Tumor Study. *Cancer*, **72**, 938–944

Pershagen, G., Hrubec, Z. & Svensson, C. (1987) Passive smoking and lung cancer in Swedish women. *Am. J. Epidemiol*., **125**, 17–24

Pershagen, G., Ericson, A. & Otterblad-Olausson, P. (1992) Maternal smoking in pregnancy: Does it increase the risk of childhood cancer? *Int. J. Epidemiol.*, **21**, 1–5

Peto, J. (1992) Meta-analysis of epidemiological studies of carcinogenesis. In: Vainio, H., Magee, P.N., McGregor, D.B. & McMichael, A.J., eds, *Mechanisms of Carcinogenesis in Risk Identification* (IARC Scientific Publications No. 116), Lyon, IARC*Press*, pp. 571–577

Preston-Martin, S., Yu, M.C., Benton, B. & Henderson, B.E. (1982) N-nitroso compounds and childhood brain tumors: A case–control study. *Cancer Res.*, **42**, 5240–5245

Rapiti, E., Jindal, S.K., Gupta, D. & Boffetta, P. (1999) Passive smoking and lung cancer in Chandigarh, India. *Lung Cancer*, **23**, 183–189

Reynolds, P., Von Behren, J., Fontham, E.T.H., Wu, A., Buffler, P. & Greenberg, R. (1996) Occupational exposure to environmental tobacco smoke [Letter]. *J. Am. med. Assoc.*, **275**, 441–442

Riboli, E., Haley, N.J., Tredaniel, J., Saracci, R., Preston-Martin, S. & Trichopolous, D. (1995) Misclassification of smoking status among women in relation to exposure to environmental tobacco smoke. *Eur. respir. J.*, **8**, 285–290

Roman, E., Watson, A., Beral, V., Buckle, S., Bull, D., Baker, K., Ryder, H. & Barton, C. (1993) Case–control study of leukaemia and non-Hodgkin's lymphoma among children aged 0–4 years living in West Berkshire and North Hampshire health districts. *Br. med. J.*, **306**, 615–621

Ryan, P., Lee, M.W., North, J.B. & McMichael, A.J. (1992) Risk factors for tumors of the brain and meninges: Results from the Adelaide Adult Brain Tumor study. *Int. J. Cancer*, **51**, 20–27

Sandler, D.P., Everson, R.B., Wilcox, A.J. & Browder, J.P. (1985a) Cancer risk in adulthood from early life exposure to parents' smoking. *Am. J. public Health*, **75**, 487–492

Sandler, D.P., Everson, R.B. & Wilcox, A.J. (1985b). Passive smoking in adulthood and cancer risk. *Am. J. Epidemiol.*, **121**, 37–48

Sandler, R.S., Sandler, D.P., Comstock, G.W., Helsing, K.J. & Shore, D.L. (1988) Cigarette smoking and the risk of colorectal cancer in women. *J. natl Cancer Inst.*, **80**, 1329–1333

Scholes, D., McBride, C., Grothaus, L., Curry, S., Albright, J. & Ludman, E. (1999) The association between cigarette smoking and low-grade cervical abnormalities in reproductive-age women. *Cancer Causes Control*, **10**, 339–344

Schwartz, A.G., Yang, P. & Swanson, G.M. (1996) Familial risk of lung cancer among nonsmokers and their relatives. *Am. J. Epidemiol.*, **144**, 554–562

Schwartzbaum, J.A. (1992) Influence of the mother's prenatal drug consumption on risk of neuroblastoma in the child. *Am. J. Epidemiol.*, **135**, 1358–1367

Severson, R.K., Buckley, J.D., Woods, W.G., Benjamin, D. & Robison, L.L. (1993) Cigarette smoking and alcohol consumption by parents of children with acute myeloid leukemia: An analysis within morphological subgroups—a report from the Childrens Cancer Group. *Cancer Epidemiol. Biomarkers Prev.*, **2**, 433–439

Shen, X.B., Wang, G.X. & Zhou, B.S. (1998) Relation of environmental tobacco smoke and pulmonary adenocarcinoma in non-smoking women: A case–control study in Nanjing. *Oncol. Rep.*, **5**, 1221–1223

Shimizu, H., Morishita, M., Mizuno, K., Masuda, T., Ogura, Y., Santo, M., Nishimura, M., Kunishima, K., Karasawa, K., Nishiwaki, K., Yamamoto, M., Hisamichi, S. & Tominaga, S. (1988) A case–control study of lung cancer in non-smoking women. *Tohoku J. exp. Med.*, **154**, 389–397

Shu, X.-O., Ross, J.A., Pendergrass, T.W., Reaman, G.H., Lampkin, B. & Robison, L.L. (1996) Parental alcohol consumption, cigarette smoking, and risk of infant leukemia: A Childrens Cancer Group study. *J. natl Cancer Inst.*, **88**, 24–31

Slattery, M.L., Robison, L.M., Schuman, K.L., French, T.K., Abbott, T.M., Overall, J.C., Jr & Gardner, J.W. (1989) Cigarette smoking and exposure to passive smoke are risk factors for cervical cancer. *J. Am. med. Assoc.*, **262**, 1593–1598

Smith, S.J., Deacon, J.M., Chilvers, C.E.D. & members of the UK National Case–Control Study Group. (1994) Alcohol, smoking, passive smoking and caffeine in relation to breast cancer risk in young women. *Br. J. Cancer*, **70**, 113–119

Sobue, T. (1990) Association of indoor air pollution and lifestyle with lung cancer in Osaka, Japan. *Int. J. Epidemiol.*, **19** (Suppl. 1), S62–S66

Sorahan, T., Lancashire, R., Prior, P., Peck, I. & Stewart, A. (1995) Childhood cancer and prenatal use of alcohol and tobacco. *Ann. Epidemiol.*, **5**, 354–359

Sorahan, T., Lancashire, R.J., Hulten, M.A., Peck, I. & Stewart, A.M. (1997a) Childhood cancer and parental use of tobacco: Deaths from 1953 to 1955. *Br. J. Cancer*, **75**, 134–138

Sorahan, T., Prior, P., Lancashire, R.J., Faux, S.P., Hulten, M.A., Peck, I.M. & Stewart, A.M. (1997b) Childhood cancer and parental use of tobacco: Deaths from 1971 to 1976. *Br. J. Cancer*, **76**, 1525–1531

Sorahan, T., McKinney, P.A., Mann, J.R., Lancashire, R.J., Stiller, C.A., Birch, J.M., Dodd, H.E. and Cartwright, R.A. (2001) Childhood cancer and parental use of tobacco: Findings from the inter-regional epidemiological study of childhood cancer (IRESCC) *Br. J. Cancer*, **84**, 141–148

Speizer, F.E., Colditz, G.A., Hunter, D.J., Rosner, B. & Hennekens, C. (1999) Prospective study of smoking, antioxidant intake, and lung cancer in middle-aged women (USA). *Cancer Causes Control*, **10**, 475–482

Stewart, A., Webb, J. & Hewitt, D. (1958) A survey of childhood malignancies. *Br. med. J.*, **5086**, 1495–1508

Stjernfeldt, M., Berglund, K., Lindsten, J. & Ludvigsson, J. (1986) Maternal smoking during pregnancy and risk of childhood cancer. *Lancet*, **i**, 1350–1352

Stockwell, H.G., Goldman, A.L., Lyman, G.H., Noss, C.I., Armstrong, A.W., Pinkham, P.A., Candelora, E.C. & Brusa, M.R. (1992) Environmental tobacco smoke and lung cancer risk in nonsmoking women. *J. natl Cancer Inst*., **84**, 1417–1422

Sun, X.-W., Dai, X.-D., Lin, C.-Y., Shi, Y.-B., Ma, Y.-Y. & Li, W. (1996) Passive smoking and lung cancer among nonsmoking women in Harbin, China. International symposium on lifestyle factors and human lung cancer, China 1994. *Lung Cancer*, **14**, 237

Svensson, C., Pershagen, G. & Klominek, J. (1988) *Smoking and Passive Smoking in Relation to Lung Cancer in Women*, Stockholm, National Institute of Environmental Medicine

Svensson, C., Pershagen, G. & Klominek, J. (1989) Smoking and passive smoking in relation to lung cancer in women. *Acta oncol*., **28**, 623–629

Trichopoulos, D. (1988) Passive smoking and lung cancer. *Scand. J. soc. Med*., **16**, 75–79

Trichopoulos, D., Kalandidi, A., Sparros, L. & MacMahon, B. (1981) Lung cancer and passive smoking. *Int. J. Cancer*, **27**, 1–4

Trichopoulos, D., Kalandidi, A. & Sparros, L. (1983) Lung cancer and passive smoking: Conclusion of Greek study. *Lancet*, **ii**, 677–678

Tweedie, R.L. & Mengersen, K.L. (1992) Lung cancer and passive smoking: Reconciling the biochemical and epidemiological approaches. *Br. J. Cancer*, **66**, 700–705

Tweedie, R.L., Scott, D.J., Biggerstaff, B.J. & Mengersen, K.L. (1996) Bayesian meta-analysis, with application to studies of ETS and lung cancer. *Lung Cancer*, **14** (Suppl. 1), S171–S194

US Environmental Protection Agency (1992) *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders (No. EPA/600/6-90/006F)*, Washington DC, Office of Research and Development, Office of Health and Environmental Assessment

Van Steensel-Moll, H.A., Valkenburg, H.A., Vandenbroucke, J.P. & Van Zanen, G.E. (1985) Are maternal fertility problems related to childhood leukaemia? *Int. J. Epidemiol.*, **14**, 555–559

de Waard, F., Kemmeren, J.M., van Ginkel, L.A. & Stolker, A.A. (1995) Urinary cotinine and lung cancer risk in a female cohort. *Br. J. Cancer*, **72**, 784–787

Wald, N.J., Nanchahal, K., Thompson, S.G. & Cuckle, H.S. (1986) Does breathing other people's tobacco smoke cause lung cancer? *Br. med. J.*, **293**, 1217–1222

Wang, L., Lubin, J.H., Zhang, S.R., Metayer, C., Xia, Y., Brenner, A., Shang, B., Wang, Z. & Kleinerman, R.A. (2000) Lung cancer and environmental tobacco smoke in a non-industrial area of China. *Int. J. Cancer*, **88**, 139–145

Wang, T.-J., Zhou, B.-S. & Shi, J.-P. (1996) Lung cancer in nonsmoking Chinese women: A case-control study. International symposium on lifestyle factors and human lung cancer, China 1994. *Lung Cancer*, **14**, 93–98

Wartenberg, D., Calle, E.E., Thun, M.J., Heath, C.W., Jr, Lally, C. & Woodruff, T. (2000) Passive smoking exposure and female breast cancer. *J. natl Cancer Inst.*, **92**, 1666–1673

Wells, A.J. (1991) Breast cancer, cigarette smoking, and passive smoking [Letter]. *Am. J. Epidemiol.*, **133**, 208–210

Wells, A.J. (1998) Lung cancer from passive smoking at work. *Am. J. public Health*, **88**, 1025–1029

Wells, A.J., English, P.B., Posner, S.F., Wagenknecht, L.E. & Perez-Stable, E.J. (1998) Misclassification rates for current smokers misclassified as nonsmokers. *Am. J. public Health*, **88**, 1053–1059

Whitehead, J. & Whitehead, A. (1991) A general parametric approach to the meta-analysis of randomised clinical trials. *Stat. Med.*, **10**, 1665–1677

Winn, D.M., Li, F.P., Robison, L.L., Mulvihill, J.J., Daigle, A.E. & Fraumeni, J.F., Jr (1992) A case–control study of the etiology of Ewing's sarcoma. *Cancer Epidemiol. Biomarkers Prev.*, **1,** 525–532

Wu, A.H., Henderson, B.E., Pike, M.C. & Yu, M.C. (1985) Smoking and other risk factors for lung cancer in women. *J. natl Cancer Inst.*, **74**, 747–751

Wu-Williams, A.H., Dai, X.D., Blot, W., Xu, Z.Y., Sun, X.W., Xiao, H.P., Stone, B.J., Yu, S.F., Feng, Y.P., Ershow, A.G., Sun, J., Fraumeni, J.F., Jr & Henderson, B.E. (1990) Lung cancer among women in north-east China. *Br. J. Cancer*, **62**, 982–987

Yuan, J.-M., Wang, X.-L., Xiang, Y.-B., Gao, Y.-T., Ross, R.K. & Yu, M.C. (2000) Non-dietary risk factors for nasopharyngeal carcinoma in Shanghai, China. *Int. J. Cancer*, **85**, 364–369

Zaridze, D.G., Zemlianaia, G.M. & Aitakov, Z.N. (1995) [Contribution of out- and indoor air pollution to the etiology of lung cancer.] *Vestn. Ross. Akad. Med. Nauk*, **4**, 6–10 (in Russian)

Zaridze, D., Maximovitch, D., Zemlyana, G., Aitakov, Z.N. & Boffetta, P. (1998) Exposure to environmental tobacco smoke and risk of lung cancer in non-smoking women from Moscow, Russia. *Int. J. Cancer*, **75**, 335–338

Zheng, W., McLaughlin, J.K., Chow, W.-H., Co Chien, H.T. & Blot, W.J. (1993) Risk factors for cancers of the nasal cavity and paranasal sinuses among white men in the United States. *Am. J. Epidemiol.*, **138**, 965–972

Zhong, L., Goldberg, M.S., Gao, Y.-T. & Jin, F. (1999) A case–control study of lung cancer and environmental tobacco smoke among non-smoking women living in Shanghai, China. *Cancer Causes Control*, **10**, 607–616

Zhong, L., Goldberg, M.S., Parent, M.-E. & Hanley, J.A. (2000) Exposure to environmental tobacco smoke and the risk of lung cancer: A meta-analysis. *Lung Cancer*, **27**, 3–18

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).

References

Bertone, E.R., Snyder, L.A. & Moore, A.S. (2002) Environmental tobacco smoke and risk of malignant lymphoma in pet cats. *Am. J. Epidemiol.*, **156**, 268–273

Bukowski, J.A. & Wartenberg, D. (1997) An alternative approach for investigating the carcinogenicity of indoor air pollution: Pets as sentinels of environmental cancer risk. *Environ. Health Perspect.*, **105**, 1312–1319

Bukowski, J.A., Wartenberg, D. & Goldschmidt, M. (1998) Environmental causes for sinonasal cancers in pet dogs, and their usefulness as sentinels of indoor cancer risk. *J. Toxicol. environ. Health*, **A54**, 579–591

Cummins, D. (1994) Pets and passive smoking [Letter to the editor]. *Br. med. J.*, **309**, 960

D'Agostini, F., Balansky, R.M., Bennicelli, C., Lubet, R.A., Kelloff, G.J. & De Flora, S. (2001) Pilot studies evaluating the lung tumor yield in cigarette smoke-exposed mice. *Int. J. Oncol.*, **18**, 607–615

De Flora, S., D'Agostini, F., Balansky, R., Camoirano, A., Bennicelli, C., Bagnasco, M. Cartiglia, C., Tampa, E., Longobardi, M.G., Lubet, R.A. & Izzotti, A. (2003) Modulation of cigarette smoke-related end-points in mutagenesis and carcinogenesis. *Mutat. Res*., **523–524**, 237–252

Glickman, L.T., Schofer, F.S., McKee, L.J., Reif, J.S. & Goldschmidt, M.H. (1989) Epidemiologic study of insecticide exposures, obesity, and risk of bladder cancer in household dogs. *J. Toxicol. environ. Health*, **28**, 407–414

Grimmer, G., Brune, H., Dettbarn, G., Naujack, K.-W., Mohr, U. & Wenzel-Hartung, R. (1988) Contribution of polycyclic aromatic compounds to the carcinogenicity of sidestream smoke of cigarettes evaluated by implantation into the lungs of rats. *Cancer Lett*., **43**, 173–177

IARC (1986) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 38, *Tobacco smoking*, Lyon, IARC*Press*

IARC (1999) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 74, *Surgical Implants and other Foreign Bodies*, Lyon, IARC*Press*, pp. 173–177

Malkinson, A.M. (1992) Primary lung tumors in mice: An experimentally manipulable model of human adenocarcinoma. *Cancer Res.*, **52** (Suppl.), 2670S–2676S

Manenti, G., Gariboldi, M., Fiorino, A., Zanesi, N., Pierotti, M.A. & Dragani, T.A. (1997) Genetic mapping of lung cancer modifier loci specifically affecting tumor initiation and progression. *Cancer Res*., **57**, 4164–4166

Mohtashamipur, E., Mohtashamipur, A., Germann, P.-G., Ernst, H., Norpoth, K. & Mohr, U. (1990) Comparative carcinogenicity of cigarette mainstream and sidestream smoke condensates on the mouse skin. *J. Cancer Res. clin. Oncol.,* **116**, 604–608

Reif, J.S., Dunn, K., Ogilvie, G.K. & Harris, C.K. (1992) Passive smoking and canine lung cancer risk. *Am. J. Epidemiol*., **135**, 234–239

Reif, J.S., Bruns, C. & Lower, K.S. (1998) Cancer of the nasal cavity and paranasal sinuses and exposure to environmental tobacco smoke in pet dogs. *Am. J. Epidemiol.*, **147**, 488–492

Shimkin, M.B. & Stoner, G.D. (1975) Lung tumours in mice: Application to carcinogenesis bioassay. *Adv. Cancer Res.*, **21**, 1–58

Teague, S.V., Pinkerton, K.E., Goldsmith, M., Gebremichael, A., Chang, S., Jenkins, R.A. & Moneyhun, J.H. (1994) Sidestream cigarette smoke generation and exposure system for environmental tobacco smoke studies. *Inhal. Toxicol*., **6**, 79–93

Witschi, H. (2000) Successful and not so successful chemoprevention of tobacco smoke-induced lung tumors. *Exp. Lung Res.*, **26**, 743–755

Witschi, H., Oreffo, V.I.C. & Pinkerton, K.E. (1995) Six-month exposure of strain A/J mice to cigarette sidestream smoke: Cell kinetics and lung tumor data. *Fundam. appl. Toxicol*., **26**, 32–40

Witschi, H., Espiritu, I., Peake, J.L., Wu, K, Maronpot, R.R. & Pinkerton, K.E. (1997a) The carcinogenicity of environmental tobacco smoke. *Carcinogenesis*, **18**, 575–586

Witschi, H., Espiritu, I., Maronpot, R.R., Pinkerton, K.E. & Jones, A.D. (1997b) The carcinogenic potential of the gas phase of environmental tobacco smoke. *Carcinogenesis*, **18**, 2035–2042

Witschi, H., Espiritu, I., Yu, M. & Willits, N.H. (1998) The effects of phenethyl isothiocyanate, *N*-acetylcysteine and green tea on tobacco smoke-induced lung tumors in strain A/J mice. *Carcinogenesis*, **19**, 1789–1794

Witschi, H., Espiritu, I. & Uyeminami, D. (1999) Chemoprevention of tobacco smoke-induced lung tumors in A/J strain mice with dietary *myo*-inositol and dexamethasone. *Carcinogenesis*, **20**, 1375–1378

Witschi, H., Uyeminami, D., Moran, D. & Espiritu, I. (2000) Chemoprevention of tobacco-smoke lung carcinogenesis in mice after cessation of smoke exposure. *Carcinogenesis*, **21**, 977–982

Witschi, H., Espiritu, I., Dance, S.T. & Miller, M.S. (2002) A mouse lung tumor model of tobacco smoke carcinogenesis. *Toxicol. Sci*., **68**, 322–330

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

The Working Group attempted to provide comprehensive coverage of the published literature on other data relevant to the evaluation of the carcinogenic hazards of secondhand smoke (since 1985), in some cases referring to recent reviews.

4.1 Absorption, distribution, metabolism and excretion

For a description of the absorption, distribution, metabolism and excretion of components of tobacco smoke, the reader is referred to the monograph on tobacco smoke.

4.1.1 *Humans*

(*a*) *Enzyme activities and metabolism*

In a study of human placental monooxygenase activity, as measured by in-vitro oxidation of 7-ethoxyresorufin, *O*-deethylase activity was significantly inhibited ($p < 0.05$) by 7,8-benzoflavone with placental microsomes from women passively exposed to cigarette smoke, but not with those from women who had not been exposed (Manchester & Jacoby, 1981).

A pharmacokinetic study reported a significantly faster clearance of theophylline in a group of seven nonsmokers exposed to secondhand tobacco smoke, as determined by questionnaire data and cotinine levels, than in a matched group of non-exposed individuals, as determined by clearance rate, terminal elimination half-time and mean residence time ($T_{½}$ = 6.93 h versus 8.69 h, $p < 0.05$) (Matsunga *et al*., 1989). Conversely, no changes in theophylline clearance rate were observed in five male subjects who were heavily exposed to secondhand tobacco smoke for 3 h/day on 5 consecutive days under controlled conditions (Casto *et al*., 1990).

(*b*) *Tobacco smoke carcinogen biomarkers*

(i) *Urinary compounds*

The use of urinary compounds as biomarkers of carcinogen uptake from environmental tobacco smoke was reviewed by Scherer and Richter (1997).

4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronides (NNAL-Gluc) are metabolites of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). The use of the assay for NNAL and NNAL-Gluc in urine for investigations of exposure to secondhand tobacco smoke offers several advantages. Firstly, it has the sensitivity required to measure relatively low concentrations (typically about 0.05 pmol/mL urine). Secondly, because NNK is a tobacco-specific compound, the detection of NNAL and NNAL-Gluc in urine specifically signals exposure to tobacco smoke. All studies reported to date have found significantly higher concentrations of NNAL plus NNAL-Gluc, or NNAL-Gluc alone, in the urine of nonsmokers exposed to secondhand tobacco smoke than in the urine of unexposed controls, and a good correlation between urinary levels of cotinine and NNAL plus NNAL-Gluc (Table 4.1). In one study, the uptake of NNK was more than six times higher in women who lived with smokers than in women who lived with nonsmokers (Anderson *et al*., 2001). In another investigation, widespread uptake of NNK was demonstrated in a group of economically disadvantaged school-children heavily exposed to tobacco smoke at home (Hecht *et al*., 2001). Correlations have been consistently observed between levels of urinary cotinine and NNAL + NNAL-Gluc in people exposed to secondhand tobacco smoke (Hecht, 2002). Because NNAL is a metabolite of the lung carcinogen NNK, these data imply that there is elevated carcinogen uptake in subjects with raised concentrations of urinary cotinine.

Mixed results have been obtained in studies on the relationship between *tt*-muconic acid, a metabolite of benzene, and exposure to secondhand tobacco smoke. Some studies have shown significantly increased concentrations in people exposed to secondhand tobacco smoke (Yu & Weisel, 1996; Taniguchi *et al.*, 1999; Carrer *et al*., 2000) whereas others found no effect (Scherer *et al*., 1995; Weaver *et al*., 1996; Ruppert *et al*., 1997; Scherer *et al*., 1999), the levels being primarily dependent on whether the subject's home is in the city or the suburbs and on dietary intake of sorbic acid rather than on exposure to secondhand tobacco smoke. The levels of 1-hydroxypyrene and hydroxyphenanthrenes in urine are generally not increased by exposure to secondhand tobacco smoke (Hoepfner *et al*., 1987; Scherer *et al*., 1992; Scherer *et al*., 2000), although significant increases have been reported under some high exposure conditions (Van Rooij *et al*., 1994; Siwinska *et al*., 1999).

The concentrations of aromatic amines (Grimmer *et al*., 2000) and 8-hydroxy-2′-deoxyguanosine (8-OHdG) (Pilger *et al*., 2001) in urine were also unaffected by exposure to secondhand tobacco smoke. The concentration of urinary 5-(hydroxymethyl)uracil was significantly elevated in nonsmokers exposed to high levels of secondhand tobacco smoke, in a dose-dependent manner (Bianchini *et al*., 1998). Exposure to secondhand tobacco smoke did not affect urinary concentrations of 3-ethyladenine (Kopplin *et al*., 1995). Elevated concentrations of thioethers, in particular of 3-hydroxypropylmercapturic acid, were observed under controlled, high exposure conditions (Scherer *et al*., 1990, 1992), but not in a field study (Scherer *et al.*, 1996).

Lackmann *et al.* (1999) first reported the presence of NNAL and NNAL-Gluc in the urine of newborns of women who smoked (Table 4.1). The available data indicate that

Table 4.1. Urinary NNAL and its glucuronides (NNAL-Gluc): biomarkers of NNK uptake in studies of involuntary exposure to tobacco smoke

Study group	Main conclusions[a]	Reference
Exposure of adults to secondhand smoke		
5 men exposed to secondhand smoke	Significantly increased levels of NNAL + NNAL-Gluc after exposure in a chamber: 127 ± 74 pmol/day (approx. 0.16 ± 74 pmol/mL urine)	Hecht *et al*. (1993)
5 men, 4 women exposed to secondhand smoke 5 unexposed controls	Significantly increased levels of NNAL-Gluc in exposed workers compared to unexposed controls: 0.059 ± 0.028 pmol/mL urine	Parsons *et al*. (1998)
29 nonsmokers (13 women)	NNAL + NNAL-Gluc levels correlated with nicotine levels from personal samplers. NNAL, 20.3 ± 21.8 pmol/day; NNAL-Gluc, 22.9 ± 28.6 pmol/day in exposed nonsmokers	Meger *et al*. (2000)
45 nonsmoking women, 23 exposed to secondhand smoke in the home, 22 non-exposed	NNAL + NNAL-Gluc significantly higher in exposed women: 0.050 ± 0.068 pmol/mL urine	Anderson *et al*. (2001)
204 nonsmoking elementary school-aged children	34% with total cotinine ≥ 5 ng/mL; 52/54 of these samples had detectable NNAL or NNAL-Gluc, 93-fold range. NNAL + NNAL-Gluc, 0.056 ± 0.076 pmol/mL urine	Hecht *et al*. (2001)
In-utero exposure to mother's smoking		
31 newborns of mothers who smoked; 17 newborns of mothers who did not smoke	NNAL-Gluc detected in 71%, NNAL in 13% of urine samples of newborns of smokers; neither detected in urine of newborns of nonsmokers ($p < 0.001$); NNAL + NNAL-Gluc in urine of newborns of smoking mothers, 0.13 ± 0.15 pmol/mL urine	Lackmann *et al*. (1999)
21 smokers and 30 nonsmokers	NNAL detected in amniotic fluid of 52.4% of smokers and 6.7% of nonsmokers ($p = 0.0006$). NNAL concentration in amniotic fluid of smokers, 0.025 ± 0.029 pmol/mL	Milunsky *et al*. (2000)
12 smokers and 10 nonsmokers	NNAL and NNAL-Gluc not detected in follicular fluid	Matthews *et al*. (2002)

[a] Values represent mean ± SD.

NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone

NNK, a transplacental carcinogen, is taken up by the fetus and metabolized to NNAL and NNAL-Gluc by fetal enzymes (Lackmann *et al*., 1999). Consistent with these results, NNAL was detected in the amniotic fluid of pregnant smokers (Milunksy *et al*., 2000). However, neither NNAL nor NNAL-Gluc could be detected in follicular fluid (Matthews *et al*., 2002).

Urinary excretion of 8-OHdG by newborn babies (n = 12) whose mothers were exposed to secondhand tobacco smoke was significantly higher (p = 0.047) than that of babies whose mothers were not exposed (n = 8). In both groups, the concentration of 8-OHdG excreted was also significantly higher for babies whose mothers had the *GSTM1* null genotype (Hong *et al*., 2001).

(ii) *Protein adducts*

To determine whether involuntary smoking increased the levels of aromatic amine-haemoglobin adducts, a group of 14 volunteers who reported negligible exposure to secondhand tobacco smoke was compared with a group of 15 nonsmokers who reported exposure to at least one pack of cigarettes per day smoked by others, and one of 15 non-smokers with unknown levels of exposure to secondhand tobacco smoke. No measurable quantities of cotinine were detected in the blood of members of any of the three groups (see Section 4.1.1.(d) for measurement of cotinine). A further group of 13 nonsmokers, including six bartenders who were heavily exposed to secondhand tobacco smoke, had measurable levels of cotinine in their blood. Background levels of adducts from 4-amino-biphenyl (ABP) and 3-aminobiphenyl were detected in all subjects, but higher levels were found in subjects with detectable cotinine levels (p = 0.05 and 0.027, respectively) (Maclure *et al.*, 1989). In another study, the levels of 4-ABP-haemoglobin adducts in 15 nonsmokers who reported being exposed to secondhand tobacco smoke were not significantly higher than those in 35 nonsmokers who were not exposed to secondhand tobacco smoke (87.9 ± 19 [SE] pg/g haemoglobin and 69.5 ± 7 pg/g, respectively). Only four out of 15 of those subjects who reported exposure to secondhand tobacco smoke and four out of 35 of those who reported no exposure had measurable levels of urinary cotinine (Bartsch *et al.*, 1990). The level of exposure of 40 nonsmoking women to secondhand tobacco smoke was determined by questionnaire, use of a diary and a personal air monitor and was stratified by average nicotine concentration. There was a significant correlation between the concentration of 4-ABP–haemoglobin and exposure category (p = 0.009) (Hammond *et al.*, 1993).

Exposure of pre-school children to secondhand tobacco smoke from their mothers was investigated by measuring plasma cotinine levels and PAH–albumin adducts in peripheral blood, the latter detected by ELISA. The study involved 87 mother–child pairs; 31 mothers smoked and 56 did not. Not only did the mothers who smoked have higher levels of adducts (see monograph on tobacco smoke), but the levels in their children were also significantly higher ($p < 0.05$). There was also a significant correlation between adduct levels in the mothers and in their children (p = 0.014) (Crawford *et al.*, 1994). In a subsequent study, PAH–albumin and 4-ABP–haemoglobin adducts were also found to be

significantly higher in children whose mothers smoked or who lived with other smokers ($p < 0.05$) (Tang *et al.*, 1999). In a study in children from three different-sized cities, levels of 4-ABP adducts and other aromatic amines correlated with the size of the city. Exposure to secondhand tobacco smoke was associated with a non-significant increase in levels of 4-ABP adducts and a significant decrease in adducts of *ortho*- and *m*-toluidine ($p < 0.05$) (Richter *et al*., 2001).

In a study of 69 adults, 27 were smokers, and 19 of the 42 nonsmokers were classified as passive smokers as determined by self-report and cotinine levels. The levels of benzo-[*a*]pyrene adducts with albumin and haemoglobin were similar for nonsmokers and passive smokers (Scherer *et al.*, 2000).

The levels of *N*-hydroxyethylvaline in haemoglobin were reported to be similar in nonsmokers who did not live or work with a smoker ($n = 74$) and in those who did ($n = 28$). Cotinine levels in passive smokers were not higher than in nonsmokers (Bono *et al.*, 1999).

There was a significantly higher level ($p = 0.02$) of nitrated proteins in blood plasma of nonsmokers who were exposed to secondhand tobacco smoke ($n = 30$) than in non-smokers who were unexposed ($n = 23$) (Pignatelli *et al*., 2001).

Measurements of maternal–fetal exchange of 4-ABP in pregnant women who smoked ($n = 14$) and in nonsmoking ($n = 38$) pregnant women (see monograph on tobacco smoke) showed consistently lower levels of haemoglobin adducts in cord blood than in maternal blood, with an average maternal to fetal ratio of 2. A significant correlation was found between maternal and fetal levels for all subjects ($p < 0.001$) and for smokers only ($p = 0.002$), but not for nonsmokers only ($p = 0.06$) (Coghlin *et al.* 1991). Another study also found that adduct levels were lower in fetal blood than in maternal blood and were correlated with the smoking status of the mothers (subjects included 74 smokers and 74 nonsmokers) (Myers *et al.*, 1996). Another study of 73 nonsmoking pregnant women whose cotinine:creatinine ratios correlated with self-reported exposure to secondhand tobacco smoke, found no association with levels of haemoglobin adducts formed by any of nine aromatic amines (Branner *et al*., 1998).

Blood samples from smoking and nonsmoking mothers and cord blood from their newborns were analysed for *N*-hydroxyethylvaline in haemoglobin. The average adduct concentration in newborns of mothers who smoked ($n = 13$; 147 ± 68 [mean ± SD] pmol/g) was significantly higher ($p < 0.01$) than in those from mothers who were nonsmokers ($n = 10$; 42 ± 18 pmol/g). There was also a significant correlation ($p < 0.01$) between adduct levels in the newborns and in their mothers (Tavares *et al.*, 1994). The same samples showed a strong correlation between the concentration of *N*-(2-cyanoethyl)valine (CEVal) adducts in the mothers who smoked and in their newborns ($p < 0.001$). The adduct levels in the babies were also strongly correlated with the numbers of cigarettes smoked per day by their mothers ($p = 0.009$). The levels of CEVal in babies of mothers who did not smoke were below the limit of detection of the assay (1 pmol/g) (Tavares *et al.*, 1996).

(iii) *DNA adducts*

Although many studies have investigated the levels of DNA adducts or other measures of DNA damage in the tissues of smokers, ex-smokers and nonsmokers (see monograph on tobacco smoke), relatively few studies have investigated the use of these biomarkers to monitor the exposure of nonsmokers to secondhand tobacco smoke, probably because they may not distinguish the effects of exposure to secondhand tobacco smoke from those of exposure to other sources of environmental carcinogens.

In a study in which declining DNA adduct levels in the white blood cells of smokers enrolled in a smoking cessation programme were measured by ELISA, the levels of PAH–DNA adducts both at baseline and 10 weeks after cessation were significantly associated with number of hours of exposure to secondhand tobacco smoke at home ($p = 0.009$ and $p = 0.02$, respectively) and were also higher if the subject lived with another smoker ($p = 0.02$). However, there was no observable influence of exposure to secondhand tobacco smoke at the workplace (Mooney *et al.*, 1995).

Using the prevalence of serum antibodies to benzo[*a*]pyrene diol epoxide (BPDE)–DNA adducts as a biomarker of exposure to environmental PAHs in an Italian population, no association between the percentage of subjects with DNA adducts and passive smoking was found (Petruzzelli *et al.*, 1998). In a study in which significant differences were observed between the levels of BPDE–DNA adducts in the peripheral lymphocytes of smokers ($n = 40$) and nonsmokers ($n = 35$), as determined by a flow cytometric method using BPDE–DNA antibodies, the mean value for nonsmokers with no or low exposure to secondhand tobacco smoke ($n = 17$) was marginally *higher* than that of exposed nonsmokers ($n = 18$), but the difference was not statistically significant (Shinozaki *et al.*, 1999). Using antibodies to BPDE–DNA adducts, immunohistochemical staining of ovarian granulosa-lutein cells from women undergoing in-vitro fertilization showed a strong correlation between smoking status and adduct levels in nonsmokers ($n = 11$), passive smokers ($n = 7$) and active smokers ($n = 14$); all pairwise comparisons were highly significant ($p < 0.0001$) (Zenzes *et al.*, 1998).

Oxidative damage caused by exposure to secondhand tobacco smoke was assessed by measuring the concentration of 8-OHdG in the blood of 74 nonsmokers. The levels were, on average, 63% higher in the subjects exposed to secondhand tobacco smoke in the workplace ($n = 27$) than in the unexposed group ($n = 29$) and this difference was statistically significant ($p < 0.05$) (Howard *et al*., 1998a). However, in another study, the levels of 8-OHdG in leukocytes were significantly *lower* in smokers than in nonsmokers (see monograph on tobacco smoke) and no association was observed with exposure to secondhand tobacco smoke (van Zeeland *et al*., 1999).

Five nonsmokers were exposed to secondhand tobacco smoke under controlled conditions (exposure to gas phase only for 8 h, followed by exposure to whole secondhand tobacco smoke for 8 h, 40 h later). When their monocyte DNA was analysed by ^{32}P-post-labelling, no changes in the adduct patterns were seen after either exposure period, when compared with the samples obtained before exposure (Holz *et al.*, 1990). In a study of biomarkers of exposure to air pollution in three Greek populations, one urban, one rural and

one on a university campus, ^{32}P-postlabelling analysis of lymphocyte DNA revealed the presence of DNA adducts that significantly ($p < 0.001$) paralleled the level of exposure to secondhand tobacco smoke, as determined by self-report, plasma cotinine concentrations and profiles of personal exposure to PAHs that were characteristic of secondhand tobacco smoke, rather than other environmental sources (Georgiadis *et al.*, 2001).

DNA adducts of PAHs were detected by ELISA in 6/14 placentas and in 5/12 matched fetal lung samples from spontaneous abortions. None of the samples were from women who reported smoking during pregnancy, suggesting that the adducts are due to some other source of hydrocarbon exposure (Hatch *et al.*, 1990). In another study using ELISA, BPDE–DNA adducts were detected in 13/15 placental samples from smokers and 3/10 from nonsmokers. There was a strong correlation between concentrations of both adducts and urinary cotinine for both placental DNA and umbilical cord DNA, the former tissue having the higher adduct levels (transfer coefficient = 0.37–0.74) (Arnould *et al.*, 1997). When placental DNA was analysed both for bulky DNA adducts by ^{32}P-postlabelling and for 8-OHdG by electrochemical detection, neither method showed a difference between 11 smokers, ten nonsmokers and nine nonsmokers exposed to passive smoking (Daube *et al.*, 1997). Using ^{32}P-postlabelling with nuclease P1 digestion, DNA adducts were detected in placental and umbilical cord DNA regardless of the smoking status of the mothers and were significantly higher in maternal tissue than in fetal tissue (maternal/fetal ratio = 2.0). When considered separately, tissues showed only marginally increased adduct levels in smokers, but total DNA adduct levels in all tissues combined were significantly higher in smokers ($n = 8$) than in nonsmokers ($n = 11$) (Hansen *et al.*, 1992, 1993).

(*c*) *Other biomarkers*

(i) *Breath compounds*

Carbon monoxide

Carbon monoxide (CO) in expired air has been reported to be an indirect measure of passive smoking both in adults and children. Given its very short half-life, CO concentration must be measured shortly after exposure.

After a 9-h period of exposure to secondhand tobacco smoke at the workplace, 100 nonsmoking waiters exhaled on average 5.0 ppm CO (the pre-exposure CO concentration was 2.0 ppm) compared to a concentration of 2.5 ppm CO exhaled by 100 medical students who spent the day in a nonsmoking environment ($p < 0.001$; Laranjeira *et al.*, 2000). A study in Japan found that mean concentrations of exhaled CO in passive smokers were also significantly higher ($p < 0.001$) than those of nonsmokers who were not exposed to secondhand tobacco smoke (Taniguchi *et al.*, 1999).

The concentrations of exhaled CO were also measured in 235 healthy and 54 asthmatic children (Ece *et al.*, 2000). Regardless of the parents' smoking habits, CO concentrations were higher in asthmatic than in healthy children (1.32 ppm versus 0.86 ppm; $p = 0.028$). Significant relationships were found between the number of cigarettes smoked

in the house and concentrations of exhaled CO in both healthy ($p = 0.003$) and asthmatic children ($p = 0.01$).

Both women exposed to secondhand smoke during pregnancy and their newborns exhaled higher concentrations of CO than non-exposed women (1.95 ppm versus 1.33 ppm and 2.51 versus 1.74 ppm, respectively) (Seidman *et al*., 1999).

Nitric oxide

Fifteen nonsmoking subjects were exposed to secondhand tobacco smoke or asked to smoke for 60 min in a ventilated chamber. Within 15 min of exposure, the concentrations of exhaled nitric oxide (NO) had fallen by 23.6% or 30.3%, respectively, and remained low during the entire time of exposure (Yates *et al*., 2001). Similarly, newborns exposed prenatally to cigarette smoke ($n = 7$) exhaled significantly less NO than non-exposed ($n = 13$) newborns (Hall *et al*., 2002).

Benzene

The concentrations of exhaled benzene in children exposed to secondhand tobacco smoke were not significantly related to the smoking status of the household members, but depended primarily on the location of the home (Scherer *et al*., 1999). Passive smokers not exposed at home, but exposed for more than 50% of their time at work had significantly higher levels of benzene, ethylbenzene, *meta*-xylene + *para*-xylene and *ortho*-xylene in their breath than did non-exposed nonsmokers (Wallace *et al*., 1987) .

(ii) *Blood compounds*

Carboxyhaemoglobin

Measurements of the concentration of carboxyhaemaglobin in subjects exposed to secondhand tobacco smoke and in subjects who were not, are consistent with measurements of CO in the environment (Russell *et al.*, 1973; Hugod *et al.*, 1978; Jarvis *et al.*, 1983). However, carboxyhaemoglobin measurements may be largely confounded by endogenous formation and environmental factors, and are thus not a reliable means for monitoring passive smoking (Scherer & Richter, 1997).

Thiocyanate

It is not possible to distinguish between nonsmokers who are exposed to secondhand smoke and those who are not by measuring serum thiocyanate concentrations (Robertson *et al*., 1987; Scherer & Richter, 1997).

(iii) *Particles*

Experimental deposition of particulate matter with a diameter of < 1 μm from secondhand tobacco smoke within the human respiratory tract was evaluated in 15 nonsmokers and three regular smokers (Morawska *et al*., 1999). On average, smokers had a higher rate of deposition than nonsmokers (65.3 ± 24.1% versus 56.0 ± 15.9% for nose breathing and 66.1 ± 17.6 % versus 48.7 ± 11.6% for mouth breathing). The large variations observed

between individuals indicate that deposition of environmental tobacco smoke is governed by an individual's airway anatomy and breathing patterns.

(*d*) *Nicotine and its metabolites as biomarkers*

Many of the biological markers other than nicotine or cotinine that are used as indicators of exposure and uptake in smokers (e.g. carboxyhaemoglobin and thiocyanate; see monograph on tobacco smoke) are not suitable for accurate measurement of exposure to secondhand tobacco smoke because of potential confounding exposure from diet and environment (US National Research Council, 1986; US Environmental Protection Agency, 1992; California Environmental Protection Agency, 1997; Benowitz, 1999).

In addition to nicotine from use of tobacco products, pharmaceutical products for nicotine replacement therapy or exposure from secondhand tobacco smoke, small quantities of nicotine may enter the body from dietary sources, mainly from consumption of tea and some solanaceous plants such as aubergine, potato peel and tomato (Castro & Monji, 1986; Sheen, 1988; Davis *et al*., 1991; Domino *et al*., 1993; reviewed in Leyden *et al*., 1999). The contribution from dietary sources has, however, been estimated to be minimal and is generally thought not to influence the concentrations of nicotine or cotinine in body fluids significantly enough to affect their use as a biomarker for exposure to secondhand tobacco smoke (Tunstall-Pedoe *et al*., 1991; Henningfield, 1993; Benowitz, 1996), although there has been some disagreement on the subject (Davis *et al.*, 1991). It has been calculated that even very high consumption of these nicotine-containing products would equal, at most, about 10% of the amount of nicotine generally taken up by nonsmokers exposed to secondhand tobacco smoke (Jarvis, 1994; Repace, 1994; Pirkle *et al*., 1996).

Measurements of nicotine and/or cotinine in body fluids of smokers have demonstrated that nicotine and cotinine are biomarkers of high sensitivity (96–97%) and specificity (99–100%) of exposure to tobacco smoke (Jarvis *et al*., 1987; see monograph on tobacco smoke). Owing to its longer half-life, cotinine measured in the blood, saliva or urine of nonsmokers is presently the most widely used biomarker for assessment of exposure to secondhand tobacco smoke (IARC, 1986; US National Research Council, 1986; US Environmental Protection Agency, 1992).

(i) *Adults*

Numerous studies have investigated the dependence of concentrations of cotinine in the serum, saliva and urine on exposure to secondhand tobacco smoke (concentration and duration of exposure) in experimental conditions as well as in nonsmokers exposed to secondhand tobacco smoke, as reviewed in the reports of IARC (1986), US National Research Council (1986), the US DHHS (1986), the US Environmental Protection Agency (1992) and the California Environmental Protection Agency (1997). Studies involving several thousands of subjects have demonstrated that cotinine concentrations measured in the blood, saliva or urine of nonsmokers exposed to secondhand tobacco smoke at home or at work are significantly higher than the concentrations in non-exposed

nonsmokers (Coultas *et al*., 1987; Cummings *et al*., 1990; Riboli *et al*., 1990; Tunstall-Pedoe *et al.*, 1991; Pirkle *et al*., 1996; Wagenknecht *et al*., 1993; Fontham *et al*., 1994; Jarvis *et al*., 2001). In nonsmokers exposed to secondhand tobacco smoke, cotinine levels are typically 0.6–2% of those detected in smokers (Hackshaw *et al.*, 1997; Jarvis *et al*., 1987, 2001; Etzel *et al*., 1990; Benowitz, 1999; Etter, 2000), and they correlate well with self-reported exposure (Jarvis *et al*., 1985; Haley *et al*., 1989; Coultas *et al*., 1987; Cummings *et al*., 1990; Riboli *et al*., 1990; Jarvis *et al*., 1991, 2001, and also discussed in the reviews of the US Environmental Protection Agency (1992) and the California Environmental Protection Agency (1997)).

Cut-points have been introduced in these studies to distinguish occasional smokers from nonsmokers exposed to secondhand smoke. The cut-off values used in the various studies are typically in the range of 10–30 ng/mL for salivary cotinine, 10–15 ng/mL for cotinine in serum, 20–40 ng/mL for cotinine in plasma, and 50–90 ng/mL for cotinine in urine (reviewed in Etzel, 1990; Pérez-Stable *et al.*, 1992; California Environmental Protection Agency, 1997), but higher values may sometimes be applied (Riboli *et al*., 1995).

The relationships between exposure to secondhand tobacco smoke and cotinine concentrations in body fluids have been investigated. Cummings and co-workers (1990) found a clear association between concentrations of urinary cotinine and the number of reported exposures to secondhand tobacco smoke in the 4 days before sampling in 663 nonsmokers. Another study that investigated almost 200 nonsmokers who were exposed to secondhand tobacco smoke at home or at work showed that concentrations of urinary cotinine increased with increasing duration of exposure (Thompson *et al*., 1990). Every additional 10-h period of exposure was found to result in an increase in urinary cotinine of 44% (95% CI, 23–67%; $p < 0.001$).

In a large multicentre, multinationality study conducted among 1300 nonsmoking women, a clear linear increase in mean concentrations of urinary cotinine was observed from the group of women not exposed to secondhand smoke either at work or at home (mean, 2.7 ng/mg creatinine) to those exposed both at work and at home (mean, 10.0 ng/mg creatinine) (Riboli *et al*., 1990). Cotinine concentrations have been demonstrated to be dependent both on the duration of exposure and the number of cigarettes smoked by others. When the number of cigarettes was corrected for duration of exposure and room volume, it was estimated that a similar increase in concentration of cotinine (5 ng/mg) is predicted with 7.2 cigarettes smoked at home versus 17.9 cigarettes smoked at the workplace. Based on the measured cotinine concentrations, the number of cigarettes smoked by the spouse was found to be the best estimate for domestic exposure, and duration of exposure provided the best estimate for occupational exposure (Riboli *et al*., 1990).

Cotinine concentrations associated with occupational exposure to secondhand tobacco smoke vary somewhat more than those related to domestic exposure. This is because occupational exposure is subject to larger variations in several variables including the number of smokers present, ventilation conditions and variation in physical workload of the nonsmokers. Studies of flight attendants and workers in restaurants, bars, casinos

and other similar public settings have found that these occupations lead to greater exposure to secondhand tobacco smoke than that of the average population, with cotinine concentrations generally reflecting those of tobacco smoke concentrations measured in the workplace (Mattson *et al*., 1989; Jarvis *et al*., 1992; Siegel, 1993; Dimich-Ward *et al*., 1997; Trout *et al*., 1998; Maskarinec *et al*., 2000). One study showed that in addition to exposure in the workplace, exposure of bartenders to secondhand smoke at home further elevated their cotinine concentrations (Maskarinec *et al*., 2000). Jarvis *et al*. (1992) reported a median salivary cotinine concentration of 7.95 ng/mL and a maximum concentration of 31.3 ng/mL among 42 nonsmoking staff working in a bar. Thus, under certain circumstances of exposure, peak values detected in people exposed to secondhand tobacco smoke may exceed the cut-points used to distinguish smokers from nonsmokers in many studies (Pérez-Stable *et al.*, 1992; California Environmental Protection Agency, 1997).

(ii) *Children*

The reports of the US Environmental Protection Agency (1992) and the California Environmental Protection Agency (1997) summarize studies that have reported increased concentrations of cotinine in children exposed to secondhand tobacco smoke at home. Many more recent studies have also found a significant correlation between cotinine concentrations in children and the amount of smoking by the parent(s) (Jarvis *et al.*, 1985; reviewed in Hovell *et al*., 2000a). A cross-sectional survey of secondary-school children conducted in 1998 found that salivary cotinine concentrations were correlated with parental smoking, but that the concentrations had halved since the late 1980s (Jarvis *et al*., 2000). Counselling, during 3 months, of non-employed mothers who smoked and who had children under school age significantly reduced the children's urine cotinine concentration at 12 months (Hovell *et al.*, 2000b).

(iii) *Newborns*

Higher concentrations of cotinine were found in amniotic fluid than in maternal urine in both smokers and nonsmokers (Jordanov, 1990). Studies of isolated perfused human placental cotyledon indicated that less than 1% of nicotine is metabolized to cotinine by the placenta. Rather, after rapid transfer across the placenta, nicotine is metabolized to cotinine by fetal tissues (Pastrakuljic *et al*., 1998; Sastry *et al*., 1998). The elimination kinetics of nicotine, cotinine, trans-3′-hydroxycotinine and their conjugates in the urine of newborns were first reported by Dempsey *et al*. (2000). The results indicated that the half-life of nicotine in newborns was 3–4 times longer than that in adults, whereas the half-life of cotinine was essentially the same in newborns as in adults. The data indicate that newborns are capable of metabolizing nicotine to cotinine and of conjugating nicotine, cotinine and 3′-OH cotinine. However, it is not known what percentage of cotinine is formed by the fetus and what percentage is acquired transplacentally, and which P450 isozymes are involved in fetal metabolism of nicotine (Dempsey *et al*., 2000).

Etzel *et al*. (1985) used a radio-immunoassay to detect cotinine in the 1-day urine of infants born to self-identified smokers and nonsmokers. The median concentration of urinary cotinine for newborns of smokers was 1233 ng/mg creatinine as opposed to 14.5 ng/mg for newborns whose mothers were nonsmokers.

A study of 31 mothers and their newborns was conducted in Bulgaria (Jordanov, 1990). Analysis of 1-day urine by a direct colorimetric method found a mean urinary cotinine concentration of 13 ± 3 μmol/L for the newborns of nonsmokers not exposed to tobacco smoke, 18 ± 4 μmol/L for the newborns of passive smokers and 44 ± 18 μmol/L for the newborns of active smokers who smoked an average of 15 cigarettes per day; all differences were statistically significant. First-day urine of newborns was analysed in a large study of 429 mothers in Barcelona, Spain (Pichini *et al*., 2000). Concentrations of urinary cotinine higher than the cut-off value of 50 ng/mL were measured in 17% of samples from newborns of nonsmoking mothers exposed to secondhand smoke, versus 2% for nonsmoking mothers who were not exposed to secondhand smoke. The concentrations of cotinine in the urine and cord serum of newborns of nonsmoking women with a calculated daily exposure to nicotine of more than 4 mg were significantly higher than the levels in newborns of nonsmoking mothers who were not exposed (30.9 versus 6.2 ng/mL; $p < 0.05$), after adjustment for creatinine, maternal age and sex. Daily intake of nicotine for active smokers was stratified into ≤ 3.6 mg nicotine per day, 3.6–9 mg per day, and > 9 mg per day. Urinary and cord serum cotinine concentrations were 515 ng/mL for newborns of mothers with intermediate daily nicotine intake and 568 ng/mL for the newborns of mothers with high daily nicotine intake and were statistically different ($p < 0.05$) from the concentrations in newborns of mothers with a low daily nicotine intake (161 ng/mL).

Nicotine has recently been demonstrated to occur in newborn urine. Lackmann *et al*. (1999) used gas chromatography–mass spectrometry with selective ion monitoring to detect nicotine in first voided urine samples in newborns of mothers who smoked an average of 12.4 cigarettes per day. The average concentration of nicotine in 18/31 (58%) samples was 0.63 nmol/mL. Nicotine was not detected in the urine of 17 newborns of women who did not smoke ($p < 0.001$). In the same study, cotinine was detected in 28/31 (90%) of the urine samples from newborns of mothers who were smokers, at a mean concentration of 0.87 nmol/mL. The newborns of women who were nonsmokers had a mean urine cotinine concentration of 0.049 nmol/mL. The difference was statistically significant ($p < 0.001$). Similarly, using high-performance liquid chromatography, Köhler *et al*. (2001) were able to detect nicotine and cotinine in the urine of newborns of active smokers (mean ± SD, 374 ± 765 nmol/L for nicotine and 500 ± 572 nmol/L for cotinine), but not in the urine of the newborns of nonsmokers, whether or not they were exposed to secondhand tobacco smoke ($p < 0.05$ and $p < 0.001$ for nicotine and cotinine, respectively). They also observed a strong correlation between the nicotine and cotinine concentrations in the mothers and in their newborns.

(iv) *Alternative nicotine-related measures of exposure*

The analysis of nicotine in hair has been suggested as an alternative and non-invasive measure of exposure to tobacco smoke, particularly in children. This method may allow past exposure to be measured over a longer time period than is possible using measurements of nicotine in blood, saliva or urine. Several studies have shown a strong correlation between nicotine levels in hair and self-reported exposure to tobacco smoke or exposure in experimental chambers (Zahlsen *et al*., 1996; Nafstad *et al*., 1997; Dimich-Ward *et al*., 1997; Al-Delaimy *et al*., 2000). In fact, this has been proposed to be a more precise indicator of exposure to secondhand tobacco smoke than concentrations of urinary cotinine (Al-Delaimy *et al*., 2002).

The concentrations in the urine of minor nicotine-related tobacco alkaloids not present in nicotine medications, such as anabasine or anatabine, have been proposed as indicators of exposure to tobacco smoke in individuals undergoing nicotine replacement therapy (Jacob *et al*., 1999).

In summary, cotinine and its parent compound nicotine have a very high specificity and sensitivity for exposure to secondhand tobacco smoke, and, as such, cotinine is presently the best suited biomarker for assessing exposure to secondhand smoke and its uptake and metabolism in adults, children and newborns.

4.1.2 *Experimental systems*

The studies in which experimental animals were exposed to sidestream smoke alone or to simulated environmental tobacco smoke are reviewed below (see Section 3.1 for definitions).

In most studies the amount of smoke administered to the animals was monitored by measuring its total particulate matter (TPM), carbon monoxide (CO) and/or nicotine content. Internal dose measurements include those of carboxyhaemoglobin (COHb) adducts and/or cotinine in blood or urine.

(*a*) *Effects of tobacco smoke on enzyme activities*

Studies in animals on the effects of sidestream smoke on enzyme concentrations have evaluated changes in phase I and phase II enzymes in liver, lung and trachea (Table 4.2). A few studies have looked at changes in enzyme activities in brain and heart.

(i) *Phase I enzymes*

The ability of sidestream smoke to induce hepatic P450 activity was investigated in male Wistar rats (Kawamoto *et al*., 1993). Animals were exposed for 8 h/day to the smoke from 1, 3 or 5 cigarettes/h for 5 days (6–500 ppm CO). Total cytochrome P450 and nicotinamide-adenine dinucleotide phosphate (reduced form; NADPH) cytochrome c reductase activities were not affected, but cytochrome b_5 was increased 1.6-fold and aryl hydrocarbon hydroxylase (AHH) activity was significantly decreased in the highest exposure

Table 4.2. Effect of sidestream or simulated environmental tobacco smoke on enzyme concentration or activity

Species	Strain/sex	Exposure conditions (mg/m^3 TPM)	Enzyme affected	Effect (tissue)	Reference
Rat	S-D/M	n.g.	Ornithine decarboxylase	+ (trachea); 0 (lung)	Olson (1985)
			S-Adenosyl-methionine decarboxylase	– (trachea, lung)	
Mouse	C57BL/M	n.g.	Aryl hydrocarbon hydroxylase	+ (lung)	Gairola (1987)
Rat	S-D/M		Aryl hydrocarbon hydroxylase	+ (lung)	
Guinea-pig	Hartley/M		Aryl hydrocarbon hydroxylase	0 (lung)	
Mouse	C57BL/F	5.21 mg/kg bw	Aryl hydrocarbon hydroxylase	+ (lung)	Gairola *et al*. (1993)
	DBA/F	7.05 mg/kg bw	Aryl hydrocarbon hydroxylase	0 (lung)	
Rat	Wistar/M	6–500 ppm CO	Total P450s	0 (liver)	Kawamoto *et al*. (1993)
			P450 1A1, 1A2, 2B1	+ (liver)	
			NADPH cytochrome C reductase	0 (liver)	
			Cytochrome b_5	+ (liver)	
			Aryl hydrocarbon hydroxylase	– (liver)	
Rat	S-D/M	1	P450 1A1	+ (lung)	Ji *et al*. (1994)
			NADPH reductase	+ (lung)	
			P450 2B	0 (lung)	
Rat	S-D/M	1	P450 1A1	0 (trachea, liver); + (lung)	Gebremichael *et al*. (1995)
			P450 2B1	0 (lung, liver)	
Ferret	European/M&F	38; 381	P450s	– (liver)	Sindhu *et al*. (1995)
			P450 reductase	– (liver)	
			7-Ethoxycoumarin *O*-deethylase	– (liver)	
			P450 1A	– (liver)	
	European/F		Cytochrome b_5	– (liver)	
			Cytochrome b_5 reductase	– (liver)	

Table 4.2 (contd)

Species	Strain/sex	Exposure conditions (mg/m^3 TPM)	Enzyme affected	Effect (tissue)	Reference
Mouse	C57BL/6N/M	1	P450 1A1	+ (lung)	Gebremichael *et al.* (1996)
	DBA/2N/M		P450 1A1	0 (lung)	
Mouse	AJ/M	87.3	P450 1A1	+ (trachea, lung)	Witschi *et al.* (1997a)
			P450 2B1, 2E1	0 (lung)	
Rat	Wistar/M	n.g.	P450s	0 (liver)	Kurata *et al*. (1998)
Rat	Sprague-Dawley/n.g.	73–93	Aryl hydrocarbon hydroxylase	+ (lung)	Izzotti *et al*. (1999)
			Glutathione-*S*-transferase	+ (lung)	
Rat	Wistar/M	n.g.	Protein kinase C	+ (lung)	Maehira *et al*. (1999)
Rat	Wistar/M	10	Inducible nitric oxide synthase*	+ (alveolar macrophages)	Morimoto *et al*. (1999)
Rat	Sprague-Dawley/ M&F	1	P450 1A1	+ (lung)	Lee *et al*. (2000)
			P450 1B1, 2B1	0 (lung)	
			NADPH reductase	0 (lung)	
Rat	Sprague-Dawley/F	1	Adenylyl cyclase	+ (brain, heart)	Slotkin *et al*. (2001)
Rat	Wistar/M	90	P450 1A1	+ (lung)	Nadadur *et al*. (2002)

TPM, total particulate matter; M, male; F, female; bw, body weight; +, significant increase; 0, unchanged; –, significant decrease; n.g., not given
* With mineral fibre treatment

group. Although total cytochrome P450s did not change, P450 1A1, P450 1A2, and P450 2B1 were elevated by the high exposure regimen.

The effect of sidestream smoke on bronchiolar epithelial cell expression of P450 1A1 was studied in postnatal male Sprague-Dawley rats that were exposed to aged and diluted sidestream smoke (1 mg/m^3 TPM; 6 ppm CO; 350 μg/m^3 nicotine) for 6 h/day, 5 days/week from birth until 7, 14, 21, 50 or 100 days of age. Exposure to sidestream smoke significantly increased the expression of P450 1A1 in Clara cells of the proximal and distal airways and in alveolar Type II cells in the lung parenchyma at all times, with a maximal expression occurring at 50 days of age. NADPH reductase was increased in bronchiolar epithelial cells at 21 and 50 days, but not at 7 or 100 days. Cytochrome P450 2B expression was not affected by sidestream smoke in any airway epithelial cells during this study (Ji *et al.*, 1994).

Sindhu *et al*. (1995) studied hepatic cytochrome P450s after the exposure of ferrets to simulated environmental tobacco smoke. Six-week old male and female European ferrets were exposed to simulated environmental tobacco smoke (38 mg/m^3 TPM (low-dose) and 381 mg/m^3 TPM (high-dose)) for 2 h/day, 5 days/week for 8 weeks. In both male and female animals, there was a significant decrease in P450 content, and in P450 reductase and 7-ethoxycoumarin *O*-deethylase activities after exposure to both high and low concentrations. Immunoblot analysis revealed a decrease in P450 1A in exposed animals compared with controls. In addition, cytochrome b_5 content and the activity of its reductase were decreased in females.

The expression of P450 1A1 and 2B1 was evaluated in newborn male rats which were exposed to aged and diluted sidestream smoke for 6 h/day, 5 days/week (1 mg/m^3 TPM). Sidestream smoke induced pulmonary P450 1A1 activity as early as day 7 after birth, whereas it was not detected in controls. Pulmonary P450 1A1 activity remained significantly (3- to 4-fold) elevated until 100 days, whereas pulmonary P450 2B1 activity did not change at any age. Hepatic P450 1A1 and P450 2B1 were generally unchanged following exposure to sidestream smoke, except that P450 2B1 activity was decreased by 30% at 100 days. The effects of short-term exposure were studied in 47-day-old rats exposed for 6 h/day for 4 days, to either filtered or unfiltered sidestream smoke (0.03 and 1 mg/m^3 TPM, respectively). Whole, but not filtered, sidestream smoke increased pulmonary P450 1A1 more than threefold; P450 2B1 was unchanged by either type of exposure (Gebremichael *et al.*, 1995).

The role of the Ah receptor in response to exposure to sidestream smoke was evaluated (Gebremichael *et al*., 1996). Male C57BL/6N and DBA/2N mice were exposed for 6 h/day for 4 days to aged and diluted sidestream smoke (1 mg/m^3 TPM; 3.4 ppm CO; 703 μg/m^3 nicotine). Sidestream smoke induced ethoxyresorufin-*O*-dealkylase activity in the lungs of C57BL/6N mice, but had no effect in mice of the DBA/2N strain, which has a reduced AhR functionality.

The induction of pulmonary tumours and P450 1A1 after exposure to simulated environmental tobacco smoke was examined in male A/J mice (Witschi *et al*., 1997a). Mice, 12 weeks of age, were exposed to simulated environmental tobacco smoke (87.3 mg/m^3

TPM) for 6 h/day, 5 days/week for 5 months. The expression of P450 1A1 was significantly increased in airway epithelium and lung parenchyma of the smoke-exposed mice after 5 months of exposure; however, after a 4-month recovery period, no expression of P450 1A1 could be detected. P450 2B1 and 2E1 were not affected by exposure to tobacco smoke. No enhanced expression of P450 1A1 was detected in lung tumours. Filtered smoke containing 0.1 mg/m^3 TPM did not induce P450 1A1 expression in female A/J mice under the same conditions (Witschi *et al.*, 1997b).

The effect of sidestream smoke on the expression of pulmonary cytochrome P450 mRNAs in rats has been examined following in-utero and postnatal exposure (Lee *et al*., 2000). Gestating Sprague-Dawley rats were exposed to aged and diluted sidestream smoke (1 mg/m^3 TPM; 7.3 ppm CO; 250 µg/m^3 nicotine) beginning on gestational day 5. None of the P450 isozymes analysed were increased in fetal lungs when evaluated at 17, 19 or 21 days of gestation. In contrast, postnatal exposure to sidestream smoke induced P450 1A1 expression as early as 1 day after birth. No induction of P450 1B1, 2B1 or NADPH cytochrome P450 reductase was observed following continuous in-utero and postnatal exposure to sidestream smoke.

Total liver content of P450 remained unchanged in male Wistar rats following exposure to sidestream smoke for 2 h/day for 25 days [no information on TPM or other measurements of smoke concentration was given] (Kurata *et al.*, 1998).

Spontaneously hypertensive (SH) rats exhibit heritable risk factors similar to those found in patients with chronic obstructive pulmonary disease, and are more susceptible to lung injury and inflammation, to oxidative stress resulting from exposure to combustion by-products and to induction of pulmonary diseases in general. Nadadur *et al*. (2002) used this model to examine the differential gene expression following exposure to sidestream smoke. Male SH rats were exposed to sidestream smoke (90 mg/m^3 TPM) for 6 h/day on 2 consecutive days. Total RNAs were isolated from lungs on the third day and cDNA was examined by gene-expression array filters containing 588 genes. Exposure to sidestream smoke resulted in a differential expression of 16 genes, including P450 1A1.

The effect of sidestream smoke on AHH activity was investigated in different species and strains. Male C57BL mice, Sprague-Dawley rats and Hartley guinea-pigs [ages not stated] were exposed to sidestream smoke once or twice daily, on 7 days/week for 16 weeks. AHH levels were significantly increased in mice and rats (3.7-fold and 2.7-fold, respectively), but remained unchanged in guinea-pigs (Gairola, 1987). In a later study by Gairola *et al.* (1993), female C57BL and DBA mice, 8–9 weeks old, were exposed to sidestream smoke daily [duration of exposure not stated] for 65–70 weeks (average TPM intake, 5.21 and 7.05 mg/kg body weight, respectively). Exposure to sidestream smoke induced pulmonary AHH activity two- to threefold in C57BL mice, but no effect was found in DBA mice. In a later study, male Sprague-Dawley rats were exposed to simulated environmental tobacco smoke (a mixture of 89% sidestream smoke and 11% mainstream smoke) for 6 h/day, 5 days/week for up to 5 weeks (73–93 mg/m^3 TPM; 350 ppm CO). Exposure to simulated environmental tobacco smoke resulted in a significant induction of AHH activity in lung microsomal fractions, which increased over the first 4

weeks of exposure; however, within 1 week after termination of the exposure, AHH activity decreased to the same levels as those measured in sham-treated rats (Izzotti *et al*., 1999).

(ii) *Phase II enzymes*

Male Sprague-Dawley rats were exposed to simulated environmental tobacco smoke for 6 h/day, 5 days/week for up to 5 weeks (73–93 mg/m^3 TPM; 350 ppm CO) (Izzotti *et al.*, 1999). This exposure resulted in the concentrations of GSH in lung post-mitochondrial (S12) fractions undergoing a progressive and consistent decrease, which became significant after 4 weeks. After 5 weeks, GSH levels in exposed animals were 67% of the levels in controls. The activity of glutathione-*S*-transferase (GST) in lung cytosolic fractions from exposed animals increased steadily and became significantly elevated after 5 weeks.

(iii) *Other enzymatic alterations*

The effect of chronic exposure to sidestream smoke on ornithine decarboxylase and *S*-adenosyl-methionine decarboxylase activity was determined in the rat trachea and lung. Male Sprague-Dawley rats were exposed for 10 min daily, 7 days/week, for 4 or 8 weeks to 25% sidestream smoke, or for 20 weeks to either 50%, 25% or 10% sidestream smoke (Olson, 1985). Ornithine decarboxylase activity in the lung was elevated in the group exposed for 8 weeks, but not in the group exposed for 20 weeks at any dose. Ornithine decarboxylase in the trachea was significantly elevated by all concentrations of sidestream smoke at all times. None of the treated rats showed any significant increase in *S*-adenosyl-methionine decarboxylase activity at any concentration or duration of exposure.

In 8-week-old male Wistar rats exposed to sidestream smoke [concentration not reported] for 1-h periods, twice daily, for 8, 12 or 20 weeks, protein kinase C activity in lung was increased by 120% at 8 weeks, and by 86% and 81% at 12 and 20 weeks, respectively (Maehira *et al*., 1999).

The synergistic effects of sidestream smoke and mineral fibres were investigated by Morimoto *et al*. (1999). Ten-week-old male Wistar rats were first given an intratracheal instillation of chrysotile or ceramic fibres and subsequently exposed to sidestream smoke for 4 h/day, 5 days/week for 4 weeks (10 mg/m^3 TPM; 79 ppm CO). Control groups included animals exposed to saline only, chrysotile only, ceramic fibres only and sidestream smoke only. Both exposure to mineral fibres and/or to sidestream smoke increased the number of cells recovered from bronchoalveolar lavage; alveolar macrophages accounted for > 95% of the total cells. Levels of IL-1α mRNA were significantly increased ($p < 0.05$) in all exposed groups (i.e. those exposed to sidestream smoke, mineral fibres, and sidestream smoke plus mineral fibres) in alveolar macrophages, but not in lung (when compared to saline-treated controls). Increased expression of IL-6 mRNA was only seen in the lung when sidestream smoke was combined with chrysotile, but neither exposure alone was sufficient to induce expression of IL-6 mRNA. No such

increase was observed in alveolar macrophages. Similarly, inducible nitric oxide synthase (iNOS) was not increased in the alveolar macrophages of rats treated with mineral fibres or sidestream smoke alone, but was significantly increased in animals that received combination treatments ($p < 0.01$). iNOS was not induced in the lungs by any treatment.

To mimic fetal and childhood exposure to secondhand smoke, gestating Sprague-Dawley rats were exposed to mainstream smoke (29 mg/m^3 TPM; 93 ppm CO; 4.6 mg/m^3 nicotine) for 6 h/day, 7 days/week, from gestational day 5 to day 20. One or two days after parturition, dams and pups were exposed to sidestream smoke (1 mg/m^3 TPM; 5.6 ppm CO; 117 μg/m^3 nicotine) until postnatal day 21. Animals were exposed either prenatally or postnatally or both. Adenylyl cyclase (AC) activity was evaluated under four different conditions in brain and heart tissues: basal AC, after isoproterenol or forskolin stimulation, and after forskolin stimulation followed by carbachol inhibition. In the brain, both prenatal and postnatal exposure were effective in upregulating AC when measured by forskolin response, but not when measured by the other methods. In the heart, AC activity as measured by all methods was significantly elevated after prenatal exposure, postnatal exposure, or both. The authors concluded that postnatal exposure to sidestream smoke elicited changes similar to, or more severe than, those observed during prenatal exposure from maternal smoking (see also Section 4.3.2(iii)) (Slotkin *et al.*, 2001).

Male SH rats were exposed to sidestream smoke (90 mg/m^3 TPM) for 6 h/day for 2 days (Nadadur *et al.*, 2002; see Section 4.1.2(*a*)(i) for details). A two- to threefold increase was observed in expression of macrophage inflammatory protein-2, suggesting the potential for lung inflammation. Over-expression of matrix metalloproteinase-7 was also observed; this may play a role in cell migration and invasion.

(*b*) *Tobacco smoke carcinogen biomarkers*

Animal studies on the formation of carcinogen biomarkers following exposure to sidestream smoke have evaluated protein and DNA adducts, including those in lung and liver. These studies are summarized in Table 4.3; only the main studies are described in detail in the text.

(i) *Urinary compounds*

Urine samples from male and female Fischer 344 rats exposed to sidestream smoke for 15 min four times/day for 5 days elicited DNA adducts in a plasmid assay *in vitro* (Takenawa *et al.*, 1994).

(ii) *DNA adducts*

Lee *et al*. (1992, 1993) evaluated the formation of DNA adducts in various tissues following 14-day and 90-day periods of exposure to sidestream smoke. In these studies, 7-week-old male Sprague-Dawley rats were exposed to aged and diluted sidestream smoke for 6 h/day for 14 or 90 days at target exposure concentrations of 0, 0.1, 1.0 and 10 mg/m^3 TPM. DNA adducts were observed only in the lung and heart of animals that received the highest dose. Adducts in lung were observed after 7 and 14 days and were

Table 4.3. Effects of sidestream or simulated environmental tobacco smoke on DNA adducts and other biomarkers

Species	Strain/sex	Biomarker	Effect (tissue)	Reference
		DNA adducts		
Rat	S-D/*	Smoke-related (14-day exposure)	+ (lung, heart/high dose) – (lung, heart/low dose)	Lee *et al*. (1992)
Rat	S-D/M	Smoke-related (90-day exposure)	+ (lung, heart, larynx) – (liver, bladder)	Lee *et al*. (1993)
Mouse	Parkes/M	Smoke-related	+++ (skin, lung, bladder) ++ (heart, kidney)	Carmichael *et al.* (1993)
Mouse	C7BL/F DBA/F	Smoke-enhanced	+ (lung); – (liver) + (lung); – (liver)	Gairola *et al*. (1993)
Rat	F344/M&F	Smoke-related	+ (bladder, kidney) – (testis)	Takenawa *et al.* (1994)
Mouse	BALB/c/F BALB/c/F	Smoke-related 8-Hydroxy-2′-deoxyguanosine	+ (lung, liver, heart) + (lung, liver, heart)	Howard *et al.* (1998b)
Rat	S-D/M	Smoke-related 8-Hydroxy-2′-deoxyguanosine	+ (lung, heart, bladder, trachea, bronchi) 0 (liver), ± (testes) + (lung)	Izzotti *et al*. (1999)
Rat	Wistar/M	8-Hydroxy-2′-deoxyguanosine	+ (lung)	Maehira *et al*. (1999)
	S-D/F	Smoke-related	+++ (lung), ++ (trachea, heart) + (bladder)	Arif *et al*. (2000)
Rat	S-D/M	Smoke-related 8-Hydroxy-2′-deoxyguanosine	+ (lung, trachea, heart) + (lung)	Izzotti *et al*. (2001)
Mouse	SKH-1	Smoke-related 8-Hydroxy-2′-deoxyguanosine	+ (skin), ++ (lung) + (lung)	De Flora *et al*. (2003)

Table 4.3 (contd)

Species	Strain/sex	Biomarker	Effect (tissue)	Reference
		Other biomarkers and metabolites		
Ferret	EUR/M&F	(+)-*Anti*-B*a*P 7,8-dihydrodiol-9,10-epoxide		Sindhu *et al*. (1995)
		- glutathione	– (liver) (female only)	
		- glucuronide	0 (liver)	
		- sulfate	0 (liver)	
		total B*a*P	– (liver)	
		(-)-7R *trans*-B*a*P-7,8-dihydrodiol-9,10-epoxide	0 (liver)	
Rat	Wistar/M	L-Ascorbic acid	+ (urine, plasma, tissues)	Kurata *et al*. (1998)
Rat	n.g./n.g.	Cotinine	+ (urine)	Oddoze *et al*. (1998)
Rat	S-D/M	8-Iso-prostaglandin-$F_{2\alpha}$	+ (urine)	Visioli *et al.* (2000)
Rat	S-D/M	B*a*P-7,8-diol-9,10-epoxide haemoglobin	+ (blood)	Izzotti *et al*. (2001)

M, male; F, female; S-D, Sprague-Dawley; +, significant increase; 0, unchanged; –, significant decrease; n.g., not given
* Sex not stated, but likely to be males (see Lee *et al.*, 1993)

still present after 14 days of recovery. Adducts in heart tissue were first seen after 14 days and persisted through the 14-day recovery period. Neither liver nor larynx exhibited exposure-related adducts at any time period or any dose. In the 90-day study, animals were killed at 28 and 90 days, and after a 90-day recovery period. After 28 and 90 days, a significant elevation in adducts in lung, heart and larynx was seen only in the animals exposed to 10 mg/m^3 TPM, and liver and bladder were unaffected by exposure at any time or any dose. After a 90-day recovery period, adduct levels in all organs in which there had been a response to exposure decreased, but were still elevated compared to the levels in controls [no statistical test performed]. These data establish a no-observed-effect-level of at least 1.0 mg/m^3 TPM for DNA adducts.

Sidestream smoke condensate was applied topically on mouse skin and DNA adducts formed from the condensate in several organs were quantified by ^{32}P-postlabelling techniques. When compared with unexposed controls, sidestream smoke condensate was found to induce approximately five- to sevenfold higher levels of adducts in skin, lung and bladder and two- to threefold higher levels in heart and kidney (Carmichael *et al*., 1993).

Long-term studies of exposure of female C57BL and DBA mice to sidestream smoke were conducted by Gairola *et al*. (1993). DNA adducts were assayed in lung and liver after 65–70 consecutive weeks of exposure (average TPM intake, 5.21 and 7.05 mg/kg body weight, respectively). Sidestream smoke enhanced DNA adducts in lung in both strains of mice; the increase was about 16-fold in C57BL mice and 8-fold in DBA mice (the difference between the two strains was not statistically significant. Adduct maps showed no qualitative difference between strains, or between treated and control mice. No increase in adduct levels was observed in the liver.

Male and female Fischer 344 rats were exposed to sidestream smoke for 15 min four times/day for 5 days (Takenawa *et al*., 1994). [No monitoring of exposure was reported.] A significant increase in DNA adducts in bladder and kidney was seen in exposed animals when compared to control samples, but not in testicular tissues; this suggests that the DNA adducts were formed in the tissues along the urinary tract.

Adult female BALB/c mice were exposed to a regimen of 30-min exposures to sidestream smoke followed by a 90-min recovery, for three consecutive cycles. The level of 8-OHdG adducts was increased by exposure to sidestream smoke in heart, lung and liver (about 1.6-fold) and remained elevated in lung and heart after the recovery period [limited statistical analysis was performed] (Howard *et al*., 1998b).

In a study to evaluate the inhibitory effect of indole-3-carbinol on cigarette smoke-related formation of DNA adducts in target organs, Arif *et al*. (2000) found that whole-body exposure of female Sprague-Dawley rats to sidestream smoke (6 h/day, 7 days/week for 4 weeks; 27 mg/m^3 TPM) induced smoke-related adducts in all tissues examined, including (in descending order) lung, heart, trachea and bladder. The adducts were qualitatively similar in all organs, but were present in different proportions.

Male Sprague-Dawley rats were exposed to simulated environmental tobacco smoke for 6 h/day, 5 days/week for up to 5 weeks (73–93 mg/m^3 TPM; 350 ppm CO) (Izzotti *et al.*, 1999, 2001). The exposure continued for 1, 2, 3, 4 or 5 weeks and rats were killed

16 h after the last exposure. Samples of heart, lung, liver, testes, bladder, bronchial alveolar macrophages and tracheal epithelium were analysed for adducts. Examination of the autoradiograph patterns revealed the existence of four major and two minor spots in tracheal epithelium, three major spots in macrophages, and one major and one minor spot in lung, heart and bladder. All organs showed a time-related increase in adducts during the first 4 weeks, and the trachea and macrophages continued to accumulate adducts through the fifth week. When animals were allowed 1 week of recovery after 4 weeks of exposure, levels of adducts decreased significantly in all tissues except heart, but remained significantly higher than in control animals. There was a slight but significant increase in 8-OHdG adducts in lung of animals exposed to smoke for 4 weeks when compared with sham-treated rats (Izzotti *et al.*, 2001).

In a preliminary experiment reported by De Flora *et al*. (2003), SKH-1 hairless mice were exposed to simulated environmental tobacco smoke for 28 days [exposure concentrations not given]. Whole-body exposure resulted in bulky DNA and 8-OHdG-adducts in the skin and lungs of treated animals. A potential synergistic effect was noted between exposure to simulated environmental tobacco smoke and exposure to sunlight-simulating lamps with respect to the induction of bulky DNA adducts in the lung.

(*c*) *Other biomarkers and metabolites*

The results of animal studies that have reported changes in metabolites and carboxyhaemoglobin levels in various tissues are summarized below and in Table 4.3.

(i) *Blood compounds*

Serum concentrations of carboxyhaemoglobin, together with nicotine and/or cotinine, are commonly used as biomarkers of exposure in experimental models as they are strongly correlated with the estimated total particulate matter (von Meyerink *et al.*, 1989; Coggins *et al.*, 1992, 1993; Zhu *et al.*, 1994; Sun *et al.*, 2001).

(ii) *Particles*

A comparison of the deposition of environmental tobacco smoke particles in human and rat tracheobronchial tree and pulmonary region was performed by Oberdörster and Pott (1986). Their calculations showed that the relative deposition of particles (mass median aerodynamic diameter of 0.2 μm) was about the same in the tracheobronchial tree of rats and humans, and was less in the pulmonary region in rats than in humans. However, the rate of deposition in the transitional region of the lung was about twice as high in rats as in humans. These data should be taken into consideration when using the results of experiments in rats to predict the results of human exposure.

(iii) *Urinary compounds including cotinine*

L-Ascorbic acid is a potential scavenger of free radicals under normal conditions and following most carcinogenic insults, including the free radicals contained in and generated by cigarette smoke. To evaluate the effect of sidestream smoke on the metabolism and excretion of L-ascorbic acid, Kurata *et al*. (1998) exposed 7-week-old male Wistar

rats to the sidestream smoke generated by two cigarettes every 30 min, four times/day, for 25 days [concentrations of TPM, CO and nicotine not stated]. The excretion of L-ascorbic acid into urine increased steadily with duration of exposure to sidestream smoke, and became significantly higher than in controls after day 12. At 25 days, L-ascorbic acid in liver, adrenal glands, lungs and kidneys in exposed animals was higher than in controls.

The exposure of rats to sidestream smoke produces a smoke-related oxidative stress, resulting in lipid peroxidation, that can be monitored by the urinary excretion of F_2 isoprostanes (e.g. 8-*iso*-prostaglandin $F_{2\alpha}$), produced from arachidonic acid by free radical-catalysed mechanisms. Visioli *et al*. (2000) evaluated the antioxidant effect of olive oil on the excretion of 8-*iso*-prostaglandin $F_{2\alpha}$. Male Sprague-Dawley rats were exposed to sidestream smoke for 20 min/day for 4 days (2600 ppm CO). The excretion of 8-*iso*-prostaglandin $F_{2\alpha}$ increased from 237 to 319 pg/mg creatinine after 2 days of exposure, an increase of 44%. After four exposures, the excretion of 8-*iso*-prostaglandin $F_{2\alpha}$ was 55% higher than in control rats. Treatment with olive oil reduced the excretion to pre-exposure levels and to a 34% increase over pre-exposure levels, after 2 and 4 days of exposure, respectively.

Oddoze *et al*. (1998) developed a rapid and sensitive assay for measuring urinary metabolites in human nonsmokers and rats. In rats exposed to sidestream smoke for 4 days [strain and sex of rats and conditions of exposure not stated], 24-h urine samples were collected before the exposure began and after the last exposure. No cotinine was found in sham-exposed samples, but the amount of cotinine in the urine of exposed rats (n = 5) ranged from 525 to 675 ng/mL and one sample had a cotinine concentration of 1587 ng/mL.

4.2 Toxic effects

Exposure to secondhand tobacco smoke is a cause of cardiovascular and respiratory disease. The studies reviewed here add to the knowledge of the adverse effects of exposure to secondhand tobacco smoke on the health of adult humans.

4.2.1 *Humans*

(*a*) *Nicotine addiction*

No data on nicotine addiction resulting from involuntary exposure to tobacco smoke were available to the Working Group.

(*b*) *Cardiovascular system*

A causal association between active smoking and coronary heart disease (CHD) is well established (US Department of Health and Human Services, 1983, 1990). Since 1984, some 20 studies have examined the association between exposure to secondhand tobacco smoke and risk of CHD in nonsmokers. The available literature was first reviewed in 1986 in a report from the US National Research Council (US National

Research Council, 1986) and a report of the Surgeon General (US DHHS, 1986). Both reviews concluded that an association between exposure to secondhand tobacco smoke and CHD was biologically plausible, but that the epidemiological evidence was inconclusive. Since then, numerous reviews and reports have become available (Wells, 1988; Wu-Williams & Samet, 1990; Glantz & Parmley, 1991; Steenland, 1992; Wells, 1994; Glantz & Parmley, 1995; Kritz *et al*., 1995; Law *et al*., 1997; Wells, 1998; He *et al*., 1999; Thun *et al*., 1999; US National Cancer Institute, 1999). Nine of these reviews included a meta-analysis to calculate a pooled relative risk for CHD in relation to exposure to secondhand tobacco smoke (Wells, 1988; Glantz & Parmley, 1991; Wells, 1994 ; Glantz & Parmley, 1995; Kritz *et al*., 1995; Law *et al*., 1997; Wells, 1998; He *et al*., 1999; Thun *et al*., 1999).

(i) *Epidemiological studies*

The results of three recent meta-analyses (Law *et al*., 1997; He *et al*., 1999; Thun *et al*., 1999) are summarized in Tables 4.4 and 4.5.

Law *et al.* (1997) carried out five sets of meta-analyses using published data (Table 4.4). In the first analysis, which included 19 studies of exposure to secondhand tobacco smoke and ischaemic heart disease (IHD), it was estimated that never-smokers living with a smoker have a 30% increased risk of IHD. In the second analysis, which included five large cohorts of men, it was estimated that the risk for CHD in nonsmokers living with a smoker was similar to the excess risk from smoking one cigarette per day. The third analysis, which included three cohorts, estimated that almost all the excess risk reversed after cessation of smoking; the residual excess risk was 6%. The fourth analysis was conducted on 18 studies to estimate the potential effect of confounding attributable to differences in diet between passive smokers and nonsmokers. People exposed to secondhand smoke were more likely than nonsmokers not exposed to tobacco smoke to consume diets with few vegetables and fruits and were less likely to take antioxidant vitamin supplements. However, clinical trials have indicated that taking β-carotene and vitamin E supplements does not reduce the risk for CHD in persons with no history of myocardial infarction (Alpha-Tocopherol β Carotene Cancer Prevention Study Group, 1994; Hennekens *et al.*, 1996). It was estimated that nonsmokers living with smokers eat a diet that gives them a 6% increased risk for IHD. The relative risk of exposure to secondhand smoke for ischaemic heart disease adjusted for diet was 1.2 (95% CI, 1.1–1.3). In the fifth analysis, which was based on eight studies, the increase in risk for IHD attributable to secondhand tobacco smoke-related platelet aggregation was estimated. It was concluded that the increase in experimentally produced platelet aggregation caused by exposure to secondhand tobacco smoke would be expected to have acute effects increasing the risk for IHD by 34%.

In the meta-analysis conducted by He *et al.* (1999), passive smoking was consistently associated with an increased relative risk for CHD. This association was observed in cohort studies, in case–control studies, in men, in women and in those exposed to

Table 4.4. Relative risk for coronary (or ischaemic) heart disease (and/or death from coronary heart disease) in never-smokers exposed to secondhand tobacco smoke in meta-analyses

Focus of meta-analysis	Relative risk (95% CI)	Exposure to tobacco smoke	Number of studies included and references
Secondhand tobacco smoke and IHD	1.30 (1.22–1.38; $p < 0.001$)	Never-smokers living with a smoker	Meta-analysis of 19 studies (Garland *et al.*, 1985; Lee *et al.*, 1986; Svendsen *et al.*, 1987; He, 1989; Hole *et al.*, 1989; Sandler *et al.*, 1989; Hirayama, 1990; Humble *et al.*, 1990; Dobson *et al.*, 1991; Lee, 1992; La Vecchia *et al.*, 1993; He *et al.*, 1994; Layard, 1995; LeVois & Layard, 1995; Muscat & Wynder, 1995; Tunstall-Pedoe *et al.*, 1995; Steenland *et al.*, 1996; Kawachi *et al.*, 1997; Ciruzzi *et al.*, 1998)
Smoking at low doses and IHD	1.39 (1.18–1.64) 1.78 (1.31–2.44)	Active smoking of 1 cig/day Active smoking of 20 cig/day	Five large cohorts of men (660 IHD events) (Hammond & Horn, 1958; Doll & Hill, 1964; 1966; Hammond, 1966; Kahn, 1966; Hammond & Garfinkel, 1969; Pooling Project Research Group, 1978)
Smoking cessation and reversibility of excess risk of IHD	1.06 (1.02–1.10)	Former smokers (smoking cessation)	Meta-analysis of 3 studies (Hammond & Garfinkel, 1969; Rogot & Murray, 1980; Doll & Peto, 1976)
Dietary differences between nonsmokers living with a smoker and nonsmokers living with a nonsmoker and IHD	1.06	Diet of nonsmokers living with a smoker	Meta-analysis of 18 studies (Keith & Driskell, 1980; Fehily *et al.*, 1984; Stryker *et al.*, 1988; Sidney *et al.*, 1989; Larkin *et al.*, 1990; Subar *et al.*, 1990; Cade & Margetts, 1991; Le Marchand *et al.*, 1991; Nuttens *et al.*, 1992; Bolton-Smith *et al.*, 1993; Margetts & Jackson, 1993; Midgette *et al.*, 1993; Tribble *et al.*, 1993; Järvinen *et al.*, 1994; McPhillips *et al.*, 1994; Thornton *et al.*, 1994; Emmons *et al.*, 1995; Zondervan *et al.*, 1996)
Secondhand tobacco smoke-related platelet aggregation and risk of IHD	1.34 (1.19–1.50)	Platelets experimentally exposed to second-hand tobacco smoke	Meta-analysis of 8 studies (cohort of 2398 men) (Davis & Davis, 1981; Davis *et al.*, 1982; Schmidt & Rasmussen, 1984; Davis *et al.*, 1985a,b, 1986; 1989; Blache *et al.*, 1992)

CI, confidence interval; IHD, ischaemic heart disease; cig, cigarettes

Table 4.5. Relative risk for coronary heart disease (and/or death from coronary heart disease) in never-smokers exposed to secondhand tobacco smoke in meta-analyses

Meta-analyses	Number of studies analysed	Number of cases of CHD	Relative risk (95% CI)	References
He *et al.* (1999)	10 cohort studies 8 case–control studies	6813	1.25 (1.17–1.32) in all studies 1.21 (1.14–1.30) in cohort studies 1.51 (1.26–1.81) in case–control studies 1.22 (1.10–1.35) in men 1.24 (1.15–1.34) in women 1.17 (1.11–1.24) at home 1.11 (1.00–1.23) at work 1.26 (1.16–1.38) pooled adjusted relative risk[a] *Intensity of exposure to secondhand smoke* 1–19 cig/day, 1.23 (1.13–1.34) ≥ 20 cig/day, 1.31 (1.21–1.42) (*p* for linear trend = 0.006) *Duration of exposure to secondhand smoke* 1–9 years, 1.18 (0.98–1.42) 10–19 years, 1.31 (1.11–1.55) ≥ 20 years, 1.29 (1.16–1.43) (*p* for linear trend = 0.01)	Cohort studies: Hirayama (1984); Garland *et al.* (1985); Svendsen *et al.* (1987); Butler (1988); Hole *et al.* (1989); Sandler *et al.* (1989); Hirayama (1990); Humble *et al.* (1990); Steenland *et al.* (1996); Kawachi *et al.* (1997) Case–control studies: Lee *et al.* (1986); He (1989); Jackson (1989); Dobson *et al.* (1991); La Vecchia *et al.* (1993); He *et al.* (1994); Muscat & Wynder (1995); Ciruzzi *et al.* (1998)
Thun *et al.* (1999)	9 cohort studies 8 case–control studies	7345	1.25 (1.17–1.33) in all studies 1.23 (1.15–1.31) in cohort studies 1.47 (1.19–1.81) in case–control studies 1.24 (1.15–1.32) in men 1.23 (1.15–1.32) in women 1.22 (1.13–1.30) in USA 1.41 (1.21–1.65) in other countries 1.22 (1.14–1.30) for fatal CHD 1.32 (1.04–1.67) for non-CHD	Cohort studies: Hirayama (1984); Garland *et al.* (1985); Svendsen *et al.* (1987); Butler (1988); Hole *et al.* (1989); Sandler *et al.* (1989); Hirayama (1990); Humble *et al.* (1990); Steenland *et al.* (1996); Kawachi *et al.* (1997) Case–control studies: Lee *et al.* (1986); He (1989); Jackson (1989); Dobson *et al.* (1991); La Vecchia *et al.* (1993); He *et al.* (1994); Muscat & Wynder (1995); Lam & He (1997); Ciruzzi *et al.* (1998)

CHD, coronary heart disease; IHD, ischaemic heart disease; CI, confidence interval; cig, cigarettes

[a] Analysis confined to 10 studies that adjusted for age, sex, blood pressure, body weight and serum cholesterol

smoking at home or in the workplace. Positive dose–response relationships for intensity and duration of exposure were observed (Table 4.5).

Thun *et al.* (1999) found that never-smokers married to smokers had an increased relative risk for fatal or non-fatal coronary events when compared with never-smokers married to nonsmokers. The increase in relative risk was similar in men and women, in cohort and case–control studies, in the USA and other countries and in studies of fatal and non-fatal coronary events (Table 4.5).

(ii) *Other human data*

Several mechanisms may increase the risk of CHD in nonsmokers exposed to secondhand tobacco smoke (US DHHS, 1990; Wells, 1994; He *et al*., 1999). The acute effects of passive smoking include alterations in heart rate (Pope *et al*., 2001), blood pressure, concentrations of carboxyhaemoglobin and carbon monoxide in the blood, in the blood's ability to use oxygen in the formation of adenosine triphosphate (ATP), and reduced exercise capability in people breathing secondhand smoke (Glantz & Parmley, 1995). An increase in the ratio of serum total cholesterol to high-density lipoprotein cholesterol (HDL-C), a decrease in the serum level of HDL-C (Feldman *et al*., 1991), an increase in platelet aggregation (Davis *et al*., 1989) and endothelial cell dysfunction (Otsuka *et al*., 2001) have also been described. Exposure to secondhand tobacco smoke may also contribute to atherosclerosis by priming and sensitizing neutrophils, resulting in their activation and subsequent oxidant-mediated tissue damage (Anderson *et al*., 1991).

(*c*) *Respiratory system*

The relationship between exposure to secondhand tobacco smoke and a variety of non-malignant respiratory health endpoints has been examined extensively in epidemiological and experimental studies. When this topic was first raised in the 1972 Report of the Surgeon General (US DHHS, 1972), the handful of studies that had addressed this issue had provided only limited information.

Since then, several reviews of the literature on secondhand tobacco smoke have addressed some aspects of the effects of secondhand tobacco smoke on the risk for non-neoplastic respiratory diseases in adults (Weiss *et al*., 1983; US DHHS, 1984, 1986; US National Research Council, 1986; Crawford, 1988; Eriksen *et al*., 1988; Spitzer *et al*., 1990; Trédaniel *et al*., 1994; Jinot & Bayard, 1996; California Environmental Protection Agency, 1997; Coultas, 1998; Weiss *et al*., 1999; US National Academy of Sciences, 2000).

A variety of adverse respiratory health outcomes in children have been causally linked to exposure to secondhand tobacco smoke or there is suggestive evidence of a causal association (see Table 4.6). For a detailed discussion of the relevant studies, the reader is referred to the recent reviews of the California Environmental Protection Agency (1997) and the US National Academy of Sciences (2000).

In adults, irritation of the eyes and nasal irritation have been causally associated with exposure to secondhand tobacco smoke and other annoyance has been described in

Table 4.6. Respiratory effects associated with exposure to secondhand tobacco smoke in children

Effects causally associated with exposure to secondhand tobacco smoke	Effects for which there is suggestive evidence of a causal association with exposure to secondhand tobacco smoke
Acute infections of the lower respiratory tract (e.g. bronchitis and pneumonia) Induction and exacerbation of asthma Chronic respiratory symptoms Middle-ear infections	Exacerbation of cystic fibrosis Decreased pulmonary function

Modified from California Environmental Protection Agency (1997)

several studies (US DHHS, 1999). For decreased pulmonary function, especially in combination with other exposures (e.g. prior exposure to occupational irritants) and for exacerbation of asthma, there is suggestive evidence of a causal association (California Environmental Protection Agency, 1997; US National Academy of Sciences, 2000). Some of the studies on exposure to secondhand tobacco smoke and respiratory health effects are briefly summarized below; for more comprehensive details, the reader is referred to some recent reviews (California Environmental Protection Agency, 1999; US National Academy of Sciences, 2000).

(i) *Acute effects of sensory irritation and annoyance*

The determination of the acute effects of secondhand tobacco smoke is difficult, because the observed reactions, although immediate, are largely subjective (Speer, 1968). A review of the irritation and annoyance attributable to exposure to secondhand tobacco smoke was published by the California Environmental Protection Agency (1997). The chemical constituents of secondhand tobacco smoke thought to be responsible for sensory irritation include organic acids (acetic acid and propionic acid), aldehydes (formaldehyde and acrolein), nicotine, ammonia, pyridine, toluene, sulfur dioxide and nitrogen oxides, among others (Ayer & Yeager, 1982; Triebig *et al*., 1984; US DHHS, 1986).

Nonsmokers seem to react significantly more than smokers (Weber, 1984a). The most common effect is tissue irritation, especially of the eyes (Speer, 1968; Basu *et al*., 1978; Shephard *et al*., 1979a; Bascom *et al*., 1991; White *et al*., 1991), but also of the nose, throat and airways (Bascom *et al*., 1991; Willes *et al*., 1992, 1998). The complaints are especially marked among aircraft passengers (US National Institute for Occupational Safety and Health, 1971; US National Academy of Sciences, 1986; Mattson *et al*., 1989).

Weber and co-workers (Weber *et al*., 1976; Weber, 1984b; Weber & Grosjean, 1987) and Muramatsu *et al*. (1983) conducted experiments in which volunteers were exposed to progressively increasing concentrations of secondhand tobacco smoke; as duration and intensity of exposure increased, subjects began to report subjective eye irritation, and blink rate also increased.

Lebowitz *et al*. (1992) found an increased prevalence of acute respiratory symptoms as levels of indoor secondhand tobacco smoke increased, especially in the households of subjects with lower socioeconomic status.

(ii) *Chronic respiratory symptoms*

In an early study, 25% of 10 320 nonsmoking office workers reported exacerbation of pre-existing pulmonary conditions when working with a smoker (Barad, 1979).

Other studies have shown no association (or a weak and statistically non-significant association) between the frequency of major respiratory symptoms and exposure to secondhand tobacco smoke from family members or spouse (Lebowitz & Burrows, 1976; Schilling *et al.*, 1977; Comstock *et al.*, 1981; Kauffmann *et al.*, 1983; Gillis *et al.*, 1984; Hole *et al.*, 1989; Kauffmann *et al.*, 1989).

Since 1990, however, several investigations have demonstrated a significant increase in risk for many respiratory symptoms (including cough, phlegm, breathlessness, wheeze, chest illness and dyspnoea) in subjects exposed to secondhand smoke at home and/or at work (Schwartz & Zeger, 1990; White *et al.*, 1991; Ng *et al.*, 1993; Leuenberger *et al.*, 1994; Janson *et al.*, 2001).

(iii) *Lung function testing*

A number of studies have been published that have examined the effects of secondhand tobacco smoke on pulmonary function in adults. These investigations were often initiated within the framework of research projects not primarily concerned with secondhand tobacco smoke; as a result, certain limitations apply regarding the validity of some of the findings, because of the low sensitivity and low power of these studies.

Acute exposure

Many studies have shown that exposure of nonsmoking adults to secondhand tobacco smoke is associated with a decrease in maximum expiratory flow at 25% (MEF25), FVC, FEV_1 and FEF25–75 and a decrease in dynamic lung volume (Pimm *et al.*, 1978; Shephard *et al.*, 1979a,b,c; Bascom *et al.*, 1991; Smith *et al.*, 2001).

Chronic exposure

A number of studies failed to detect any association between exposure to secondhand tobacco smoke and ventilatory parameters of lung function (Schilling *et al*., 1977; Comstock *et al.*, 1981; Jones *et al.*, 1983; Lebowitz, 1984a,b; Kentner *et al.*, 1984; Laurent *et al.*, 1992; Jaakkola *et al.*, 1995; Frette *et al.*, 1996).

Other investigators have reported an association between exposure to secondhand tobacco smoke and pulmonary function determined using different test parameters. In numerous studies, FEV_1 and/or FVC were reported to be significantly decreased (Brunekreef *et al.*, 1985; Svendsen *et al.*, 1987; Hole *et al.*, 1989; Kauffmann *et al.*, 1989; Masjedi *et al.*, 1990; Xu & Li, 1995; Carey *et al.*, 1999; Chen *et al.*, 2001). Other studies reported a significant decrease in the ventilatory parameters FEF25–75, PEF or FEF75–85 (Kauffmann & Perdrizet, 1981; Kauffmann *et al.*, 1983; Salem *et al.*, 1984; Masi *et al.*,

1988; White & Froeb, 1980; Masjedi *et al.*, 1990; Lebowitz *et al.*, 1992). Decreases in MEF50 and/or MEF75 were reported to occur only in nonsmoking men exposed at home (Masi *et al.*, 1988) or nonsmoking women exposed at home (Brunekreef *et al.*, 1985).

(iv) *Chronic obstructive pulmonary disease*

Few studies have examined the possible association between exposure to secondhand tobacco smoke and development of chronic obstructive pulmonary disease (COPD). With the exception of two studies that reported a negative association (Hirayama, 1981; Lee *et al.*, 1986), most of them found an increased risk for COPD including emphysema and bronchitis, airways obstructive disease (AOD) and obstructive respiratory disease associated with exposure to secondhand smoke (Euler *et al.*, 1987; Kalandidi *et al.*, 1987; Sandler *et al.*, 1989; Kalandidi *et al.*, 1990; Robbins *et al.*, 1993; Dayal *et al.*, 1994).

(v) *Asthma*

Many patients regard secondhand tobacco smoke as a major factor in the exacerbation of asthma (Cockcroft, 1988).

Symptoms and lung function. Many studies have shown that patients with allergies and/or asthma experienced more nasal symptoms, headache, cough, wheezing, sore throat, hoarseness (Speer, 1968), eye irritation (Weber & Fisher, 1980), aggravation of the asthma (Dales *et al.*, 1992) and restrictions in activity (Ostro *et al.*, 1994) in response to secondhand smoke. Other studies have reported a statistically significant association between the new onset of asthma, asthma ever diagnosed by a physician or current asthma and exposure to secondhand tobacco smoke at the workplace (Greer *et al.*, 1993), in the home environment and among young adults exposed to parental smoking (Hu *et al.*, 1997; Thorn *et al.*, 2001).

Two studies have found no statistically significant change in dynamic lung volume of asthmatic subjects exposed for 1 or 2 h to tobacco smoke (Shephard *et al.*, 1979b; Wiedeman *et al.*, 1986), whereas other studies have reported a statistically significant decrease in FEV_1, FVC and FEF25–75 in asthmatic subjects exposed to smoke in a chamber study (Dahms *et al.*, 1981), to secondhand tobacco smoke from the spouse and/or other close contacts (Jindal *et al.*, 1994) or in the workplace, particularly in asthmatic women (Künzli *et al.*, 2000).

Chamber studies. Chamber studies have been used to investigate potential relationships between controlled exposure to secondhand smoke and lung function and airway reactivity in asthmatic subjects. The principal advantage of this methodology over epidemiological studies is that the exposure to secondhand tobacco smoke can, in theory, be measured precisely.

Most of the studies of exposure to secondhand tobacco smoke in inhalation chambers reported slight-to-moderate transient effects on lung function in at least some of the study subjects. In several studies, some participants experienced decreases in lung function of more than 20% and a marked increase in bronchial reactivity to inhaled histamine or methacholine. These changes in lung function are considered clinically significant, parti-

cularly when they occur in conjunction with lower respiratory symptoms such as chest tightness, dyspnoea and cough (Dahms *et al.*, 1981; Knight & Breslin, 1985; Stankus *et al.*, 1988; Menon *et al.*, 1991, 1992; Nowak *et al.*, 1997). However, these results were not confirmed by Magnussen and colleagues (Jörres & Magnussen, 1992; Magnussen *et al.*, 1992) who exposed adults with mild and moderate asthma to secondhand tobacco smoke for a short period (1 h) and then conducted a bronchoprovocation test with methacholine.

Suggestion can induce an attack of asthma (Spector *et al.*, 1976). Most of the above-mentioned studies were unable to exclude the possibility that the changes reported in asthmatic subjects were emotionally related to cigarette smoke which might result in psychological suggestion being the cause of the observed symptoms, such as changes in lung function and others (Witorsch, 1992). Urch *et al.* (1988) argued that, if physiological responses were dominant, changes in pulmonary function should show a dose–response relationship to secondhand tobacco smoke, whereas, if psychological reactions were dominant, correlations between functional changes and specific measures of suggestibility would be expected. Sixteen nonsmoking asthmatic subjects were exposed to high or low concentrations of secondhand tobacco smoke or to ambient air for 65 min. Cigarette smoke was generated by a machine located outside the exposure chamber, but visible to the subjects; during sham-exposure, the smoke from the cigarettes was diverted from the study chamber. Subjects with asthma showed significant dose–response relationships for MEF50 at 5 min, and for FVC and FEV_1 at 30 min of exposure; these results support a physiological rather than psychological explanation of the findings. In the study by Danuser *et al.* (1993), the subjects wore noseclips and were exposed to secondhand tobacco smoke administered by a mouthpiece, thus blinding them to the differences in the concentrations of secondhand tobacco smoke delivered. In these conditions subjective airway symptoms were weak, but most of the symptomatic responses of the subjects with airway hyperresponsiveness appeared to be dose-related.

4.2.2 *Experimental systems*

Studies in which experimental animals were exposed to sidestream smoke alone or to simulated environmental tobacco smoke were reviewed, and the results of studies on adult animals are summarized in Tables 4.7 and 4.8 (see also Witschi *et al.*, 1997c) (see Section 3.1 for definitions).

(*a*) *Exposure of adult animals*

(i) *Effects on the respiratory tract*

Rats and hamsters were exposed to sidestream smoke (4 mg/m^3 TPM; 25–30 ppm CO) for 10 h/day, 5 days/week for 90 days. Hyperplasia and metaplasia in the epithelium of the dorsal nasal turbinates were the only changes seen in the rats. The changes partially receded after 30 days and had completely reversed 60 days after exposure. No signs of toxicity were observed in the hamster respiratory tract (Von Meyerinck *et al.*, 1989).

Table 4.7. Toxicity of sidestream or simulated environmental tobacco smoke on respiratory tract in adult animals

Species	Strain/sex	Exposure concentration (mg/m^3 TPM)	Exposure duration; conditions	Effects	Reference
Rat	F344/CrlBr/M+F	4	90 days; 10 h/d; 5 d/wk	Hyperplasia/metaplasia of the dorsal nasal epithelium	von Meyerinck *et al.* (1989)
Hamster	Syrian golden/M+F			No effect	
Rat	SD/M+F	0.1; 1; 10	14 d; 6 h/d	Slight-to-mild hyperplasia and inflammation in rostral nasal cavity at high dose only	Coggins *et al.* (1992)
Rat	SD/M	0.1; 1; 10	4 d; 28 d; 90 d; 6 h/d; 5 d/wk	Slight-to-mild hyperplasia and inflammation in rostral nasal cavity at high dose only	Coggins *et al.* (1993)
Rat	SD/F	1	3 h; 4 d	No effect	Joad *et al.* (1993)
Mouse	A/J/M	1	3 d; 5 d; 6 h/day	Increased cell proliferation in airways	Rajini & Witschi (1994)
Mouse	C57BL/6/M		5 d	No effect	
Hamster	Syrian golden/M	1	1 wk; 6 h/d; 7 d/wk	Increased cell proliferation in respiratory epithelium of nasal septum; increase after 1-week recovery period in terminal bronchioles	Witschi & Rajini (1994)
Rat	Wistar/M+F	35 ppm CO	3 mths; 90 min/d; 5 d/wk	Emphysema in lungs	Escolar *et al.* (1995)
Mouse	A/J/M	83.5	20 wks; 6 h/d; 5 d/wk	Increased cell proliferation in airways during the first 2 wks. No changes in lung parameters (volume and cell number)	Witschi *et al.* (1997a)

TPM, total particulate matter; M, male; F, female; h, hour; d, day; wk, week; mths, months; SD, Sprague-Dawley

Table 4.8. Toxicity of sidestream or simulated environmental tobacco smoke on cardiovascular system in adult animals

Species	Strain/sex	Exposure concentration (mg/m^3 TPM)	Exposure duration; conditions	Effects	Reference
Cockerel	–	8	16 wks; 6 h/d; 5 d/wk	Increase in size of arteriosclerotic plaques, but not in number or distribution	Penn & Snyder (1993)
Rabbit	New Zealand/M	4 or 33	10 wks; 6 h/d; 5 d/wk	Dose-dependent increase in formation of arteriosclerotic plaques in cholesterol-fed animals	Zhu *et al.* (1993)
Cockerel	–	2.5	16 wks; 6 h/d; 5 d/wk	Increase in size of arteriosclerotic plaques, but not in number or distribution	Penn *et al.* (1994)
Rat	SD/not given	60	3 d; 3 wks; 6 wks; 6 h/d; 7 d/wk	Time-dependent increase in infarct size	Zhu *et al.* (1994)
Mouse	Apolipoprotein $E^{-/-}$/F	25	7, 10, 14 wks; 6 h/d; 5 d/wk	Increased percentage of atherosclerotic lesions in aortic intimal surface	Gairola *et al.* (2001)
Rabbit	New Zealand White/M	24	10 wk; 6 h/d; 5 d/wk	Increased percentage of surface lipid lesions in aorta and pulmonary artery	Sun *et al.* (2001)

TPM, total particulate matter; h, hour; d, day; wk, week; M, male; F, female; SD, Sprague-Dawley

Rats were exposed, nose-only, for 6 h/day for 4, 14, 28 or 90 days to sidestream smoke at concentrations of 0.1, 1 or 10 mg/m^3 TPM. The only pathological response observed was slight to mild epithelial hyperplasia and chronic active inflammation in the most rostral part of the nasal cavity, in the group exposed to the high dose (10 mg/m^3 TPM). No time-dependent increase in the severity of the lesions was observed. After a 14-day recovery period, the changes had completely reversed (Coggins *et al*., 1992, 1993).

Male A/J and C57BL/6 mice were exposed for 6 h/day for up to 5 days to aged and diluted sidestream smoke (1 mg/m^3 TPM; 5.9 ppm CO; 549 μg/m^3 nicotine). Labelling indices in the epithelium of the large intrapulmonary airways and terminal bronchioles, but not in the alveoli, were significantly increased after 3 and 5 days of exposure in A/J mice. No signs of increased cell proliferation in the respiratory tract were seen in C57BL/6 mice (Rajini & Witschi, 1994).

Hamsters were exposed to aged and diluted sidestream smoke containing 1 mg/m^3 TPM for 6 h/day for 1–3 weeks, after which some subgroups were allowed a 1-week recovery period. Increased cell proliferation was observed in the respiratory epithelium of nasal septum after 1 week of exposure, but not at later time points. After 1 week of exposure and 1 week of recovery, cell proliferation in the terminal bronchioles was significantly increased when compared to concomitant controls and to the levels observed before recovery (Witschi & Rajini, 1994).

A similar initial increase in cell proliferation was seen in alveoli and terminal bronchioles in male A/J mice during the first 2 weeks of exposure to simulated environmental tobacco smoke (83.5 mg/m^3 TPM; 233 ppm CO; 18.9 mg/m^3 nicotine) (Witschi *et al.*, 1997a).

Wistar rats were exposed for 90 min/day, 5 days/week, for 3 months to sidestream smoke containing 35 ppm CO. Emphysematous changes (decreased number of distal airspaces and increase in alveolar chord) were observed in the lungs. These changes were accompanied by decreases in tissue density, internal alveolar perimeter, wall thickness and density and perimeter of elastic fibres (Escolar *et al.*, 1995).

Exposure of female rats to sidestream smoke (1 mg/m^3 TPM; 6.5 ppm CO) either on 1 day for 3 h or for 6 h/day on 4 days had no effect on dynamic compliance, lung resistance, lung weight/body weight, pulmonary artery pressure, or airway reactivity to methacholine (all $p > 0.4$) (Joad *et al.*, 1993).

(ii) *Cardiovascular effects*

Cardiovascular changes resulting from exposure to sidestream smoke have been demonstrated in several animal models.

Male New Zealand rabbits, fed a cholesterol-rich diet, were exposed to low-dose or high-dose sidestream smoke (4 and 33 mg/m^3 TPM, respectively) for 6 h/day, 5 days/week for 10 weeks. A dose-dependent significant increase in the size of arteriosclerotic plaques was found in the aorta and the pulmonary artery when compared with control rabbits receiving the same diet but exposed to clean air (Zhu *et al*., 1993).

Sprague-Dawley rats were exposed to sidestream smoke (60 mg/m^3 TPM; 92 ppm CO; 1103 µg/m^3 nicotine) 6 h/day, 5 days/week for 3 days, 3 weeks or 6 weeks. Infarct sizes increased in a time-dependent manner ($p = 0.023$) (Zhu *et al.*, 1994).

Exposure of 6-week old cockerels for 6 h/day, 5 days/week to sidestream smoke containing 8 mg/m^3 TPM (Penn & Snyder, 1993) or 2.5 mg/m^3 TPM (Penn *et al.*, 1994) resulted in a significant increase in the size of arteriosclerotic plaques in the aorta.

Roberts *et al.* (1996) developed a model to measure the rate of accumulation of low-density lipoproteins (LDL) in rat carotid arteries. First, rats were exposed to simulated environmental tobacco smoke for 4 h (3.3 mg/m^3 TPM; 18 ppm CO; 615 µg/m^3 nicotine) to obtain simulated tobacco smoke-plasma). Second, carotid arteries from unexposed rats were perfused with control plasma containing fluorescently labelled LDL and subsequently with tobacco smoke-plasma containing fluorescently labelled LDL. Photometric measurements were made during perfusion with labelled LDL. Perfusion with tobacco smoke-plasma increased the rate of LDL accumulation measured as fluorescence intensity (6.9 ± 1.8 mV/min (mean ± SEM)) when compared with control animals (1.6 ± 0.40 mV/min, $p < 0.01$). The maximal increase was observed after 40–60 min perfusion. LDL accumulation was primarily dependent on the interaction of tobacco smoke-plasma with LDL, which occurred before perfusion, rather than interaction with the artery wall. It was also noted that LDL accumulation resulted from its increased binding to artery wall rather than an increase in its permeability. Perfusion with tobacco smoke-plasma increased the lumen volume measured as fluorescence intensity (43.3 ± 5.1 mV versus 35.1 ± 4.4 mV; $p < 0.05$) in treated and untreated animals, respectively.

Rabbits receiving a 0.5% cholesterol diet and exposed for 6 h/day, 5 days/week for 10 weeks, to sidestream smoke (24 mg/m^3 TPM; 45 ppm CO) were compared with control animals. There was no difference in serum lipids between cholesterol fed and control animals. Exposure to sidestream smoke significantly increased the percentage of surface lipid lesions in the aorta (54 ± 5% versus 39 ± 4%; $p = 0.049$) and in the pulmonary artery (66 ± 4% versus 43 ± 3%; $p < 0.001$). Exposure to nicotine-free cigarettes (35 mg/m^3 TPM; 53 ppm CO) had the same effects as standard cigarettes. Vascular tension was measured in intact aortic rings. Endothelium-dependent and endothelium-independent relaxation were measured with acetylcholine and the calcium ionophore A23187, and nitroglycerin, respectively. There were no significant differences with any treatment between exposed and control animals (Sun *et al*., 2001).

Female ApoE-deficient mice, which are used as a mouse model of human atherosclerosis, were exposed to sidestream smoke (25 mg/m^3 TPM) 6 h/day, 5 days/week for 7, 10 and 14 weeks. There were no consistent differences in serum concentrations of cholesterol between control mice and those exposed to sidestream smoke. In exposed mice, atherosclerotic lesions in the aorta covered a larger part of the intimal area at all time points than in non-exposed mice. Also the total affected area increased at a higher rate than in controls. The increase was most evident in the thoracic region. Lesions appeared thicker, as reflected by increased amounts of esterified and unesterified cholesterol in the aortic tissues of mice exposed to sidestream smoke (Gairola *et al*., 2001).

(iii) *Immunological effects*

BALB/c mice, sensitized with aluminium hydroxide-precipitated ovalbumin (OVA/AL) antigen, were exposed for 6 h/day, 5 days/week to simulated environmental tobacco smoke (1 mg/m^3 TPM; 6.1 ppm CO; 269 µg/m^3 nicotine), from days 15 to 58 after sensitization. Sensitized mice, with or without smoke exposure, had elevated levels of IgE. Exposure to simulated environmental tobacco smoke enhanced and prolonged the IgE response in sensitized mice, and the levels were significantly increased at all time points at which measurements were made (day 19 to day 58); the concentrations of OVA-specific IgG1 were elevated in the smoke-exposed group from days 34 to 54. For both IgE and IgG1 the increase was strongest at 54 days. The numbers of eosinophils were increased in the blood and lungs of smoke-exposed, pre-sensitized mice. The total number of bronchoalveolar lavage cells was increased ($p = 0.016$); about 90% of the increase was due to alveolar macrophages. The concentrations of cytokines IL-4 and IL-10 were significantly higher in the smoke-exposed group than in the control animals. The demonstration of an exaggerated inflammatory response in sensitized mice may have relevance to the early events in carcinogenesis where an inflammatory response often precedes mild hyperplasia (Seymour *et al*., 1997).

(iv) *Effects on gastric ulceration*

A smoke chamber was designed to investigate the effects of exposure to secondhand smoke on gastric ulceration. Different concentrations of cigarette smoke (0%, 1%, 2% and 4%) were perfused during one hour into a chamber in which male Sprague-Dawley rats were placed. This exposure potentiated ethanol (70% v/v, oral administration)-induced gastric mucosal damage and increased serum nicotine concentrations, but did not affect the pH, pCO_2 or pO_2 and the concentration of HCO_3 in blood, or the systemic blood pressure and heart rate. Under these experimental conditions, exposure to cigarette smoke produced no significant changes in the blood acid/base balance or stress in the animals, but significantly potentiated ethanol-induced gastric mucosal damage. This experimental model is suitable for studying adverse interactions between passive smoking and alcohol drinking in gastric ulcer formation in rats (Chow *et al*., 1996).

(*b*) *Effects of perinatal exposure*

(i) *Effects on lung development and lung function*

Exposure of Sprague-Dawley rats to aged and diluted sidestream smoke from birth (1 mg/m^3 TPM; 6 h/day, 5 days/week) significantly reduced the labelling index of epithelial cells in distal airways at 7 and 14 days of age, but not at later times or in proximal bronchi (Ji *et al.*, 1994).

Gestating Sprague-Dawley rats were exposed to aged and diluted sidestream smoke (1 mg/m^3 TPM; 4.9 ppm CO) from gestational day 5 until gestational day 14, 18 or 21. Maternal exposure to sidestream smoke significantly increased fetal expression of Clara cell secretory protein and mRNA in the terminal bronchioles at gestational day 21, but not at gestational day 14 or 18 (Ji *et al*., 1998).

A series of studies was designed to determine the effects of perinatal exposure to sidestream smoke on airway reactivity in Sprague-Dawley rats. Female rats were exposed 6 h/day, 5 days/week from day 2 of life to week 8 or week 15 of age (1 mg/m^3 TPM; 6.5 ppm CO). Exposure to sidestream smoke did not change the ratio of lung weight/body weight or the baseline values for lung resistance, dynamic compliance or pulmonary artery pressure. Airway reactivity to methacholine was also unaffected at either time-point (all $p > 0.2$). In animals exposed from day 2 of life to week 11 of age, sidestream smoke reduced airway ($p = 0.004$), but not pulmonary artery ($p = 0.63$) reactivity to serotonin (Joad *et al*., 1993). In a further study, Joad *et al*. (1999) exposed rats to aged and diluted sidestream smoke (1 mg/m^3 TPM; 6.9 ppm CO) for 4–6 h/day from gestational day 3 until 21 days of age. The airway responsiveness of one female pup from each litter was assessed at 8 weeks of age. Perinatal exposure to sidestream smoke did not affect baseline lung function, but enhanced methacholine-induced changes in lung resistance (three-fold increase; $p = 0.02$), dynamic compliance ($p = 0.004$), and pulmonary pressure ($p = 0.007$). These changes occurred in the absence of any increase in pulmonary neuroendocrine cells, neuroepithelial bodies or mast cells. In another study, rats were exposed prenatally and/or postnatally to sidestream smoke (1 mg/m^3 TPM; 4.9 ppm CO; 344 µg/m^3 nicotine) for 4 h/day, 7 days/week from gestational day 3 until 7–10 weeks of age. Pulmonary pressure was not affected by any type of exposure. Prenatal or postnatal exposure alone did not affect baseline values or metacholine-induced changes in lung responsiveness. Prenatal followed by postnatal exposure to sidestream smoke reduced dynamic lung compliance at baseline ($p = 0.0006$) and increased lung responsiveness to methacholine ($p = 0.0001$). This reaction was accompanied by an increase in the number of neuroendocrine cells and neuroepithelial bodies (Joad *et al.*, 1995a).

Male guinea-pigs were exposed 6 h/day, 5 days/week from age 8 days to age 37–48 days (1 mg/m^3 TPM; 5.6 ppm CO; 586 µg/m^3 nicotine). Exposure to sidestream smoke did not change lung morphology, collagen or elastin deposition, lung volume, surface area or mean linear intercept length of alveolar airspace. Baseline dynamic lung compliance ($p = 0.05$), but not lung resistance ($p = 0.61$) was increased by exposure to sidestream smoke (see also Section 4.2.2(*b*)(iii)) (Joad *et al.*, 1995b).

(ii) *Cardiovascular effects*

Sprague-Dawley rats were exposed to filtered air or sidestream smoke (33 mg/m^3 TPM; 60 ppm CO) for 6 h/day, 5 days/week, for 3 weeks before birth and/or for 12 weeks in the neonatal to adolescent period. Exposure to sidestream smoke postnatally increased endothelin-1 levels in plasma ($p = 0.001$) independently of in-utero exposure. Infarct size (infarct mass/risk area × 100) was greater in all animals exposed postnatally than in unexposed controls ($p = 0.005$), and was greater in males than in females ($p < 0.001$) (Zhu *et al*., 1997).

In rats exposed under the same conditions, aortic rings were excised and isometric force responses to phenylephrine, acetylcholine, the calcium ionophore A23187 and nitroglycerin were studied in organ baths. In-utero exposure to sidestream smoke increased the

sensitivity of aortic rings to phenylephrine ($p < 0.0005$) and reduced the half-maximal contraction (EC_{50}; $p = 0.04$). It reduced the maximal endothelium-dependent relaxation response to acetylcholine ($p = 0.04$) and increased its half-maximal contraction value ($p = 0.05$). Finally, in-utero exposure decreased the sensitivity to the endothelium-independent vasodilator nitroglycerin ($p = 0.003$). The sensitivity of aortic rings to phenylephrine was reduced after neonatal exposure ($p = 0.01$) (Hutchison *et al*., 1998).

(iii) *Neurological effects*

Female Sprague-Dawley rats were exposed to filtered air or sidestream smoke for 4 h/day, 7 days/week from day 3 of gestation until birth and/or for 9 weeks postnatally (1 mg/m^3 TPM; 4.9 ppm CO; 344 μg/m^3 nicotine). Postnatal exposure to sidestream smoke increased the mortality of the pups during the first 18 days of life ($p < 0.001$) and significantly reduced body weights at 9 weeks of age ($p = 0.016$). In-utero exposure had no effect on DNA, protein, or cholesterol concentration or on the weight of forebrain or hindbrain. Postnatal exposure reduced DNA concentration in the hindbrain, an indicator of cellular density, by 4.4% ($p < 0.001$) and increased the hindbrain protein/DNA ratio, an index of cell size, by 8.4% ($p = 0.001$). The weight of the hindbrain was not affected by exposure to sidestream smoke (Gospe *et al*., 1996).

Rhesus monkeys were exposed to aged and diluted sidestream smoke (1 mg/m^3 TPM; 5.3 ppm CO; 190 μg/m^3 nicotine) from gestational day 100 until 70–80 days after birth. Expression of beta-adrenergic and m2-muscarinic cholinergic receptors in heart and lungs of the offspring were not changed by exposure to smoke. Whereas there were no changes in the heart, a strong induction of adenylyl cyclase was observed in the lungs (Slotkin *et al*., 2000).

To mimic fetal and childhood exposure to secondhand smoke, gestating Sprague-Dawley rats were exposed to mainstream smoke (29 mg/m^3 TPM; 94 ppm CO; 4600 μg/m^3 nicotine) for 6 h/day, 7 days/week from gestational days 5 to 20. One to two days after delivery, dams and pups were exposed to sidestream smoke (1 mg/m^3 TPM; 5.6 ppm CO; 117 μg/m^3 nicotine) until postnatal day 21. Animals were exposed either prenatally, postnatally, or both. Prenatal and/or postnatal exposure significantly increased total adenylyl cyclase activity in brain and heart when monitored with the direct enzymatic stimulant forskolin (see Section 4.1.2(*a*)(iii) for details). In the brain, the specific coupling of beta-adrenergic receptors to adenylyl cyclase was inhibited in all exposed animals, despite normal expression of beta-receptors. In the heart, a decrease in m2-receptor expression was observed after postnatal or continuous exposure, but no inhibition of beta-adrenergic receptors was seen. In both tissues, and for all parameters, the effects of combined prenatal and postnatal exposure were equivalent to those seen in response to postnatal exposure alone (Slotkin *et al*., 2001).

In a series of studies, guinea-pigs were exposed to sidestream smoke (1 mg/m^3 TPM; 6.2 ppm CO; 224 μg/m^3 nicotine) for 6 h/day, 5 days/week from age 1 to 6 weeks (age equivalent of human childhood). Sidestream smoke reduced capsaicin-induced changes in lung resistance ($p = 0.02$) and lung dynamic compliance ($p = 0.04$), indicating a down-

regulation of the lung C-fibre reflex response (Joad *et al.*, 1995b). Primary bronchopulmonary C-fibres were tested for their responsiveness to chemical and mechanical stimuli. Exposure to sidestream smoke had no effect on baseline activity of C-fibres but augmented the responsiveness to left atrial injection of capsaicin ($p = 0.047$) and to lung hyperinflation ($p = 0.03$) (Mutoh *et al.*, 1999). A study on the impulse activity of bronchopulmonary C-fibre-activated nucleus tractus solitarii neurons showed that exposure to sidestream smoke significantly augmented the peak ($p = 0.02$) and duration ($p = 0.01$) of the neuronal response to C-fibre activation, and prolonged the expiratory time (apnoea) ($p = 0.003$), at the higher dose of capsaicin (2.0 µg/kg). Exposure to sidestream smoke did not alter baseline values or capsaicin-induced changes in tracheal pressure, arterial blood pressure or heart rate (Mutoh *et al*., 2000). A recent study presented data to suggest that actions of the neuropeptide substance P in the nucleus tractus solitarius may contribute to these effects (Bonham *et al.*, 2001).

In summary, exposure of experimental animals to sidestream smoke can produce changes that are similar to those observed in response to exposure of humans to secondhand tobacco smoke, such as inflammatory changes in the airways and accelerated formation of arteriosclerotic plaques. The results obtained from studies of perinatal exposure may provide a potential mechanism to explain the association between exposure to secondhand smoke and sudden infant death syndrome.

4.3 Reproductive, developmental and hormonal effects

4.3.1 *Humans*

(*a*) *Reproductive effects*

There are inherent ambiguities in the interpretation of data on reproductive effects: if involuntary smoking in women is defined in terms of household exposure to secondhand smoke, reproductive effects could be due either to the exposure to secondhand smoke of the female or to a direct effect of active smoking on the fertility of the male partner. In most of the published studies, the effects of secondhand smoke have been estimated on the basis of paternal smoking. A possible direct effect of smoking on the father's sperm cannot be ruled out when the father has been the source of exposure to secondhand smoke (Lindbohm *et al.*, 2002).

(i) *Fertility and fecundability*

The available data regarding the effects of passive smoking by women on fertility and fecundity are conflicting (US DHHS, 2001): some studies have reported an increased risk of delayed conception (Hull *et al*., 2000), whereas others have found no association (US DHHS, 2001). The results of investigations of the association between passive smoking during the prenatal period or childhood and later fertility have also been inconsistent: in some studies such exposure has been associated with reduced fecundability (in the case of prenatal exposure) or an *increased* fecundability (in the case of childhood exposure),

whereas others have reported no association (Weinberg *et al.*, 1989; Wilcox *et al.*, 1989; Jensen *et al.*, 1998; US DHHS, 2001; Lindbohm *et al.*, 2002). These investigations are particularly hampered by potential exposure measurement error, confounding factors and other biases.

(ii) *Pregnancy outcomes*

The data regarding the association between maternal exposure to secondhand smoke and preterm birth are not entirely consistent, but in aggregate they suggest a modestly increased risk associated with high exposure (Lindbohm *et al*., 2002).

(iii) *Birth outcomes*

The adverse effect of cigarette smoking on birth weight is well-established; on average, women who smoke cigarettes deliver term infants that weigh about 150–250 g less than those of nonsmokers (Andres & Day, 2000; US DHHS, 2001). When expressed as relative risks, mothers who smoke have more than a doubled risk for having low-birth-weight babies (US DHHS, 2001). There is a similar association between maternal smoking and delivery of small-for-gestational-age infants (US DHHS, 2001). The association is characterized by a dose–response relationship that persists after adjustment for possible confounding factors, and seems to be more pronounced for older mothers (US DHHS, 2001).

Numerous studies have also investigated the association between fetal growth and maternal passive smoking (US DHHS, 2001). On average the birth weight of infants born to nonsmoking mothers exposed to secondhand smoke after adjustment for important potential confounders seems to be about 25–50 g lower than that of babies born to mothers who were not exposed (California EPA, 1997; Windham *et al.*, 1999a; US DHHS, 2001; Lindbohm *et al.*, 2002). However, some studies have not found such an adverse effect (Sadler *et al*., 1999; US DHHS, 2001).

There has been little investigation of the association between maternal exposure to secondhand smoke and spontaneous abortion or stillbirth. The available data are inconsistent, although some studies have shown effects as large as those seen in investigations of the effects of active smoking (Windham *et al*., 1999b; US DHHS, 2001; Lindbohm *et al*., 2002).

The association between maternal smoking during pregnancy and the risk of birth defects has been extensively investigated (US DHHS, 2001). When the focus is on major defects as a single end-point, generally no association has been found. When separate classes of malformations are considered individually, there are indications that maternal smoking during pregnancy is associated with oral clefts, limb reductions, and perhaps malformations of the urinary tract (US DHHS, 2001).

(*b*) *Body weight*

In contrast to the extensive and consistent literature describing the effects of active smoking on body weight, findings on the effects of passive smoking on weight are sparse.

The available data suggest that women exposed to secondhand smoke weigh more than women who are not exposed. However, this association may be confounded by a more sedentary and less healthy lifestyle being adopted by nonsmokers exposed to secondhand smoke (Cress *et al.*, 1994; Thornton *et al.*, 1994; Bernstein, 1996).

(*c*) *Hormones*

No data regarding involuntary exposure to tobacco smoke and levels of estrogens, androgens or vitamin D were available to the Working Group. In one study cord blood from mothers who smoke seemed to contain higher concentrations of insulin-like growth factor 1 (IGF-1) than specimens obtained from nonsmoking mothers (Beratis *et al.*, 1994). In other studies, a decreased concentration of IGF-1 in cord blood has been reported (Heinz-Erian *et al.*, 1998; Coutant *et al.*, 2001).

(*d*) *Menopause*

Three studies addressed the association between exposure to secondhand smoke and age at menopause. One study reported that passive smoking was associated with an advancement in the age at menopause similar to that reported for active smoking, but the study population was small (Everson *et al*., 1986). More recent investigations reported no association between exposure to secondhand smoke at home and age at menopause (Cramer *et al*., 1995; Cooper *et al*., 1999).

4.3.2 *Experimental systems*

A few studies have reported the effects of exposure of gestating female animals to sidestream smoke on embryo implantations, size of litters, mortality rate or body weight of pups in the first weeks of life.

Female hamsters were exposed to the smoke of 1, 2 or 3 cigarettes, twice a day, 7 days/week, from 14 days before mating until the third day of pregnancy. Transport of pre-implantation embryos through the hamster oviduct was retarded in exposed females at all three doses. In a study of exposure to a single dose of smoke, the rate of oviductal muscle contraction decreased significantly within 15 min of exposure and failed to return to baseline rates during a 25-min recovery period. Both pre-implantation embryo transport and muscle contraction were more sensitive to sidestream smoke than to mainstream smoke (see monograph on tobacco smoke, Section 4.3) (DiCarlantonio & Talbot, 1999).

Rats were exposed for 2 h/day, from days 1 to 20 of gestation, to the smoke of 10 king-size cigarettes/2 h [exposure concentrations not reported]. Exposure to smoke significantly reduced food consumption of gestating dams. The average fetal weight ($n = 8$) in the animals exposed to sidestream smoke was reduced to 91% of the pair-fed control values ($p < 0.05$). Litter size and proportion of resorptions were not significantly affected. Combination of smoke with alcohol had a synergistic effect that led to significantly smaller litter size and fetal weight than in pair-fed animals [no comparison was made with smoke exposure alone] (Leichter, 1989). In another study, gestating Sprague-Dawley rats

were exposed to aged and diluted sidestream smoke (1 mg/m^3 TPM; 5.5 ppm CO; 405 µg/m^3 nicotine) for 6 h/day on days 3, 6–10 and 13–17 of pregnancy and killed on day 20. Maternal body weight gain, average daily food consumption and the number of fetuses and of implantation sites per litter were comparable between smoke-exposed and pair-fed controls. However, there was a small, but significant reduction in mean pup weight ($p < 0.05$). This was not accompanied by any significant decrease in fetal ossification, an index of gestational age (Rajini *et al*., 1994). In a similar study, animals were exposed for 6 h/day to aged and diluted sidestream smoke (1 mg/m^3 TPM) from day 3 to day 11 of gestation. Average pup weight per litter was not affected by exposure to smoke, but the average number of implantations and of live pups per litter were significantly lower ($p < 0.05$) in the smoke-exposed animals (Witschi *et al.*, 1994).

Gestating rats were exposed for 3 weeks before delivery to sidestream smoke, 4 cigarettes/15 min, 6 h/day, 5 days/week. Mortality at birth was higher in the exposed animals than in controls (11.9% versus 2.8%; $p < 0.001$), and body weights at 3 and 4 weeks of age were lower than those of controls ($p < 0.001$) (Zhu *et al.*, 1997). In a later study under the same conditions, mortality at birth was also greater in rats exposed *in utero* than in those not exposed (12% versus 3%, $p < 0.001$), but in-utero exposure did not reduce body weight at 4 weeks (Hutchison *et al.*, 1998). Other studies found that exposure of rats to aged and diluted sidestream smoke (1 mg/m^3 TPM) *in utero* did not affect fetal body weight at any gestational age (Ji *et al.*, 1998) or at birth (Joad *et al.*, 1999).

4.4 Genetic and related effects

4.4.1 *Humans*

(*a*) *Mutagenicity, sister chromatid exchange and* HPRT *mutations*

(i) *Urinary mutagenicity*

Mutagenicity of urine from smokers has been detected by use of the *Salmonella* (Ames) mutagenicity test in a large number of studies ever since the first report by Yamasaki and Ames (1977). Urinary mutagenicity correlates significantly with the number of cigarettes smoked daily and with urinary nicotine and/or cotinine concentrations (e.g. Bartsch *et al*., 1990; Vermeulen *et al*., 2000).

Urine voided by nonsmokers exposed to secondhand tobacco smoke or to diluted sidestream smoke also shows bacterial mutagenicity (Bos *et al.*, 1983; Sorsa *et al*., 1985; IARC, 1986; Kado *et al*., 1987; Bartsch *et al*., 1990; Smith, C.J. *et al*., 2000; Vermeulen *et al*., 2000). This is in accordance with the mutagenicity of sidestream smoke and samples of airborne particulate matter or the vapour-phase of the air collected from environments contaminated with secondhand tobacco smoke (see Section 4.4.2). However, the increase in urinary mutagenicity was small in many of the studies (Sorsa *et al*., 1985; Husgafvel-Pursiainen *et al*., 1987; Kado *et al*., 1987; US Environmental Protection Agency, 1992; Smith C.J. *et al*., 2000), and no increase in mutagenicity was found in the urine of volunteers (nonsmokers) after 8 h of exposure to the gaseous phase of second-

hand tobacco smoke or to whole secondhand tobacco smoke under experimental conditions (Scherer *et al*., 1990). The small increases in urinary mutagenicity that have been detected are subject to confounding from dietary, occupational and environmental exposures. Such confounding factors affect the sensitivity and specificity of the assay for secondhand tobacco smoke exposure in the same manner as they do in smokers (Sasson *et al*., 1985; Malaveille *et al*., 1989; US Environmental Protection Agency, 1992; Scherer *et al*., 1996; Vermeulen *et al*., 2000).

Increased urinary mutagenicity was clearly associated with exposure to secondhand tobacco smoke in two studies that used urinary cotinine concentrations to indicate exposure to tobacco smoke in smokers and nonsmokers (Bartsch *et al*., 1990; Vermeulen *et al*., 2000). Bartsch *et al.* (1990) found urinary mutagenicity to be a specific indicator of exposure to secondhand tobacco smoke. In the study by Vermeulen *et al.* (2000), an increase in urinary mutagenicity was found to follow an increase in urinary cotinine in a manner similar to that seen in smokers. In fact, cotinine-adjusted urinary mutagenicity levels showed an almost identical increase for both nonsmokers exposed to secondhand smoke and smokers (Vermeulen *et al*., 2000).

(ii) *Sister chromatid exchange*

Significantly higher levels of sister chromatid exchange, chromosomal aberrations and micronuclei have been found in cultured peripheral lymphocytes of smokers than in nonsmokers (IARC, 1986). However, studies on nonsmokers exposed to secondhand tobacco smoke in experimental or field conditions, where cotinine measurements were used as indicators of exposure and uptake, have shown predominantly negative results for sister chromatid exchange in cultured lymphocytes of peripheral blood (Sorsa *et al*., 1985; Collman *et al*., 1986; Husgafvel-Pursiainen, 1987; Husgafvel-Pursiainen *et al*., 1987). A study of 106 adult nonsmokers who were divided into two groups according to whether they experienced high or low levels of exposure to secondhand tobacco smoke as determined from plasma cotinine levels, found no difference in sister chromatid exchange frequencies between the two groups (Gorgels *et al*., 1992). More recently, sister chromatid exchange was investigated in 109 preschool children, aged 1–6 years, whose mothers or other persons living in the same household smoked. Exposure to secondhand tobacco smoke at home, based on interview data and plasma cotinine measurements, was found to be associated with an almost significant increase in sister chromatid exchange ($p = 0.076$) when compared with the level measured in children living in nonsmoking households. The increase paralleled statistically significant increases ($p < 0.05$) in 4-ABP-haemoglobin and PAH-albumin adducts in the children exposed to secondhand smoke (Tang *et al*., 1999).

The frequencies of sister chromatid exchange in cord blood lymphocytes from mothers who smoked or who were exposed to secondhand tobacco smoke were not elevated when compared with those in non-exposed mothers (Sorsa & Husgafvel-Pursiainen, 1988). Chromosomal aberrations were not increased in nonsmoking waitresses and

waiters exposed to secondhand tobacco smoke who had increased cotinine levels (Sorsa *et al*., 1989).

In summary, studies on sister chromatid exchange have found marginal effects in nonsmokers exposed to secondhand tobacco smoke. However, the lack of sensitivity of the assay for exposure to low doses of this complex mixture needs to be taken into account.

(iii) HPRT *gene mutations*

Smokers have been found to have higher frequencies of *HPRT* mutant lymphocytes than nonsmokers in most of the populations studied (Ammenheuser *et al*., 1997; Curry *et al*., 1999; see monograph on tobacco smoke). A set of studies has been conducted on *HPRT* mutations in the newborns of mothers who were exposed or not exposed to secondhand tobacco smoke. After an initial study that found no difference between *HPRT* mutant frequencies in T lymphocytes from the cord blood of infants born to mothers exposed to secondhand tobacco smoke and to non-exposed mothers (Finette *et al*., 1997), the same authors carried out another study, in which the types of *HPRT* mutations were investigated (Finette *et al*., 1998). Maternal exposure was based on self-reported smoking status, interview data on exposure to secondhand tobacco smoke at home or at work and on measured concentrations of cotinine in cord blood plasma. Analysis of 30 *HPRT* mutants from 12 infants whose mothers were classified as not exposed and 37 mutant isolates from 12 infants born to mothers who were exposed found a significant difference between the mutation spectra in these groups. The difference was attributed to *HPRT* exon 2–3 deletions, which are mutational events presumably mediated by illegitimate combinatorial rearrangement of multiple V (variable), D (diversity) and J (junctional) coding gene segments (V(D)J) recombinase activity (Finette *et al*., 1998).

In another study, cord blood T lymphocytes from 60 newborns were investigated and were found not to show an independent effect of (self-reported) maternal exposure to secondhand tobacco smoke on *HPRT* mutant frequencies. However, the exon 2–3 deletions comprised 26.3 and 28.6% of all mutants in cord blood of infants of mothers who were not exposed or were passively exposed to secondhand smoke, respectively. In infants born to mothers who smoked, this percentage was 85.7% (Bigbee *et al*., 1999).

(iv) *Other*

A study of lift workers conducted in China examined DNA damage in lymphocytes with the single-cell gel electrophoresis (comet) assay. It was found that in 255 never-smokers, the tail moment in the assay was significantly increased by any reported exposure to secondhand tobacco smoke at home or at work. Analysis of covariance showed a significant, independent effect of domestic, but not of occupational, exposure to secondhand tobacco smoke, measured by the number of smokers nearby, on the comet tail moment (Lam *et al*., 2002).

(*b*) *Mutations in* TP53*,* KRAS *and related genes*

(i) TP53 *gene mutations*

The frequency of mutations of the *TP53* gene is higher in lung tumours from smokers than in those from nonsmokers (as reviewed in Hussain & Harris, 1998; Hernandez-Boussard *et al*., 1999; see monograph on tobacco smoke) and this correlates with lifetime cigarette consumption or duration of smoking (Takeshima *et al*., 1993; Wang *et al*., 1995; Kondo *et al*., 1996; Husgafvel-Pursiainen *et al*., 1999). In addition, a significant difference has been observed between mutation spectra in smokers and nonsmokers (see monograph on tobacco smoke).

Frequencies of *TP53* mutations found in lung cancer tissues from lifetime nonsmokers vary between 10 and 35% (Huang *et al*., 1998; Marchetti *et al*., 1998; Takagi *et al*., 1998; Gealy *et al*., 1999; Husgafvel-Pursiainen *et al*., 2000; Vähäkangas *et al*., 2001). A few studies have investigated lung tumours from patients who, as determined from interview data, were lifetime nonsmokers who had experienced long-term exposure to secondhand tobacco smoke at home and compared the mutation frequencies with those recorded in lifetime nonsmokers without exposure to secondhand smoke (Husgafvel-Pursiainen *et al*., 2000; Vähäkangas *et al*., 2001). Life-long nonsmokers studied as a single group (i.e. irrespective of exposure to secondhand tobacco smoke) were found to have a significantly lower prevalence of *TP53* mutations than smokers (odds ratio, 2.9; 95% CI, 1.2–7.2; n = 91 for never-smokers) (Husgafvel-Pursiainen *et al*., 2000) or ex-smokers (odds ratio, 9.1; 95% CI, 2.1–40.0; n = 117 for never-smokers) (Vähäkangas *et al*., 2001). When the prevalence of mutations in the lifetime nonsmokers who reported exposure to secondhand tobacco smoke from spousal smoking was compared with that in cases who reported no exposure to secondhand tobacco smoke at home, mutations were more common in exposed cases who reported exposure from spousal smoking (odds ratio, 2.0; 95% CI, 0.5–8.7; based on six exposed cases with mutation and 42 exposed cases without mutation) (Husgafvel-Pursiainen *et al*., 2000). In addition, the predominant type of mutation detected in nonsmokers was GC→AT transition, but the number of mutations was too small to allow comparisons to be made between the exposure groups (Husgafvel-Pursiainen *et al*., 2000; Vähäkangas *et al*., 2001).

(ii) KRAS *mutations*

Mutations of the *KRAS* gene (codons 12, 13 or 61) occur in approximately 30% of lung adenocarcinomas obtained from smokers (Rodenhuis *et al*., 1988; Slebos *et al*., 1991; Husgafvel-Pursiainen *et al*., 1993; Westra *et al*., 1993; Gealy *et al*., 1999). Studies that have looked for *KRAS* mutations in lung tumours from nonsmokers (typically codon 12) have found low frequencies of mutation: 0% (0/35) (Marchetti *et al*., 1998), 5% (2/40) (Rodenhuis & Slebos, 1992), 7% (2/27) (Westra *et al*., 1993), 9% (2/23) (Gealy *et al*., 1999) and 11% (13/117) (Vähäkangas *et al*., 2001). Only Vähäkangas *et al.* (2001) studied *KRAS* mutations in lifetime nonsmokers exposed to secondhand tobacco smoke: of the 13 nonsmokers with a *KRAS* mutation in codon 12, seven had been exposed to secondhand smoke and six had not.

(*c*) *Polymorphisms in xenobiotic metabolizing genes*

Many studies have investigated smokers for associations between polymorphisms of genes involved in xenobiotic metabolism, proposed as markers of susceptibility, and various end-points of genotoxicity and related effects (Vineis & Malats, 1999). However, many of the data from such studies are contradictory and were frequently based on small numbers. Few studies have addressed the influence of genetic polymorphisms on nonsmokers exposed to secondhand tobacco smoke, and no firm conclusion can be drawn regarding the influence of polymorphisms on smoking-associated biomarkers.

4.4.2 *Experimental systems*

(*a*) *In-vitro studies on genotoxicity*

The genotoxicity of whole sidestream smoke or fractions of sidestream smoke or secondhand tobacco smoke has been investigated in many studies. Sidestream smoke or secondhand tobacco smoke collected from indoor environments has been shown to be mutagenic in the *Salmonella* (Ames) mutagenicity assay (Husgafvel-Pursiainen *et al*., 1986; Löfroth & Lazaridis, 1986; Ling *et al*., 1987; Claxton *et al*., 1989; Doolittle *et al*., 1990) as reviewed by Sorsa and Löfroth (1989). Condensates of mainstream smoke and cigarette smoke were mutagenic in the presence of S9 activation systems (IARC, 1986; see monograph on tobacco smoke), and some studies found that sidestream smoke or secondhand tobacco smoke also induced bacterial mutagenicity in the absence of S9 (Ling *et al*., 1987; Claxton *et al*., 1989). One study that found that secondhand tobacco smoke condensate induced mutations in the *Salmonella* assay also observed a genotoxic response in the SOS chromotest with *Escherichia coli* (Chen & Lee, 1996). Another study investigated the particulate matter of secondhand tobacco smoke collected near the breathing zone of nonsmoking individuals and detected mutagenicity that correlated with the concentrations of nicotine in air (Kado *et al*., 1991).

Several studies have shown sidestream smoke, secondhand tobacco smoke and their fractions to be potent inducers of sister chromatid exchange in Chinese hamster ovary cells in the presence and absence of metabolic activation (Husgafvel-Pursiainen *et al*., 1986; Salomaa *et al*., 1988; Doolittle *et al*., 1990). Other studies have reported smaller effects (e.g. Chen & Lee, 1996). Sidestream smoke has also been found to induce chromosomal aberrations, but not *Hprt* gene mutations, in Chinese hamster ovary cells (Doolittle *et al*., 1990).

(*b*) *In-vivo studies on genotoxicity*

Studies in rodents have indicated in-vivo genotoxicity of sidestream smoke, or of the combination of sidestream smoke and mainstream smoke, as reviewed by IARC (1986). Various studies have been conducted on the clastogenic effects of sidestream cigarette smoke in mice or rats under whole-body or nose-only exposure conditions. In mice exposed to sidestream smoke in an exposure chamber (whole-body exposure), a signifi-

cant increase in the frequency of micronucleated polychromatic erythrocytes in the bone marrow was observed (Mohtashamipur *et al*., 1987). Similarly, sidestream smoke and mainstream smoke condensates injected either separately or in a mixture increased the formation of micronuclei in polychromatic erythrocytes in treated mice in a dose-dependent manner (Mohtashamipur *et al*., 1988). In agreement with chemical analyses showing that the concentrations of several genotoxic and carcinogenic substances are higher in sidestream smoke than in mainstream smoke, sidestream smoke condensate induced significantly more micronuclei than mainstream smoke condensate. This difference was more pronounced in animals pretreated with the enzyme inducer Arochlor 1254 (Mohtashamipur *et al*., 1988).

Aged and diluted sidestream smoke was not found to induce chromosomal aberrations in alveolar macrophages in rats after nose-only exposure for 7 days (Lee *et al*., 1992), or after 28 days or 90 days (Lee *et al*., 1993). More recently, whole-body exposure of rats to a mixture of mainstream (11%) and sidestream (89%) cigarette smoke for 28 consecutive days was found to induce DNA adducts and cytogenetic damage in all tissues examined. The frequencies of micronucleated and polynucleated pulmonary alveolar macrophages as well as those of micronucleated polychromatic erythrocytes in bone marrow were significantly increased in animals exposed to sidestream smoke when compared with sham-exposed animals (Izzotti *et al*., 2001).

4.5 Mechanistic considerations

Biological measurements have demonstrated uptake and metabolism of tobacco smoke constituents in nonsmokers who reported regular exposure to secondhand tobacco smoke. In particular, cotinine concentrations measured in the body fluids of nonsmokers have provided both qualitative and quantitative evidence of exposure to secondhand tobacco smoke. In addition, the presence of tobacco-specific nitrosamines and their metabolites in the urine of nonsmokers exposed to secondhand tobacco smoke, with a correlation between the metabolites and cotinine concentration in the urine, provides clear evidence of the exposure of nonsmokers to carcinogenic constituents of tobacco smoke. The results of current studies on individual variation due to environmental or genetic factors are insufficient to permit conclusions regarding the influence of these factors on the response of people to exposure to secondhand tobacco smoke.

Evidence is provided in this monograph for the genotoxicity of secondhand tobacco smoke in humans. Exposure of nonsmokers to secondhand tobacco smoke has often been demonstrated by measurements of both cotinine and protein adducts. Studies analysing somatic mutations in the *TP53* and *KRAS* genes in lung tumours from life-long nonsmokers have suggested that the mutation burden in nonsmokers who are exposed to secondhand tobacco smoke may be higher than that in nonsmokers who have not been exposed. These observations in humans are supported by the findings from animal studies and other experimental systems that have demonstrated the genotoxicity of sidestream smoke (a major component of secondhand tobacco smoke), of a mixture of mainstream

and sidestream smoke, and of secondhand tobacco smoke collected in indoor environments.

The evidence from studies of nonsmokers exposed to secondhand tobacco smoke, supported by other data from experimental systems, is compatible with the current concept of tobacco-related carcinogenesis. According to this concept, tobacco smoke carcinogens, regardless of the type of smoke in which they occur, are associated with genetic effects that disrupt crucial biological processes of normal cellular growth and differentiation in smokers as well as in nonsmokers (see monograph on tobacco smoke).

References

Al-Delaimy, W.K., Crane, J. & Woodward, A. (2000) Questionnaire and hair measurement of exposure to tobacco smoke. *J. Expo. anal. environ. Epidemiol*., **10**, 378–384

Al-Delaimy, W.K., Crane, J. & Woodward, A. (2002) Is the hair nicotine level a more accurate biomarker of environmental tobacco smoke exposure than urine cotinine? *J. Epidemiol. Community Health*, **56**, 66–71

Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group (1994) The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *New Engl. J. Med*., **330**, 1029–1035

Ammenheuser, M.M., Hastings, D.A., Whorton, E.B., Jr & Ward, J.B., Jr (1997) Frequencies of *Hprt* mutant lymphocytes in smokers, non-smokers, and former smokers. *Environ. mol. Mutag.*, **30**, 131–138

Anderson, R., Theron, A.J., Richards, G.A., Myer, M.S. & van Rensburg, A.J. (1991) Passive smoking by humans sensitizes circulating neutrophils. *Am. Rev. respir. Dis*., **144**, 570–574

Anderson, K.E., Carmella, S.G., Ye, M., Bliss, R.L., Le, C., Murphy, L. & Hecht, S.S. (2001) Metabolites of a tobacco-specific lung carcinogen in nonsmoking women exposed to environmental tobacco smoke. *J. natl Cancer Inst.*, **93**, 378–381

Andres, R.L. & Day, M.C. (2000) Perinatal complications associated with maternal tobacco use. *Semin. Neonatol.*, **5**, 231–241

Arif, J.M., Gairola, C.G., Kelloff, G.J., Lubet, R.A. & Gupta, R.C. (2000) Inhibition of cigarette smoke-related DNA adducts in rat tissues by indole-3-carbinol. *Mutat. Res.*, **452**, 11–18

Arnould, J.P., Verhoest, P., Bach, V., Libert, J.P. & Belegaud, J. (1997) Detection of benzo[*a*]-pyrene–DNA adducts in human placenta and umbilical cord blood. *Hum. exp. Toxicol.*, **16**, 716–721

Ayer, H.E. & Yeager, D.W. (1982) Irritants in cigarette smoke plumes. *Am. J. public Health*, **72**, 1283–1285

Barad, C.B. (1979) Smoking on the job: The controversy heats up. *Occup. Health Saf*., **48**, 21–24

Bartsch, H., Caporaso, N., Coda, M., Kadlubar, F., Malaveille, C., Skipper, P., Talaska, G., Tannenbaum, S.R. & Vineis, P. (1990) Carcinogen hemoglobin adducts, urinary mutagenicity, and metabolic phenotype in active and passive cigarette smokers. *J. natl. Cancer Inst.*, **82**, 1826–1831

Bascom, R., Kulle, T., Kagey-Sobotka, A. & Proud, D. (1991) Upper respiratory tract environmental tobacco smoke sensitivity. *Am. Rev. respir. Dis*., **143**, 1304–1311

Basu, P.K., Pimm, P.E., Shephard, R.J. & Silverman, F. (1978) The effect of cigarette smoke on the human tear film. *Can. J. Ophthalmol.*, **13**, 22–26

Benowitz, N.L. (1996) Cotinine as a biomarker of environmental tobacco smoke exposure. *Epidemiol. Rev.*, **18**, 188–204

Benowitz, N.L. (1999) Biomarkers of environmental tobacco smoke exposure. *Environ. Health Perspect.*, **107** (Suppl. 2), 349–355

Beratis, N.G., Varvarigou, A., Makri, M. & Vagenakis, A.G. (1994) Prolactin, growth hormone and insulin-like growth factor-I in newborn children of smoking mothers. *Clin. Endocrinol.*, **40**, 179–185

Bernstein, M., Morabia, A., Héritier, S. & Katchatrian, N. (1996) Passive smoking, active smoking, and education: Their relationship to weight history in women in Geneva. *Am. J. public Health*, **86**, 1267–1272

Bianchini, F., Donato, F., Faure, H., Ravanat, J.-L., Hall, J. & Cadet, J. (1998) Urinary excretion of 5-(hydroxymethyl)uracil in healthy volunteers: Effect of active and passive tobacco smoke. *Int. J. Cancer*, **77**, 40–46

Bigbee, W.L., Day, R.D., Grant, S.G., Keohavong, P., Xi, L., Zhang, L. & Ness, R.B. (1999) Impact of maternal lifestyle factors on newborn *HPRT* mutant frequencies and molecular spectrum — Initial results from the Prenatal Exposures and Preeclampsia Prevention (PEPP) Study. *Mutat. Res.*, **431**, 279–289

Blache, D., Bouthillier, D. & Davignon, J. (1992) Acute influence of smoking on platelet behaviour, endothelium and plasma lipids and normalization by aspirin. *Atherosclerosis*, **93**, 179–188

Bolton-Smith, C., Woodward, M., Brown, C.A. & Tunstall-Pedoe, H. (1993) Nutrient intake by duration of ex-smoking in the Scottish Heart Health Study. *Br. J. Nutr.*, **69**, 315–332

Bonham, A.C., Chen, C.Y., Mutoh, T. & Joad, J.P. (2001) Lung C-fiber CNS reflex: Role in the respiratory consequences of extended environmental tobacco smoke exposure in young guinea pigs. *Environ. Health Perspect.*, **109** (Suppl. 4), 573–578

Bono, R., Vincenti, M., Meineri, V., Pignata, C., Saglia, U., Giachino, O. & Scursatone, E. (1999) Formation of *N*-(2-hydroxyethyl)valine due to exposure to ethylene oxide via tobacco smoke: A risk factor for onset of cancer. *Environ. Res.*, **81**, 62–71

Bos, R.P., Theuws, J.L.G. & Henderson, P.T. (1983) Excretion of mutagens in human urine after passive smoking. *Cancer Lett.*, **19**, 85–90

Branner, B., Kutzer, C., Zwickenpflug, W., Scherer, G., Heller, W.-D. & Richter, E. (1998) Haemoglobin adducts from aromatic amines and tobacco-specific nitrosamines in pregnant smoking and non-smoking women. *Biomarkers*, **3**, 35–47

Brunekreef, B., Fischer, P., Remijn, B., van der Lende, R., Schouten, J. & Quanjer, P. (1985) Indoor air pollution and its effect on pulmonary function of adult non-smoking women: III. Passive smoking and pulmonary function. *Int. J. Epidemiol.*, **14**, 227–230

Butler, T.L. (1988) *The Relationship of Passive Smoking to Various Health Outcomes Among Seventh-Day Adventists in California*, Doctor of Public Health Dissertation, Los Angeles, University of California

Cade, J.E. & Margetts, B.M. (1991) Relationship between diet and smoking — Is the diet of smokers different? *J. Epidemiol. Community Health*, **45**, 270–272

California Environmental Protection Agency (1997) *Health Effects of Exposure to Environmental Tobacco Smoke*, Sacramento, CA

Carey, I.M., Cook, D.G. & Strachan, D.P. (1999) The effects of environmental tobacco smoke exposure on lung function in a longitudinal study of British adults. *Epidemiology*, **10**, 319–326

Carmichael, P.L., Hewer, A., Jacob, J., Grimmer, G. & Phillips, D.H. (1993) Comparison of total DNA adduct levels induced in mouse tissues and human skin by mainstream and sidestream cigarette smoke condensates. In: Phillips, D.H., Castegnaro, M. & Bartsch, H., *Postlabelling Methods for Detection of DNA Adducts* (IARC Scientific Publications No. 124), Lyon, IARC*Press*, pp. 321–326

Carrer, P., Maroni, M., Alcini, D., Cavallo, D., Fustinoni, S., Lovato, L. & Visigalli, F. (2000) Assessment through environmental and biological measurements of total daily exposure to volatile organic compounds of office workers in Milan, Italy. *Indoor Air*, **10**, 258–268

Casto, D.T., Schnapf, B.M. & Clotz, M.A. (1990) Lack of effect of short-term passive smoking on the metabolic disposition of theophylline. *Eur. J. clin. Pharmacol*., **39**, 399–402

Castro, A. & Monji, N. (1986) Dietary nicotine and its significance in studies on tobacco smoking. *Biochem. Arch.*, **2**, 91–97

Chen, C.-C. & Lee, H. (1996) Genotoxicity and DNA adduct formation of incense smoke condensates: Comparison with environmental tobacco smoke condensates. *Mutat. Res*., **367**, 105–114

Chen, R., Tunstall-Pedoe, H. & Tavendale, R. (2001) Environmental tobacco smoke and lung function in employees who never smoked: The Scottish MONICA study. *Occup. environ. Med*., **58**, 563–568

Chow, J.Y., Ma, L. & Cho, C.H. (1996) An experimental model for studying passive cigarette smoking effects on gastric ulceration. *Life Sci.*, **58**, 2415–2422

Ciruzzi, M., Pramparo, P., Esteban, O., Rozlosnik, J., Tartaglione, J., Abecasis, B., César, J. , De Rosa, J., Paterno, C. & Schargrodsky, H. (1998) Case–control study of passive smoking at home and risk of acute myocardial infarction. *J. Am. Coll. Cardiol*., **31**, 797–803

Claxton, L.D., Morin, R.S., Hughes, T.J. & Lewtas, J. (1989) A genotoxic assessment of environmental tobacco smoke using bacterial bioassays. *Mutat. Res*., **222**, 81–99

Cockcroft, D.W. (1988) Cigarette smoking, airway hyperresponsiveness, and asthma. *Chest*, **94**, 675–676

Coggins, C.R.E., Ayres, P.H., Mosberg, A.T., Ogden, M.W., Sagartz, J.W. & Hayes, A.W. (1992) Fourteen-day inhalation study in rats, using aged and diluted sidestream smoke from a reference cigarette. I. Inhalation toxicology and histopathology. *Fundam. appl. Toxicol*., **19**, 133–140

Coggins, C.R.E., Ayres, P.H., Mosberg, A.T., Sagartz, J.W.& Hayes, A.W. (1993) Subchronic inhalation study in rats using aged and diluted sidestream smoke from a reference cigarette. *Inhal. Toxicol*., **5**, 77–96

Coghlin, J., Gann, P.H., Hammond, S.K., Skipper, P.L., Taghizadeh, K., Paul, M. & Tannenbaum, S.R. (1991) 4-Aminobiphenyl hemoglobin adducts in fetuses exposed to the tobacco smoke carcinogen *in utero*. *J. natl Cancer Inst.*, **83**, 274–280

Collman, G.W., Lundgren, K., Shore, D., Thompson, C.L. & Lucier, G.W. (1986) Effects of α-naphthoflavone on levels of sister chromatid exchanges in lymphocytes from active and passive cigarette smokers: Dose–response relationships. *Cancer Res.*, **46**, 6452–6455

Comstock, G.W., Meyer, M.B., Helsing, K.J. & Tockman, M.S. (1981) Respiratory effects on household exposures to tobacco smoke and gas cooking. *Am. Rev. respir. Dis*., **124**, 143–148

Cooper, G.S., Sandler, D.P. & Bohlig, M. (1999) Active and passive smoking and the occurrence of natural menopause. *Epidemiology*, **10**, 771–773

Coultas, D.B. (1998) Health effects of passive smoking. 8. Passive smoking and risk of adult asthma and COPD: An update. *Thorax*, **53**, 381–387

Coultas, D.B., Howard, C.A., Peake, G.T., Skipper, B.J. & Samet, J.M. (1987) Salivary cotinine levels and involuntary tobacco smoke exposure in children and adults in New Mexico. *Am. Rev. respir. Dis*., **136**, 305–309

Coutant, R., Boux de Casson, F., Douay, O., Mathieu, E., Rouleau, S., Beringue, F., Gillard, P., Limal, J.M. & Descamps, P. (2001) Relationships between placental GH concentration and maternal smoking, newborn gender, and maternal leptin: Possible implications for birth weight. *J. clin. Endocrinol.*, **86**, 4854–4859

Cramer, D.W., Harlow, B.L., Xu, H., Fraer, C. & Barbieri, R. (1995) Cross-sectional and case-controlled analyses of the association between smoking and early menopause. *Maturitas*, **22**, 79–87

Crawford, W.A. (1988) On the health effects of environmental tobacco smoke. *Arch. environ. Health*, **43**, 34–37

Crawford, F.G., Mayer, J., Santella, R.M., Cooper, T.B., Ottman, R., Tsai, W.-Y., Simon-Cereijido, G., Wang, M., Tang, D. & Perera, F.P. (1994) Biomarkers of environmental tobacco smoke in preschool children and their mothers. *J. natl Cancer Inst.*, **86**, 1398–1402

Cress, R.D., Holly, E.A., Aston, D.A., Ahn, D.K. & Kristiansen, J.J. (1994) Characteristics of women nonsmokers exposed to passive smoke. *Prev. Med.*, **23**, 40–47

Cummings, K.M., Markello, S.J., Mahoney, M., Bhargava, A.K., McElroy, P.D. & Marshall, J.R. (1990) Measurement of current exposure to environmental tobacco smoke. *Arch. environ. Health*, **45**, 74–79

Curry, J., Karnaoukhova, L., Guenette, G.C. & Glickman, B.W. (1999) Influence of sex, smoking and age on human *hprt* mutation frequencies and spectra. *Genetics*, **152**, 1065–1077

Dahms, T.E., Bolin, J.F. & Slavin, R.G. (1981) Passive smoking. Effects on bronchial asthma. *Chest*, **80**, 530–534

Dales, R.E., Kerr, P.E., Schweitzer, I., Reesor, K., Gougeon, L. & Dickinson, G. (1992) Asthma management preceding an emergency department visit. *Arch. intern. Med*., **152**, 2041–2044

Danuser, B., Weber, A., Hartmann, A.L. & Krueger, H. (1993) Effects of a bronchoprovocation challenge test with cigarette sidestream smoke on sensitive and healthy adults. *Chest*, **103**, 353–358

Daube, H., Scherer, G., Riedel, K., Ruppert, T., Tricker, A.R., Rosenbaum, P. & Adlkofer, F. (1997) DNA adducts in human placenta in relation to tobacco smoke exposure and plasma antioxidant status. *J. Cancer Res. clin. Oncol.*, **123**, 141–151

Davis, J.W. & Davis, R.F. (1981) Prevention of cigarette smoking-induced platelet aggregate formation by aspirin. *Arch. intern. Med*., **141**, 206–207

Davis, J.W., Davis, R.F. & Hassanein, K.M. (1982) In healthy habitual smokers acetylsalicylic acid abolishes the effects of tobacco smoke on the platelet aggregate ratio. *Can. med. Assoc. J*., **126**, 637–639

Davis, J.W., Hartman, C.R., Lewis, H.D., Jr, Shelton, L., Eigenberg, D.A., Hassanein, K.M., Hignite, C.E. & Ruttinger, H.A. (1985a) Cigarette smoking-induced enhancement of platelet function: Lack of prevention by aspirin in men with coronary artery disease. *J. Lab. clin. Med*., **105**, 479–483

Davis, J.W., Shelton, L., Eigenberg, D.A., Hignite, C.E. & Watanabe, I.S. (1985b) Effects of tobacco and non-tobacco cigarette smoking on endothelium and platelets. *Clin. Pharmacol. Ther*., **37**, 529–533

Davis, J.W., Shelton, L., Hartman, C.R., Eigenberg, D.A. & Ruttinger, H.A. (1986) Smoking-induced changes in endothelium and platelets are not affected by hydroxyethylrutosides. *Br. J. exp. Pathol.*, **67**, 765–771

Davis, J.W., Shelton, L., Watanabe, I.S. & Arnold, J. (1989) Passive smoking affects endothelium and platelets. *Arch. intern. Med*., **149**, 386–389

Davis, R.A., Stiles, M.F., deBethizy, J.D. & Reynolds, J.H. (1991) Dietary nicotine: A source of urinary cotinine. *Food chem. Toxicol.*, **29**, 821–827

Dayal, H.H., Khuder, S., Sharrar, R. & Trieff, N. (1994) Passive smoking in obstructive respiratory diseases in an industrialized urban population. *Environ. Res*., **65**, 161–171

De Flora, S., D'Agostini, F., Balansky, R., Camoirano, A., Bennicelli, C., Bagnasco, M., Cartiglia, C., Tampa, E., Longobardi, M.G., Lubet, R.A., & Izzotti, A. (2003) Modulation of cigarette smoke-related end-points in mutagenesis and carcinogenesis. *Mutat. Res.*, **523–524**, 237–252

Dempsey, D., Jacob, P., III & Benowitz, N.L. (2000) Nicotine metabolism and elimination kinetics in newborns. *Clin. Pharmacol. Ther*., **67**, 458–465

DiCarlantonio, G. & Talbot, P. (1999) Inhalation of mainstream and sidestream cigarette smoke retards embryo transport and slows muscle contraction in oviducts of hamsters (*Mesocricetus auratus*). *Biol. Reprod*., **61**, 651–656

Dimich-Ward, H., Gee, H., Brauer, M. & Leung, V. (1997) Analysis of nicotine and cotinine in the hair of hospitality workers exposed to environmental tobacco smoke. *J. occup. environ. Med*., **39**, 946–948

Dobson, A.J., Alexander, H.M., Heller, R.F. & Lloyd, D.M. (1991) Passive smoking and the risk of heart attack or coronary death. *Med. J. Aust*., **154**, 793–797

Doll, R. & Hill, A.B. (1964) Mortality in relation to smoking: Ten years' observations of British doctors. *Br. med. J*., **i**, 1399–1410

Doll, R. & Hill, A.B. (1966) Mortality of British doctors in relation to smoking: Observations on coronary thrombosis. *Natl Cancer Inst. Monogr*., **19**, 205–268

Doll, R. & Peto, R. (1976) Mortality in relation to smoking: 20 years' observations on male British doctors. *Br. med. J.*, **ii**, 1525–1536

Domino, E.F., Hornbach, E. & Demana, T. (1993) The nicotine content of common vegetables. *New Engl. J. Med*., **329**, 437

Doolittle, D.J., Lee, C.K., Ivett, J.L., Mirsalis, J.C., Riccio, E., Rudd, C.J., Burger, G.T. & Hayes, A.W. (1990) Genetic toxicology studies comparing the activity of sidestream smoke from cigarettes which burn or only heat tobacco. *Mutat. Res*., **240**, 59–72

Ece, A., Gürkan, F., Haspolat, K., Derman, O. & Kirbas, G. (2000) Passive smoking and expired carbon monoxide concentrations in healthy and asthmatic children. *Allergol. Immunopathol*., **28**, 255–260

Emmons, K.M., Thompson, B., Feng, Z., Hebert, J.R., Heimendinger, J. & Linnan, L. (1995) Dietary intake and exposure to environmental tobacco smoke in a worksite population. *Eur. J. clin. Nutr*., **49**, 336–345

Eriksen, M.P., LeMaistre, C.A. & Newell, G.R. (1988) Health hazards of passive smoking. *Ann. Rev. public Health*, **9**, 47–70

Escolar, J.D., Martínez, M.N., Rodríguez, F.J., Gonzalo, C., Escolar, M.A. & Roche, P.A. (1995) Emphysema as a result of involuntary exposure to tobacco smoke: Morphometrical study of the rat. *Exp. Lung Res*., **21**, 255–273

Etter, J.-F., Duc, T.V. & Perneger, T.V. (2000) Saliva cotinine levels in smokers and nonsmokers. *Am. J. Epidemiol.*, **151**, 251–258

Etzel, R.A. (1990) A review of the use of saliva cotinine as a marker of tobacco smoke exposure. *Prev. Med*., **19**, 190–197

Etzel, R.A., Greenberg, R.A., Haley, N.J. & Loda, F.A. (1985) Urine cotinine excretion in neonates exposed to tobacco smoke products in utero. *J. Pediatr*., **107**, 146–148

Euler, G.L., Abbey, D.E., Magie, A.R. & Hodgkin, J.E. (1987) Chronic obstructive pulmonary disease symptom effects of long-term cumulative exposure to ambient levels of total suspended particulates and sulfur dioxide in California Seventh-Day Adventist residents. *Arch. environ. Health*, **42**, 213–222

Everson, R.B., Sandler, D.P., Wilcox, A.J., Schreinemachers, D., Shore, D.L. & Weinberg, C. (1986) Effect of passive exposure to smoking on age at natural menopause. *Br. med. J.*, **293**, 792

Fehily, A.M., Phillips, K.M. & Yarnell, J.W.G. (1984) Diet, smoking, social class, and body mass index in the Caerphilly Heart Disease Study. *Am. J. clin. Nutr*., **40**, 827–833

Feldman, J., Shenker, I.R., Etzel, R.A., Spierto, F.W., Lilienfield, D.E., Nussbaum, M. & Jacobson, M.S. (1991) Passive smoking alters lipid profiles in adolescents. *Pediatrics*, **88**, 259–264

Finette, B.A., Poseno, T., Vacek, P.M. & Albertini, R.J. (1997) The effects of maternal cigarette smoke exposure on somatic mutant frequencies at the *hprt* locus in healthy newborns. *Mutat. Res.*, **377**, 115–123

Finette, B.A., O'Neill, J.P., Vacek, P.M. & Albertini, R.J. (1998) Gene mutations with characteristic deletions in cord blood T lymphocytes associated with passive maternal exposure to tobacco smoke. *Nat. Med.*, **4**, 1144–1151

Fontham, E.T.H., Correa, P., Reynolds, P., Wu-Williams, A., Buffler, P.A., Greenberg, R.S., Chen, V.W., Alterman, T., Boyd, P., Austin, D.F. & Liff, J. (1994) Environmental tobacco smoke and lung cancer in nonsmoking women. A multicenter study. *J. Am. med. Assoc.*, **271**, 1752–1759

Frette, C., Barrett-Connor, E. & Clausen, J.L. (1996) Effect of active and passive smoking on ventilatory function in elderly men and women. *Am. J. Epidemiol*., **143**, 757–765

Gairola, C.G. (1987) Pulmonary aryl hydrocarbon hydroxylase activity of mice, rats and guinea pigs following long term exposure to mainstream and sidestream cigarette smoke. *Toxicology*, **45**, 177–184

Gairola, C.G., Wu, H., Gupta, R.C. & Diana, J.N. (1993) Mainstream and sidestream cigarette smoke-induced DNA adducts in C57B1 and DBA mice. *Environ. Health Perspect.*, **99**, 253–255

Gairola, C.G., Drawdy, M.L., Block, A.E. & Daugherty, A. (2001) Sidestream cigarette smoke accelerates atherogenesis in apolipoprotein $E^{-/-}$ mice. *Atherosclerosis*, **156**, 49–55

Garland, C., Barrett-Connor, E., Suarez, L., Criqui, M.H. & Wingard, D.L. (1985) Effects of passive smoking on ischemic heart disease mortality of nonsmokers. A prospective study. *Am. J. Epidemiol*., **121**, 645–650

Gealy, R., Zhang, L., Siegfried, J.M., Luketich, J.D. & Keohavong, P. (1999) Comparison of mutations in the p53 and K-ras genes in lung carcinomas from smoking and nonsmoking women. *Cancer Epidemiol. Biomarkers Prev.*, **8**, 297–302

Gebremichael, A., Chang, A.M., Buckpitt, A.R., Plopper, C.G. & Pinkerton, K.E. (1995) Postnatal development of cytochrome P4501A1 and 2B1 in rat lung and liver: Effect of aged and diluted sidestream cigarette smoke. *Toxicol. appl. Pharmacol.*, **135**, 246–253

Gebremichael, A., Tullis, K., Denison, M.S., Cheek, J.M. & Pinkerton, K.E. (1996) Ah-receptor-dependent modulation of gene expression by aged and diluted sidestream cigarette smoke. *Toxicol. appl. Pharmacol.*, **141**, 76–83

Georgiadis, P., Topinka, J., Stoikidou, M., Kaila, S., Gioka, M., Katsouyanni, K., Sram, R., Autrup, H. & Kyrtopoulos, S.A. on behalf of the AULIS Network (2001) Biomarkers of genotoxicity of air pollution (the AULIS project): Bulky DNA adducts in subjects with moderate to low exposures to airborne polycyclic aromatic hydrocarbons and their relationship to environmental tobacco smoke and other parameters. *Carcinogenesis*, **22**, 1447–1457

Gillis, C.R., Hole, D.J., Hawthorne, V.M. & Boyle, P. (1984) The effect of environmental tobacco smoke in two urban communities in the west of Scotland. *Eur. J. respir. Dis.*, **133** (Suppl.), 121–126

Glantz, S.A. & Parmley, W.W. (1991) Passive smoking and heart disease. Epidemiology, physiology, and biochemistry. *Circulation*, **83**, 1–12

Glantz, S.A. & Parmley, W.W. (1995) Passive smoking and heart disease. Mechanisms and risk. *J. Am. med. Assoc.*, **273**, 1047–1053

Gorgels, W.J.M.J., van Poppel, G., Jarvis, M.J., Stenhuis, W. & Kok, F.J. (1992) Passive smoking and sister-chromatid exchanges in lymphocytes. *Mutat. Res.*, **279**, 233–238

Gospe, S.M., Jr, Zhou, S.S. & Pinkerton, K.E. (1996) Effects of environmental tobacco smoke exposure in utero and/or postnatally on brain development. *Pediatr. Res.*, **39**, 494–498

Greer, J.R., Abbey, D.E. & Burchette, R.J. (1993) Asthma related to occupational and ambient air pollutants in nonsmokers. *J. occup. Med.*, **35**, 909–915

Grimmer, G., Dettbarn, G., Seidel, A. & Jacob, J. (2000) Detection of carcinogenic aromatic amines in the urine of non-smokers. *Sci. total Environ.*, **247**, 81–90

Haley, N.J., Colosimo, S.G., Axelrad, C.M., Harris, R. & Sepkovic, D.W. (1989) Biochemical validation of self-reported exposure to environmental tobacco smoke. *Environ. Res.*, **49**, 127–135

Hall, G.L., Reinmann, B., Wildhaber, J.H. & Frey, U. (2002) Tidal exhaled nitric oxide in healthy, unsedated newborn infants with prenatal tobacco exposure. *J. appl. Physiol.*, **92**, 59–66

Hammer, D.I., Hasselblad, V., Portnoy, B. & Wehrle, P.F. (1974) Los Angeles Student Nurse study. Daily symptom reporting and photochemical oxidants. *Arch. environ. Health*, **28**, 255–260

Hammond, E.C. (1966) Smoking in relation to the death rates of one million men and women. *Natl Cancer Inst. Monogr.*, **19**, 127–204

Hammond, E.C. & Garfinkel, L. (1969) Coronary heart disease, stroke, and aortic aneurysm. *Arch. environ. Health*, **19**, 167–182

Hammond, E.C. & Horn, D. (1958) Smoking and death rates — Report on forty-four months of follow-up of 187,783 men. *J. Am. med. Assoc.*, **166**, 2840–2853

Hammond, S.K., Coghlin, J., Gann, P.H., Paul, M., Taghizadeh, K., Skipper, P.L. & Tannenbaum, S.R. (1993) Relationship between environmental tobacco smoke exposure and carcinogen–hemoglobin adduct levels in nonsmokers. *J. natl Cancer Inst.*, **85**, 474–478

Hansen, C., Sørensen, L.D., Asmussen, I. & Autrup, H. (1992) Transplacental exposure to tobacco smoke in human-adduct formation in placenta and umbilical cord blood vessels. *Teratog. Carcinog. Mutag.*, **12**, 51–60

Hansen, C., Asmussen, I. & Autrup, H. (1993) Detection of carcinogen–DNA adducts in human fetal tissues by the ^{32}P-postlabeling procedure. *Environ. Health Perspect.*, **99**, 229–231

Hatch, M.C., Warburton, D. & Santella, R.M. (1990) Polycyclic aromatic hydrocarbon–DNA adducts in spontaneously aborted fetal tissue. *Carcinogenesis*, **11**, 1673–1675

He, Y. (1989) [Women's passive smoking and coronary heart disease.] *Zhonghua Yu Fang Yi Xue Za Zhi*, **23**, 19–22 (in Chinese)

He, Y., Lam, T.H., Li, L.S., Li, L.S., Du, R.Y., Jia, G.L., Huang, J.Y. & Zheng, J.S. (1994) Passive smoking at work as a risk factor for coronary heart disease in Chinese women who have never smoked. *Br. med. J.*, **308**, 380–384

He, J., Vupputuri, S., Allen, K., Prerost, M.R., Hughes, J. & Whelton, P.K. (1999) Passive smoking and the risk of coronary heart disease — A meta-analysis of epidemiologic studies. *New Engl. J. Med.*, **340**, 920–926

Hecht, S.S. (2002) Human urinary carcinogen metabolites: Biomarkers for investigating tobacco and cancer. *Carcinogenesis*, **23**, 907–922

Hecht, S.S., Carmella, S.G., Murphy, S.E., Akerkar, S., Brunnemann, K.D. & Hoffmann, D. (1993) A tobacco-specific lung carcinogen in the urine of men exposed to cigarette smoke. *New Engl. J. Med.*, **329**, 1543–1546

Hecht, S.S., Ye, M., Carmella, S.G., Fredrickson, A., Adgate, J.L., Greaves, I.A., Church, T.R., Ryan, A.D., Mongin, S.J. & Sexton, K. (2001) Metabolites of a tobacco-specific lung carcinogen in the urine of elementary school-aged children. *Cancer Epidemiol. Biomarkers Prev.*, **10**, 1109–1116

Heinz-Erian, P., Spitzmüller, A., Schröcksnadel, H. & Birnbacher, R. (1998) Maternal smoking and inhibition of fetal growth factor (Letter to the Editor). *J. Am. med. Assoc.*, **279**, 1954

Hennekens, C.H., Buring, J.E., Manson, J.E., Stampfer, M., Rosner, B., Cook, N.R., Belanger, C., LaMotte, F., Gaziano, J.M., Ridker, P.M., Willett, W. & Peto, R. (1996) Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *New Engl. J. Med.*, **334**, 1145–1149

Henningfield, J.E. (1993) More on the nicotine content of vegetables. *New Engl. J. Med.*, **329**, 1581–1582

Hernandez-Boussard, T., Montesano, R. & Hainaut, P. (1999) Analysis of somatic mutations of the *p53* gene in human cancers: A tool to generate hypotheses about the natural history of cancer. In: McGregor, D.B., Rice, J.M. & Venitt, S., eds, *The Use of Short- and Medium-term Tests for Carcinogens and Data on Genetic Effects in Carcinogenic Hazard Evaluation* (IARC Scientific Publications No. 146), Lyon, IARC*Press*, pp. 43–53

Hirayama, T. (1981) Non-smoking wives of heavy smokers have a higher risk of lung cancer: A study from Japan. *Br. med. J.*, **282**, 183–185

Hirayama, T. (1984) Lung cancer in Japan: Effects of nutrition and passive smoking. In: Mizell, M. & Correa, P., eds, *Lung Cancer: Causes and Prevention*, New York, Verlag Chemie International, pp. 175–195

Hirayama, T. (1990) Passive smoking. *N.Z. med. J.*, **103**, 54

Hoepfner, I., Dettbarn, G., Scherer, G., Grimmer, G. & Adlkofer, F. (1987) Hydroxy-phenanthrenes in the urine of non-smokers and smokers. *Toxicol. Lett.*, **35**, 67–71

Hole, D.J., Gillis, C.R., Chopra, C. & Hawthorne, V.M. (1989) Passive smoking and cardiorespiratory health in a general population in the west of Scotland. *Br. med. J.*, **299**, 423–427

Holz, O., Krause, T., Scherer, G., Schmidt-Preuss, U. & Rüdiger, H.W. (1990) ^{32}P-postlabelling analysis of DNA adducts in monocytes of smokers and passive smokers. *Int. Arch. occup. environ. Health*, **62**, 299–303

Hong, Y.C., Kim, H., Im, M.W., Lee, K.H., Woo, B.H. & Christiani, D.C. (2001) Maternal genetic effects on neonatal susceptibility to oxidative damage from environmental tobacco smoke. *J. natl Cancer Inst*., **93**, 645–647

Hovell, M.F., Zakarian, J.M., Wahlgren, D.R. & Matt, G.E. (2000a) Reported measures of environmental tobacco smoke exposure: Trials and tribulations. *Tob. Control*, **9** (Suppl. 3), 22–28

Hovell, M.F., Zakarian, J.M., Matt, G.E., Hofstetter, C.R., Bernert, J.T. & Pirkle, J. (2000b) Effect of counselling mothers on their children's exposure to environmental tobacco smoke: Randomised controlled trial. *Br. med. J.*, **321**, 337–342

Howard, D.J., Ota, R.B., Briggs, L.A., Hampton, M. & Pritsos, C.A. (1998a) Environmental tobacco smoke in the workplace induces oxidative stress in employees, including increased production of 8-hydroxy-2′-deoxyguanosine. *Cancer Epidemiol. Biomarkers Prev.*, **7**, 141–146

Howard, D.J., Briggs, L.A. & Pritsos, C.A. (1998b) Oxidative DNA damage in mouse heart, liver, and lung tissue due to acute side-stream tobacco smoke exposure. *Arch. Biochem. Biophys*., **352**, 293–297

Hu, F.B., Persky, V., Flay, B.R. & Richardson, J. (1997) An epidemiological study of asthma prevalence and related factors among young adults. *J. Asthma*, **34**, 67–76

Huang, C., Taki, T., Adachi, M., Konishi, T., Higashiyama, M. & Miyake, M. (1998) Mutations in exon 7 and 8 of *p53* as poor prognostic factors in patients with non-small cell lung cancer. *Oncogene*, **16**, 2469–2477

Hugod, C., Hawkins, L.H. & Astrup, P. (1978) Exposure of passive smokers to tobacco smoke constituents. *Int. Arch. occup. environ. Health*, **42**, 21–29

Hull, M.G.R., North, K., Taylor, H., Farrow, A., Ford, W.C.L. & the Avon Longitudinal Study of Pregnancy and Childhood Study Team (2000) Delayed conception and active and passive smoking. *Fertil. Steril.*, **74**, 725–733

Humble, C., Croft, J., Gerber, A., Casper, M., Hames, C.G. & Tyroler, H.A. (1990) Passive smoking and 20-year cardiovascular disease mortality among nonsmoking wives, Evans County, Georgia. *Am. J. public Health*, **80**, 599–601

Husgafvel-Pursiainen, K. (1987) Sister-chromatid exchange and cell proliferation in cultured lymphocytes of passively and actively smoking restaurant personnel. *Mutat. Res*., **190**, 211–215

Husgafvel-Pursiainen, K., Sorsa, M., Møller, M. & Benestad, C. (1986) Genotoxicity and polynuclear aromatic hydrocarbon analysis of environmental tobacco smoke samples from restaurants. *Mutagenesis*, **1**, 287–292

Husgafvel-Pursiainen, K., Sorsa, M., Engström, K. & Einistö, P. (1987) Passive smoking at work: Biochemical and biological measures of exposure to environmental tobacco smoke. *Int. Arch. occup. environ. Health*, **59**, 337–345

Husgafvel-Pursiainen, K., Hackman, P., Ridanpää, M., Anttila, S., Karjalainen, A., Partanen, T., Taikina-Aho, O., Heikkilä, L. & Vainio, H. (1993) K-*ras* mutations in human adenocarcinoma of the lung: Association with smoking and occupational exposure to asbestos. *Int. J. Cancer*, **53**, 250–256

Husgafvel-Pursiainen, K., Karjalainen, A., Kannio, A., Anttila, S., Partanen, T., Ojajärvi, A. & Vainio, H. (1999) Lung cancer and past occupational exposure to asbestos: Role of *p53* and *K-ras* mutations. *Am. J. respir. Cell mol. Biol.*, **20**, 667–674

Husgafvel-Pursiainen, K., Boffetta, P., Kannio, A., Nyberg, F., Pershagen, G., Mukeria, A., Constantinescu, V., Fortes, C. & Benhamou, S. (2000) *p53* Mutations and exposure to environmental tobacco smoke in a multicenter study on lung cancer. *Cancer Res.*, **60**, 2906–2911

Hussain, S.P. & Harris, C.C. (1998) Molecular epidemiology of human cancer: Contribution of mutation spectra studies of tumor suppressor genes. *Cancer Res.*, **58**, 4023–4037

Hutchison, S.J., Glantz, S.A., Zhu, B.Q., Sun, Y.P., Chou, T.M., Chatterjee, K., Deedwania, P.C., Parmley, W.W. & Sudhir, K. (1998) In-utero and neonatal exposure to secondhand smoke causes vascular dysfunction in newborn rats. *J. Am. Coll. Cardiol*., **32**, 1463–1467

IARC (1986) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*,Vol. 38, *Tobacco Smoking*, Lyon, IARC*Press*

Izzotti, A., Bagnasco, M., D'Agostini, F., Cartiglia, C., Lubet, R.A., Kelloff, G.J. & De Flora, S. (1999) Formation and persistence of nucleotide alterations in rats exposed whole-body to environmental cigarette smoke. *Carcinogenesis*, **20**, 1499–1505

Izzotti, A., Balansky, R.M,. D'Agostini, F., Bennicelli, C., Myers, S.R., Grubbs, C.J., Lubet, R.A., Kelloff, G.J. & De Flora, S. (2001) Modulation of biomarkers by chemopreventive agents in smoke-exposed rats. *Cancer Res*., **61**, 2472–2479

Jaakkola, M.S., Jaakkola, J.J.K., Becklake, M.R. & Ernst, P. (1995) Passive smoking and evolution of lung function in young adults. An 8-year longitudinal study. *J. clin. Epidemiol*., **48**, 317–327

Jackson, R.T. (1989) *The Auckland Heart Study: A Case–Control Study of Coronary Heart Disease*, PhD Thesis, Auckland, University of Auckland

Jacob, P., III, Yu, L., Shulgin, A.T. & Benowitz, N.L. (1999) Minor tobacco alkaloids as biomarkers for tobacco use: Comparison of users of cigarettes, smokeless tobacco, cigars, and pipes. *Am. J. public Health*, **89**, 731–736

Janson, C., Chinn, S., Jarvis, D., Zock, J.-P., Torén, K. & Burney, P. (2001) Effect of passive smoking on respiratory symptoms, bronchial responsiveness, lung function, and total serum IgE in the European Community Respiratory Health Survey: A cross-sectional study. *Lancet*, **358**, 2103–2109

Järvinen, R., Knekt, P., Seppänen, R., Reunanen, A., Heliövaara, M., Maatela, J. & Aromaa, A. (1994) Antioxidant vitamins in the diet: Relationships with other personal characteristics in Finland. *J. Epidemiol. Community Health*, **48**, 549–554

Jarvis, M.J. (1994) Dietary nicotine. …unless subjects eat 90 kg tomatoes a day. *Br. med. J.*, **308**, 62

Jarvis, M.J., Russell, M.A.H. & Feyerabend, C. (1983) Absorption of nicotine and carbon monoxide from passive smoking under natural conditions of exposure. *Thorax*, **38**, 829–833

Jarvis, M.J., Russell, M.A.H., Feyerabend, C., Eiser, J.R., Morgan, M., Gammage, P. & Gray, E.M. (1985) Passive exposure to tobacco smoke: Saliva cotinine concentrations in a representative population sample of non-smoking schoolchildren. *Br. med J*., **291**, 927–929

Jarvis, M.J., Phil, M., Tunstall-Pedoe, H., Feyerabend, C., Vesey, C. & Saloojee, Y. (1987) Comparison of tests used to distinguish smokers from nonsmokers. *Am. J. public Health*, **77**, 1435–1438

Jarvis, M.J., McNeill, A.D., Bryant, A. & Russell, M.A. (1991) Factors determining exposure to passive smoking in young adults living at home: Quantitative analysis using saliva cotinine concentrations. *Int. J. Epidemiol.*, **20**, 126–131

Jarvis, M.J., Foulds, J. & Feyerabend, C. (1992) Exposure to passive smoking among bar staff. *Br. J. Addict.*, **87**, 111–113

Jarvis, M.J., Goddard, E., Higgins, V., Feyerabend, C., Bryant, A. & Cook, D.G. (2000) Children's exposure to passive smoking in England since the 1980s: Cotinine evidence from population surveys. *Br. med. J.*, **321**, 343–345

Jarvis, M.J., Feyerabend, C., Bryant, A., Hedges, B. & Primatesta, P. (2001) Passive smoking in the home: Plasma cotinine concentrations in non-smokers with smoking partners. *Tob. Control*, **10**, 368–374

Jensen, T.K., Henriksen, T.B., Hjollund, N.H.I., Scheike, T., Kolstad, H., Giwercman, A., Ernst, E., Bonde, J.P., Skakkebaek, N.E. & Olsen, J. (1998) Adult and prenatal exposures to tobacco smoke as risk indicators of fertility among 430 Danish couples. *Am. J. Epidemiol.*, **148**, 992–997

Ji, C.M., Plopper, C.G., Witschi, H.P. & Pinkerton, K.E. (1994) Exposure to sidestream cigarette smoke alters bronchiolar epithelial cell differentiation in the postnatal rat lung. *Am. J. respir. Cell mol. Biol.*, **11**, 312–320

Ji, C.M., Royce, F.H., Truong, U., Plopper, C.G., Singh, G. & Pinkerton, K.E. (1998) Maternal exposure to environmental tobacco smoke alters Clara cell secretory protein expression in fetal rat lung. *Am. J. Physiol.*, **275** , L870–L876

Jindal, S.K., Gupta, D. & Singh, A. (1994) Indices of morbidity and control of asthma in adult patients exposed to environmental tobacco smoke. *Chest*, **106**, 746–749

Jinot, J. & Bayard, S. (1996) Respiratory health effects of exposure to environmental tobacco smoke. *Rev. environ. Health*, **11**, 89–100

Joad, J.P., Pinkerton, K.E. & Bric, J.M. (1993) Effects of sidestream smoke exposure and age on pulmonary function and airway reactivity in developing rats. *Pediatr. Pulmonol.*, **16**, 281–288

Joad, J.P., Ji, C., Kott, K.S., Bric, J.M. & Pinkerton, K.E. (1995a) In utero and postnatal effects of sidestream cigarette smoke exposure on lung function, hyperresponsiveness, and neuroendocrine cells in rats. *Toxicol. appl. Pharmacol.*, **132**, 63–71

Joad, J.P., Bric, J.M. & Pinkerton, K.E. (1995b) Sidestream smoke effects on lung morphology and C-fibers in young guinea pigs. *Toxicol. appl. Pharmacol.*, **131**, 289–296

Joad, J.P., Bric, J.M., Peake, J.L. & Pinkerton, K.E. (1999) Perinatal exposure to aged and diluted sidestream cigarette smoke produces airway hyperresponsiveness in older rats. *Toxicol. appl. Pharmacol.*, **155**, 253–260

Jones, J.R., Higgins, I.T.T., Higgins, M.W. & Keller, J.B. (1983) Effects of cooking fuels on lung function in nonsmoking women. *Arch. environ. Health*, **38**, 219–222

Jordanov, J.S. (1990) Cotinine concentrations in amniotic fluid and urine of smoking, passive smoking and non-smoking pregnant women at term and in the urine of their neonates on 1st day of life. *Eur. J. Pediatr.*, **149**, 734–737

Jörres, R. & Magnussen, H. (1992) Influence of short-term passive smoking on symptoms, lung mechanics and airway responsiveness in asthmatic subjects and healthy controls. *Eur. respir. J.*, **5**, 936–944

Kado, N.Y., Tesluk, S.J., Hammond, S.K., Woskie, S.R., Samuels, S.J. & Schenker, M.B. (1987) Use of a Salmonella micro pre-incubation procedure for studying personal exposure to muta-

gens in environmental tobacco smoke: Pilot study of urine and airborne mutagenicity from passive smoking. In: Sandhu, S.S., DeMarini, D.M., Mass, M.J., Moore, M.M. & Mumford, J.L., eds, *Short-term Bioassays in the Analysis of Complex Environmental Mixtures V*, New York, Plenum Press, pp. 375–390

Kado, N.Y., McCurdy, S.A., Tesluk, S.J., Hammond, S.K., Hsieh, D.P.H., Jones, J. & Schenker, M.B. (1991) Measuring personal exposure to airborne mutagens and nicotine in environmental tobacco smoke. *Mutat. Res*., **261**, 75–82

Kahn, H.A. (1966) The Dorn study of smoking and mortality among US veterans: Report on eight and one-half years of observation. *Natl Cancer Inst. Monogr*., **19**, 1–125

Kalandidi, A., Trichopoulos, D., Hatzakis, A., Tzannes, S. & Saracci, R. (1987) Passive smoking and chronic obstructive lung disease. *Lancet*, **ii**, 1325–1326

Kalandidi, A., Trichopoulos, D., Hatzakis, A., Tzannes, S. & Saracci, R. (1990) The effect of involuntary smoking on the occurrence of chronic obstructive pulmonary disease. *Soz. Präventivmed*., **35**, 12–16

Kauffmann, F. & Perdrizet, S. (1981) Effect of passive smoking on respiratory function. *Eur. J. respir. Dis*., **62** (Suppl. 113), 109–110

Kauffmann, F., Tessier, J.-F. & Oriol, P. (1983) Adult passive smoking in the home environment: A risk factor for chronic airflow limitation. *Am. J. Epidemiol.*, **117**, 269–280

Kauffmann, F., Dockery, D.W., Speizer, F.E. & Ferris, B.G., Jr (1989) Respiratory symptoms and lung function in relation to passive smoking: A comparative study of American and French women. *Int. J. Epidemiol*., **18**, 334–344

Kawachi, I., Colditz, G.A., Speizer, F.E., Manson, J.E., Stampfer, M.J., Willett, W.C. & Hennekens, C.H. (1997) A prospective study of passive smoking and coronary heart disease. *Circulation*, **95**, 2374–2379

Kawamoto, T., Yoshikawa, M., Matsuno, K., Kayama, F., Oyama, T., Arashidani, K. & Kodama, Y. (1993) Effect of side-stream cigarette smoke on the hepatic cytochrome P450. *Arch. environ. Contam. Toxicol.*, **25**, 255–259

Keith, R.E. & Driskell, J.A. (1980) Effects of chronic cigarette smoking on vitamin C status, lung function, and resting and exercise cardiovascular metabolism in humans. *Nutr. Rep. int*., **21**, 907–912

Kentner, M., Triebig, G. & Weltle, D. (1984) The influence of passive smoking on pulmonary function — A study of 1351 office workers. *Prev. Med*., **13**, 656–669

Knight, A. & Breslin, A.B.X. (1985) Passive cigarette smoking and patients with asthma. *Med. J. Aust*., **142**, 194–195

Köhler, E., Bretschneider, D., Rabsilber, A., Weise, W. & Jorch, G. (2001) Assessment of prenatal smoke exposure by determining nicotine and its metabolites in maternal and neonatal urine. *Hum. exp. Toxicol*., **20**, 1–7

Kondo, K., Tsuzuki, H., Sasa, M., Sumitomo, M., Uyama, T. & Monden, Y. (1996) A dose–response relationship between the frequency of p53 mutations and tobacco consumption in lung cancer patients. *J. surg. Oncol*., **61**, 20–26

Kopplin, A., Eberle-Adamkiewicz, G., Glüsenkamp, K.-H., Nehls, P. & Kirstein, U. (1995) Urinary excretion of 3-methyladenine and 3-ethyladenine after controlled exposure to tobacco smoke. *Carcinogenesis*, **16**, 2637–2641

Kritz, H., Schmid, P. & Sinzinger, H. (1995) Passive smoking and cardiovascular risk. *Arch. intern. Med*., **155**, 1942–1948

Künzli, N., Schwartz, J., Stutz, E.Z., Ackermann-Liebrich, U. & Leuenberger, P. (2000) Association of environmental tobacco smoke at work and forced expiratory lung function among never smoking asthmatics and non-asthmatics. (The SAPALDIA-Team, Swiss Study on Air Pollution and Lung Disease in Adults). *Soz. Präventivmed.*, **45**, 208–217

Kurata, T., Suzuki, E., Hayashi, M. & Kaminao, M. (1998) Physiological role of L-ascorbic acid in rats exposed to cigarette smoke. *Biosci. Biotechnol. Biochem.*, **62**, 842–845

La Vecchia, C., D'Avanzo, B., Franzosi, M.G. & Tognoni, G. (1993) Passive smoking and the risk of acute myocardial infarction. *Lancet*, **341**, 505–506

Lackmann, G.M., Salzberger, U., Töllner, U., Chen, M., Carmella, S.G. & Hecht, S.S. (1999) Metabolites of a tobacco-specific carcinogen in urine from newborns. *J. natl Cancer Inst*., **91**, 459–465

Lam, T.H., Zhu, C.Q. & Jiang, C.Q. (2002) Lymphocyte DNA damage in elevator manufacturing workers in Guangzhou, China. *Mutat. Res.*, **515**, 147–157

Laranjeira, R., Pillon, S. & Dunn, J. (2000) Environmental tobacco smoke exposure among non-smoking waiters: Measurement of expired carbon monoxide levels. *Sao Paulo med. J.*, **118**, 89–92

Larkin, F.A., Basiotis, P.P., Riddick, H.A., Sykes, K.E. & Pao, E.M. (1990) Dietary patterns of women smokers and non-smokers. *J. Am. Diet. Assoc*., **90**, 230–237

Laurent, A.M., Bevan, A., Chakroun, N., Courtois, Y., Valois, B., Roussel, M., Festy, B. & Pretet, S. (1992) [Effects of chronic exposure to tobacco smoke on the health of non-smokers]. *Rev. Pneumol. clin*., **48**, 65–70 (in French)

La Vecchia, C., D'Avanzo, B., Franzosi, M.G. & Tognoni, G. (1993) Passive smoking and the risk of acute myocardial infarction. *Lancet*, **341**, 505–506

Law, M.R., Morris, J.K. & Wald, N.J. (1997) Environmental tobacco smoke exposure and ischaemic heart disease: An evaluation of the evidence. *Br. med. J*., **315**, 973–980

Layard, M.W. (1995) Ischemic heart disease and spousal smoking in the National Mortality Followback Survey. *Regul. Toxicol. Pharmacol*., **21**, 180–183

Lebowitz, M.D. (1984a) Influence of passive smoking on pulmonary function: A survey. *Prev. Med*., **13**, 645–655

Lebowitz, M.D. (1984b) The effects of environmental tobacco smoke exposure and gas stoves on daily peak flow rates in asthmatic and non-asthmatic families. *Eur. J. respir. Dis.*, **65** (Suppl. 133), 90–97

Lebowitz, M.D. & Burrows, B. (1976) Respiratory symptoms related to smoking habits of family adults. *Chest*, **69**, 48–50

Lebowitz, M.D., Quackenboss, J.J., Krzyzanowski, M., O'Rourke, M.K. & Hayes, C. (1992) Multipollutant exposures and health responses to particulate matter. *Arch. environ. Health*, **47**, 71–75

Lee, P.N. (1992) *Environmental Tobacco Smoke and Mortality*, Basel, Karger

Lee, P.N., Chamberlain, J. & Alderson, M.R. (1986) Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. *Br. J. Cancer*, **54**, 97–105

Lee, C.K., Brown, B.G., Reed, E.A., Rahn, C.A., Coggins, C.R.E., Doolittle, D.J. & Hayes, A.W. (1992) Fourteen-day inhalation study in rats, using aged and diluted sidestream smoke from a reference cigarette. II. DNA adducts and alveolar macrophage cytogenetics. *Fundam. appl. Toxicol*., **19**, 141–146

Lee, C.K., Brown, B.G., Reed, E.A., Coggins, C.R.E., Doolittle, D.J. & Hayes, A.W. (1993) Ninety-day inhalation study in rats, using aged and diluted sidestream smoke from a reference cigarette: DNA adducts and alveolar macrophage cytogenetics. *Fundam. appl. Toxicol.*, **20**, 393–401

Lee, C.Z., Royce, F.H., Denison, M.S. & Pinkerton, K.E. (2000) Effect of in utero and postnatal exposure to environmental tobacco smoke on the developmental expression of pulmonary cytochrome P450 monooxygenases. *J. biochem. Toxicol.*, **14**, 121–130

Leichter, J. (1989) Growth of fetuses of rats exposed to ethanol and cigarette smoke during gestation. *Growth Dev. Aging*, **53**, 129–134

Le Marchand, L., Wilkens, L.R., Hankin, J.H. & Haley, N.J. (1991) Dietary patterns of female nonsmokers with and without exposure to environmental tobacco smoke. *Cancer Causes Control,* **2**, 11–16

Leuenberger, P., Schwartz, J., Ackermann-Liebrich, U., Blaser, K., Bolognini, G., Bongard, J.P., Brandli, O., Braun, P., Bron, C., Brutsche, M., Domenighetti, G., Elsasser, S., Guldimann, P., Hollenstein, C., Hufschmid, P., Karrer, W., Keller, R., Keller-Wossidlo, H., Kunzli, N., Luthi, J.C., Martin, B.W., Medici, T., Perruchoud, A.P., Radaelli, A., Schindler, C., Schoeni, M.H., Solari, G., Tschopp, J.M., Villiger, B., Wuthrich, B., Zellweger, J.P. & Zemp, E. (Swiss Study on Air Pollution and Lung Diseases in Adults, SAPALDIA Team) (1994) Passive smoking exposure in adults and chronic respiratory symptoms (SAPALDIA Study). *Am. J. respir. crit. Care Med*., **150**, 1222–1228

LeVois, M.E. & Layard, M.W. (1995) Publication bias in the environmental tobacco smoke/coronary heart disease epidemiologic literature. *Regul. Toxicol. Pharmacol*., **21**, 184–191

Leyden, D.E., Leitner, E. & Siegmund, B. (1999) Determination of nicotine in pharmaceutical products and dietary sources. In: Gorrod, J.W. & Jacob, P., III, *Analytical Determination of Nicotine and Related Compounds and their Metabolites*, Amsterdam, Elsevier, pp. 393–421

Lindbohm, M.-L., Sallmén, M. & Taskinen, H. (2002) Effects of exposure to environmental tobacco smoke on reproductive health. *Scand. J. Work Environ. Health*, **28** (Suppl. 2), 84–96

Ling, P.I., Löfroth, G. & Lewtas, J. (1987) Mutagenic determination of passive smoking. *Toxicol. Lett*., **35**, 147–151

Löfroth, G. & Lazaridis, G. (1986) Environmental tobacco smoke: Comparative characterization by mutagenicity assays of sidestream and mainstream cigarette smoke. *Environ. Mutag*., **8**, 693–704

Maclure, M., Katz, R.B.-A., Bryant, M.S., Skipper, P.L. & Tannenbaum, S.R. (1989) Elevated blood levels of carcinogens in passive smokers. *Am. J. public Health*, **79**, 1381–1384

Maehira, F., Miyagi, I., Asato, T., Eguchi, Y., Takei, H., Nakatsuki, K., Fukuoka, M. & Zaha, F. (1999) Alterations of protein kinase C, 8-hydroxydeoxyguanosine, and K-ras oncogene in rat lungs exposed to passive smoking. *Clin. chim. Acta*, **289**, 133–144

Magnussen, H., Jörres, R. & Oldigs, M. (1992) Effect of one hour of passive cigarette smoking on lung function and airway responsiveness in adults and children with asthma. *Clin. Invest*., **70**, 368–371

Malaveille, C., Vineis, P., Estève, J., Ohshima, H., Brun, G., Hautefeuille, A., Gallet, P., Ronco, G., Terracini, B. & Bartsch, H. (1989) Levels of mutagens in the urine of smokers of black and blond tobacco correlate with their risk of bladder cancer. *Carcinogenesis*, **10**, 577–586

Manchester, D.K. & Jacoby, E.H. (1981) Sensitivity of human placental monooxygenase activity to maternal smoking. *Clin. Pharmacol. Ther.*, **30**, 687–692

Marchetti, A., Pellegrini, S., Sozzi, G., Bertacca, G., Gaeta, P., Buttitta, F., Carnicelli, V., Griseri, P., Chella, A., Angeletti, C.A., Pierotti, M. & Bevilacqua, G. (1998) Genetic analysis of lung tumours of non-smoking subjects: p53 Gene mutations are constantly associated with loss of heterozygosity at the FHIT locus. *Br. J. Cancer*, **78**, 73–78

Margetts, B.M. & Jackson, A.A. (1993) Interactions between people's diet and their smoking habits: The dietary and nutritional survey of British adults. *Br. med. J*., **307**, 1381–1384

Masi, M.A., Hanley, J.A., Ernst, P. & Becklake, M.R. (1988) Environmental exposure to tobacco smoke and lung function in young adults. *Am. Rev. respir. Dis*., **138**, 296–299

Masjedi, M.-R., Kazemi, H. & Johnson, D.C. (1990) Effects of passive smoking on the pulmonary function of adults. *Thorax*, **45**, 27–31

Maskarinec, M.P., Jenkins, R.A., Counts, R.W. & Dindal, A.B. (2000) Determination of exposure to environmental tobacco smoke in restaurant and tavern workers in one US city. *J. Expo. anal. environ. Epidemiol*., **10**, 36–49

Matsunga, S.K., Plezia, P.M., Karol, M.D., Katz, M.D., Camilli, A.E. & Benowitz, N.L. (1989) Effects of passive smoking on theophylline clearance. *Clin. Pharmacol. Ther*., **46**, 399–407

Matthews, S.J., Hecht, S.S., Picton, H.M., Ye, M., Carmella, S.G., Shires, S., Wild, C.P. & Hay, A.W.M. (2002) No association between smoking and the presence of tobacco-specific nitrosamine metabolites in ovarian follicular fluid. *Cancer Epidemiol. Biomarkers Prev.*, **11**, 321–322

Mattson, M.E., Boyd, G., Byar, D., Brown, C., Callahan, J.F., Corle, D., Cullen, J.W., Greenblatt, J., Haley, N.J., Hammond, S.K., Lewtas, J. & Reeves, W. (1989) Passive smoking on commercial airline flights. *J. Am. med. Assoc*., **261**, 867–872

McPhillips, J.B., Eaton, C.B., Gans, K.M., Derby, C.A., Lasater, T.M., McKenney, J.L. & Carleton, R.A. (1994) Dietary differences in smokers and nonsmokers from two southeastern New England communities. *J. Am. Diet. Assoc*., **94**, 287–292

Meger, M., Meger-Kossien, I., Riedel, K. & Scherer, G. (2000) Biomonitoring of environmental tobacco smoke (ETS)-related exposure to 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). *Biomarkers*, **5**, 33–45

Menon, P.K., Stankus, R.P., Rando, R.J., Salvaggio, J.E. & Lehrer, S.B. (1991) Asthmatic responses to passive cigarette smoke: Persistence of reactivity and effect of medications. *J. Allergy clin. Immunol*., **88**, 861–869

Menon, P.K., Rando, R.J., Stankus, R.P., Salvaggio, J.E. & Lehrer, S.B. (1992) Passive cigarette smoke-challenge studies: Increase in bronchial hyperreactivity. *J. Allergy clin. Immunol*., **89**, 560–566

von Meyerinck, L., Scherer, G., Adlkofer, F., Wenzel-Hartung, R., Brune, H. & Thomas, C. (1989) Exposure of rats and hamsters to sidestream smoke from cigarettes in a subchronic inhalation study. *Exp. Pathol.*, **37**, 186–189

Midgette, A.S., Baron, J.A. & Rohan, T.E. (1993) Do cigarette smokers have diets that increase their risks of coronary heart disease and cancer? *Am. J. Epidemiol*., **137**, 521–529

Milunsky, A., Carmella, S.G., Ye, M. & Hecht, S.S. (2000) A tobacco-specific carcinogen in the fetus. *Prenat. Diagn.*, **20**, 307–310

Mohtashamipur, E., Norpoth, K. & Straeter, H. (1987) Clastogenic effect of passive smoking on bone marrow polychromatic erythrocytes of NMRI mice. *Toxicol. Lett*., **35**, 153–156

Mohtashamipur, E., Steinforth, T. & Norpoth, K. (1988) Comparative bone marrow clastogenicity of cigarette sidestream, mainstream and recombined smoke condensates in mice. *Mutagenesis*, **3**, 419–422

Mooney, L.A., Santella, R.M., Covey, L., Jeffrey, A.M., Bigbee, W., Randall, M.C., Cooper, T.B., Ottman, R., Tsai, W.-Y., Wazneh, L., Glassman, A.H., Young, T.-L. & Perera, F.P. (1995) Decline of DNA damage and other biomarkers in peripheral blood following smoking cessation. *Cancer Epidemiol. Biomarkers Prev.*, **4**, 627–634

Morawska, L., Barron, W. & Hitchins, J. (1999) Experimental deposition of environmental tobacco smoke submicrometer particulate matter in the human respiratory tract. *Am. ind. Hyg. Assoc. J.*, **60**, 334–339

Morimoto, Y., Tsuda, T., Hori, H., Yamato, H., Ohgami, A., Hagashi, T., Nagata, N., Kido, M. & Tanaka, I. (1999) Combined effect of cigarette smoke and mineral fibers on the gene expression of cytokine mRNA. *Environ. Health Perspect.*, **107**, 495–500

Muramatsu, T., Weber, A., Muramatsu, S. & Akermann, F. (1983) An experimental study on irritation and annoyance due to passive smoking. *Int. Arch. occup. environ. Health*, **51**, 305–317

Muscat, J.E. & Wynder, E.L. (1995) Exposure to environmental tobacco smoke and the risk of heart attack. *Int. J. Epidemiol.*, **24**, 715–719

Mutoh, T., Bonham, A.C., Kott, K.S. & Joad, J.P. (1999) Chronic exposure to sidestream tobacco smoke augments lung C-fiber responsiveness in young guinea pigs. *J. appl. Physiol.*, **87**, 757–768

Mutoh, T., Joad, J.P. & Bonham, A.C. (2000) Chronic passive cigarette smoke exposure augments bronchopulmonary C-fibre inputs to nucleus tractus solitarii neurones and reflex output in young guinea-pigs. *J. Physiol.*, **523**, 223–233

Myers, S.R., Spinnato, J.A. & Pinorini-Godly, M.T. (1996) Characterization of 4-aminobiphenyl–hemoglobin adducts in maternal and fetal blood samples. *J. Toxicol. environ. Health*, **47**, 553–566

Nadadur, S.S., Pinkerton, K.E. & Kodavanti, U.P. (2002) Pulmonary gene expression profiles of spontaneously hypertensive rats exposed to environmental tobacco smoke. *Chest*, **121**, 83S–84S

Nafstad, P., Jaakkola, J.J.K., Hagen, J.A., Zahlsen, K. & Magnus, P. (1997) Hair nicotine concentrations in mothers and children in relation to parental smoking. *J. Expo. anal. environ. Epidemiol.*, **7**, 235–239

Ng, T.P., Hui, K.P. & Tan, W.C. (1993) Respiratory symptoms and lung function effects of domestic exposure to tobacco smoke and cooking by gas in non-smoking women in Singapore. *J. Epidemiol. Community Health*, **47**, 454–458

Nowak, D., Jörres, R., Schmidt, A. & Magnussen, H. (1997) Effect of 3 hours' passive smoke exposure in the evening on airway tone and responsiveness until next morning. *Int. Arch. occup. environ. Health*, **69**, 125–133

Nuttens, M.C., Romon, M., Ruidavets, J.B., Arveiler, D., Ducimetiere, P., Lecerf, J.M., Richard, J.L., Cambou, J.P., Simon, C. & Salomez, J.L. (1992) Relationship between smoking and diet: The MONICA-France project. *J. intern. Med.*, **231**, 349–356

Oberdörster, G. & Pott, F. (1986) Extrapolation from rat studies with environmental tobacco smoke (ETS) to humans: Comparison of particle mass deposition and of clearance behavior of ETS compounds. *Toxicol. Lett.*, **35**, 107–112

Oddoze, C., Pauli, A.M. & Pastor, J. (1998) Rapid and sensitive high-performance liquid chromatographic determination of nicotine and cotinine in nonsmoker human and rat urines. *J. Chromatogr.*, **B708**, 95–101

Olson, J.W. (1985) Chronic cigarette sidestream smoke exposure increases rat trachea ornithine decarboxylase activity. *Life Sci.*, **37**, 2165–2171

Ostro, B.D., Lipsett, M.J., Mann, J.K., Wiener, M.B. & Selner, J. (1994) Indoor air pollution and asthma. Results from a panel study. *Am. J. respir. crit. Care Med*., **149**, 1400–1406

Otsuka, R., Watanabe, H., Hirata, K., Tokai, K., Muro, T., Yoshiyama, M., Takeuchi, K. & Yoshikawa, J. (2001) Acute effects of passive smoking on the coronary circulation in healthy young adults. *J. Am. med. Assoc*., **286**, 436–441

Parsons, W.D., Carmella, S.G., Akerkar, S., Bonilla, L.E. & Hecht, S.S. (1998) A metabolite of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in the urine of hospital workers exposed to environmental tobacco smoke. *Cancer Epidemiol. Biomarkers Prev.*, **7**, 257–260

Pastrakuljic, A., Schwartz, R., Simone, C., Derewlany, L.O., Knie, B. & Koren, G. (1998) Transplacental transfer and biotransformation studies of nicotine in the human placental cotyledon perfused in vitro. *Life Sci*., **63**, 2333–2342

Penn, A. & Snyder, C.A. (1993) Inhalation of sidestream cigarette smoke accelerates development of arteriosclerotic plaques. *Circulation*, **88**, 1820–1825

Penn, A., Chen, L.-C. & Snyder, C.A. (1994) Inhalation of steady-state sidestream smoke from one cigarette promotes arteriosclerotic plaque development. *Circulation*, **90**, 1363–1367

Pérez-Stable, E.J,. Marín, G., Marín, B.V. & Benowitz, N.L. (1992) Misclassification of smoking status by self-reported cigarette consumption. *Am. Rev. respir. Dis*., **145**, 53–57

Petruzzelli, S., Celi, A., Pulerà, N., Baliva, F., Viegi, G., Carrozzi, L., Ciacchini, G., Bottai, M., Di Pede, F., Paoletti, P. & Giuntini, C. (1998) Serum antibodies to benzo(*a*)pyrene diol epoxide–DNA adducts in the general population: Effects of air pollution, tobacco smoking, and family history of lung diseases. *Cancer Res.*, **58**, 4122–4126

Pichini, S., Basagaña, X., Pacifici, R., Garcia, O., Puig, C., Vall, O., Harris, J., Zuccaro, P., Segura, J. & Sunyer, J. (2000) Cord serum cotinine as a biomarker of fetal exposure to cigarette smoke at the end of pregnancy. *Environ. Health Perspect*., **108**, 1079–1083

Pignatelli, B., Li, C.-Q., Boffetta, P., Chen, Q., Ahrens, W., Nyberg, F., Mukeria, A., Bruske-Hohlfeld, I., Fortes, C., Constantinescu, V., Ischiropoulos, H. & Ohshima, H. (2001) Nitrated and oxidized plasma proteins in smokers and lung cancer patients. *Cancer Res.*, **61**, 778–784

Pilger, A., Germadnik, D., Riedel, K., Meger-Kossien, I., Scherer, G. & Rüdiger, H.W. (2001) Longitudinal study of urinary 8-hydroxy-2′-deoxyguanosine excretion in healthy adults. *Free Radic. Res.*, **35**, 273–280

Pimm, P.E., Shephard, R.J. & Silverman, F. (1978) Physiological effects of acute passive exposure to cigarette smoke. *Arch. environ. Health*, **33**, 201–213

Pirkle, J.L., Flegal, K.M., Bernert, J.T., Brody, D.J., Etzel, R.A. & Maurer, K.R. (1996) Exposure of the US population to environmental tobacco smoke: The Third National Health and Nutrition Examination Survey, 1988 to 1991. *J. Am. med. Assoc*., **275**, 1233–1240

Pooling Project Research Group (1978) Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: Final report of the pooling project. *J. chron. Dis*., **31**, 201–306

Pope, C.A., III, Eatough, D.J., Gold, D.R., Pang, Y., Nielsen, K.R., Nath, P., Verrier, R.L. & Kanner, R.E. (2001) Acute exposure to environmental tobacco smoke and heart rate variability. *Environ. Health Perspect*., **109**, 711–716

Rajini, P. & Witschi, H. (1994) Short-term effects of sidestream smoke on respiratory epithelium in mice: Cell kinetics. *Fundam. appl. Toxicol*., **22**, 405–410

Rajini, P., Last, J.A., Pinkerton, K.E., Hendrickx, A.G. & Witschi, H. (1994) Decreased fetal weights in rats exposed to sidestream cigarette smoke. *Fundam. appl. Toxicology*, **22**, 400–404

Repace, J.L. (1994) Dietary nicotine. Won't mislead on passive smoking… *Br. med. J.*, **308**, 61–62

Riboli, E., Preston-Martin, S., Saracci, R., Haley, N.J., Trichopoulos, D., Becher, H., Burch, J.D., Fontham, E.T.H., Gao, Y.-T., Jindal, S.K., Koo, L.C., Le Marchand, L., Segnan, N., Shimizu, H., Stanta, G., Wu-Williams, A.H. & Zatonski, W. (1990) Exposure of nonsmoking women to environmental tobacco smoke: A 10-country collaborative study. *Cancer Causes Control*, **1**, 243–252

Riboli, E., Haley, N.J., Trédaniel, J., Saracci, R., Preston-Martin, S. & Trichopoulos, D. (1995) Misclassification of smoking status among women in relation to exposure to environmental tobacco smoke. *Eur. respir. J.*, **8**, 285–290

Richter, E., Rösler, S., Scherer, G., Gostomzyk, J.G., Grübl, A., Krämer, U. & Behrendt, H. (2001) Haemoglobin adducts from aromatic amines in children in relation to area of residence and exposure to environmental tobacco smoke. *Int. Arch. occup. environ. Health*, **74**, 421–428

Robbins, A.S., Abbey, D.E. & Lebowitz, M.D. (1993) Passive smoking and chronic respiratory disease symptoms in non-smoking adults. *Int. J. Epidemiol*., **22**, 809–817

Roberts, K.A., Rezai, A.A., Pinkerton, K.E. & Rutledge, J.C. (1996) Effect of environmental tobacco smoke on LDL accumulation in the artery wall. *Circulation*, **94**, 2248–2253

Robertson, A.S., Burge, P.S. & Cockrill, B.L. (1987) A study of serum thiocyanate concentrations in office workers as a means of validating smoking histories and assessing passive exposure to cigarette smoke. *Br. J. ind. Med.*, **44**, 351–354

Rodenhuis, S. & Slebos, R.J.C. (1992) Clinical significance of *ras* oncogene activation in human lung cancer. *Cancer Res.*, **52** (Suppl.), 2665s–2669s

Rodenhuis, S., Slebos, R.J.C., Boot, A.J.M., Evers, S.G., Mooi, W.J., Wagenaar, S.S., van Bodegom, P.C. & Bos, J.L. (1988) Incidence and possible clinical significance of K-*ras* oncogene activation in adenocarcinoma of the human lung. *Cancer Res.*, **48**, 5738–5741

Rogot, E. & Murray, J.L. (1980) Smoking and causes of death among US veterans: 16 years of observation. *Public Health Rep.*, **95**, 213–222

Ruppert, T., Scherer, G., Tricker, A.R. & Adlkofer, F. (1997) *trans*,*trans*-Muconic acid as a biomarker of non-occupational environmental exposure to benzene. *Int. Arch. occup. environ. Health*, **69**, 247–251

Russell, M.A.H., Cole, P.V. & Brown, E. (1973) Absorption by non-smokers of carbon monoxide from room air polluted by tobacco smoke. *Lancet*, **i**, 576–579

Sadler, L., Belanger, K., Saftlas, A., Leaderer, B., Hellenbrand, K., McSharry, J.-E. & Bracken, M.B. (1999) Environmental tobacco smoke exposure and small-for-gestational-age birth. *Am. J. Epidemiol.*, **150**, 695–705

Salem, E.S., El Zahby, M., Senna, G.A. & Malek, A. (1984) [Pulmonary manifestations among 'passive smokers'.] *Bull. Union int. Tubercul.*, **59**, 52–56 (in French)

Salomaa, S., Tuominen, J. & Skyttä, E. (1988) Genotoxicity and PAC analysis of particulate and vapour phases of environmental tobacco smoke. *Mutat. Res.*, **204**, 173–183

Sandler, D.P., Comstock, G.W., Helsing, K.J. & Shore, D.L. (1989) Deaths from all causes in non-smokers who lived with smokers. *Am. J. public Health*, **79**, 163–167

Sasson, I.M., Coleman, D.T., LaVoie, E.J., Hoffmann, D. & Wynder, E.L. (1985) Mutagens in human urine: Effects of cigarette smoking and diet. *Mutat. Res.*, **158**, 149–157

Sastry, B.V.R., Chance, M.B., Hemontolor, M.E. & Goddijn-Wessel, T.A.W. (1998) Formation and retention of cotinine during placental transfer of nicotine in human placental cotyledon. *Pharmacology*, **57**, 104–116

Scherer, G. & Richter, E. (1997) Biomonitoring exposure to environmental tobacco smoke (ETS): A critical reappraisal. *Hum. exp. Toxicol.*, **16**, 449–459

Scherer, G., Conze, C., von Meyerinck, L., Sorsa, M. & Adlkofer, F. (1990) Importance of exposure to gaseous and particulate phase components of tobacco smoke in active and passive smokers. *Int. Arch. occup. environ. Health*, **62**, 459–466

Scherer, G., Conze, C., Tricker, A.R. & Adlkofer, F. (1992) Uptake of tobacco smoke constituents on exposure to environmental tobacco smoke (ETS). *Clin. Invest.*, **70**, 352–367

Scherer, G., Ruppert, T., Daube, H., Kossien, I., Riedel, K., Tricker, A.R. & Adlkofer, F. (1995) Contribution of tobacco smoke to environmental benzene exposure in Germany. *Environ. int.*, **21**, 779–789

Scherer, G., Doolittle, D.J., Ruppert, T., Meger-Kossien, I., Riedel, K., Tricker, A.R. & Adlkofer, F. (1996) Urinary mutagenicity and thioethers in nonsmokers: Role of environmental tobacco smoke (ETS) and diet. *Mutat. Res*., **368**, 195–204

Scherer, G., Meger-Kossien, I., Riedel, K., Renner, T. & Meger, M. (1999) Assessment of the exposure of children to environmental tobacco smoke (ETS) by different methods. *Hum. exp. Toxicol.*, **18**, 297–301

Scherer, G., Frank, S., Riedel, K., Meger-Kossien, I. & Renner, T. (2000) Biomonitoring of exposure to polycyclic aromatic hydrocarbons of nonoccupationally exposed persons. *Cancer Epidemiol. Biomarkers Prevent.*, **9**, 373–380

Schilling, R.S.F., Letai, A.D., Hui, S.L., Beck, G.J., Schoenberg, J.B. & Bouhuys, A. (1977) Lung function, respiratory disease, and smoking in families. *Am. J. Epidemiol*., **106**, 274–283

Schmidt, K.G. & Rasmussen, J.W. (1984) Acute platelet activation induced by smoking. *In vivo* and *ex vivo* studies in humans. *Thromb. Haemostas*., **51**, 279–282

Schwartz, J. & Zeger, S. (1990) Passive smoking, air pollution, and acute respiratory symptoms in a diary study of student nurses. *Am. Rev. respir. Dis*., **141**, 62–67

Seidman, D.S., Paz, I., Merlet-Aharoni, I., Vreman, H., Stevenson, D.K. & Gale, R. (1999) Non-invasive validation of tobacco smoke exposure in late pregnancy using end-tidal carbon monoxide measurements. *J. Perinatol.*, **19**, 358–361

Seymour, B.W.P., Pinkerton, K.E., Friebertshauser, K.E., Coffman, R.L. & Gershwin, L.J. (1997) Second-hand smoke is an adjuvant for T helper-2 responses in a murine model of allergy. *J. Immunol.*, **159**, 6169–6175

Sheen, S.J. (1988) Detection of nicotine in foods and plant materials. *J. Food Sci.*, **53**, 1572–1573

Shephard, R.J., Collins, R. & Silverman, F. (1979a) Responses of exercising subjects to acute 'passive' cigarette smoke exposure. *Environ. Res*., **19**, 279–291

Shephard, R.J., Collins, R. & Silverman, F. (1979b) 'Passive' exposure of asthmatic subjects to cigarette smoke. *Environ. Res*., **20**, 392–402

Shephard, R.J., Ponsford, E., LaBarre, R. & Basu, P.K. (1979c) Effect of cigarette smoke on the eyes and airway. *Int. Arch. occup. environ. Health*, **43**, 135–144

Shinozaki, R., Inoue, S., Choi, K.-S. & Tatsuno, T. (1999) Association of benzo[*a*]pyrene-diol-epoxide–deoxyribonucleic acid (BPDE–DNA) adduct level with aging in male smokers and nonsmokers. *Arch. environ. Health*, **54**, 79–85

Sidney, S., Caan, B.J. & Friedman, G.D. (1989) Dietary intake of carotene in nonsmokers with and without passive smoking at home. *Am. J. Epidemiol*., **129**, 1305–1309

Siegel, M. (1993) Involuntary smoking in the restaurant workplace. A review of employee exposure and health effects. *J. Am. med. Assoc.*, **270**, 490–493

Sindhu, R.K., Rasmussen, R.E., Yamamoto, R., Fujita, I. & Kikkawa, Y. (1995) Depression of hepatic cytochrome P450 monooxygenases after chronic environmental tobacco smoke exposure of young ferrets. *Toxicol. Lett.*, **76**, 227–238

Siwinska, E., Mielzynska, D., Bubak, A. & Smolik, E. (1999) The effect of coal stoves and environmental tobacco smoke on the level of urinary 1-hydroxypyrene. *Mutat. Res.*, **445**, 147–153

Slebos, R.J.C., Hruban, R.H., Dalesio, O., Mooi, W.J., Offerhaus, G.J.A. & Rodenhuis, S. (1991) Relationship between K-ras oncogene activation and smoking in adenocarcinoma of the human lung. *J. natl Cancer Inst.*, **83**, 1024–1027

Slotkin, T.A., Pinkerton, K.E. & Seidler, F.J. (2000) Perinatal exposure to environmental tobacco smoke alters cell signaling in a primate model: Autonomic receptors and the control of adenylyl cyclase activity in heart and lung. *Dev. Brain Res*., **124**, 53–58

Slotkin, T.A., Pinkerton, K.E., Garofolo, M.C., Auman, J.T., McCook, E.C. & Seidler, F.J. (2001) Perinatal exposure to environmental tobacco smoke induces adenylyl cyclase and alters receptor-mediated cell signaling in brain and heart of neonatal rats. *Brain Res*., **898**, 73–81

Smith, C.J., Bombick, D.W., Ryan, B.A., Morgan, W.T. & Doolittle, D.J. (2000) Urinary mutagenicity in nonsmokers following exposure to fresh diluted sidestream cigarette smoke. *Mutat. Res.*, **470**, 53–70

Smith, C.J., Bombick, D.W., Ryan, B.A., Morton, M.J. & Doolittle, D.J. (2001) Pulmonary function in nonsmokers following exposure to sidestream cigarette smoke. *Toxicol. Pathol*., **29**, 260–264

Sorsa, M. & Husgafvel-Pursiainen, K. (1988) Assessment of passive and transplacental exposure to tobacco smoke. In: Bartsch, H., Hemminki, K. & O'Neill, I.K., eds, *Methods for Detecting DNA Damaging Agents in Humans: Applications in Cancer Epidemiology and Prevention* (IARC Scientific Publications No. 89), Lyon, IARC*Press*, pp. 129–132

Sorsa, M. & Löfroth, G., eds (1989) *Environmental Tobacco Smoke and Passive Smoking*, Amsterdam, Elsevier Science

Sorsa, M., Einistö, P., Husgafvel-Pursiainen, K., Järventaus, H., Kivistö, H., Peltonen, Y., Tuomi, T., Valkonen, S. & Pelkonen, O. (1985) Passive and active exposure to cigarette smoke in a smoking experiment. *J. Toxicol. environ. Health*, **16**, 523–534

Sorsa, M., Husgafvel-Pursiainen, K., Järventaus, H., Koskimies, K., Salo, H. & Vainio, H. (1989) Cytogenetic effects of tobacco smoke exposure among involuntary smokers. *Mutat. Res*., **222**, 111–116

Spector, S., Luparello, T.J., Kopetzky, M.T., Souhrada, J. & Kinsman, R.A. (1976) Response of asthmatics to methacholine and suggestion. *Am. Rev. respir. Dis*., **113**, 43–50

Speer, F. (1968) Tobacco and the nonsmoker. A study of subjective symptoms. *Arch. environ. Health*, **16**, 443–446

Spitzer, W.O., Lawrence, V., Dales, R., Hill, G., Archer, M.C., Clark, P., Abenhaim, L., Hardy, J., Sampalis, J., Pinfold, S.P. & Morgan, P.P. (1990) Links between passive smoking and disease:

A best-evidence synthesis. A report of the Working Group on Passive Smoking. *Clin. invest. Med*., **13**, 17–42

Stankus, R.P., Menon, P.K., Rando, R.J., Glindmeyer, H., Salvaggio, J.E. & Lehrer, S.B. (1988) Cigarette smoke-sensitive asthma: Challenge studies. *J. Allergy clin. Immunol*., **82**, 331–338

Steenland, K. (1992) Passive smoking and the risk of heart disease. *J. Am. med. Assoc*., **267**, 94–99

Steenland, K., Thun, M., Lally, C. & Heath, C., Jr (1996) Environmental tobacco smoke and coronary heart disease in the American Cancer Society CPS-II cohort. *Circulation*, **94**, 622–628

Stryker, W.S., Kaplan, L.A., Stein, E.A., Stampfer, M.J., Sober, A. & Willett, W.C. (1988) The relation of diet, cigarette smoking, and alcohol consumption to plasma beta-carotene and alpha-tocopherol levels. *Am. J. Epidemiol*., **127**, 283–296

Subar, A.F., Harlan, L.C. & Mattson, M.E. (1990) Food and nutrient intake differences between smokers and non-smokers in the US. *Am. J. public Health*, **80**, 1323–1329

Sun, Y.P., Zhu, B.Q., Browne, A.E., Sievers, R.E., Bekker, J.M., Chatterjee, K., Parmley, W.W. & Glantz, S.A. (2001) Nicotine does not influence arterial lipid deposits in rabbits exposed to second-hand smoke. *Circulation*, **104**, 810–814

Svendsen, K.H., Kuller, L.H., Martin, M.J. & Ockene, J.K. (1987) Effects of passive smoking in the Multiple Risk Factor Intervention Trial. *Am. J. Epidemiol*., **126**, 783–795

Takagi, Y., Osada, H., Kuroishi, T., Mitsudomi, T., Kondo, M., Niimi, T., Saji, S., Gazdar, A.F., Takahashi, T., Minna, J.D. & Takahashi, T. (1998) p53 Mutations in non-small-cell lung cancers occurring in individuals without a past history of active smoking. *Br. J. Cancer*, **77**, 1568–1572

Takenawa, J., Kaneko, Y., Okumura, K., Nakayama, H., Fujita, J. & Yoshida, O. (1994) Urinary excretion of mutagens and covalent DNA damage induced in the bladder and kidney after passive smoking in rats. *Urol. Res.*, **22**, 93–97

Takeshima, Y., Seyama, T., Bennett, W.P., Akiyama, M., Tokuoka, S., Inai, K., Mabuchi, K., Land, C.E. & Harris, C.C. (1993) p53 Mutations in lung cancers from non-smoking atomic-bomb survivors. *Lancet*, **342**, 1520–1521

Tang, D., Warburton, D., Tannenbaum, S.R., Skipper, P., Santella, R.M., Cereijido, G.S., Crawford, F.G. & Perera, F.P. (1999) Molecular and genetic damage from environmental tobacco smoke in young children. *Cancer Epidemiol. Biomarkers Prev.*, **8**, 427–431

Taniguchi, S., Niitsuya, M., Inoue, Y., Katagiri, H., Kadowaki, T. & Aizawa, Y. (1999) Evaluation of passive smoking by measuring urinary trans,trans-muconic acid and exhaled carbon monoxide levels. *Ind. Health*, **37**, 88–94

Tavares, R., Ramos, P., Palminha, J., Bispo, M.A., Paz, I., Bras, A., Rueff, J., Farmer, P.B. & Bailey, E. (1994) Transplacental exposure to genotoxins. Evaluation in haemoglobin of hydroxyethylvaline adduct levels in smoking and non-smoking mothers and their newborns. *Carcinogenesis*, **15**, 1271–1274

Tavares, R., Borba, H., Monteiro, M., Proença, M.J., Lynce, N., Rueff, J., Bailey, E., Sweetman, G.M.A., Lawrence, R.M. & Farmer, P.B. (1996) Monitoring of exposure to acrylonitrile by determination of *N*-(2-cyanoethyl)valine at the N-terminal position of haemoglobin. *Carcinogenesis*, **17**, 2655–2660

Thompson, S.G., Stone, R., Nanchahal, K. & Wald, N.J. (1990) Relation of urinary cotinine concentrations to cigarette smoking and to exposure to other people's smoke. *Thorax*, **45**, 356–361

Thorn, J., Brisman, J. & Torén, K. (2001) Adult-onset asthma is associated with self-reported mold or environmental tobacco smoke exposures in the home. *Allergy*, **56**, 287–292

Thornton, A., Lee, P. & Fry, J. (1994) Differences between smokers, ex-smokers, passive smokers and non-smokers. *J. clin. Epidemiol*., **47**, 1143–1162

Thun, M., Henley, J. & Apicella, L. (1999) Epidemiologic studies of fatal and nonfatal cardiovascular disease and ETS exposure from spousal smoking. *Environ. Health Perspect*., **107** (Suppl. 6), 841–846

Trédaniel, J., Boffetta, P., Saracci, R. & Hirsch, A. (1994) Exposure to environmental tobacco smoke and adult non-neoplastic respiratory diseases. *Eur. respir. J*., **7**, 173–185

Tribble, D.L., Giuliano, L.J. & Fortmann, S.P. (1993) Reduced plasma ascorbic acid concentrations in nonsmokers regularly exposed to environmental tobacco smoke. *Am. J. clin. Nutr.*, **58**, 886–890

Triebig, G. & Zober, M.A. (1984) Indoor air pollution by smoke constituents — A survey. *Prev. Med*., **13**, 570–581

Trout, D., Decker, J., Mueller, C., Bernert, J.T. & Pirkle, J. (1998) Exposure of casino employees to environmental tobacco smoke. *J. occup. environ. Med.*, **40**, 270–276

Tunstall-Pedoe, H., Woodward, M. & Brown, C.A. (1991) The drinking, passive smoking, smoking deception and serum cotinine in the Scottish Heart Health Study. *J. clin. Epidemiol*., **44**, 1411–1414

Tunstall-Pedoe, H., Brown, C.A., Woodward, M. & Tavendale, R. (1995) Passive smoking by self report and serum cotinine and the prevalence of respiratory and coronary heart disease in the Scottish Heart Health Study. *J. Epidemiol. Community Health*, **49**, 139–143

Urch, R.B., Silverman, F., Corey, P., Shephard, R.J., Cole, P. & Goldsmith, L.J. (1988) Does suggestibility modify acute reactions to passive cigarette smoke exposure? *Environ. Res*., **47**, 34–47

US Department of Health, Education and Welfare (DHEW) (1972) *The Health Consequences of Smoking. A Report of the Surgeon General* (DHEW Publ. No. (PHS) 72-7516), Washington DC

US Department of Health and Human Services (DHHS) (1983) *The Health Consequences of Smoking. Cardiovascular Disease. A Report of the Surgeon General* (DHHS Publ. No. (CDC) 84-50204), Rockville, MD

US Department of Health and Human Services (DHHS) (1984) *The Health Consequences of Smoking. Chronic Obstructive Disease. A Report of the Surgeon General* (DHHS Publ. No. (PHS) 84-50205), Rockville, MD

US Department of Health and Human Services (DHHS) (1986) *The Health Consequences of Involuntary Smoking. A Report of the Surgeon General* (DHHS Publ. No. (CDC) 86-8398), Rockville, MD

US Department of Health and Human Services (DHHS) (1990) *The Health Benefits of Smoking Cessation. A Report of the Surgeon General* (DHHS Publ. No. (CDC) 90-8416), Rockville, MD

US Department of Health and Human Services (DHHS) (2001) *Women and Smoking. A Report of the Surgeon General*, Rockville, MD [available at http://www.cdc.gov/tobacco/sgr/sgr_forwomen/index]

US Environmental Protection Agency (EPA, 1992) *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders. The Report of the US Environmental Protection Agency*

(Smoking and Tobacco Control Monograph No. 4; NIH Publ. No. 93-3605), Washington DC [available at http://cfpub.epa.gov/ncea/cfm/ets/etsindex.cfm]

US National Academy of Sciences (1986) *The Airliner Cabin Environment — Air Quality and Safety*, Washington DC, National Academy Press

US National Academy of Sciences (2000) *Clearing the Air: Asthma and Indoor Air Exposures*, Washington DC, National Academy Press

US National Institute for Occupational Safety and Health (NIOSH) (1971) *Health Aspects of Smoking in Transports Aircrafts*, Washington DC, US Government Printing Office

US National Research Council (1986) *Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects*, Washington DC, National Academy Press

Vähäkangas, K.H., Bennett, W.P., Castrén, K., Welsh, J.A., Khan, M.A., Blömeke, B., Alavanja, M.C.-R. & Harris, C.C. (2001) *p53* and K-*ras* Mutations in lung cancers from former and never-smoking women. *Cancer Res.*, **61**, 4350–4356

Van Rooij, J.G.M., Veeger, M.M.S., Bodelier-Bade, M.M., Scheepers, P.T.J. & Jongeneelen, F.J. (1994) Smoking and dietary intake of polycyclic aromatic hydrocarbons as sources of inter-individual variability in the baseline excretion of 1-hydroxypyrene in urine. *Int. Arch. occup. environ. Health*, **66**, 55–65

Vermeulen, R., Wegh, H., Bos, R.P. & Kromhout, H. (2000) Weekly patterns in smoking habits and influence on urinary cotinine and mutagenicity levels: Confounding effect of nonsmoking policies in the workplace. *Cancer Epidemiol. Biomarkers Prev.*, **9**, 1205–1209

Vineis, P. & Malats, N. (1999) Strategic issues in the design and interpretation of studies on metabolic polymorphisms and cancer. In: Vineis, P., Malats, N., Lang, M., d'Errico, A., Caporaso, N., Cuzick, J. & Boffetta, P., eds, *Metabolic Polymorphisms and Susceptibility to Cancer* (IARC Scientific Publication No. 148), Lyon, IARC*Press*, pp. 51–61

Visioli, F., Galli, C., Plasmati, E., Viappiani, S., Hernandez, A., Colombo, C. & Sala, A. (2000) Olive phenol hydroxytyrosol prevents passive smoking-induced oxidative stress. *Circulation*, **102**, 2169–2171

Wagenknecht, L.E., Manolio, T.A., Sidney, S., Burke, G.L. & Haley, N.J. (1993) Environmental tobacco smoke exposure as determined by cotinine in black and white young adults: The CARDIA study. *Environ. Res.*, **63**, 39–46

Wallace, L., Pellizzari, E., Hartwell, T.D., Perritt, R. & Ziegenfus, R. (1987) Exposures to benzene and other volatile compounds from active and passive smoking. *Arch. environ. Health*, **42**, 272–279

Wang, X., Christiani, D.C., Wiencke, J.K., Fischbein, M., Xu, X., Cheng, T.J., Mark, E., Wain, J.C. & Kelsey, K.T. (1995) Mutations in the *p53* gene in lung cancer are associated with cigarette smoking and asbestos exposure. *Cancer Epidemiol. Biomarkers Prev.*, **4**, 543–548

Weaver, V.M., Davoli, C.T., Heller, P.J., Fitzwilliam, A., Peters, H.L., Sunyer, J., Murphy, S.E., Goldstein, G.W. & Groopman, J.D. (1996) Benzene exposure, assessed by urinary *trans*,*trans*-muconic acid, in urban children with elevated blood lead levels. *Environ. Health Perspect.*, **104**, 318–323

Weber, A. (1984a) Annoyance and irritation by passive smoking. *Prev. Med.*, **13**, 618-625

Weber, A. (1984b) Acute effects of environmental tobacco smoke. *Eur. J. respir. Dis.*, **Suppl. 133**, 98–108

Weber, A. & Fischer, T. (1980) Passive smoking at work. *Int. Arch. occup. environ. Health*, **47**, 209–221

Weber, A. & Grandjean, E. (1987) Acute effects of environmental tobacco smoke. In: O'Neill, I.K., Brunnemann, K.D., Dodet, B. & Hoffmann, D., eds, *Environmental Carcinogens: Methods of Analysis and Exposure Measurement* (IARC Scientific Publications No. 81), Lyon, IARC*Press*, pp. 59–68

Weber, A., Jermini, C. & Grandjean, E. (1976) Irritating effects on man of air pollution due to cigarette smoke. *Am. J. public Health*, **66**, 672–676

Weinberg, C.R., Wilcox, A.J. & Baird, D.B. (1989) Reduced fecundability in women with prenatal exposure to cigarette smoking. *Am. J. Epidemiol.*, **129**, 1072–1078

Weiss, S.T., Tager, I.B., Schenker, M. & Speizer, F.E. (1983) The health effects of involuntary smoking. *Am. Rev. respir. Dis*., **128**, 933–942

Weiss, S.T., Utell, M.J. & Samet, J.M. (1999) Environmental tobacco smoke exposure and asthma in adults. *Environ. Health Perspect*., **107** (Suppl. 6), 891–895

Wells, A.J. (1988) An estimate of adult mortality in the United States from passive smoking. *Environ. int*., **14**, 249–265

Wells, A.J. (1994) Passive smoking as a cause of heart disease. *J. Am. Coll. Cardiol*., **24**, 546–554

Wells, A.J. (1998) Heart disease from passive smoking in the workplace. *J. Am. Coll. Cardiol*., **31**, 1–9

Westra, W.H., Slebos, R.J.C., Offerhaus, G.J.A., Goodman, S.N., Evers, S.G., Kensler, T.W., Askin, F.B., Rodenhuis, S. & Hruban, R.H. (1993) K-*ras* oncogen activation in lung adenocarcinoma from former smokers. *Cancer*, **72**, 432–438

White, J.R. & Froeb, H.F. (1980) Small-airways dysfunction in nonsmokers chronically exposed to tobacco smoke. *New Engl. J. Med*., **302**, 720–723

White, J.R., Froeb, H.F. & Kulik, J.A. (1991) Respiratory illness in nonsmokers chronically exposed to tobacco smoke in the work place. *Chest*, **100**, 39–43

Wiedemann, H.P., Mahler, D.A., Loke, J., Virgulto, J.A., Snyder, P. & Matthay, R.A. (1986) Acute effects of passive smoking on lung function and airway reactivity in asthmatic subjects. *Chest*, **89**, 180–185

Wilcox, A.J., Baird, D.D. & Weinberg, C.R. (1989) Do women with childhood exposure to cigarette smoking have increased fecundability? *Am. J. Epidemiol.*, **129**, 1079–1083

Willes, S.R., Fitzgerald, T.K. & Bascom, R. (1992) Nasal inhalation challenge studies with sidestream tobacco smoke. *Arch. environ. Health*, **47**, 223–230

Willes, S.R., Fitzgerald, T.K., Permutt, T., Proud, D., Haley, N.J. & Bascom, R. (1998) Acute respiratory response to prolonged, moderate levels of sidestream tobacco smoke. *J. Toxicol. environ. Health*, **A53**, 193–209

Windham, G.C., Eaton, A. & Hopkins, B. (1999a) Evidence for an association between environmental tobacco smoke exposure and birthweight: A meta-analysis and new data. *Paediatr. perinat. Epidemiol.*, **13**, 35–57

Windham, G.C., Von Behren, J., Waller, K. & Fenster, L. (1999b) Exposure to environmental and mainstream tobacco smoke and risk of spontaneous abortion. *Am. J. Epidemiol.*, **149**, 243–247

Witorsch, P. (1992) Does environmental tobacco smoke (ETS) cause adverse health effects in susceptible individuals? A critical review of the scientific literature: I. Respiratory disorders, atopic allergy and related conditions. *Environ. Technol*., **13**, 323–340

Witschi, H. & Rajini, P. (1994) Cell kinetics in the respiratory tract of hamsters exposed to cigarette sidestream smoke. *Inhal. Toxicol.*, **6**, 321–333

Witschi, H., Lundgaard, S.M., Rajini, P., Hendrickx, A.G. & Last, J.A. (1994) Effects of exposure to nicotine and to sidestream smoke on pregnancy outcome in rats. *Toxicol. Lett.*, **71**, 279–286

Witschi, H., Espiritu, I., Maronpot, R.R., Pinkerton, K.E. & Jones, A.D. (1997a) The carcinogenic potential of the gas phase of environmental tobacco smoke. *Carcinogenesis*, **18**, 2035–2042

Witschi, H., Espiritu, I., Peake, J.L., Wu, K., Maronpot, R.R. & Pinkerton, K.E. (1997b) The carcinogenicity of environmental tobacco smoke. *Carcinogenesis*, **18**, 575–586

Witschi, H., Joad, J.P. & Pinkerton, K.E. (1997c) The toxicology of environmental tobacco smoke. *Ann. Rev. Pharmacol. Toxicol.*, **37**, 29–52

Wu-Williams, A.H. & Samet, J.M. (1990) Environmental tobacco smoke: Exposure–response relationships in epidemiologic studies. *Risk Anal*., **10**, 39–48

Xu, X. & Li, B. (1995) Exposure–response relationship between passive smoking and adult pulmonary function. *Am. J. respir. crit. Care Med*., **151**, 41–46

Yamasaki, E. & Ames, B.N. (1977) Concentration of mutagens from urine by absorption with the nonpolar resin XAD-2: Cigarette smokers have mutagenic urine. *Proc. natl Acad. Sci. USA*, **74**, 3555–3559

Yates, D.H., Breen, H. & Thomas, P.S. (2001) Passive smoke inhalation decreases exhaled nitric oxide in normal subjects. *Am. J. respir. crit. Care Med.*, **164**, 1043–1046

Yu, R. & Weisel, C.P. (1996) Measurement of the urinary benzene metabolite *trans*,*trans*-muconic acid from benzene exposure in humans. *J. Toxicol. environ. Health*, **48**, 453–477

Zahlsen, K., Nilsen, T. & Nilsen, O.G. (1996) Interindividual differences in hair uptake of air nicotine and significance of cigarette counting for estimation of environmental tobacco smoke exposure. *Pharmacol. Toxicol.*, **79**, 183–190

van Zeeland, A.A., de Groot, A.J.L., Hall, J. & Donato, F. (1999) 8-Hydroxydeoxyguanosine in DNA from leukocytes of healthy adults: Relationship with cigarette smoking, environmental tobacco smoke, alcohol and coffee consumption. *Mutat. Res.*, **439**, 249–257

Zenzes, M.T., Puy, L.A. & Bielecki, R. (1998) Immunodetection of benzo[*a*]pyrene adducts in ovarian cells of women exposed to cigarette smoke. *Mol. hum. Reprod.*, **4**, 159–165

Zhu, B.-Q., Sun, Y.-P., Sievers, R.E., Isenberg, W.M., Glantz, S.A. & Parmley, W.W. (1993) Passive smoking increases experimental atherosclerosis in cholesterol-fed rabbits. *J. Am. Coll. Cardiol.*, **21**, 225–232

Zhu, B.Q., Sun, Y.P., Sievers, R.E., Glantz, S.A., Parmley, W.W. & Wolfe, C.L. (1994) Exposure to environmental tobacco smoke increases myocardial infarct size in rats. *Circulation*, **89**, 1282–1290

Zhu, B.Q., Sun, Y.P., Sudhir, K., Sievers, R.E., Browne, A.E., Gao, L., Hutchison, S.J., Chou, T.M., Deedwania, P.C., Chatterjee, K., Glantz, S.A. & Parmley, W.W. (1997) Effects of second-hand smoke and gender on infarct size of young rats exposed in utero and in the neonatal to adolescent period. *J. Am. Coll. Cardiol*., **30**, 1878–1885

Zondervan, K.T., Ocké, M.C., Smit, H.A. & Seidell, J.C. (1996) Do dietary and supplementary intakes of antioxidants differ with smoking status? *Int. J. Epidemiol*., **25**, 70–79

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Involuntary (or passive) smoking is exposure to secondhand tobacco smoke, which is a mixture of exhaled mainstream smoke and sidestream smoke released from the smouldering cigarette or other smoking device (cigars, pipes, bidis, etc.) and diluted with ambient air. Involuntary smoking involves inhaling carcinogens, as well as other toxic components, that are present in secondhand tobacco smoke. Secondhand tobacco smoke is sometimes referred to as 'environmental' tobacco smoke. Carcinogens that occur in secondhand tobacco smoke include benzene, 1,3-butadiene, benzo[*a*]pyrene, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and many others.

Secondhand tobacco smoke consists of a gas phase and a particulate phase; it changes during its dilution and distribution in the environment and upon ageing. The concentrations of respirable particles may be elevated substantially in enclosed spaces containing secondhand tobacco smoke. The composition of tobacco smoke inhaled involuntarily is variable quantitatively and depends on the smoking patterns of the smokers who are producing the smoke as well as the composition and design of the cigarettes or other smoking devices. The secondhand tobacco smoke produced by smoking cigarettes has been most intensively studied.

Secondhand tobacco smoke contains nicotine as well as carcinogens and toxins. Nicotine concentrations in the air in homes of smokers and in workplaces where smoking is permitted typically range on average from 2 to 10 μg/m^3.

5.2 Human carcinogenicity data

Lung cancer

Involuntary smoking involves exposure to the same numerous carcinogens and toxic substances that are present in tobacco smoke produced by active smoking, which is the principal cause of lung cancer. As noted in the previous *IARC Monograph* on tobacco smoking, this implies that there will be some risk of lung cancer from exposure to secondhand tobacco smoke.

More than 50 studies of involuntary smoking and lung cancer risk in never-smokers, especially spouses of smokers, have been published during the last 25 years. These studies

have been carried out in many countries. Most showed an increased risk, especially for persons with higher exposures. To evaluate the information collectively, in particular from those studies with a limited number of cases, meta-analyses have been conducted in which the relative risk estimates from the individual studies are pooled together. These meta-analyses show that there is a statistically significant and consistent association between lung cancer risk in spouses of smokers and exposure to secondhand tobacco smoke from the spouse who smokes. The excess risk is of the order of 20% for women and 30% for men and remains after controlling for some potential sources of bias and confounding. The excess risk increases with increasing exposure. Furthermore, other published meta-analyses of lung cancer in never-smokers exposed to secondhand tobacco smoke at the workplace have found a statistically significant increase in risk of 12–19%. This evidence is sufficient to conclude that involuntary smoking is a cause of lung cancer in never-smokers. The magnitudes of the observed risks are reasonably consistent with predictions based on studies of active smoking in many populations.

Breast cancer

The collective evidence on breast cancer risk associated with involuntary exposure of never-smokers to tobacco smoke is inconsistent. Although four of the 10 case–control studies found statistically significant increases in risks, prospective cohort studies as a whole and, particularly, the two large cohort studies in the USA of nurses and of volunteers in the Cancer Prevention Study II provided no support for a causal relation between involuntary exposure to tobacco smoke and breast cancer in never-smokers. The lack of a positive dose–response also argues against a causal interpretation of these findings. Finally, the lack of an association of breast cancer with active smoking weighs heavily against the possibility that involuntary smoking increases the risk for breast cancer, as no data are available to establish that different mechanisms of carcinogenic action operate at the different dose levels of active and of involuntary smoking.

Childhood cancer

Overall, the findings from studies of childhood cancer and exposure to parental smoking are inconsistent and are likely to be affected by bias. There is a suggestion of a modest association between exposure to maternal tobacco smoke during pregnancy and childhood cancer for all cancer sites combined; however, this is in contrast with the null findings for individual sites. Studies on paternal tobacco smoking suggest a small increased risk for lymphomas, but bias and confounding cannot be ruled out.

Other cancer sites

Data are conflicting and sparse for associations between involuntary smoking and cancers of the nasopharynx, nasal cavity, paranasal sinuses, cervix, gastrointestinal tract and cancers at all sites combined. It is unlikely that any effects are produced in passive

smokers that are not produced to a greater extent in active smokers or that types of effects that are not seen in active smokers will be seen in passive smokers.

5.3 Animal carcinogenicity data

Secondhand tobacco smoke for carcinogenicity studies in animals is produced by machines that simulate human active smoking patterns and combine mainstream and sidestream smoke in various proportions. Such mixtures have been tested for carcinogenicity by inhalation studies in rodents. The experimental model systems for exposure to secondhand tobacco smoke do not fully simulate human exposures, and the tumours that develop in animals are not completely representative of human cancer. Nevertheless, the animal data provide valuable insights regarding the carcinogenic potential of secondhand tobacco smoke.

A mixture of 89% sidestream smoke and 11% mainstream smoke has been tested for carcinogenic activity in mouse strains that are highly susceptible to lung tumours (strains A/J and Swiss). In strain A/J mice, this mixture consistently produces a significant, modest increase in lung tumour incidence and lung tumour multiplicity when the mice are exposed for 5 months followed by a 4-month recovery period. These lung tumours are predominantly adenomas. Continuous exposure of strain A/J mice to the above mixture of mainstream and sidestream tobacco smoke for 9 months with no recovery period did not increase the incidence of lung tumours. In Swiss strain mice, the same mixture induced lung tumours by both protocols, i.e. when the animals were exposed for 5 months followed by a 4-month recovery period and when they were exposed continuously for 9 months with no recovery period. In addition, exposure of Swiss mice to the tobacco smoke mixture for a shorter period was sufficient to induce lung tumours.

Condensates of sidestream and of mainstream cigarette smoke have been tested for carcinogenicity. Both kinds of condensates produced a spectrum of benign and malignant skin tumours in mice following topical application, and the sidestream condensate exhibited higher carcinogenic activity. Sidestream smoke condensate was shown to produce a dose–dependent increase in lung tumours in rats following implantation into the lungs.

Increased relative risks for lung and sinonasal cancer have been reported in companion animals (dogs) exposed to secondhand tobacco smoke in homes.

5.4 Other relevant data

Involuntary smoking has been associated with a number of non-neoplastic diseases and adverse effects in never-smokers, including both children and adults. Epidemiological studies have demonstrated that exposure to secondhand tobacco smoke is causally associated with coronary heart disease. From the available meta-analyses, it has been estimated that involuntary smoking increases the risk of an acute coronary heart disease event by 25–35%. Adverse effects of involuntary smoking on the respiratory system have also been detected. In adults, the strongest evidence for a causal relation exists for chronic

respiratory symptoms. Some effects on lung function have been detected, but their medical relevance is uncertain.

Data on the hormonal and metabolic effects of involuntary smoking are sparse. However, female involuntary smokers do not appear to weigh less than women who are not exposed to secondhand tobacco smoke, a pattern that contrasts with the findings for active smoking. No consistent association of maternal exposure to secondhand smoke with fertility or fecundity has been identified. There is no clear association of passive smoking with age at menopause.

Maternal cigarette smoking has repeatedly been associated with adverse effects on fetal growth; full-term infants born to women who smoke weigh about 200 g less than those born to nonsmokers. A smaller adverse effect has been attributed to maternal passive smoking.

Cotinine, and its parent compound nicotine, are highly specific for exposure to secondhand smoke. Because of its favourable biological half-life and the sensitivity of techniques for quantifying it, cotinine is currently the most suitable biomarker for assessing recent exposure to secondhand tobacco smoke uptake and metabolism in adults, children and newborns.

Several studies in humans have shown that concentrations of adducts of carcinogens to biological macromolecules, including haemoglobin adducts of aromatic amines and albumin adducts of polycyclic aromatic hydrocarbons, are higher in adult involuntary smokers and in the children of smoking mothers than in individuals not exposed to secondhand tobacco smoke. Protein adduct concentrations in fetal cord blood correlate with those in maternal blood but are lower. Fewer studies have investigated DNA adduct levels in white blood cells of exposed and unexposed nonsmokers, and most studies have not shown clear differences.

In studies of urinary biomarkers, metabolites of the tobacco-specific carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, have been found to be consistently elevated in involuntary smokers. Levels of these metabolites are 1–5% as great as those found in smokers. The data demonstrating uptake of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, a lung carcinogen in rodents, by nonsmokers are supportive of a causal link between exposure to secondhand tobacco smoke and development of lung cancer.

The exposure of experimental animals, primarily rodents, to secondhand tobacco smoke has several biological effects that include (i) increases or decreases in the activity of phase I enzymes involved in carcinogen metabolism; (ii) increased expression of nitric oxide synthase, xanthine oxidase and various protein kinases; (iii) the formation of smoke-related DNA adducts in several tissues; and (iv) the presence of urinary biomarkers of exposure to tobacco smoke.

In adult experimental animals, sidestream tobacco smoke has been found to produce changes that are similar to those observed with exposure of humans to secondhand tobacco smoke. These include inflammatory changes in the airways and accelerated formation of arteriosclerotic plaques. Although the changes are often comparatively minor and require exposure to rather elevated concentrations of sidestream smoke, they support

the results of human epidemiological studies. During pre- and postnatal exposure, sidestream smoke produces intrauterine growth retardation, changes the pattern of metabolic enzymes in the developing lung, and gives rise to hyperplasia of the pulmonary neuroendocrine cell population. In addition, it adversely affects pulmonary compliance and airway responsiveness to pharmacological challenges.

In humans, involuntary smoking is associated with increased concentrations of mutagens in urine. Some studies have shown a correlation of urinary mutagenicity with concentrations of urinary cotinine. Increased levels of sister chromatid exchange have not been observed in involuntary smokers; however, there is some indication of elevated levels in exposed children. Lung tumours from nonsmokers exposed to tobacco smoke contain *TP53* and *KRAS* mutations that are similar to those found in tumours from smokers. The genotoxicity of sidestream smoke, 'environmental' tobacco smoke, sidestream smoke condensate or a mixture of sidestream and mainstream smoke condensates has been demonstrated in experimental systems *in vitro* and *in vivo*.

5.5 Evaluation

There is *sufficient evidence* that involuntary smoking (exposure to secondhand or 'environmental' tobacco smoke) causes lung cancer in humans.

There is *limited evidence* in experimental animals for the carcinogenicity of mixtures of mainstream and sidestream tobacco smoke.

There is *sufficient evidence* in experimental animals for the carcinogenicity of sidestream smoke condensates.

In addition, the Working Group noted that there are published reports on possible carcinogenic effects of secondhand tobacco smoke in household pet dogs.

Overall evaluation

Involuntary smoking (exposure to secondhand or 'environmental' tobacco smoke) is *carcinogenic to humans (Group 1)*.