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A REVIEW OF HUMAN CARCINOGENS

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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

SECOND-HAND TOBACCO SMOKE

Second-hand tobacco smoke was considered by a previous IARC Working Group in 2002 as "involuntary smoking" (IARC, 2004). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

Second-hand tobacco smoke comprises the smoke released from the burning tip of a cigarette (or other burned tobacco product) between puffs (called sidestream smoke (SM)) and the smoke exhaled by the smoker (exhaled mainstream smoke (MS)). Small additional amounts are contributed from the tip of the cigarette and through the cigarette paper during a puff, and through the paper and from the mouth end of the cigarette between puffs (Jenkins *et al.*, 2000).

Second-hand tobacco smoke is also referred as 'environmental tobacco smoke', 'passive smoking' or 'involuntary smoking' (IARC, 2004). The terms 'passive smoking' or 'involuntary smoking' suggest that while involuntary or passive smoking is not acceptable, voluntary or active smoking is acceptable. In this document, we use the term second-hand tobacco smoke (WHO, 2010).

1.1 Chemical composition

Many studies have examined the concentrations of cigarette smoke constituents in mainstream and sidestream smoke. The composition of mainstream and sidestream smoke is qualitatively similar but quantitatively different. The ratios of sidestream to mainstream smoke vary greatly depending on the constituent. Some representative SS:MS ratios are: nicotine, 7.1; carbon monoxide, 4.8; ammonia, 455; formaldehyde, 36.5; acrolein, 18.6; benzo[*a*]pyrene, 16.0; N'-nitrosonornicotine (NNN), 0.43; (methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 0.40 (Jenkins *et al.*, 2000; IARC, 2004).

The physicochemical properties of second-hand tobacco smoke are different from those of mainstream smoke and sidestream smoke because of its rapid dilution and dispersion into the indoor environment (IARC, 2004). Concentrations of individual constituents in second-hand tobacco smoke can vary with time and environmental conditions. Field studies of these constituents and representative data have been extensively summarized (Jenkins *et al.*, 2000; IARC, 2004). Some representative data are presented in Table 1.1 (Jenkins *et al.*, 2000; IARC, 2004; US Department of Health and Human Services, 2006).

Table 1.1 Concentration of selected constituents in second-hand tobacco smoke

Constituent	Concentration
Nicotine	10–100 µg/m^3
Carbon monoxide	5–20 ppm
Benzene	15–30 µg/m^3
Formaldehyde	100–140 µg/m^3
Acetaldehyde	200–300 µg/m^3
1,3-Butadiene	20–40 µg/m^3
Benzo[a]pyrene	0.37–1.7 ng/m^3
NNK	0.2–29.3 ng/m^3
NNN	0.7–23 ng/m^3

1.2 Sources of exposure

Second-hand tobacco smoke is present in virtually all places where smoking takes place (Navas-Acien et al., 2004): at home, in the workplace, in bars, restaurants, public buildings, hospitals, public transport and educational institutions. The setting that represents the most important source of exposure differs depending on the population. For example in children, the home environment may constitute a significant source of exposure, while other sources that may contribute are schools and public transportation. Likewise, for most women, the home environment is the primary source of second-hand tobacco smoke, which may be enhanced by exposure at the workplace.

Biomarker studies have evaluated carcinogen uptake in non-smokers to second-hand tobacco smoke. The NNK metabolites NNAL and its glucuronides (total NNAL) are consistently elevated in non-smokers exposed to second-hand tobacco smoke, in studies conducted in various living and occupational environments, and from infancy through adulthood (Hecht et al., 2006; Hecht, 2008). Levels of the biomarker of PAHs, urinary 1-hydroxypyrene, were significantly elevated in a large study of non-smokers exposed to second-hand tobacco smoke (Suwan-ampai et al., 2009).

1.3 Measures of exposure

A conceptual framework for considering exposure to second-hand tobacco smoke is the "microenvironmental model," which takes the weighted sum of the concentrations of second-hand tobacco smoke in the microenvironments where time is spent, with the weights the time spent in each, as a measure of personal exposure (Jaakkola & Jaakkola, 1997). Direct measures of exposure use concentrations of second-hand tobacco smoke components in the air in the home, workplace, or other environments, combined with information on the time spent in the microenvironments where exposure took place. Measurements of tobacco smoke biomarker(s) in biological specimens also represent a direct measure of exposure to second-hand smoke (Samet & Yang, 2001; Table 1.2). Indirect measures are generally obtained by survey questionnaires. These include self-reported exposure and descriptions of the source of second-hand tobacco smoke in relevant microenvironments, most often the home and workplace (Samet & Yang, 2001).

One useful surrogate measure, and the only available in many countries, is the prevalence of smoking among men and women. It provides a measure of the likelihood of exposure. In most countries in Asia and the Middle East,

Table 1.2 Types of indicators measuring exposure to second-hand tobacco smoke

Measure	Suggested indicators

Direct	Concentration of second-hand tobacco smoke components in the air:
	    - Nicotine
	    - Respirable particles
	    - Other markers
	Biomarker concentrations:
	    - Cotinine
	    - Carboxyhaemoglobin

Indirect	Report of second-hand tobacco smoke exposure at:
	Home
	    - Number of smokers
	    - Smoking of parents
	    - Intensity (number of cigarettes smoked)
	Workplace
	    - Presence of second-hand tobacco smoke
	    - Number of smokers

Surrogate	Pre Prevalence of smoking tobacco in men and in women Sel Self reported smoking habits of parents Nic Nicotine concentration in house dust

From Samet & Yang (2001) and Whitehead *et al.* (2009)

for example, the very high prevalence of smoking among men combined with the low prevalence among women would imply that most women are exposed to second-hand tobacco smoke at home (Samet & Yang, 2001).

To measure exposure to second-hand tobacco smoke in children, self-reported smoking habits of their parents are used as a surrogate (US Department of Health and Human Services, 2006). More recently, other surrogate measures such as nicotine concentrations in house dust have been considered less biased than parental smoking as they reflect cumulative smoking habits and long-term exposure rather than current patterns of smoking (Whitehead *et al.*, 2009).

1.4 Prevalence of exposure

1.4.1 Exposure among children

(a) Overview

The most extensive population-based data on exposure to second-hand tobacco smoke among children are available through the Global Youth Tobacco Survey (GYTS) (CDC/WHO, 2009). GYTS is part of the Global Tobacco Surveillance System (GTSS), developed by the WHO and the United States' Centers for Disease Control and Prevention (CDC) in 1998. The GYTS is a school-based survey designed to measure tobacco use and some key tobacco control measures among youth (13–15 years) using a common methodology and core questionnaire. While most GYTS are national surveys, in some countries they are limited to subnational locations. Further, countries conduct the GYTS in different years, rendering comparison across countries for the same year difficult. The GYTS questionnaire

Fig. 1.1 Average prevalence (in%) of 13–15 year old children living in a home where others smoke, by WHO region, 2007
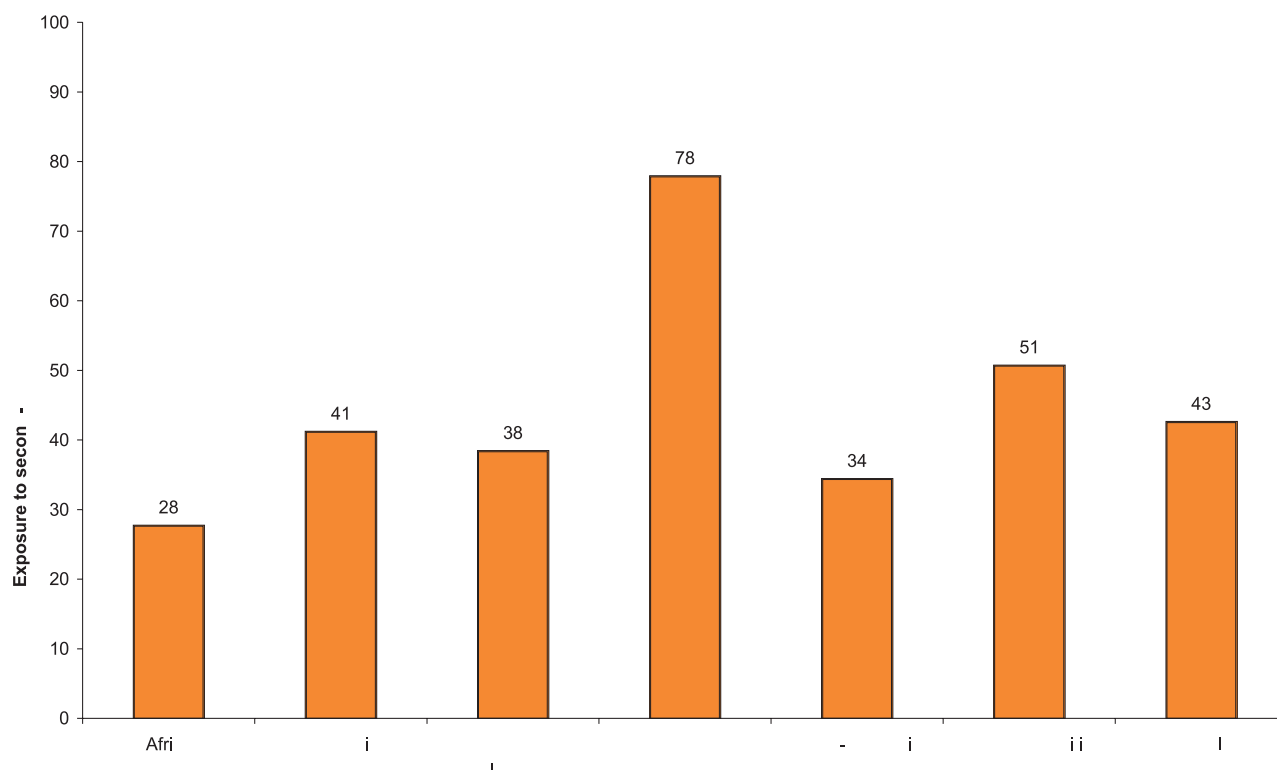
From CDC (2008)

asks about children's exposure to second-hand tobacco smoke in their home or in other places in the last 7 days preceding the survey. Since its inception in 1999, over 2 million students in 160 countries representing all six WHO regions have participated in the GYTS (WHO, 2008, 2009a).

Country-level estimates on second-hand tobacco smoke exposure at home and in public places among youth are available in the WHO Reports on the global tobacco epidemic (WHO, 2008, 2009a, 2011).

(b) Exposure at home

Nearly half of youth aged 13–15 years are exposed to second-hand tobacco smoke in their homes (Fig. 1.1; CDC, 2008). Among the six WHO regions, exposure to second-hand tobacco smoke at home was highest in the European Region

(77.8%) and lowest in the African region (27.6%). In the other four regions, exposure to second-hand tobacco smoke at home ranged from 50.6% in the Western Pacific Region to 34.3% in the South East Asian Region.

Fig. 1.2 shows the range of exposure to second-hand tobacco smoke at home by WHO region for boys and girls and for both sexes combined. The largest variations are observed in the Eastern Mediterranean Region and the European Region irrespective of sex. These variations are predominantly due to differences in parental smoking prevalence between countries, as well as the impact of the smoke-free places campaigns in place in various countries.

Country-level estimates from the Global Youth Tobacco Survey (1999–2009) are presented in Table 1.3.

Fig. 1.2 Range of prevalence (in%) of exposure of 13–15 year old children to second-hand tobacco smoke at home, by WHO region, 2009

Percent
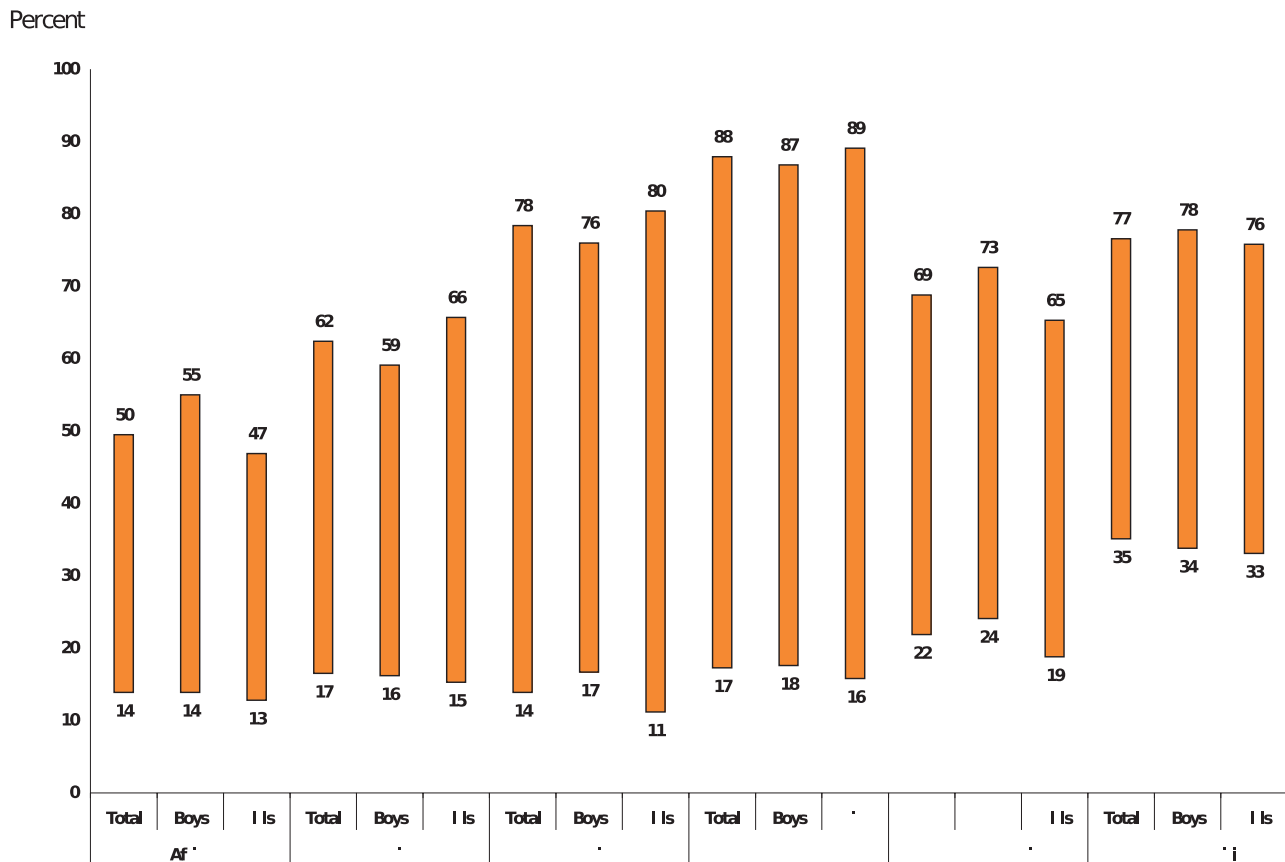
From CDC/WHO (2009)

Öberg and colleagues have estimated the worldwide exposure to second-hand tobacco smoke among children by using parent's current smoking status as an indicator of exposure among children (WHO, 2010). Four out of ten children (approximately 700 million children globally) have at least one parent who currently smokes, predisposing them to exposure to second-hand tobacco smoke at home (Table 1.4). Children in the Western Pacific Region had the highest level of potential exposure (68%) while Africa had the lowest, with about 13% of children having at least one parent who smoked. In the 2010 WHO Report on global estimate of the burden of disease from second-hand smoke (WHO, 2010), country-level estimates were collected or modelled from various sources. [Data partially overlap with those of the Global Youth Tobacco Survey].

(c)   Exposure outside home

Similar to second-hand tobacco smoke exposure at home, almost half of the youth are exposed to second-hand tobacco smoke in public places, according to estimates from the Global Youth Tobacco Survey (Fig. 1.3; CDC, 2008). Exposure was highest in Europe (86.1%); for the other five regions, exposure to second-hand tobacco smoke in public places ranged from 64.1% in the Western Pacific to 43.7% in Africa.

Table 1.3 Prevalence of exposure to second-hand tobacco smoke at home and outside home among 13–15 year olds, by country and sex, from the Global Youth Tobacco Survey (participating countries only) — 1999–2009

Country	WHO region	National survey, or jurisdiction where survey conducted	Year	Exposed to second-hand tobacco smoke at home			Exposed to second-hand tobacco smoke outside their homes		
				Total	Boys	Girls	Total	Boys	Girls
Afghanistan	EMRO	Kabul	2004	38.8	43.4	33.3	45.0	60.2	23.6
Albania	EURO	National	2009	49.7	48.6	50.9	64.5	65.3	63.9
Algeria	AFRO	Constantine	2007	38.7	39.8	37.9	60.2	66.0	56.2
Antigua and Barbuda	AMRO	National	2009	26.7	22.5	29.7	47.5	45.0	49.6
Argentina	AMRO	National	2007	54.7	51.7	57.7	68.6	66.4	70.7
Armenia	EURO	National	2009	70.6	69.2	71.6	78.3	80.7	76.4
Bahamas	AMRO	National	2009	25.1	23.4	27.0	51.0	50.8	52.7
Bahrain	EMRO	National	2002	38.7	37.2	39.5	45.3	49.7	40.9
Bangladesh	SEARO	National	2007	34.7	37.8	32.4	42.2	47.1	38.7
Barbados	AMRO	National	2007	25.9	25.9	26.0	59.6	59.7	59.6
Belize	AMRO	National	2008	25.7	26.2	25.1	50.4	52.1	48.6
Benin	AFRO	Atlantique Littoral	2003	21.5	23.7	18.3	38.0	41.3	33.5
Bhutan	SEARO	National	2009	29.5	29.2	29.5	59.4	58.6	59.7
The Plurinational State of Bolivia	AMRO	La Paz	2003	34.3	34.3	34.4	52.9	54.4	51.4
Bosnia and Herzegovina	EURO	National	2008	77.3	74.0	80.3	84.0	82.3	85.6
Botswana	AFRO	National	2008	38.5	38.2	38.6	62.1	60.0	63.7
Brazil	AMRO	São Paulo	2009	35.5	31.9	38.7	51.3	48.2	54.1
Bulgaria	EURO	National	2008	63.9	61.5	66.3	70.1	66.7	73.7
Burkina Faso	AFRO	Ouagadougou	2009	29.2	28.9	29.2	47.5	53.5	42.2
Burundi	AFRO	National	2008	33.9	35.2	31.7	49.3	54.0	45.3
Cambodia	WPRO	National	2003	47.0	48.9	44.5	58.5	60.6	56.5
Cameroon	AFRO	Yaounde	2008	21.7	25.0	19.1	45.8	49.3	42.4
Cape Verde	AFRO	National	2007	13.9	13.9	13.7	25.4	27.0	24.2
Central African Republic	AFRO	Bangui	2008	35.2	29.9	40.7	52.4	49.9	53.8
Chad	AFRO	National	2008	33.9	34.1	31.2	55.1	54.0	56.2
Chile	AMRO	Santiago	2008	51.7	48.9	54.4	68.3	63.4	73.0
China	WPRO	Shanghai	2005	47.0	46.6	47.4	35.2	34.2	36.2
Colombia	AMRO	Bogota	2007	26.2	25.3	27.0	56.1	55.1	56.9
Comoros	AFRO	National	2007	35.2	35.7	34.9	58.3	66.7	52.9
Congo	AFRO	National	2009	22.3	24.7	19.6	44.4	46.8	41.5
Cook Islands	WPRO	National	2008	61.9	58.8	64.5	73.8	70.3	76.8

Table 1.3 (continued)

Country	WHO region	National survey, or jurisdiction where survey conducted	Year	Exposed to second-hand tobacco smoke at home			Exposed to second-hand tobacco smoke outside their homes		
				Total	Boys	Girls	Total	Boys	Girls
Costa Rica	AMRO	National	2008	21.6	20.8	22.1	41.5	40.0	42.8
Côte d'Ivoire	AFRO	National	2009	33.1	33.1	33.0	74.4	75.9	72.3
Croatia	EURO	National	2007	73.4	71.4	75.7	82.5	81.2	84.2
Cuba	AMRO	Havana	2004	62.4	59.1	65.7	65.0	64.6	65.8
Cyprus	EURO	National	2005	87.9	86.8	89.1	87.8	85.4	90.4
Czech Republic	EURO	National	2007	38.0	37.3	38.9	75.2	71.6	79.5
Democratic Republic of the Congo	AFRO	Kinshasa	2008	30.2	32.5	27.0	36.8	37.4	34.7
Djibouti	EMRO	National	2009	36.0	36.2	35.3	44.7	44.8	44.8
Dominica	AMRO	National	2009	26.9	25.2	27.4	62.3	61.4	62.5
Dominican Republic	AMRO	National	2004	33.1	31.1	34.5	41.9	38.5	44.9
Ecuador	AMRO	Quito	2007	28.9	27.5	30.2	52.5	49.5	54.6
Egypt	EMRO	National	2009	47.6	50.1	45.9	52.2	57.7	47.5
El Salvador	AMRO	National	2009	17.9	19.3	16.5	33.7	36.7	30.7
Equatorial Guinea	AFRO	National	2008	47.5	47.8	45.8	61.7	64.0	59.8
Eritrea	AFRO	National	2006	18.4	20.4	14.8	37.3	40.4	32.3
Estonia	EURO	National	2007	41.1	39.3	42.8	68.5	68.2	68.7
Ethiopia	AFRO	Addis Ababa	2003	14.9	15.5	12.8	41.2	45.1	37.4
Fiji	WPRO	National	2009	42.1	45.4	39.6	55.1	55.2	54.9
Gambia	AFRO	Banjul	2008	45.8	45.8	44.4	59.2	61.6	57.2
Georgia	EURO	National	2008	62.7	62.4	62.8	74.4	75.5	73.4
Ghana	AFRO	National	2009	19.1	19.6	17.9	32.3	33.9	30.4
Greece	EURO	National	2005	…	…	…	…	…	…
Grenada	AMRO	National	2009	27.3	24.9	29.7	53.1	50.5	55.7
Guatemala	AMRO	National	2008	23.1	23.9	22.1	40.8	43.8	37.9
Guinea	AFRO	National	2008	27.7	27.6	28.1	52.3	57.0	48.1
Guinea-Bissau	AFRO	Bissau	2008	31.0	32.1	29.7	35.3	36.6	34.1
Guyana	AMRO	National	2004	33.4	36.6	30.6	61.1	62.9	59.1
Haiti	AMRO	Port-au-Prince	2005	32.3	34.7	29.6	43.2	46.2	40.4
Honduras	AMRO	Tegucigalpa	2003	29.6	26.2	31.6	42.2	46.9	38.4
Hungary	EURO	National	2008	43.0	39.9	45.3	72.6	70.0	74.7
India	SEARO	National	2009	21.9	24.1	18.8	36.6	39.0	33.1
Indonesia	SEARO	National	2009	68.8	72.6	65.3	78.1	83.7	73.1

Table 1.3 (continued)

Country	WHO region	National survey, or jurisdiction where survey conducted	Year	Exposed to second-hand tobacco smoke at home			Exposed to second-hand tobacco smoke outside their homes		
				Total	Boys	Girls	Total	Boys	Girls
Islamic Republic of Iran	EMRO	National	2007	35.4	38.1	32.7	44.8	49.8	39.6
Iraq	EMRO	Baghdad	2008	32.3	30.3	34.4	29.2	27.8	30.7
Jamaica	AMRO	National	2006	32.5	32.2	32.5	60.5	59.9	61.6
Jordan	EMRO	National	2009	53.6	50.6	55.5	50.5	50.6	49.7
Kenya	AFRO	National	2007	24.7	25.4	23.6	48.2	48.6	47.6
Kiribati	WPRO	National	2009	68.3	68.7	68.3	65.8	67.9	64.0
Kuwait	EMRO	National	2009	49.8	46.9	52.0	53.3	54.3	52.4
Kyrgyzstan	EURO	National	2008	33.4	35.1	31.9	57.7	58.7	56.8
Lao People's Democratic Republic	WPRO	Vientiane Capital	2007	40.3	41.2	39.5	55.4	57.7	53.2
Latvia	EURO	National	2007	55.2	55.1	55.1	72.7	73.2	72.3
Lebanon	EMRO	National	2005	78.4	76.0	80.4	74.4	73.9	74.7
Lesotho	AFRO	National	2008	36.9	34.2	37.3	52.6	50.2	53.2
Liberia	AFRO	Monrovia	2008	23.6	22.2	24.5	45.5	45.1	45.4
Lithuania	EURO	National	2009	38.3	34.1	42.6	64.9	66.5	63.3
Madagascar	AFRO	National	2008	49.5	55.0	44.9	62.9	69.5	57.5
Malawi	AFRO	National	2009	19.7	25.0	14.0	29.5	32.9	26.1
Malaysia	WPRO	National	2009	48.7	49.6	47.6	64.1	67.7	60.2
Maldives	SEARO	National	2007	48.3	49.4	47.1	68.0	70.6	65.4
Mali	AFRO	National	2008	48.5	50.1	46.9	81.4	83.1	79.2
Marshall Islands	WPRO	National	2009	52.1	54.7	50.5	59.7	60.5	60.6
Mauritania	AFRO	National	2009	37.5	39.8	35.0	50.9	55.4	47.1
Mauritius	AFRO	National	2008	36.1	38.5	34.1	73.6	77.2	70.7
Mexico	AMRO	Mexico City	2006	46.2	46.3	45.5	60.2	61.6	59.0
Federated States of Micronesia	WPRO	National	2007	60.7	60.4	59.6	71.3	73.3	68.7
Mongolia	WPRO	National	2007	54.4	53.7	54.3	55.5	60.7	50.7
Montenegro	EURO	National	2008	76.8	73.5	79.9	69.9	68.8	70.8
Morocco	EMRO	National	2006	27.1	24.7	29.2	41.1	41.1	40.9
Mozambique	AFRO	Maputo	2007	22.5	25.2	19.6	26.2	28.6	23.0
Myanmar	SEARO	National	2007	34.1	38.8	29.4	46.4	51.2	42.1
Namibia	AFRO	National	2008	38.1	38.0	37.9	49.9	47.7	51.5
Nepal	SEARO	National	2007	35.3	38.5	31.7	47.3	49.5	44.7
New Zealand	WPRO	National	2008	36.0	38.5	33.1	67.2	63.3	71.3

Table 1.3 (continued)

Country	WHO region	National survey, or jurisdiction where survey conducted	Year	Exposed to second-hand tobacco smoke at home			Exposed to second-hand tobacco smoke outside their homes		
				Total	Boys	Girls	Total	Boys	Girls
Nicaragua	AMRO	Centro Managua	2003	43.7	43.9	43.2	54.1	56.4	51.9
Niger	AFRO	National	2009	24.1	28.1	20.4	54.3	58.8	50.2
Nigeria	AFRO	Abuja	2008	21.7	29.2	12.8	39.7	43.6	36.0
Oman	EMRO	National	2007	13.9	16.7	11.2	27.4	29.8	25.2
Pakistan	EMRO	Islamabad	2003	26.6	32.1	21.7	33.9	42.5	26.4
Palau	WPRO	National	2009	…	…	…	79.2	70.4	85.3
Panama	AMRO	National	2008	21.9	22.2	21.5	40.3	38.9	41.4
Papua New Guinea	WPRO	National	2007	73.9	75.4	72.2	86.4	87.0	85.6
Paraguay	AMRO	National	2008	32.5	35.1	30.1	55.3	57.3	53.4
Peru	AMRO	National	2007	25.5	26.2	24.2	46.8	46.9	46.4
Philippines	WPRO	National	2007	54.5	55.7	53.1	64.8	67.2	62.8
Poland	EURO	Warsaw	2009	49.1	42.8	54.6	76.8	75.5	77.8
Qatar	EMRO	National	2007	35.7	36.3	35.2	45.9	52.1	42.8
Republic of Korea	WPRO	National	2008	37.6	33.8	41.6	70.8	67.3	74.8
Republic of Moldova	EURO	National	2008	20.3	20.6	20.1	57.0	59.4	54.8
Romania	EURO	National	2009	52.8	50.0	55.4	59.1	57.1	61.3
Russian Federation	EURO	National	2004	76.4	74.3	78.5	89.4	89.0	89.9
Rwanda	AFRO	National	2008	19.2	19.9	18.0	…	…	…
Saint Kitts and Nevis	AMRO	National	2002	16.5	16.2	15.3	48.8	48.0	49.0
Saint Lucia	AMRO	National	2007	25.2	28.4	22.6	64.0	61.1	65.7
Saint Vincent and the Grenadines	AMRO	National	2007	31.5	31.7	30.9	59.7	56.5	61.8
Samoa	WPRO	National	2007	59.1	60.8	56.4	62.8	64.8	60.5
San Marino	EURO	National	2009	32.9	31.8	34.0	65.8	62.8	69.3
Saudi Arabia	EMRO	National	2007	27.9	28.9	26.4	38.2	45.1	31.6
Senegal	AFRO	National	2007	47.6	49.9	42.5	48.3	48.3	45.0
Serbia	EURO	National	2008	76.9	73.4	80.0	71.9	68.1	74.8
Seychelles	AFRO	National	2007	42.3	38.2	46.1	57.1	54.3	60.6
Sierra Leone	AFRO	National	2008	44.2	46.3	42.9	56.5	59.9	53.4
Singapore	WPRO	National	2000	35.1	34.8	35.2	65.1	64.0	66.0
Slovakia	EURO	National	2007	44.9	42.4	46.9	69.3	68.0	70.5
Somalia	EMRO	Somaliland	2007	29.1	30.8	21.9	48.7	50.2	41.8
South Africa	AFRO	National	2008	32.1	32.7	31.5	41.1	43.5	39.4

Table 1.3 (continued)

Country	WHO region	National survey, or jurisdiction where survey conducted	Year	Exposed to second-hand tobacco smoke at home			Exposed to second-hand tobacco smoke outside their homes		
				Total	Boys	Girls	Total	Boys	Girls
Sri Lanka	SEARO	National	2007	35.4	37.6	33.4	65.9	66.5	65.1
Sudan	EMRO	National	2009	27.6	26.0	28.7	33.1	33.8	32.0
Suriname	AMRO	National	2009	46.6	44.2	47.7	53.3	51.4	53.8
Swaziland	AFRO	National	2009	23.3	21.8	24.3	55.6	52.1	58.0
Syrian Arab Republic	EMRO	National	2010	60.1	58.7	61.7	58.4	61.1	55.7
Thailand	SEARO	National	2009	45.7	46.6	44.7	67.6	68.0	67.1
The former Yugoslav Republic of Macedonia	EURO	National	2008	67.5	64.7	70.5	66.0	63.7	68.3
Timor-Leste	SEARO	National	2009	59.4	66.7	52.1	61.3	66.7	56.0
Togo	AFRO	National	2007	20.2	23.5	15.7	41.6	45.1	36.7
Trinidad and Tobago	AMRO	National	2007	40.1	36.3	43.6	64.2	62.8	65.9
Tunisia	EMRO	National	2007	51.9	53.1	50.6	65.2	69.7	61.0
Turkey	EURO	National	2009	48.6	43.8	53.0	79.9	80.1	79.6
Tuvalu	WPRO	National	2006	76.6	77.8	75.8	76.7	72.0	79.3
Uganda	AFRO	National	2007	20.0	20.7	18.8	45.6	46.1	45.2
United Arab Emirates	EMRO	National	2005	25.3	24.3	25.4	31.6	34.3	28.4
United Republic of Tanzania	AFRO	Arusha	2008	15.7	16.4	14.9	34.7	35.2	33.9
United States of America	AMRO	National	2009	35.7	35.3	36.1	42.8	38.2	47.6
Uruguay	AMRO	National	2007	50.5	47.6	52.5	68.6	64.0	72.1
Uzbekistan	EURO	Tashkent	2008	17.3	17.6	15.8	46.7	47.5	42.4
Vanuatu	WPRO	National	2007	59.3	62.8	56.7	75.9	78.7	73.9
Venezuela (Bolivarian Republic of)	AMRO	National	1999	43.5	40.7	45.3	47.8	47.0	48.4
Viet Nam	WPRO	National	2007	58.5	59.0	58.0	71.2	71.4	71.0
West Bank*	EMRO	West Bank	2009	63.0	61.6	64.4	61.6	67.6	55.8
Gaza Strip*	EMRO	Gaza Strip	2005	47.4	48.0	46.5	46.1	51.9	40.6
Yemen	EMRO	National	2008	44.9	48.2	37.8	42.7	49.8	30.7
Zambia	AFRO	Lusaka	2007	23.1	21.2	24.3	45.5	43.2	47.1
Zimbabwe	AFRO	Harare	2008	20.9	22.0	19.4	40.1	40.5	39.5

* Refers to a territory
From WHO (2008, 2009a)

Table 1.4 Proportion of children under 15 years with one or more parent who smokes, by WHO subregion (based on survey data and modeling)

Subregion	Parental smoking (%)
Africa (D)	13
Africa (E)	13
The Americas (A)	25
The Americas (B)	29
The Americas (D)	22
Eastern Mediterranean (B)	37
Eastern Mediterranean (D)	34
Europe (A)	51
Europe (B)	61
Europe (C)	61
South-eastern Asia (B)	53
South-eastern Asia (D)	36
Western Pacific (A)	51
Western Pacific (B)	68
GLOBAL	41

WHO subregional country grouping (adapted from WHO, 2002):

Africa. *Region D*: Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, The Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Togo; *Region E*: Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe

The Americas. *Region A*: Canada, Cuba, USA; *Region B*: Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, El Salvador, Grenada, Guyana, Honduras, Jamaica, Mexico, Panama, Paraguay, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela; *Region D*: Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru

Eastern Mediterranea. *Region B*: Bahrain, Islamic Republic of Iran, Jordan, Kuwait, Lebanon, Libyan Arab Jamahirya, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, United Arab Emirates; *Region D*: Afghanistan, Djibouti, Egypt, Iraq, Morocco, Pakistan, Somalia, Sudan, Yemen

Europe. *Region A*: Andorra, Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom; *Region B*: Albania, Armenia, Azerbaijan, Bosnia and Herzegovina, Bulgaria, Georgia, Kyrgyzstan, Poland, Romania, Serbia and Montenegro, Slovakia, Tajikistan, Former Yugoslav Republic of The former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Uzbekistan; *Region C*: Belarus, Estonia, Hungary, Kazakhstan, Latvia, Lithuania, Republic of the Republic of Moldova, Russian Federation, Ukraine

South-eastern Asia. *Region B*: Indonesia, Sri Lanka, Thailand; *Region D*: Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar (Burma), Nepal, Timor-Leste

Western Pacific. *Region A*: Australia, Brunei Darussalam, Japan, New Zealand, Singapore; *Region B*: Cambodia, China, Cook Islands, Fiji, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Federated States of Micronesia, Mongolia, Nauru, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam

Regions are categorized as follows (WHO-approved classifications): A = very low child mortality and very low adult mortality; B = low child mortality and low adult mortality; C = low child mortality and high adult mortality; D = high child mortality and high adult mortality; E = high child mortality and very high adult mortality.

Fig. 1.3 Average prevalence (in%) of exposure of 13–15 year old children to second-hand tobacco smoke in public places, by WHO region, 2007
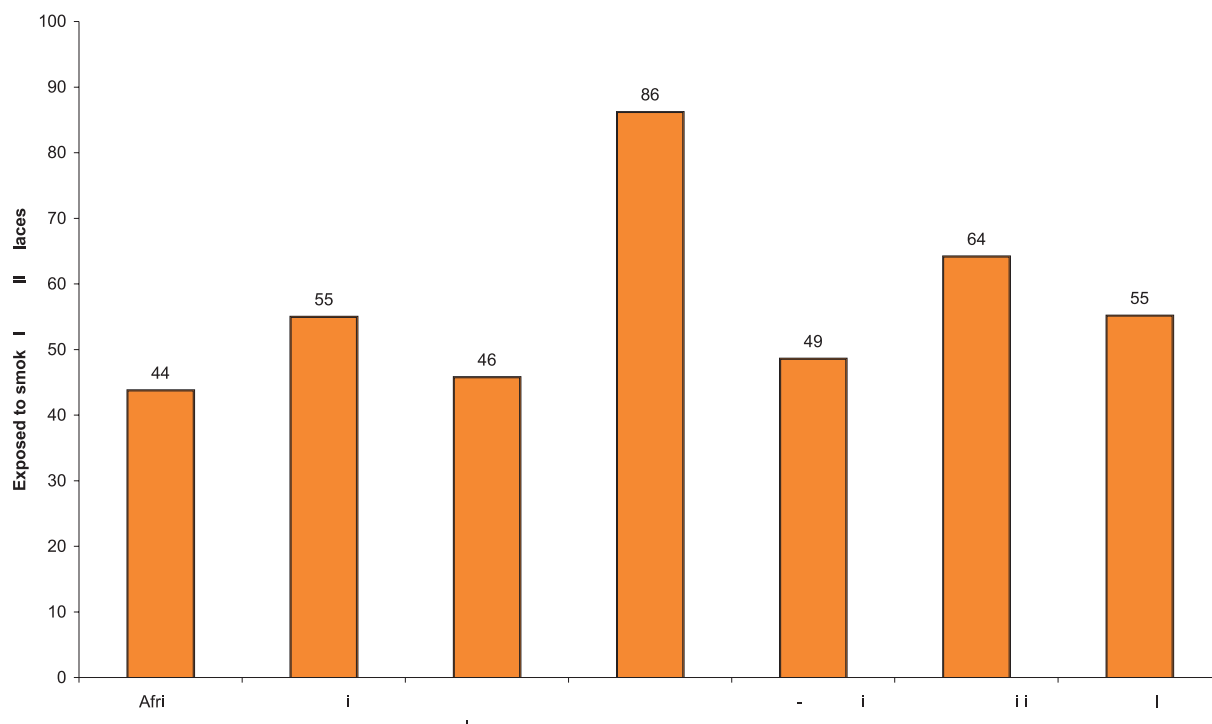
From CDC (2008)

Fig. 1.4 presents the range of exposure to second-hand tobacco smoke outside home by WHO region for boys and girls and for both sexes combined. There are wide variations in second-hand tobacco smoke exposure outside home within each region. The largest variations are observed in the African region and the Western Pacific region irrespective of sex. This is largely influenced by the presence of smoke-free legislation for public paces in the countries, as well as levels of enforcement and public's compliance with these laws.

1.4.2. Exposure among adults

(a) Overview

While the GYTS offers a valuable global source for estimating exposure to second-hand tobacco smoke among children, there is no such extensive source of data for adults. Estimates of second-hand tobacco smoke exposure among adults have used the definitions of exposure based on having a spouse who smokes or exposure to tobacco smoke at work. For the countries lacking such data, exposure was estimated using a model based on smoking prevalence among men from the WHO Global InfoBase.

About one third of adults worldwide are regularly exposed to second-hand tobacco smoke (Table 1.5). The highest exposure was estimated in European Region C with 66% of the population

Fig. 1.4 Range of prevalence (in%) of exposure of 13–15 year old children to second-hand tobacco smoke outside their home, by WHO region, 2009
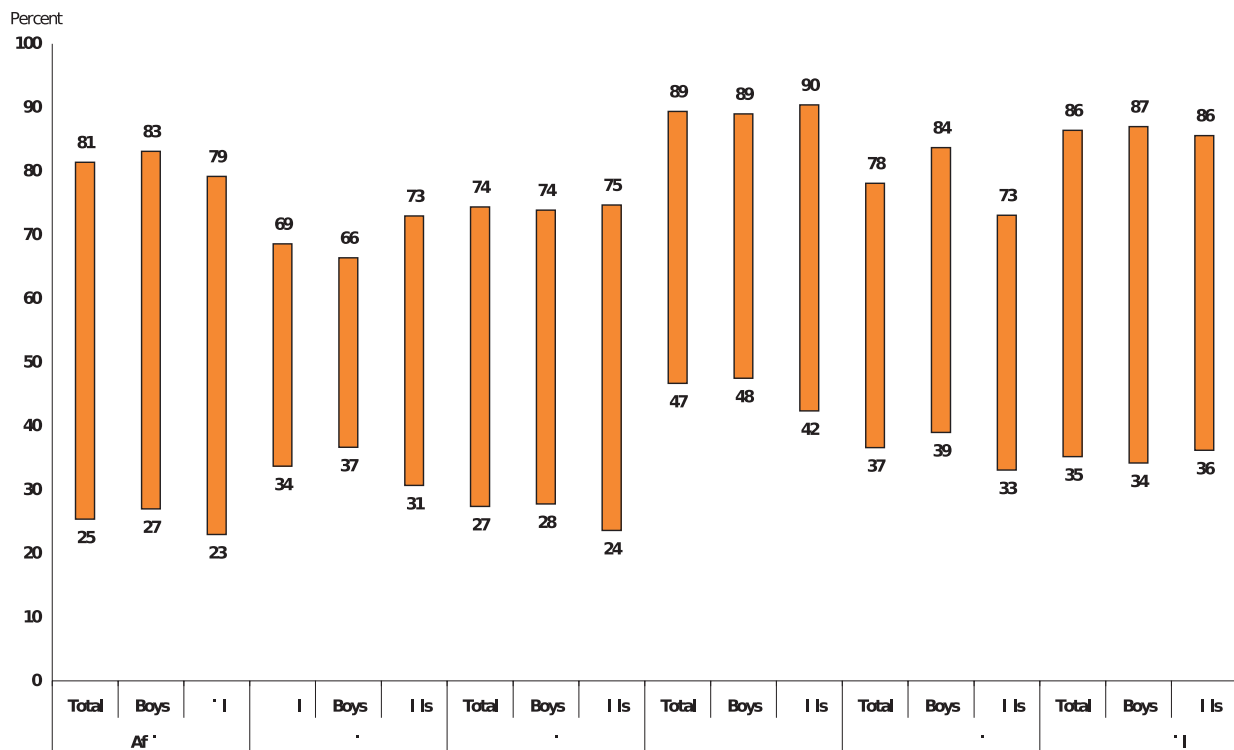
From CDC/WHO (2009)

being regularly exposed to second-hand tobacco smoke. The lowest regional exposure was estimated in the African region (4%). Differences between men and women were generally small, except in Eastern Mediterranean Region D and South East Asia Region B.

(b) Exposure at home

The Global Tobacco Surveillance System, through its adult household survey "Global Adult Tobacco Survey" (GATS), collects information on key tobacco control indicators including information on second-hand tobacco smoke exposure at home, at work and several public places (WHO, 2009b). GATS is a nationally representative survey conducted among persons aged ≥ 15 years using a standardized questionnaire, sample design, data

collection method, and analysis protocol. GATS results are available from 14 countries with a high tobacco burden. Additionally since 2008, The WHO STEPwise approach to surveillance (STEPS) surveys have started to collect information on exposure to second-hand tobacco smoke at home and at work, now available for 7 countries (WHO, 2009c).

In the 21 countries that have reported data on exposure to second-hand tobacco smoke, large numbers of people are exposed at home (Fig. 1.5). Exposure was highest in Sierra Leone (74%) and lowest in the British Virgin Islands (3%). Overall, differences between men and women were relatively small in most countries; in China, Cambodia and Mongolia, more women reported being exposed to second-hand tobacco smoke

Table 1.5 Proportion of non-smoking adults exposed regularly to second-hand tobacco smoke, by WHO region (based on survey data and modeling)

WHO Subregion	Exposure in men (%)	Exposure in women (%)
Africa (D)	7	11
Africa (E)	4	9
The Americas (A)	16	16
The Americas (B)	13	21
The Americas (D)	15	18
Eastern Mediterranean (B)	24	22
Eastern Mediterranean (D)	21	34
Europe (A)	34	32
Europe (B)	52	53
Europe (C)	66	66
South-eastern Asia (B)	58	41
South-eastern Asia (D)	23	18
Western Pacific (A)	50	54
Western Pacific (B)	53	51
GLOBAL	33	31

From WHO (2010)

For the WHO subregional country grouping, see footnote of Table 1.4.

in their homes then men. This lack of difference implies that even when prevalence of smoking among women is low, they are exposed to second-hand tobacco smoke at home as much as men.

(c)   Exposure at the workplace

The same magnitude of second-hand tobacco smoke exposure at the workplace was reported as at home (Fig. 1.6). Exposure to second-hand tobacco smoke at the workplace was highest in Sierra Leone (74%) and lowest in the British Virgin Islands (3%). However, more men reported being exposed to others' smoke at their workplace as compared to women in all countries. This difference was most significant in Libyan Arab Jamahirya and Bangladesh. These differences could be explained by the fact that women either tend to work in places where smoking is banned, such as education or health facilities, or work predominantly with other women.

1.5 Regulations

The World Health Organization's Framework Convention on Tobacco Control (WHO FCTC) is a multilateral treaty with legally binding obligations for its 174 Parties (as of November 2011) (WHO, 2003). This comprehensive treaty contains supply and demand reduction measures available to countries to counter the tobacco epidemic. Article 8 of the Treaty specifically addresses the need for protection from second-hand tobacco smoke, and articulates the "adoption and implementation of effective legislative, executive, administrative and /or other measures" by Parties to the Convention to this effect. Guidelines to Article 8 specify key elements needed in legislation to help countries meet the highest standards of protection from second-hand tobacco smoke and provide a clear time-line for Parties to adopt appropriate measures (within five years after entry into Force of the WHO FCTC) (WHO, 2007).

Fig. 1.5 Prevalence of adults exposed to second-hand tobacco smoke in their homes, in the countries that completed the Global Adult Tobacco Survey (GATS) and WHO STEPwise approach to surveillance (STEPS) surveys, 2008–2009
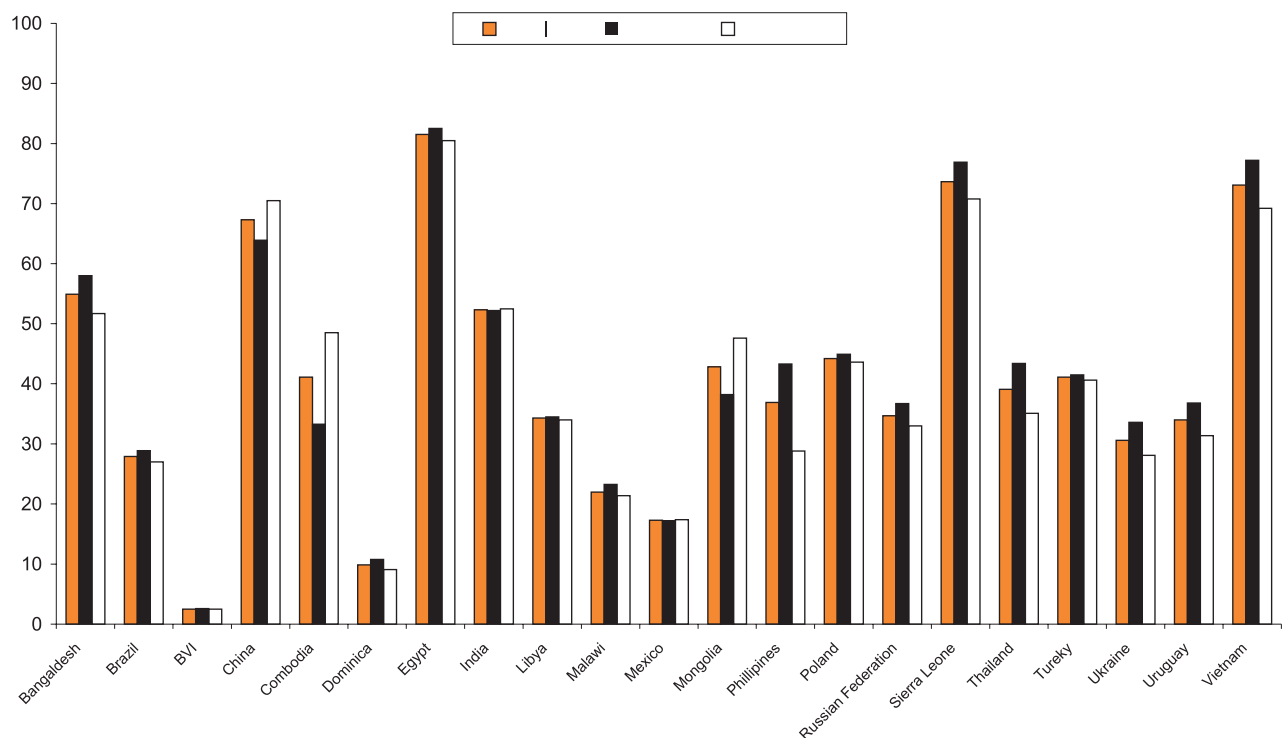
From WHO (2009b, c)
GATS defines second-hand tobacco smoke exposure at home as reporting that smoking inside their home occurs daily, weekly, or monthly.
STEPS defines second-hand tobacco smoke exposure at home as reporting exposure in the home on one or more days in the past 7 days.

All countries, regardless of their FCTC ratification status, are taking steps to reduce second-hand tobacco smoke in public places, through either planning the steps to or implementing national smoke-free laws for public places or workplaces. In 2008, approximately 5% of the world's population (354 million) had national smoke-free laws. Fig. 1.7 provides details on the number of public places with national smoke-free legislation for all WHO Member States.

As of December 2008, fifteen countries across the globe have legislation that provide the highest level of protection against second-hand tobacco smoke exposure. These include: Albania, Australia, Bhutan, Canada, Colombia, Guatemala, Islamic Republic of Iran, Ireland, Marshall Islands, New Zealand, Panama, Turkey, Turkmenistan, United Kingdom of Great Britain and Northern Ireland and Uruguay.

2 Cancer in Humans

2.1 Cancer of the lung

More than 50 epidemiological studies since 1981 have examined the association between second-hand tobacco smoke and lung cancer resulting in the conclusion that exposure of non-smokers to second-hand tobacco smoke is causally associated with lung cancer risk (IARC, 2004). Many studies previously

Fig. 1.6 Prevalence of adults exposed to second-hand tobacco smoke in their workplaces, in the countries that completed the Global Adult Tobacco Survey and WHO STEPwise approach to surveillance (STEPS) surveys, 2008–2009
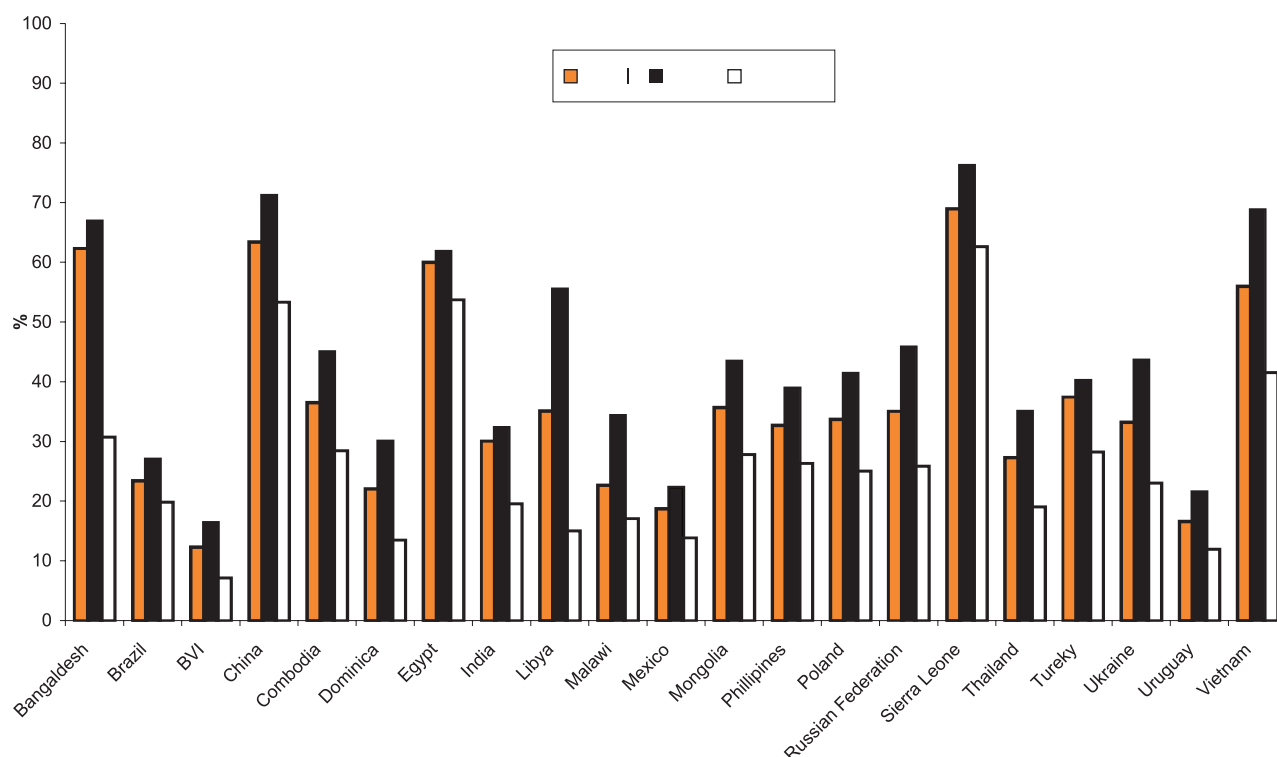
GATS defines second-hand tobacco smoke exposure at work as indoor workers who were exposed at work in the past 30 days.
STEPS defines second-hand tobacco smoke exposure at work as reporting exposure in the workplace on one or more days in the past 7 days
From WHO (2009b, c)

available assessed the lung cancer risk among the nonsmoking spouses of smokers since it is one of the sources of adult exposure to second-hand tobacco smoke that is less likely to be subject to exposure misclassification or other bias. Several important new, cohort, case–control studies and meta-analyses have been published since 2004 that provide additional evidence confirming the causal association (Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.1.pdf, Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.2.pdf, and Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.3.pdf). These new studies also expand our assessment of

the effect of second-hand tobacco smoke in the workplace allowing for more refined estimates of lung cancer risk. Preliminary data also suggest significant interactions between several genetic polymorphisms, second-hand tobacco smoke and lung cancer risk.

In a meta-analysis of 55 studies, including 7 cohort, 25 population based case–control studies and 23 hospital based case–control studies the pooled relative risk (RR) for lung cancer for never smoking women exposed to second-hand tobacco smoke from spouses was 1.27 (95%CI: 1.17–1.37). The relative risk for studies in North America was 1.15 (95%CI: 1.03–1.28), in Asia 1.31 (95%CI: 1.16–1.48) and Europe 1.31 (1.24–1.52) (Taylor et al., 2007).

Fig. 1.7 Number and percentage of countries with number of public places covered by smoke free legislations, by income status (as of 31 December 2008)
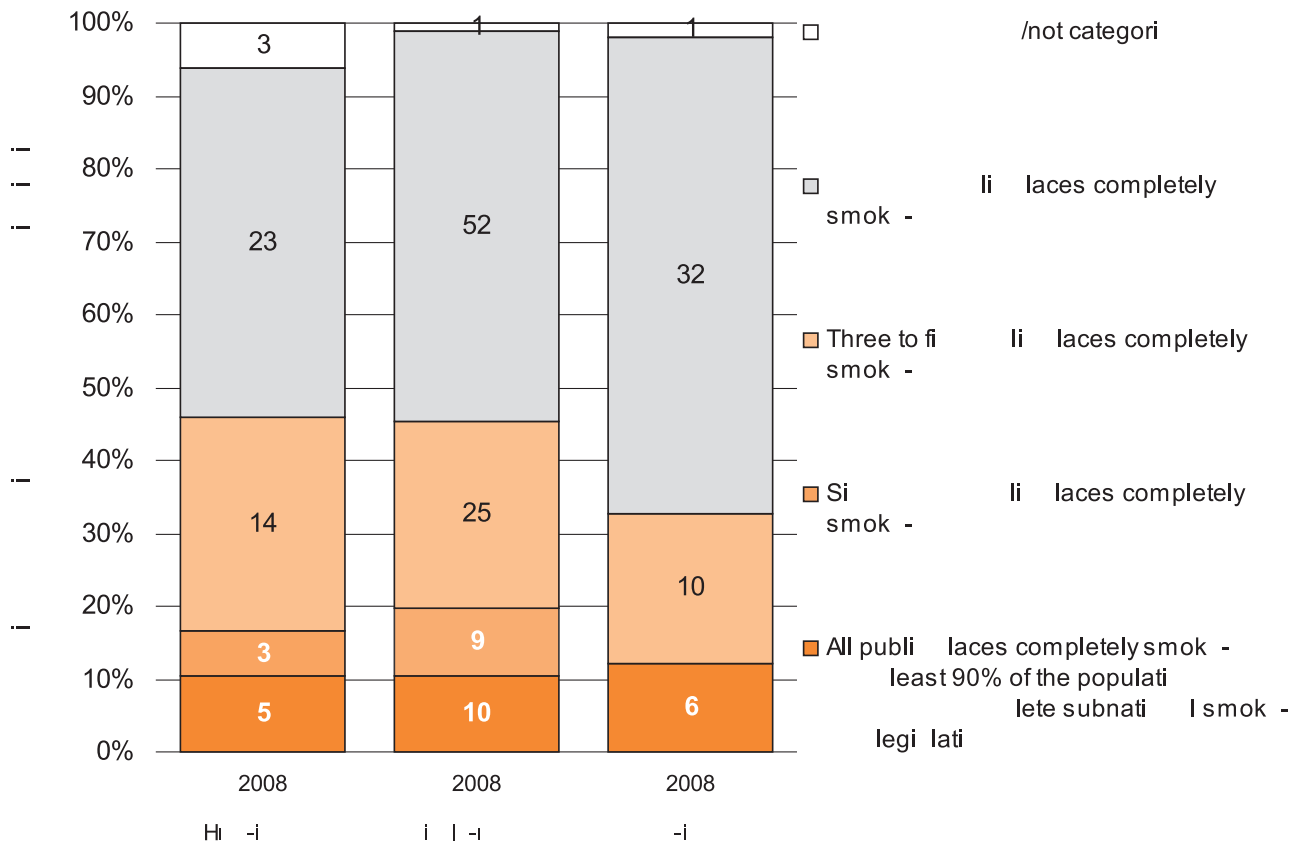
From WHO (2009a)

In a meta-analysis of 22 studies that assessed the effect of second-hand tobacco smoke exposures at work, the relative risk for lung cancer among exposed non-smokers was 1.24 (95%CI: 1.18–1.29) and among those workers classified as highly exposed to second-hand tobacco smoke at work 2.01 (95%CI: 1.33–2.60) compared to those with no exposure at work (Stayner et al., 2007).

In a large cohort study conducted in 10 European countries (European Prospective Investigation into Cancer and Nutrition, EPIC), it was estimated that the hazard ratio (HR) for lung cancer risk from second-hand tobacco smoke exposure at home and/or at work for never smokers and ex-smokers (at least 10 years) was 1.34 (0.85–2.13) (Vineis et al., 2007a). The main component of this risk was attributable to exposure at the workplace, resulting in a hazard ratio of 1.65 (1.04–2.63). The overall hazard ratio between childhood exposure and the risk of lung cancer in adulthood was 2.00 (0.94–4.28); among children with daily exposure for many hours each day the hazard ratio was 3.63 (1.19–11.12). In a separate analysis of workplace exposure to second-hand tobacco smoke in this cohort women were observed to have a lung cancer hazard ratio of 2.13 (1.6–3.4) (Veglia et al., 2007).

In a large population-based cohort study conducted in Japan, findings confirmed that exposure to second-hand tobacco smoke is

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a risk factor for lung cancer among Japanese women (Kurahashi *et al.*, 2008). Compared with women married to never smokers, the hazard ratio for all lung cancer incidence was 1.34 (95%CI:0.81–2.21) and for adenocarcinoma 2.03 (95%CI:1.07–3.86). For adenocarcinoma dose–response relationships were seen for both intensity (*P* for trend = 0.02) and total amount (*P* for trend = 0.03) of the husband's smoking. Exposure to second-hand tobacco smoke at the workplace also increased the risk of lung cancer (HR, 1.32; 95%CI: 0.85–2.04).

Data from a cohort study of women from Shanghai, China also found that exposure to second-hand tobacco smoke is associated with lung cancer mortality. Exposure to second-hand tobacco smoke at work was associated with a significantly increased mortality to lung cancer (HR 1.79, 95%CI: 1.09–2.93) but the risk was not significant for exposure to husband's second-hand tobacco smoke (HR 1.09, 95%CI: 0.74–1.61) (Wen *et al.*, 2006). In a case–control study of lung cancer among lifetime non-smoking Chinese men living in Hong Kong Special Administrative Region a non-significant association between all lung cancer and ever being exposed to household and/or workplace second-hand tobacco smoke was observed (OR, 1.11, 95%CI: 0.74–1.67) but a significant increase was observed for adenocarcinoma (OR, 1.68, 95%CI: 1.00–2.38) (Tse *et al.*, 2009).

In a long-term case–control study of lung cancer cases at the Massachusetts General Hospital, study participants exposed to second-hand tobacco smoke at work and at leisure were at a significantly greater risk (OR, 1.30, 95%CI: 1.08–1.57) if the exposure occurred between birth and 25 years of age. If the exposures occurred after the age of 25 years the risk was not elevated (OR, 0.66, 95%CI: 0.21–1.57) but the confidence limits are wide for this subgroup analysis (Asomaning *et al.*, 2008).

In two other cohort studies, one conducted in California (Enstrom & Kabat, 2003) and another in New Zealand (Hill *et al.*, 2007) no excess risk was observed among lifelong non-smokers exposed to second-hand tobacco smoke. In the California study the relative risk was 0.99 (95%CI: 0.72–1.37) based on 126 lung cancer cases. [The confidence intervals in this study are relatively wide and they include the current IARC estimate of lung cancer risk from second-hand tobacco smoke exposure. In addition the opportunity for substantial misclassification of second-hand tobacco smoke exposure is great because exposures outside the home were not assessed and the second-hand tobacco smoke exposures were not re-evaluated after enrollment into the study.] Hill *et al.* (2007) observed no association between second-hand tobacco smoke exposure in a census enumeration of current second-hand tobacco smoke exposure at home and linkage to cancer registries three years later. The authors suggest that this may be a result of either the misclassification of total second-hand tobacco smoke exposure since exposures outside the home were not assessed and/or the fact that a 3-year follow-up after exposure ascertainment may have been too short to capture important exposures before the diagnosis of lung cancer.

One case–control study (Wenzlaff *et al.*, 2005) and one case-only study (Bonner *et al.*, 2006) assessed lung cancer risk associated with second-hand tobacco smoke exposure and several polymorphisms. In the case–control study, individuals were stratified by household second-hand tobacco smoke exposure (yes/no), those with *CYP1B1 Leu^{432}Val* genotype alone or in combination with Phase II enzyme polymorphisms were more strongly associated with lung cancer risk if they also were exposed to at least some household second-hand tobacco smoke exposure compared to those that had no exposure. In the case-only study a significant interaction was observed between lung cancer risk, second-hand tobacco smoke and a GSTM1 (null) genotype (OR, 2.28, 95%CI:1.15–4.51).

2.2 Cancer of the breast

2.2.1 Overview of studies

The relationship between exposure to second-hand tobacco smoke and breast cancer has been comprehensively reviewed in the peer reviewed literature (Johnson, 2005; Miller *et al.*, 2007) and in reports from national and international committees (IARC, 2004, 2009; California Environmental Protection Agency, 2005; US. Department of Health and Human Services, 2006; Collishaw *et al.*, 2009). These reviews have drawn different conclusions. IARC (2004) characterized the evidence as "inconsistent," based on studies published or in press by June, 2002. A US Surgeon General Report (2006) concluded that the evidence was "suggestive but not sufficient" to infer a causal relationship between second-hand tobacco smoke and breast cancer, whereas reviews by the California Environmental Protection Agency (CalEPA) in 2005 and by a panel of researchers in this area convened in Canada (Collishaw *et al.*, 2009) designated the evidence for second-hand tobacco smoke as "consistent with a causal association in younger primarily premenopausal women."

A total of 16 new studies have been published since the previous *IARC Monograph* (IARC, 2004). These include three cohort studies (Reynolds *et al.*, 2004; Hanaoka *et al.*, 2005; Pirie *et al.*, 2008) (Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.4.pdf), and 13 new case–control studies (Lash & Aschengrau, 2002; Alberg *et al.*, 2004; Gammon *et al.*, 2004; Shrubsole *et al.*, 2004; Bonner *et al.*, 2005; Sillanpää *et al.*, 2005; Lissowska *et al.*, 2006; Mechanic *et al.*, 2006; Roddam *et al.*, 2007; Rollison *et al.*, 2008; Slattery *et al.*, 2008; Ahern *et al.*, 2009; Young *et al.*, 2009) (Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.5.pdf). Table 2.5 also presents two case–control studies not discussed previously (Zhao *et al.*, 1999; Liu *et al.*, 2000). Several meta-analyses have also been published as new data became available (California Environmental Protection Agency, 2005; Johnson, 2005; US. Department of Health and Human Services, 2006; Pirie *et al.*, 2008; IARC, 2009).

The largest of the cohort studies, identified 2518 incident breast cancers among 224917 never smokers followed for an average of 3.5 years in the British Million Women Study (Pirie *et al.*, 2008). The cohort was drawn from women, age 50–64 years, participating in mammography screening programmes. Nearly all cases were post-menopausal and the overall analyses pertain to postmenopausal breast cancer. No relationship was observed between breast cancer risk and smoking by a parent at the time of birth and/or age 10 years (HR, 0.98; 95%CI: 0.88–1.08); the results were also null for smoking by a current partner (HR, 1.02; 95%CI: 0.89–1.16) or exposure to the combination of parental and spousal smoking (HR, 1.03; 95%CI: 0.90–1.19). Pirie *et al.* (2008) also present a meta-analysis of studies of second-hand smoke and breast cancer risk, separating studies by cohort or case–control design. No overall association was observed in the cohort studies. These largely represent post-menopausal breast cancer, so the analysis was not stratified by menopausal status. An overall association was seen in the case–control studies, similar to the findings of other meta-analyses (California Environmental Protection Agency, 2005; US. Department of Health and Human Services, 2006; IARC, 2009). [Pirie *et al.* (2008) focus on the discrepancy between the cohort and case–control results and propose that the associations observed in early case–control studies can likely be explained by recall bias. The study has been criticized for the lack of information on occupational exposures to second-hand smoke (Collishaw *et al.*, 2009).]

A second large cohort study (Reynolds *et al.*, 2004) identified 1998 women diagnosed with breast cancer during five years of follow-up of the

California Teachers Study. Analyses were based on 433 women with pre/peri-menopausal breast cancer and 1361 women with postmenopausal cancer. No association was observed between post-menopausal breast cancer and residential exposure to second-hand tobacco smoke in childhood or adulthood. No association was initially reported with pre/peri-menopausal breast cancer in analyses based on menopausal status at enrollment (RR 0.93, 95%CI: 0.71–1.22). When menopausal status was defined by age at diagnosis rather than by age at enrollment, the hazard ratio for premenopausal breast cancer among women exposed in both childhood and adulthood increased to 1.27 (95%CI: 0.84–1.92) (Reynolds et al., 2006).

Hanaoka et al. (2005) identified 162 incident breast cancer cases during a nine-year follow-up of 20169 Japanese women, age 40–59 years, who reported no history of active smoking when enrolled in the Japan Public Health Center (JPHC) study in 1990. Nearly three quarters (72%) of the women reported exposure to second-hand tobacco smoke. About half of the women were premenopausal when enrolled in the study, although there were only nine unexposed cases among the pre-menopausal women. The multivariate-adjusted relative risk for breast cancer among all exposed women irrespective of menopausal status was 1.1 (95%CI: 0.8–1.6) compared to those classified as unexposed. The corresponding relative risks for women who were pre- or postmenopausal at baseline were 2.6 (95%CI: 1.3–5.2) and 0.7 (95%CI: 0.4–1.0), respectively.

Six of the 13 new population-based case–control studies included more than 1000 cases each (Shrubsole et al., 2004; Bonner et al., 2005; Lissowska et al., 2006; Mechanic et al., 2006; Slattery et al., 2008; Young et al., 2009; Table 2.5 on-line). None of these 13 studies showed an overall increase in breast cancer risk associated with second-hand tobacco smoke exposure in Caucasians. The incidence of premenopausal breast cancer was associated with one or more indices of second-hand tobacco smoke exposure in all four studies that stratified the results by menopausal status (Gammon et al., 2004; Shrubsole et al., 2004; Bonner et al., 2005; Slattery et al., 2008) although the association was not always statistically significant (Gammon et al., 2004; Bonner et al., 2005; Fig. 2.1). Associations were also reported between second-hand tobacco smoke exposure and overall breast cancer risk in African Americans (Mechanic et al., 2006) and with premenopausal breast cancer in Hispanics/American Indians (Slattery et al., 2008). The associations observed in these case–control studies are generally weaker than those reported in earlier case–control studies. Whereas the relative risk estimates reported in the earlier studies often equalled or exceeded 2.0 (Sandler et al., 1985a; Lash & Aschengrau, 1999; Zhao et al., 1999; Johnson & Repace, 2000; Liu et al., 2000) or 3.0 (Smith et al., 1984; Morabia et al., 1996; Liu et al., 2000; Morabia et al., 2000), the estimates in the later studies were mostly under 1.5, even in studies that reported positive associations.

2.2.2 Issues affecting the interpretation of studies

One important consideration in evaluating these data has been the lack of a strong and convincing relationship between active smoking and breast cancer. Several theories have been advanced to explain why second-hand tobacco smoke might have a stronger effect on breast cancer than active smoking (California Environmental Protection Agency, 2005; Johnson, 2005; Collishaw et al., 2009). Central to these is the hypothesis that active smoking may have counterbalancing protective and detrimental effects on breast cancer risk that, in combination, produce little or no overall association, whereas second-hand tobacco smoke may have only an adverse effect on risk. The weakness of this theory is that there is little direct evidence (see Section 4) identifying the

Fig. 2.1 Relative risk of pre-menopausal breast cancer associated with second-hand tobacco smoke. Ever versus never.
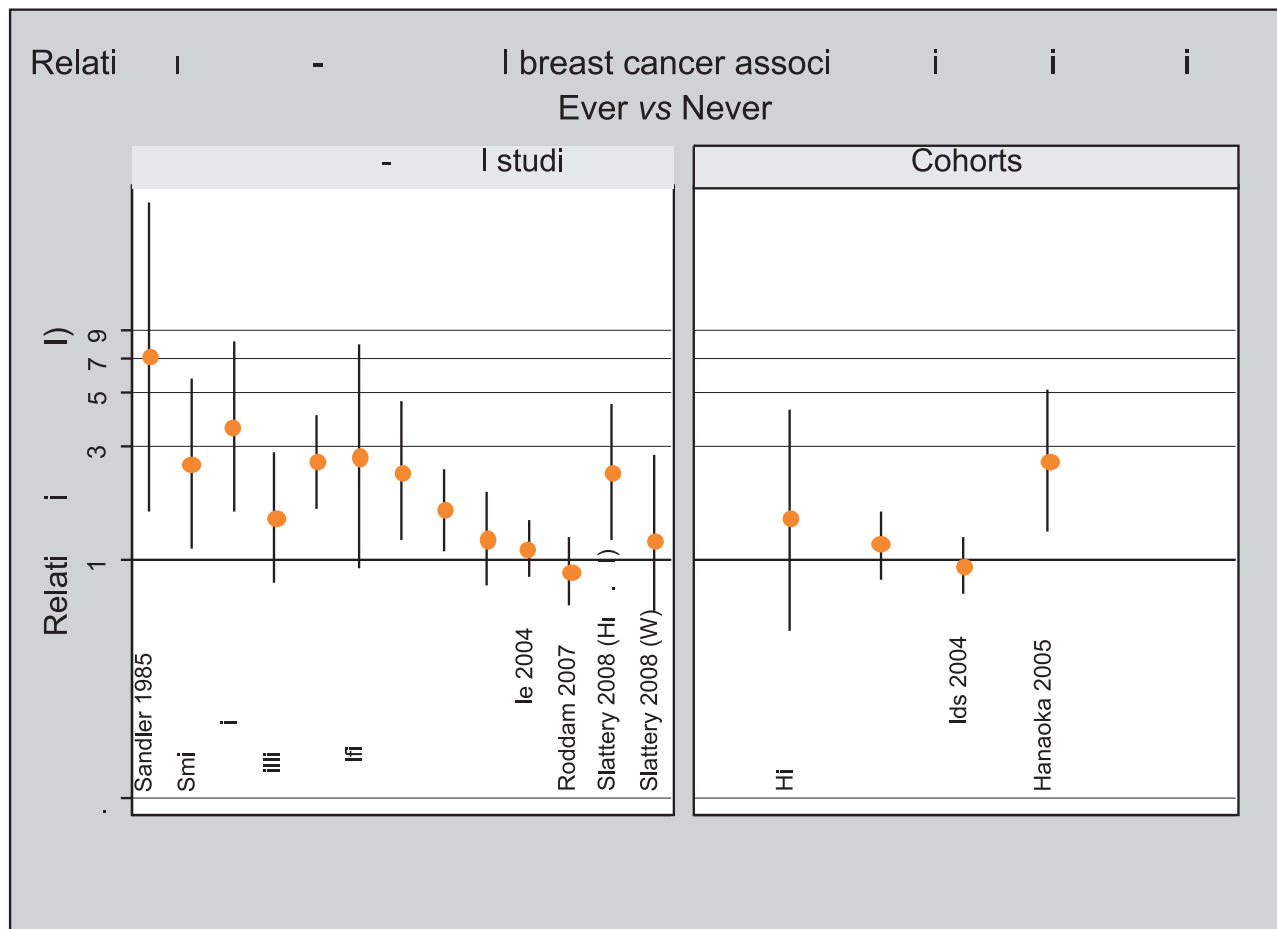
Study sorted by calendar year

mechanism by which active smoking may cause the proposed [protective] antiestrogenic effects. Without knowing the mechanism, it has been impossible to prove that active smoking has this effect but exposure to second-hand tobacco smoke does not. A second hypothesis that has been advanced is that second-hand tobacco smoke may have a greater effect on pre- than on postmenopausal breast cancer. This theory was proposed by CalEPA in 2005 (Johnson & Glantz, 2008) based on analyses of studies available at the time, and was subsequently questioned by some (US. Department of Health and Human Services, 2006) but not all (Collishaw *et al.*, 2009) subsequent reviews. [Because this arose as an a posteriori observation rather than as an a priori hypothesis, it must be confirmed by independent studies.] The strongest support for the hypothesis comes from a cohort study in Japan (Hanaoka *et al.*, 2005), which reported significantly increased risk (RR 2.6, 95%CI: 1.3–5.2) of premenopausal breast cancer in women who previously reported having ever lived with a regular smoker or ever being exposed to second-hand tobacco smoke for at least one hour per day in settings outside the home. However, the

referent group in this analysis included only nine unexposed cases. No associations were observed with post-menopausal breast cancer. A weak association between second-hand tobacco smoke exposure and premenopausal breast cancer was reported in the California Teachers cohort, when menopausal status was defined by age at diagnosis rather than age at entry into the study (Reynolds *et al.*, 2006). In case–control studies published since the CalEPA review (California Environmental Protection Agency, 2005) that reported results stratified by menopausal status, Bonner *et al.* (2005) and Slattery *et al.* (2008) reported stronger associations with pre- than with post-menopausal breast cancer, although the only statistically significant association with premenopausal breast cancer was in Hispanic or American Indian women who had second-hand tobacco smoke exposure of more than ten hours per week (OR, 2.3, 95%CI:1.2–4.5) (Slattery *et al.*, 2008). In a case–control study of breast cancer in women age 36–45 years Roddam *et al.* (2007) observed no increased risk in premenopausal women who, since age 16, were married to or lived with a boyfriend who smoked for at least one year.

Two other explanations for inconsistencies in the evidence relate to the fundamental design differences between cohort and case–control studies. A critical advantage of cohort studies is that they collect information on exposures before the disease of interest is diagnosed, thus preventing knowledge of disease status influencing how participants recall and/or report their exposures. Recall bias is especially challenging in case–control studies of exposures that are difficult to measure, when recollection of the frequency and intensity of exposure is necessarily subjective. In counterpart, an important advantage of case–control studies is that they can collect more detailed information on the exposure of interest than is usually possible in cohort studies. Together, these factors create what has been described as "a tension" between the potential for

recall or selection bias in case–control studies, and the reduced possibility of collecting full "lifetime exposure histories" in cohort studies (Collishaw *et al.*, 2009). The discrepancy in the results from case–control and cohort studies is seen especially in the earlier case–control studies, which found much stronger associations than those observed in most recent studies. Five studies in particular (Smith *et al.*, 1984; Morabia *et al.*, 1996; Zhao *et al.*, 1999; Johnson & Repace, 2000; Kropp & Chang-Claude, 2002) were considered by Collishaw *et al.* (2009) as having the most complete information on lifetime exposure to second-hand tobacco smoke from all sources. At the same time, these studies are among the most susceptible to recall bias for two reasons. The first is a general problem of case–control studies, in that cases are more likely to remember and report potentially hazardous exposures than controls. Second, recall bias is potentially more problematic when subjective considerations can influence reporting. It is easier to report smoking by a parent or spouse than it is to remember exposures from other sources that possibly occurred many years ago in daily life. Exposure to second-hand tobacco smoke was highly prevalent in the decades following World War II in Europe and North America. It would be unusual for someone not to be exposed. The studies that the California Environmental Protection Agency (2005) considered to have the best information on exposure to second-hand tobacco smoke are also those which rely more heavily on recall of past exposures outside the home. Moreover, inclusion in the referent group in these studies is also vulnerable to recall bias. Previous reviews by IARC (2004) and the US Surgeon General (US. Department of Health and Human Services, 2006) have expressed concern about potential biases that may be introduced by relying on a small and unusual subgroup (the unexposed to active smoking and second-hand tobacco smoke) as the referent category in these studies. Recall bias remains a plausible explanation for why the

association with second-hand tobacco smoke is stronger in studies that collect "lifetime exposure histories" than in those that rely on parental or spousal smoking. In addition, publication bias cannot be ruled out because the reporting of association limited by subgroup (pre-menopausal) could have been selective.

[The Working Group noted that adjustment for potential confounders using the questionnaire data on other established risk factors for breast cancer did not eliminate the association with second-hand tobacco smoke in these studies. However, this does not resolve concerns about the possibility of recall or publication bias.]

Several meta-analyses have been published, largely showing similar results but leading to substantially different interpretations of the evidence (California Environmental Protection Agency, 2005; US Department of Health and Human Services, 2006; Johnson, 2007; IARC, 2009). The California Environmental Protection Agency (2005) calculated a pooled estimate for second-hand tobacco smoke and breast cancer risk of 1.11 (95%CI: 1.04–1.19) in all women and 1.38 (95%CI: 1.21–1.56) in premenopausal women, based on 19 studies and a fixed effects model. These estimates increased to 1.89 (95%CI: 1.57–2.27) for all women and 2.18 (95%CI: 1.70–2.79) in premenopausal women when the analysis was restricted to the subset of studies considered to have the best exposure data.

Based on these analyses, the California Environmental Protection Agency (2005) and Collishaw et al. (2009) emphasized the positive association with premenopausal breast cancer in their conclusion that the evidence is "consistent with a causal relationship" whereas the US Surgeon General (US Department of Health and Human Services, 2006) was more cautious in characterizing the evidence as "suggestive but not sufficient."

[The Working Group noted that the criterion used by IARC specifies "sufficient evidence of carcinogenicity in which chance, bias and confounding could be ruled out with reasonable confidence." This is a more stringent definition than "consistent with a causal relationship."]

2.3 Cancers of the upper aerodigestive tract

2.3.1 Upper areodigestive tract combined

Cancers of the upper aerodigestive tract traditionally comprise cancers of the oral cavity, pharynx, larynx and oesophagus. However, some epidemiological studies have examined only head and neck cancers restricted to tumours of the oral cavity, pharynx and larynx. Four case–control studies (Tan et al., 1997; Zhang et al., 2000; Lee et al., 2008; Ramroth et al., 2008) assessed the effects of second-hand tobacco smoke on head and neck cancers combined and separately for oral cavity, oropharynx or larynx cancers (Table 2.6 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.6.pdf).

In a hospital-based case–control study in the USA, including only non smoking cases and controls, Tan et al. (1997) detected high risk of head and neck cancer among those ever exposed to second-hand tobacco smoke at home or at work. Women presented higher risk at home (OR, 7.3; $P < 0.001$) than men (OR, 1.1; $P < 0.79$). On the other hand, men showed higher risk at work (OR, 11.6; $P < 0.001$) than women (OR, 8.9; $P < 0.002$). [The authors did not provide the percentages of the telephone interviews done with the spouses of cases and controls. Probably, this is the main weakness of this study and differential misclassification of exposure to second-hand tobacco smoke could not be excluded. The analysis was performed without adjustment for potential confounding variables.] In a study in the USA, Zhang et al. (2000) observed an increased risk (OR, 2.4; 95%CI: 0.9–6.8) with lifetime second-hand tobacco smoke exposure (ever/never) for head and neck cancers, adjusted for age, sex, ethnicity, education, alcohol drinking,

pack-years of cigarette smoking, and marijuana consumption.

Lee *et al.* (2008) pooled the data from several studies including cases of head and neck cancers and controls (population and hospital) from central Europe, Latin America and United States. Two groups were examined separately, never tobacco users and never tobacco and alcohol users. Among never tobacco users, no association was observed between ever exposure to second-hand tobacco smoke at home or at work and the risk for head and neck cancers. Among never tobacco and alcohol users, a non-statistically significant risk (or 1.30; 95%ci: 0.94–1.81) was observed. When considering specific anatomical sites, only laryngeal cancer risk was increased when ever exposed to second-hand tobacco smoke in a lifetime, detected among never tobacco users (OR, 1.71; 95%CI: 0.98–3.00) and among never tobacco and alcohol users (OR, 2.90; 95%CI: 1.09–7.73).

In Germany, in a population-based case–control study on laryngeal cancer, Ramroth *et al.* (2008) observed a non-statistically significant risk (OR, 2.0; 95%CI: 0.39–10.7) for exposure to second-hand tobacco smoke (ever/never) at home and in workplaces among nonsmokers.

(a) Evidence of a dose–response

Zhang *et al.* (2000) observed a dose–response relationship with the intensity of exposure to second-hand tobacco smoke (never, moderate and heavy) on head and neck cancers ($P = 0.025$); those at heavy level of exposure at home or at work showed highest risk for head and neck cancer (OR, 3.6; 95%CI: 1.1–11.5). However, the classification of exposure to second-hand tobacco smoke at work as never, occasionally or regularly did not show any dose–response effect; and the risk for the groups of occasionally or regularly exposed at home were similar and non statistically significant.

Lee *et al.* (2008) explored the intensity and duration of sexposure to second-hand tobacco smoke. For intensity the number of hours of exposure per day was considered at home (0–3 hours, > 3 hours) or at the workplace (never, 1–3 hours and > 3 hours). Among both groups of never tobacco users and never tobacco and alcohol users non-statistically significant risks of head and neck cancers were observed for those exposed for > 3 hours per day at home or at work. For duration the number of years of exposure at home and at work was considered (never, 1–15 years, and > 15 years). Among never tobacco users, there was a trend of increase in risk for head and neck cancers with greater number of years of exposure at home, but not at work. Among never tobacco and alcohol users, the duration of exposure showed a trend for exposure both at work or at home.

Considering specific anatomical sites, for cancer of the oral cavity no dose–response effect was observed with increasing number of years of exposure to second-hand tobacco smoke at home or at work. For cancer of the pharynx, a dose–response effect was observed with increasing number of years of exposure to second-hand tobacco smoke with only at home, in both never tobacco users and never tobacco and alcohol users. For cancer of the larynx, a dose–response effect was noted with increasing number of years of exposure to second-hand tobacco smoke at home among never tobacco users and at work among never tobacco and alcohol users. Among never tobacco and alcohol users, all the odd ratios (OR) were statistically significantly elevated for > 15 years of exposure at home or at work for head and neck cancers overall and separately for cancer of the pharynx, and only at work for cancer of the larynx.

2.3.2 Cancers of the nasopharynx, and nasal cavity and sinonasal cavity

The relationship between exposure to second-hand tobacco smoke and risk for these rare cancers of the upper respiratory tract has

been examined in one cohort study (Hirayama, 1984; Table 2.7 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.7.pdf) and five case–controls studies (Fukuda & Shibata, 1990; Yu et al., 1990; Zheng et al., 1993; Cheng et al., 1999; Yuan et al., 2000; Table 2.6 on-line). A positive association was found in most of these studies.

Hirayama (1984) found an increased risk of sinonasal cancer in women (histology not noted) associated with increasing numbers of cigarettes smoked by husbands of nonsmoking 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 & Shibata (1990) reported the results of a 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 second-hand tobacco smoke from one or more smokers. Active smoking was associated with an increased risk for squamous-cell carcinoma of the maxillary sinus 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 second-hand tobacco smoke in white men. A total of 147 deaths from cancer of the nasal cavity and sinuses was compared to 449 controls who had died from other 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 (RR, 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 (RR 4.8; 95%CI: 0.9–24.7). The risks reported for active smoking and exposure to second-hand tobacco smoke were of similar magnitude in this study.

Neither second-hand tobacco smoke exposure during childhood nor exposure during adulthood were positively associated with an increased risk for nasopharyngeal cancer in a study in Taiwan, China (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 second-hand tobacco smoke (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 for 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 second-hand tobacco smoke during childhood was noted. The relative risk was 3.4 (95%CI: 1.4–8.1) if the mother smoked; 3.0 (95%CI: 1.4–6.2) if the father smoked; 2.7 (95%CI: 1.1–6.9) if another household member smoked and 3.0 (95%CI: 1.4–6.2)

if any household member smoked. Risks associated with exposure to second-hand tobacco smoke during adulthood in women were also statistically significantly increased. For male never-smokers, the associations were weaker and were not statistically significantly elevated for exposure during childhood and adulthood. [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 Leukaemia and lymphomas

Kasim *et al.* (2005) analysed the risk of leukaemia in adults after exposure to second-hand tobacco smoke (Table 2.8 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.8.pdf). This case–control study was based on postal questionnaires. There was a slightly increased risk (*P* for trend = 0.001) with increasing duration of exposure to second-hand tobacco smoke. The association was limited to chronic lymphocytic leukaemia and was stronger for occupational exposures to second-hand tobacco smoke.

2.5 Other cancers in adults

2.5.1 All cancer combined

Hirayama (1984), Sandler *et al.* (1985b), and Miller (1990) observed a significant association between exposure to second-hand tobacco smoke and overall cancer incidence or mortality. Nishino *et al.* (2001) also studied all cancers combined and reported a relative risk of 1.1 (95%CI: 0.92–1.4) associated with husband's smoking.

2.5.2 Cancers of the gastrointestinal tract

In addition to the studies reviewed previously (Sandler *et al.* 1988; Gerhardsson de Verdier *et al.*, 1992; Mao et.al., 2002), ten new studies

have been identified: two cohort (Nishino *et al.*, 2001; Hooker *et al.*, 2008; Table 2.13 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.13.pdf); seven case–control (Sandler *et al.*, 1985a, b; Slattery *et al.*, 2003; Lilla *et al.*, 2006; Wang *et al.*, 2006; Duan *et al.*, 2009; Verla-Tebit *et al.*, 2009; Table 2.14 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.14.pdf) and one case-only study (Peppone *et al.*, 2008; Table 2.15 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.15.pdf). Two studies (Sandler *et al.*, 1985a; Wang *et al.*, 2006) did not provide risk estimates of gastrointestinal cancers for never smokers and are not discussed further. [No data for these studies are included in the tables.]

Sandler *et al.* (1985b) observed a relative risk of 0.7 and 1.3 for cancer of the digestive system from exposure to maternal and paternal passive smoke, respectively. [No CIs were provided and the numbers of never smokers exposed were small.] Verla-Tebit *et al.* (2009) found no evidence of an increased risk for colorectal cancer associated with exposure to second-hand tobacco smoke overall.

(a) Cancer of the colorectum

Nishino *et al.* (2001) observed no association with husband's smoking for cancer of the colon (RR 1.3; CI: 0.65–2.4) or of the rectum (RR 1.8; 0.85–3.9).

Four studies investigated risk for cancer or the colon and/or rectum by sex. Sandler *et al.* (1988) reported an increased risk for colorectal cancer in men (RR 3.0; 95%CI: 1.8–5.0) but a protective effect in women (RR 0.7; 95%CI: 0.6–1.0). Slattery *et al.* (2003) noted that rectal cancer was significantly associated with exposure to second-hand tobacco smoke in men (OR, 1.5; 95%CI: 1.1–2.2 for never smokers) but not in women. Hooker *et al.* (2008) reported an effect among men only, with a significantly increased risk for rectal cancer in the 1963 cohort (RR 5.8, 95%CI: 1.8–18.4) but not

the 1975 cohort. Gerhardsson de Verdier *et al.* (1992) found an increased risk for rectal cancer in men (RR 1.9; 95%CI: 1.0–3) and for colon cancer in women (RR 1.8; 95%CI: 1.2–2.8). [The Working Group noted that it is unclear whether the analysis was restricted to never-smokers.]

When analysing different sources of exposure to second-hand tobacco smoke, Verla-Tebit *et al.* (2009) found no evidence of an increased risk for cancer of the colorectum associated with exposure to second-hand tobacco smoke specifically during childhood or at work, but observed a significant increase in risk associated with spousal exposure.

Peppone *et al.* (2008) noted that considerable exposure to second-hand tobacco smoke, especially during childhood, was more likely to lead to an earlier-age diagnosis of cancer of the colorectum.

In exploring the association of cancer of the colorectum with exposure to second-hand tobacco smoke and NAT1 and NAT2 status, Lilla *et al.* (2006) noted that risk may only be relevant among genetically susceptible (NAT1 and NAT2 status) individuals.

(b) Cancer of the stomach

Nishino *et al.* (2001) observed no association with husband's smoking for cancer of the stomach (RR, 0.95; 95%CI: 0.58–1.6).

The two studies on the association of exposure to second-hand tobacco smoke with stomach cancer by subsite (cardia versus distal) gave contradictory results. In one study (Mao *et al.*, 2002) a positive trend ($P = 0.03$) in risk for cancer of the gastric cardia was associated with lifetime exposure to second-hand tobacco smoke (residential plus occupational) in never smoking men, with a relative risk of 5.8 (95%CI: 1.2–27.5) at the highest level of exposure ($\geq$ 43 years); no increased risks or trends were observed for distal gastric cancer. In the other study, Duan *et al.* (2009) an increased risk for distal gastric cancer

was found, but not for gastric cardia [Data were not analysed by sex due to small sample size].

2.5.3 Cancer of the pancreas

Six studies have been identified on the association of exposure to second-hand tobacco smoke with cancer of the pancreas: three cohort (Nishino *et al.*, 2001; Gallicchio *et al.*, 2006; Bao *et al.*, 2009; the latter two are summarized in Table 2.17 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.17.pdf) and three case–control (Villeneuve *et al.*, 2004; Hassan *et al.*, 2007; Lo *et al.*, 2007; the former two studies are summarized in Table 2.18 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.18.pdf).

(a) Exposure in adulthood

Data from the majority of the studies (Nishino *et al.*, 2001; Villeneuve *et al.*, 2004; Gallicchio *et al.*, 2006; Hassan *et al.*, 2007; Bao *et al.*, 2009) suggested lack of an association of cancer of the pancreas with never smokers exposed to second-hand tobacco smoke in adulthood at home or at work. (RR 1.2 (95%CI: 0.45–3.1) and 1.21 (95%CI: 0.60–2.44) respectively).

Lo *et al.* (2007) reported an odd ratio of 6.0 (95%CI: 2.4 –14.8) for never smokers (both sexes combined) exposed to second-hand tobacco smoke in Egypt. [The Working Group noted the small numbers of cases, the use of hospital controls and the small proportion of the cases (35%) with histopathological confirmation. Data are not included in Table 2.18 on-line].

(b) Exposure during childhood

In the Nurses' Health Study, Bao *et al.* (2009) noted an increased risk for cancer of the pancreas (RR 1.42; 95%CI: 1.07–1.89) for maternal but not for paternal smoking (RR 0.97; 95%CI: 0.77–1.21) during childhood.

2.5.4 Cancer of the kidney (renal cell carcinoma)

Two case–control studies have been published on the association of exposure to second-hand tobacco smoke with cancer of the kidney (specifically renal cell carcinoma) since IARC (2004) (Hu et al., 2005; Theis et al., 2008; Table 2.19 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.19.pdf). In both studies a significantly increased risk associated with exposure to second-hand tobacco smoke among never smokers was reported.

2.5.5 Cancer of the urinary bladder

A total of seven studies and one meta-analysis have considered the association between exposure to second-hand tobacco smoke and cancer of the urinary bladder: three cohort studies (Zeegers et al., 2002; Bjerregaard et al., 2006; Alberg et al., 2007; Table 2.9, available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.9.pdf), four case–control studies (Burch et al., 1989; Chen et al., 2005a; Samanic et al., 2006; Jiang et al., 2007; Table 2.10 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.10.pdf), and one meta-analysis (Van Hemelrijck et al., 2009).

(a) Population-based exposure-response relationship

Burch et al. (1989) and Zeegers et al. (2002) reported no increased risk for cancer of the urinary bladder [Data are not included in the Tables]. Van Hemelrijck et al. (2009) reported a meta-relative risk of 0.99 (95%CI: 0.86–1.14) for never smokers exposed to second-hand tobacco smoke. [Data not included in Table. The Working Group noted the marked variation in risk in the analyses by sex and by timing of exposure to second-hand tobacco smoke during adulthood or childhood].

In the European Prospective Investigation into Cancer and Nutrition (EPIC) study,

Bjerregaard et al. (2006) compared ever versus never exposed to second-hand tobacco smoke as an adult or a child: the risk for cancer of the urinary bladder increased for exposures during childhood (OR, 1.38; 95%CI: 1.00–1.90), and was stronger for never-smokers (OR, 2.02; 95%CI: 0.94–4.35).

Alberg et al. (2007) analysed data from two cohorts of non-smoking women in the USA exposed to second-hand smoke at home. An association with exposure to second-hand tobacco smoke was found in the 1963 cohort (RR, 2.3; 95%CI: 1.0–5.4) but not in the 1975 cohort (RR, 0.9; 95%CI: 0.4–2.3). [The Working Group noted the small number of cases available for some of the risk estimates.]

In a study assessing occupational exposure to second-hand tobacco smoke (Samanic et al., 2006), the risk for cancer of the urinary bladder was increased in the highest exposure category among women (RR, 3.3; 95%CI: 1.1–9.5) but not among men (RR, 0.6; 95%CI: 0.2–1.4).

(b) Molecular-based exposure-response relationship

4-aminobiphenyl (4-ABP) can form DNA adducts and induce mutations, and cigarette smoke is the most prominent source of exposure to 4-aminobiphenyl in humans (see Section 4). Jiang et al. (2007) used variation in 4-ABP-haemoglobin adducts levels to assess exposure to second-hand tobacco smoke and reported a significantly increased risk with increasing lifetime exposure among never-smoking women exposed in adulthood or childhood.

Chen et al. (2005a) hypothesized that the ability to detoxify arsenic (a risk factor urinary bladder cancer) through methylation may modify risk related to second-hand tobacco smoke exposure. Results of the adjusted analyses show that a high primary methylation index associates with lower risk of cancer of the urinary bladder (OR, 0.37; 95%CI: 0.14–0.96, p interaction = 0.11) in second-hand tobacco smoke exposed subjects

compared to unexposed. In endemic area the ability to methylate arsenic may play a role in reducing the risk of cancer of the urinary bladder associated with second-hand tobacco smoke exposure. [The Working Group noted that the small number of cases and the use of hospital controls limit the validity of inferences from this study].

Using case–control data for never and former smokers nested within the EPIC study Vineis et al. (2007b) examined susceptibility in genes involved in oxidative stress (such as *NQO1*, *MPO*, *COMT*, *MnSOD*), in phase I (such as *CYP1A1* and *CYP1B1*) and phase II (such as *GSTM1*, and *GSTT1*) metabolizing genes, and in methylenetetrahydrofolate (*MTHFR*). *GSTM1* deletion was strongly associated with risk for urinary bladder cancer in never smokers (OR, 1.75; 95%CI: 0.89–3.43), and a similar association was noted for former smokers and for men.

2.5.6 Cancer of the cervix

The cohort studies evaluated previously (Hirayama, 1984; Jee et al., 1999; Nishino et al., 2001) consistently indicated the lack of association between exposure to second-hand tobacco smoke and cancer of the uterine cervix, while the informative case–control studies (Sandler et al., 1985b; Slattery et al., 1989; Scholes et al., 1999) suggested a non-statistically significant increase in risk.

A total of 10 new studies have been identified: one cohort study (Table 2.11 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.11.pdf) and nine case–control studies (Buckley et al., 1981; Brown et al., 1982; Hellberg et al., 1986; Hirose et al., 1996; Coker et al., 2002; Wu et al., 2003; Tay & Tay, 2004; Sobti et al., 2006; Tsai et al., 2007; Table 2.12 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.12.pdf). Three early case–control studies (Buckley et al., 1981; Brown et al., 1982; Hellberg et al.,

1986) did not look at risk of exposure to second-hand tobacco smoke in never smoking women, and are not further discussed.

(a) Squamous cell carcinoma of the cervix

A significant increase risk for invasive cancer of the uterine cervix associated with exposure to second-hand tobacco smoke during adulthood was found in three case–control studies (Hirose et al., 1996; Wu et al., 2003; Tay & Tay, 2004) and one cohort study (Trimble et al., 2005).

(b) Cervical intraepithelial lesions and neoplasia

An earlier case–control study (Coker et al., 1992) found no statistically significant association between exposure to second-hand tobacco smoke and CIN II/III in non-smokers, after adjustment for age, race, education, number of partners, contraceptive use, history of sexually transmitted disease and history of Pap smear. A later study (Coker et al., 2002) looked at risk of low grade and high grade cervical squamous intraepithelial lesions (LSIL and HSIL, respectively) in HPV positive never-smokers and reported a significant association with exposure to second-hand tobacco smoke. In a community-based case–control study, Tsai et al. (2007) observed a markedly increased risk for both CIN1 and CIN2 in both HPV-positive and HPV-negative women exposed to second-hand tobacco smoke. Only Coker et al. (2002) and Tsai et al. (2007) controlled for HPV status in women.

Sobti et al. (2006) reported that cervical cancer risk is increased in individuals exposed to second-hand tobacco smoke with *GSTM1* (null), *GSTT1* (null) and *GSTP1* (Ile[105]Val) genotypes, with odd ratios ranging from 6.4 to 10.2.

2.5.7 Cancer of the ovary

One cohort study (Nishino et al., 2001) and two case–control studies (Goodman & Tung, 2003; Baker et al., 2006; Table 2.16 available at http://monographs.iarc.fr/ENG/Monographs/

vol100E/100E-02-Table2.16.pdf) have been published on the association of exposure to second-hand tobacco smoke with cancer of the ovary. In all three studies a null or inverse association of cancer of the ovary for never smokers exposed to second-hand tobacco smoke was found. Nishino *et al.* (2001) observed no association with husband's smoking (RR 1.7; 95%CI: 0.6- 5.2). Goodman & Tung (2003) reported no association of exposure to second-hand tobacco smoke during childhood with risk of cancer of the ovary. Baker *et al.* (2006) reported a decreased risk of cancer of the ovary for never smokers exposed to second-hand tobacco smoke (OR, 0.68; 95%CI: 0.46–0.99), with similar findings for former and current smokers.

2.5.8 Tumours of the brain and CNS

A total of three case–control studies (Ryan *et al.*, 1992; Hurley *et al.*, 1996; Phillips *et al.*, 2005) have considered the association of second-hand tobacco smoke and cancers of the brain and central nervous system. Ryan *et al.* (1992) reported an increased risk of meningioma associated with spousal exposure, particularly among women (RR 2.7; 95%CI: 1.2–6.1). In a case–control study of gliomas in Australia no association was found for exposure to second-hand tobacco smoke in never smokers (RR 0.97, 95%CI: 0.61–1.53) (both sexes combined) (Hurley *et al.*, 1996). However Phillips *et al.* (2005) found that spousal smoking was associated with an increased risk for intracranial meningioma in both sexes combined (OR, 2.0; 95%CI: 1.1–3.5), the risk increased with increasing duration of exposure (*P* for trend = 0.02).

2.5.9 Other cancers

One case–control study on hepatocellular cancer (Hassan *et al.*, 2008) and one on cancer of the testis (McGlynn *et al.*, 2006) were published since IARC (2004). Hassan *et al.* (2008) did not find an association with exposure to second-hand tobacco smoke and hepatocellular cancer, while that of McGlynn *et al.* (2006) did not support the hypothesis that maternal smoking is related to the development of cancer of the testis (Table 2.20 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.20.pdf). However, these studies provide limited information on the association of exposure to second-hand tobacco smoke with the risk of these cancers.

2.6 Parental tobacco smoking and childhood cancers

2.6.1. Overview

A large number of studies have evaluated the association of cancer risk in childhood with exposure to parental smoking. However, childhood cancers are extremely heterogeneous, both between major cancer sites and within subtypes. In addition, given the rarity of childhood cancers, studies of specific cancer sites and subtypes that have adequate sample sizes and detailed exposure assessments are difficult to achieve.

(a) Smoking exposure assessment

Parental smoking before and during pregnancy exposes germ cells (spermatozoa and ova) and/or the fetus to the same chemical mixture and levels of tobacco smoke as during active smoking, while post-natal exposure to parental tobacco smoking exposes the offspring to second-hand tobacco smoke. Some studies distinguish whether exposure to parental smoking was preconceptional, *in utero* or postnatal. Even when a study reports only on one time period, exposure may have occurred at all three periods. Exposures to tobacco smoking during each of these periods tend to correlate, in particular, paternal smoking is less likely to change during and after pregnancy. In addition, paternal and

maternal smoking habits are highly correlated (Boffetta *et al.*, 2000).

Most studies assessed the number of cigarettes smoked per day (e.g. 0–10, 11–20, 20+) and, when data were available, some assessed continuous consumption of cigarettes per day. One study reported exposure in pack-years (Lee *et al.*, 2009). The SEARC international case–control study assessed polycyclic aromatic hydrocarbons (PAHs) as the main exposure of interest and obtained information on both tobacco smoke and occupational exposures (Cordier *et al.*, 2004).

(b) Bias and confounding

Whitehead *et al.* (2009) evaluated the adequacy of self-reported smoking histories on 469 homes of leukaemia cases and controls and found that nicotine concentrations derived from interview responses to a structured questionnaire strongly correlated to measured levels in dust samples.

The major confounders for the relationship between parental smoking and childhood cancers were markers of socioeconomic status, race or ethnicity, birth weight or gestational age, parental age, sex and age of the case child. In most studies matching or adjusting for these confounders was performed as appropriate. In some studies matching was performed for birth order and centre of diagnosis.

2.6.2 All childhood cancers combined

In addition to the four cohort and 10 case–control studies reviewed by IARC (2004), three case–control studies have examined the role of second-hand tobacco smoke in relation to risk for all childhood cancers combined (Sorahan *et al.*, 2001; Pang *et al.*, 2003; Sorahan & Lancashire, 2004; Table 2.21 available at http://monographs. iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.21.pdf).

(a) Intensity and timing of parental smoking

In a follow-up of the Inter-Regional Epidemiological Study of Childhood Cancer (IRESCC) by McKinney *et al.* (1987), a statistically significant positive trend with daily paternal smoking before pregnancy was observed when cases were compared with controls selected from General Practitioners' (GPs') lists, but not from hospitals; an inverse trend was noted for maternal smoking before pregnancy when cases were compared with hospital, but not with General Practitioners, controls (Sorahan *et al.*, 2001).

In the United Kingdom Childhood Cancer Study (UKCCS), Pang *et al.* (2003) observed a similar pattern of increasing risk with increasing intensity of paternal preconception smoking, and of decreasing risk for increasing maternal smoking before and during pregnancy for all diagnoses combined, and for most individual diagnostic groups.

In the most recent report from the Oxford Survey of Childhood Cancers (OSCC), the risk of death from all childhood cancers combined was not associated with maternal smoking, but was consistently associated with paternal smoking alone or in combination with maternal smoking, in both adjusted and unadjusted analyses [Ex-smokers of more than 2 years before birth of the survey child were assimilated to non-smokers] (Sorahan & Lancashire, 2004).

(b) Bias and confounding

The significant trends observed by Sorahan *et al.* (2001) and Pang & Birch (2003) did not diminish when adjusted for potential confounding covariates or with simultaneous analysis of parental smoking habits. The relationship between maternal smoking and birth weight reported by Sorahan *et al.* (2001) suggested that self-reported maternal smoking was equally reliable for cases and for controls. However, comparisons of smoking patterns with national data suggested that control parents in this study were heavier smokers.

2.6.3 Leukaemias and lymphomas

Since IARC (2004), one cohort study (Mucci et al., 2004) (Table 2.22 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.22.pdf), eleven case–control studies (Table 2.23 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.23.pdf), and one meta-analysis (Lee et al., 2009) (Table 2.24 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.24.pdf) have evaluated the association of parental tobacco smoking with the risk for lymphatic and haematopoietic cancers.

(a) Duration and intensity of exposure

From a meta-analysis of 30 studies published before 1999 Boffetta et al. (2000) reported no statistically significant association for all lymphatic and haematopoietic neoplasms and noted evidence of publication bias for the available data.

Lee et al. (2009) performed a meta-analysis of twelve studies on paternal smoking and risk of childhood leukaemia. Paternal smoking before conception of the index child was significantly associated with the risk for acute leukaemia (AL) and acute lymphoblastic leukaemia (ALL) (Fig. 2.2).

In a cohort study, maternal smoking was associated with a lower risk of acute lymphoblastic leukaemia, a higher risk of acute myeloid leukaemia (AML) particularly among heavy smokers, and a slight excess risk for non-Hodgkin lymphoma (NHL) (Mucci et al., 2004).

Because of the diversity of types of exposure (paternal, maternal, parental), of timing of exposure (preconception, in utero, post-natally) and of the outcome, the case–control studies are briefly summarized individually.

Schüz et al. (1999) showed that the risk for acute childhood leukaemias was inversely related to maternal smoking during pregnancy. Paternal smoking before pregnancy showed no association with leukaemia risk for any smoking category. Sorahan et al. (2001) reported a non-significant positive association between risk for acute lymphoblastic leukaemia and daily cigarette smoking by fathers before pregnancy, and a non-significant inverse association between risk for acute lymphoblastic leukaemia and daily smoking by mothers before pregnancy. Down Syndrome children are highly susceptible to the development of acute leukaemia. In a case–control study of 27 children with acute leukaemia and Down Syndrome compared with 58 Down Syndrome children without acute leukaemia Mejía-Aranguré et al. (2003) found that paternal smoking of more than 10 cigarettes/day, both preconception and after birth of the index child was associated with acute leukaemia. In the UKCC case–control study (Pang et al., 2003), paternal but not maternal preconception tobacco smoking of 1–19 cigarettes/day was associated with an increased risk of leukaemia, and a similar pattern was reported for lymphoma. Menegaux et al. (2005) reported no increased risk of acute lymphoblastic leukaemia or acute nonlymphocytic leukaemia (ANLL) associated with any category of post-natal exposure to tobacco smoking (i.e. maternal smoking during breastfeeding or after, paternal smoking after birth, other smokers at home), except for an increased risk of acute nonlymphocytic leukaemia with paternal smoking. In a later study, (Menegaux et al., 2007) reported no association between acute and parental smoking, by subtype (acute myeloid leukaemia or acute lymphoblastic leukaemia) or by time of exposure, with the exception of an increased risk of acute lymphoblastic leukaemia associated with maternal smoking during pregnancy. Chang et al. (2006) reported no risk for acute leukaemia, acute lymphoblastic leukaemia or acute myeloid leukaemia associated with maternal smoking either by period of smoking (preconception, during pregnancy, post-natally) or by amount smoked. Paternal preconception smoking was strongly associated

Fig. 2.2 Meta-analysis of the association between paternal smoking and childhood leukaemia

(A) *Overall paternal smoking staus*

Author	Year	Country	Cases		OR 95% CI	*P*
Sorahan	1997	UK	2254			
Ji	1997	China	151			
Brondum	1999	CCG	1618			
Chang	2006	US	228			
MacArthur	2008	Canada	388			
Our study		Korea	164			
All Leukemia (N=6)			4830		1.13 (1.04-1.24)	0.006
ALL (N=5)			2865		1.07 (1.00-1.14)	0.04
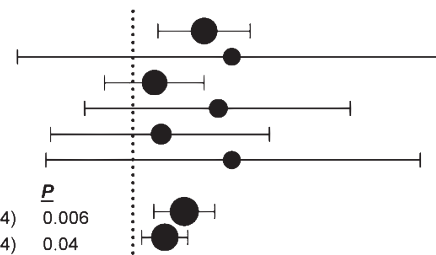
(B) *Paternal smoking status before pregnancy of the child*

Author	Year	Country	Cases		OR 95% CI	*P*
Magnani	1990	Italy	138			
John	1991	US	47			
Ji	1997	China	136			
Brondum	1999	CCG	1618			
Schuz	1999	Germany	955			
Sorahan	2001	UK	139			
Pang	2003	UK	1308			
Chang	2006	US	227			
Menegaux	2007	France	415			
MacArthur	2008	Canada	386			
Our study		Korea	148			
All Leukemia (N=11)			5540		1.12 (1.04-1.21)	0.002
ALL (N=9)			3073		1.17 (1.04-1.30)	0.007
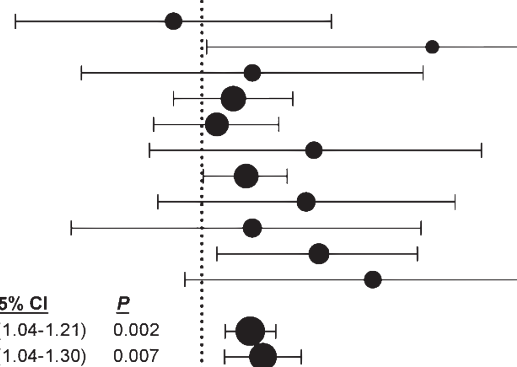
(C) *Paternal smoking status after birth of the child*

Author	Year	Country	Cases		OR 95% CI	*P*
Ji	1997	China	164			
Infante-Rivard	2000	Canada	486			
Menegaux	2007	France	472			
Our study		Korea	158			
All Leukemia (N=4)			1280		1.12 (0.96-1.32)	0.16
ALL (N=4)			1111		1.15 (0.94-1.39)	0.17

0.5　　　　1.0　　　　2.0

OR (95% CI)
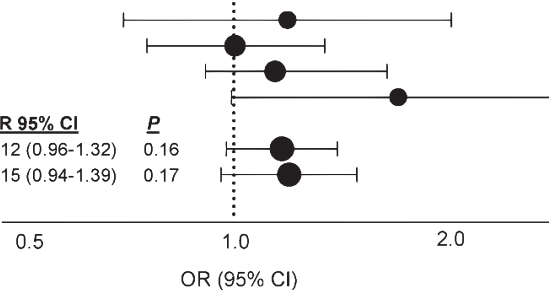
with risk for acute myeloid leukaemia both by period and intensity of smoking. When both paternal preconception smoking and maternal postnatal smoking were considered, the risk for acute lymphoblastic leukaemia was stronger. Rudant *et al.* (2008) reported a significant positive association between paternal smoking and acute lymphoblastic leukaemia, acute myeloid leukaemia, Burkitt lymphoma, and anaplastic large cell non-Hodgkin lymphoma, with increasing relative risks (RR) with increasing

number of cigarettes smoked. No associations with Hodgkin lymphoma or other types of non-Hodgkin lymphoma were observed. Non-significantly elevated risks were observed for maternal smoking during pregnancy for acute lymphoblastic leukaemia and non-Hodgkin lymphoma, but not in the highest category of 10 or more cigarettes/day. MacArthur *et al.* (2008) reported non-significantly elevated risk estimates for acute lymphoblastic leukaemia and acute myeloid leukaemia with maternal smoking, but

not with paternal smoking, before and during pregnancy. Lee *et al.* (2009) in Seoul, Republic of Korea, reported that paternal smoking was associated with a significantly increased risk of acute leukaemia and acute lymphoblastic leukaemia in a dose–response manner. The proportion of mothers who smoked was too low (6.1% in controls) to analyse risk in association with maternal smoking.

(b) Potential confounders

In the study of Down Syndrome children (Mejía-Aranguré *et al.*, 2003), the adjustment models did not show any interaction between paternal alcoholism and smoking. Menegaux *et al.* (2005) examined the association of parental smoking and maternal alcohol and coffee intake during pregnancy with the risk for childhood leukaemia. They found no association of acute lymphoblastic leukaemia or acute nonlympho-cytic leukaemia with maternal smoking during pregnancy but an association with maternal alcohol and coffee consumption.

(c) Effect modification

Cigarette smoke is a known germ-cell mutagen in mice (Yauk *et al.*, 2007), a likely germ-cell mutagen in humans (see Section 4.1.3a) and alters gene expression (see Section 4.1.4). Infante-Rivard *et al.* (2000) first assessed the role of parental smoking and *CYP1A1* genetic polymorphisms with leukaemia and reported no statistically significant association with leukaemia overall. However, a case-only subanalysis suggested that the effect of parental smoking may be modified by variant alleles in the *CYP1A1* gene: *CYP1A1*2B* tended to decrease risks and *CYP1A1*2A* and *CYP1A1*4* increased the risks associated with smoking in the second and third trimesters of pregnancy. Clavel *et al.* (2005) examined the role of metabolic polymorphisms in the *CYP1A1*, *GSTM1*, *GSTP1*, *GSTT1* and *NQO1* genes. The slow *EPHX1* allele (exon 3 homozygous geno-type) was negatively associated with leukaemia,

in particular acute lymphoblastic leukaemia, whereas the fast *EPHX1* allele (exon 4 homozy-gous genotype) was positively associated with leukaemia overall. A non-significant association with acute lymphoblastic leukaemia was noted for the homozygous *NQO1*2* genotype. There was a significant interaction of the *CYP1A1*2A* allele with smoking in the case-only analysis and a not significant interaction, but similar in magnitude, in the case–control analysis. A significant interaction was also observed with the *GSTM1* deletion in the case-only analysis, but not in the case–control analysis. Lee *et al.* (2009) genotyped five single-nucleotide *CYP1A1* poly-morphisms: acute lymphoblastic leukaemia risk was significantly increased for cases without the *CGACC* haplotype and with paternal smoking or the presence of at least one smoker in the home.

RAS is the second most mutated gene in smoking-associated lung tumours (Section 4.1.3b). *RAS* mutations have been consistently correlated with myeloid leukaemias in adults and children, in particular with occupationally-associated adult myeloid leukemias (Taylor *et al.*, 1992; Barletta *et al.*, 2004). Wiemels *et al.* (2005) studied the relationship of *RAS* mutations, hyperdiploidy (> 50 chromosomes) and smoking in a case series of 191 acute leukaemia. Smoking was negatively associated with hyperdiploidy (possibly due to the sensitivity of the hyperdip-loid clone and consequent differential survival) and hyperdiploid acute leukaemia cases had the highest rates of *RAS* mutations. [Paternal smoking in the three months before pregnancy was less frequent among hyperdiploids than among non-hyperdiploids.]

2.6.4 Cancers of the brain and central nervous system

Since IARC (2004), the association of expo-sure to parental smoking and risk for childhood brain and central nervous system (CNS) tumours has been examined in one cohort study (Brooks

et al., 2004; Table 2.25 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.25.pdf), six case–control studies (Schüz *et al.*, 1999; Sorahan *et al.*, 2001; Filippini *et al.*, 2002; Pang *et al.*, 2003; Cordier *et al.*, 2004; Plichart *et al.*, 2008; Table 2.26 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.26.pdf), and one meta-analysis (Huncharek *et al.*, 2002; Table 2.27 available at http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-02-Table2.27.pdf).

A meta-analysis of 30 studies published before 1999 indicated no significant increase in risk for CNS tumours associated with maternal smoking during pregnancy and an increased risk for brain tumours with paternal smoking (Boffetta *et al.*, 2000).

Huncharek *et al.* (2002) included one cohort and eleven case–control studies in a meta-analysis and found no clear association of maternal smoking during pregnancy with risk for childhood brain tumours, and a null risk estimate for all CNS tumours (even when the analysis was restricted to astrocytomas, the main brain tumour type). The results were comparable and consistently null for all sensitivity analyses conducted (Table 2.27 on-line).

Brooks *et al.* (2004) analysing the Swedish birth cohort study observed that children, in particular those aged 2–4 years, whose mother smoked during pregnancy, had an increased incidence of childhood brain tumours; the increase in risk was similar for benign and malignant brain tumours and most apparent for astrocytomas (Table 2.25 on-line).

Schüz *et al.* (1999) evaluated parental smoking and CNS tumour risk in children < 15 years from the German Childhood Cancer Registry (see Table 2.26 on-line). No association with risk of CNS tumours was observed for either maternal smoking during pregnancy or paternal smoking before pregnancy. Sorahan *et al.* (2001) found no significant association or trends of risk of CNS tumours with either paternal or maternal

smoking, except for low level of maternal exposure [the latter analysis is based on only eleven exposed cases and one control, yielding a very wide confidence interval]. Filippini *et al.* (2002) observed no association between risk of childhood brain tumours and parental smoking before pregnancy, maternal smoking, regular maternal exposure to second-hand tobacco smoke during pregnancy, or exposure of the child to second-hand tobacco smoke during its first year of life. The results did not vary by child's age at diagnosis, type of CNS tumour or study centre. Plichart *et al.* (2008) reported no association for maternal smoking during pregnancy with CNS tumours, while paternal smoking preconception showed a significant association, especially for astrocytomas. When assessing parental exposure to PAHs, Cordier *et al.* (2004) observed an association of paternal exposure to occupational PAHs preconception with all childhood brain tumours and with astroglial tumours, but no trend of increasing risk with increased exposure. Paternal smoking alone was associated with a risk for astroglial tumours when compared with non-smoking, non-occupationally-exposed fathers. Pang *et al.* (2003) found a decreased CNS risk with maternal smoking of more than 20 cigarettes/day preconception, in both unadjusted and adjusted analyses. In the analyses by histological subgroups a statistically significant decreased risk was associated with maternal smoking during pregnancy for primitive neuroectodermal tumours.

2.6.5 Hepatoblastoma

Hepatoblastoma is an embryonal tumour presumably of fetal origin and prenatal exposures are likely more important than post-natal. In some children, a diagnosis of hepatoblastoma is evident at birth or shortly thereafter, with a median age at diagnosis of 12 months. The ability of hepatoblastoma tumour cells to synthesize α-fetoprotein (AFP), a major serum protein

synthesized by fetal liver cells, also suggests a fetal origin. Also, hepatoblastomas, like many other embryonal tumours, are associated with Beckwith-Wiedemann syndrome and hemi-hypertrophy, further suggesting a gestational oncogenic event (DeBaun & Tucker, 1998). Data were available for both maternal and paternal exposures from two studies (Pang *et al.*, 2003; Sorahan & Lancashire, 2004) while two other studies (McLaughlin *et al.*, 2006; Pu *et al.*, 2009) were limited to data on maternal smoking, available from birth certificates and medical records, respectively (Table 2.28). Most of these studies had limited sample sizes given the extreme rarity of these tumours.

(a)   Parental smoking exposure

After adjustment for relevant covariates, Pang *et al.* (2003) observed a statistically significant increased risk of hepatoblastoma in association with maternal preconception smoking (OR, 2.68; 95%CI: 1.16–6.21, $P = 0.02$) in a somewhat dose-dependent manner ($P = 0.058$). The association with parental smoking was strongest (relative to neither parent smoking) when both parents smoked (OR, 4.74; 95%CI: 1.68–13.35, $P = 0.003$). Sorahan & Lancashire (2004) found no increased risk associated with maternal or paternal smoking alone compared to non-smokers, in both adjusted and unadjusted analyses. In contrast, parental smoking (paternal and maternal smoking combined) was strongly and consistently associated with an increased risk for hepatoblastoma in both adjusted and unadjusted analyses.

In a record-based case–cohort study only maternal smoking was examined (McLaughlin *et al.*, 2006). Extremely low birth weight (< 1000 g) was strongly associated with hepatoblastoma. After adjustement for birth weight, a statistically significant elevated risk for hepatoblastoma was found with maternal smoking (RR 2.1; 95%CI: 1.0–4.2). The increased risk was stronger for children diagnosed at the age of two years or

older (RR 6.0 versus 1.4). Also, the relarive risk for maternal smoking and hepatoblastoma was stronger for children with normal birth weight [> 2500 g] than for low birth weight children. For cases of hepatoblastoma diagnosed after the age of two years, the relative risk for maternal smoking among children with normal birth weight was also stronger than that among children with low birth weight.

Another study on maternal smoking only was conducted in Chonquing, China (Pu *et al.*, 2009). After adjustment for birth weight, a significantly increased risk for hepatoblastoma was found for maternal smoking (RR 2.9; 95%CI: 1.1–4.2). Adjustments for maternal age, maternal body mass index and sex of the baby did not change the odd ratios. When analyses were stratified by birth weight, the odd ratio associated with maternal smoking for children with a birth weight greater than 2500 g was increased almost fourfold. Stratification by age at diagnosis showed that the risk increased almost fivefold with diagnosis at the age of two years or over. [The Working Group noted that since information regarding mother's smoking status for both cases and controls was obtained before diagnosis the potential for biased recall of maternal exposures during pregnancy is reduced].

(b)   Bias and confounding

The known risk factors for hepatoblastoma include low and very low birth weights (< 2000 g and < 1000 g, respectively), maternal age and use of assisted reproductive technologies. All studies adjusted for maternal age, and low birth weight was addressed in three of them (Pang & Birch, 2003; McLaughlin *et al.*, 2006; Pu *et al.*, 2009). Assisted reproductive technologies were not considered to be an important potential confounder of these studies.

Spector & Ross (2003) argued that the association of hepatoblastoma with parental smoking observed by Pang *et al.* (2003) might be confounded by birth weight. In their response,

Table 2.28 Studies of parental tobacco smoking and childhood hepatoblastoma

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories (case/control)	(Cases/ controls)	OR (95% CI)* * P < 0.05 ** P < 0.01	Adjustment for potential confounders	Comments
Pang et al. (2003) United Kingdom	3838 childhood cancer cases, of which 28 hepatoblastoma; Hospital based; < 15 yr of age; 1991–94 in Scotland; 1992–94 in England and Wales	7581 controls; matched for sex, date of birth and geographical area of residence at diagnosis; randomly selected from Family Health Services Authorities in England and Wales and Health boards in Scotland	Face-to-face structured interviews; Computerized self-administered questionnaires to parents of index child	*Parental smoking* Neither parent Mother only Father only Both parents *Paternal preconception smoking (cigarettes per d)* 0 1–19 20+ Trend *P* *Maternal preconception smoking (cigarettes per d)* 0 1–19 20+ *P* for trend	(8/3142) (2/574) (3/1008) (10/1249) ** (11/3082) (6/1003) (7/1440) (10/3916) (9/1490) (4/882)	1.00 (ref) 2.02 (0.40–10.2) 1.86 (0.46–7.55) 4.74 (1.68–13.35) 1 (ref) 1.88 (0.67–5.26) 1.65 (0.61–4.45) 0.272 1 (ref) 2.99 (1.15–7.76)* 2.17 (0.65–7.20) 0.058	Deprivation and parental age at birth of index child	Underreporting of smoking by case mothers
Pang & Birch (2003) United Kingdom	Birch and Kelsey diagnostic subgroups, which group biologically similar tumours together (UKCCS Investigators, 2000) excluding diagnostic subgroups with less than 10 cases			*Maternal preconception smoking* *Both parents preconception smoking* § *Maternal preconception smoking* § *Both parents preconception smoking*	(28/7581) (27/6987)	2.68 (1.16–6.21)* 4.74** 2.50* 4.97**	§ As above, additionally adjusted for birth weight	

Table 2.28 (continued)

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories (case/control)	(Cases/ controls)	OR (95% CI)* * P < 0.05 ** P < 0.01	Adjustment for potential confounders	Comments
Sorahan & Lancashire (2004) United Kingdom, 1953–84	43 deaths from hepatoblastoma < 16 yr of age	5777 matched controls, (analysed as unmatched series)	Parental smoking during yr 1953–55, 1971–76, 1977–81	*Maternal cigarette smoking* Non-smoker Smoker *Paternal cigarette smoking* Non-smoker Smoker *Parental cigarette smoking* Neither parent Mother only Father only Both parents	(19/3191) (24/2524) (12/2267) (28/3359) (9/1601) (3/662) (8/1545) (20/1800)	1 (ref) 1.73 (0.93–3.21) 1 (ref) 2.10 (1.03–4.25)* 1.0 (ref) 0.85 (0.23–3.19) 1.23 (0.46–3.28) 2.69 (1.18–6.13)*	Sex, age at death, yr of death, social class, sibship position, age of mother and father at birth of child, obstetric radiography	
McLaughlin et al. (2006), New York, USA, 1985–2001	58 cases of hepatoblastoma, identified from New York State Cancer Registry	Matched on yr of birth, electronic birth records for 1985–2001 from New York State	Routinely recorded data on birth certificate	*Maternal smoking* Non-smoker Smoker Birth weight > 2500 g Birth weight > 2500 g and age > 2 yr *Maternal smoking*	(36/3439) (12/742)	1 (ref) 2.1 (1.0–4.2) 2.7 (1.2–5.5) 5.8 (1.4–25.1)	Birth yr and birth weight	Association of maternal smoking was stronger in children with birth weights over 2.5kg.
Pu et al. (2009), Chongquing China, 1990–97	58 cases	92 controls, appendicitis patients, matched on age, sex, yr	Medical record of mother or follow-up interviews as needed	Non-smoker Smoker	(43/84) (15/8)	1 (ref) 2.9 (1.1–4.2)	Birth weight	

d, day or days; yr, year or years

Pang & Birch (2003) showed evidence supporting their initial conclusion: the comparable results for maternal smoking, smoking by both parents and maternal smoking for cases diagnosed at an older age, i.e. one year or older, before and after adjustment for birth weight, appear to rule out low birth weight as an explanation for the association.

Also, both later studies (McLaughlin *et al.*, 2006; Pu *et al.*, 2009) reported higher relative risks for children with normal birth weight compared to those with low birth weight, particularly in cases diagnosed after the age of two years.

2.6.6 Other childhood cancers

Several other childhood cancers have been studied in relation to parental tobacco smoke exposures, namely neuroblastoma, nephroblastoma, bone tumours, Wilms tumour, soft tissue sarcomas, other neoplasms of the reticuloendothelial system, and childhood germ cell tumours. The data are few and inconsistent (Schüz *et al.*, 1999; Sorahan *et al.*, 2001; Chen *et al.*, 2005b; Table 2.28).

2.7 Synthesis

2.7.1 Lung

The totality of evidence available to date firmly establishes that exposure to second-hand tobacco smoke at home and at the workplace is causally associated with lung cancer risk in both men and women. This association has been observed in studies from North America, Europe, and Asia. Emerging evidence is also suggesting that exposure to second-hand tobacco smoke among children significantly enhances the risk of lung cancer in adulthood.

2.7.2 Breast

A large number of cohort studies, case–control studies and meta-analyses have assessed the association between exposure to second-hand tobacco smoke and breast cancer. Recent large cohort studies in Europe and North America showed no association between second-hand tobacco smoke and breast cancer. Positive associations in one or more subgroups were reported from some case–control studies; however, these associations were weaker in more recent studies compared with earlier studies.

Explorative analyses focusing on premenopausal breast cancer have suggested that second-hand tobacco smoke may preferentially cause premenopausal breast cancer. Positive associations were largely reported from case–control studies, in which both recall and publication bias cannot be ruled out. Case–control studies that collect a lifetime exposure history are particularly vulnerable to subjective and differential reporting of exposures that occurred long in the past from sources that are difficult to quantify. Overall, the results for an association with premenopausal breast cancer are also inconsistent.

2.7.3 Upper aerodigestive tract combined

Most evidence of the association between second-hand tobacco smoke and upper aerodigestive tract cancers, and the subsites of the oral cavity, pharynx and larynx, comes from a pooled analysis. Overall, the association between second-hand tobacco smoke exposure and cancers of the larynx and pharynx is less than causal.

2.7.4 Nasopharynx, and nasal cavity and accesory sinuses

There is some evidence from a cohort and case–control study that exposure to second-hand tobacco smoke increases the risk of sinonasal cancer; for cancer of the nasopharynx, the evidence is contradictory.

2.7.5 Others sites

Overall, data are conflicting and sparse for the association of exposure to second-hand tobacco smoke with all cancers combined, cancers of the gastrointestinal tract combined, and cancers of the stomach, colon, rectum, pancreas, liver (hepatocellular carcinoma), kidney (renal cell carcinoma), urinary bladder, cervix, ovary, testes, and brain and central nervous system.

2.7.6 Childhood cancers

(a) All childhood cancers combined

Four cohort studies, 13 case–control studies and one meta-analysis have assessed the association of parental tobacco smoking with childhood cancers, all sites combined, in offspring. Most of the early studies only assessed the contribution of maternal smoking, whereas recent studies generally assessed both paternal and maternal smoking, and at various time periods (preconception, during pregnancy, post-natally). Overall, the evidence for an association between parental smoking and childhood cancer (all sites combined) remains inconsistent and may be subject to bias. Nevertheless, a fairly consistent association of paternal tobacco smoking with childhood cancers is beginning to emerge, which is stronger in studies with more specific exposure assessments.

(b) Leukaemias and lymphomas

Two cohort studies, 27 case–control studies and 2 meta-analyses have examined the association of childhood haematopoietic malignancies (leukaemia and lymphoma) with exposure to parental smoking (paternal, maternal or both). All studies examined leukaemia, and a large number of these addressed non-Hodgkin lymphoma.

The body of evidence suggests a consistent association of leukaemia (and lymphoma) with paternal smoking preconception and with combined parental smoking, with risk ratios ranging from 1.5 to 4.0. Maternal tobacco smoking during pregnancy generally showed modest increases in risk, or null or inverse relationships. The combined effects of preconception and post-conception exposures to tobacco smoke were highly significant.

Several studies on lymphoma risk associated with parental smoking showed significantly elevated risks associated with paternal tobacco smoking preconception. The analyses had small samples sizes, and biases due to participation, recall and response, especially related to exposure, cannot be ruled out.

(c) Brain and central nervous system

The association of childhood tumours of the brain and central nervous system with parental smoking was assessed in two cohort studies, 21 case–control studies and 2 meta-analyses. Overall these studies do not show an association with either paternal smoking, largely preconception, or maternal smoking prior, during or after pregnancy, or by CNS types, gliomas and primitive neuroectodermal tumours. The strongly positive associations noted in some studies for paternal tobacco smoking with astrocytomas are offset by the lack of association with childhood brain tumours reported by the large UK Childhood Cancer Study.

(d) Hepatoblastoma

Four informative case–control studies provided data on the association between parental smoking and hepatoblastomas. Two studies reported on both maternal and paternal smoking, while the two others assessed only maternal smoking. In one study where a large number of categories of childhood cancers ($n = 25$) were assessed, the only childhood cancer that showed an association with parental smoking was hepatoblastoma. This original observation was confirmed in three later studies, with relative risks ranging from 2.0 to 5.5. Chance, bias and

confounding were adequately addressed in the data from the studies available. The evidence for the association of parental smoking with hepatoblastoma is convincing, with an emphasis on prenatal exposures.

(e) Other childhood cancers

Most of the associations reported for the other childhood cancers, notably soft tissue sarcomas, rhabdomyosarcomas, Ewing's sarcoma, neuroblastoma, Wilms tumour, reticuloendothelial sarcomas and germ cell tumours were null, with a few isolated and inconsistent positive observations.

3. Cancer in Experimental Animals

3.1 Simulated second-hand tobacco smoke

Simulated second-hand tobacco smoke, frequently a mixture of 89% sidestream and 11% mainstream smoke, generated from cigarettes by smoking machines (Teague et al., 1994) has been tested for carcinogenicity in adult mice of strains that are genetically susceptible to induction of lung tumours (Malkinson, 1992). Mice were exposed in inhalation chambers. Several studies reported no increase in lung tumour incidence or multiplicity in mice exposed to simulated second-hand tobacco smoke for 5–9 months and killed immediately thereafter (Witschi et al., 1995, 1997a; Finch et al., 1996). It was suggested that the lack of tumour response in simulated second-hand tobacco smoke-exposed mice might be due to treatment-induced stress (as determined by the increased plasma corticosterone level) that has been shown to attenuate lung tumorigenesis (Stinn et al., 2005a).

In subsequent studies from several laboratories (Table 3.1), an increased multiplicity and often increased incidence of lung tumours was reported in male and female A/J mice exposed for five months and kept in filtered air for another four months (Witschi et al., 1997a, b, 1998, 1999; D'Agostini et al., 2001) or longer (Witschi et al., 2006) before the mice were killed. Similar results were obtained with Swiss albino mice (Witschi et al., 2002). In these studies, no nasal tumours were observed in smoke-exposed mice.

In one study, male and female transgenic mice with a dominant negative p53 mutation on an A/J background were exposed to simulated second-hand tobacco smoke for 9.5 continuous months or for 5 months followed by recovery in air for 4.5 months. Transgenic mice exposed by either regimen developed significantly higher incidence and multiplicity of lung tumours than sham-exposed control transgenic mice (DeFlora et al., 2003). Neither lung tumour incidence nor multiplicity was increased in smoke-exposed wild-type control mice in this study.

In one study, male and female rats exposed to room-aged sidestream cigarette smoke by nose-only inhalation for 24 months and then killed had no increased incidence of lung or other tumours in comparison with fresh-air controls. Lung tumours were not significantly increased in rats exposed for 24 months and kept until 30 months of age (Stinn et al., 2005b).

3.2 Sidestream smoke condensate

In one study, sidestream cigarette smoke condensate applied to the shaved skin of female NMRI mice lower back, at total weekly doses of 5, 10 and 15 mg, for 3 months caused benign and malignant skin tumours and mammary carcinomas in mice observed for their lifespan and was more potently carcinogenic in this assay than mainstream smoke condensate. No cutaneous or subcutaneous tumours developed in any of three control groups ($P < 0.001$) (Mohtashamipur et al., 1990). In one study, fractionated sidestream cigarette smoke condensates were implanted into the lungs of female rats. The fraction containing

Table 3.1 Carcinogenicity studies of inhalation exposure to simulated second-hand tobacco smoke[a] in A/J mice, transgenic mice with a dominant negative *p53* mutation, and Wistar rats as a function of length of the post-exposure recovery period

Species, strain (sex) Reference	Animals/group at start Dosing regimen Duration	Results Target organ Incidence and/or multiplicity of tumours (%)	Significance	Comments
Mice, A/J (M) Witschi *et al.* (1997a)	48 animals/group Chamber concentration, 0 or 87 mg/m³ total suspended particulates; 6 h/d, 5 d/wk for 5 mo followed by 0 or 4 mo post-exposure recovery 9 mo	5 mo: 2/24 (8%, 0.1 ± 0.1); 6/24 (25%, 0.3 ± 0.1) 9 mo: 9/24 (38%, 0.5 ± 0.2); 20/24 (83%, 1.4 ± 0.2)	NS Incidence: $P < 0.05$ Multiplicity: $P < 0.05$	> 80% of tumours were adenomas; the rest were adenocarcinomas
Mice, A/J (F) D'Agostini *et al.* (2001)	20 animals/group Chamber concentration, 0 or 120 mg/m³ total suspended particulates; 6 h/d, 5 d/wk, for 5 mo followed by 4 mo post-exposure recovery 9 mo	5/20 (25%, 0.25 ± 0.10); 15/20 (75%, 1.05 ± 0.17)	Incidence: $P < 0.01$ Multiplicity: $P < 0.01$	
A/J mice (sex NR) Witschi *et al.* (2006)	24, 25 controls (12 mo) 19, 17 controls (24 mo) Chamber concentration, 0 (control) or 158 mg/m³ total suspended particulates; 6 h/d, 5 d/wk, for 6 mo followed by 4 or 16 mo post-exposure recovery 24 mo	12 mo: 13/24 (54%, 0.9 ± 0.2); 24/25 (96%, 1.8 ± 0.2) 24 mo: 8/9 (89%, 2.1 ± 0.5); 10/10 (100%, 4.3 ± 0.7)	Incidence: $P < 0.05$ Multiplicity: $P < 0.05$ Incidence: NS Multiplicity: $P < 0.05$	80% of tumours were adenomas
(UL53–3xA/J)F₁, Transgenic mice (M, F) De Flora *et al.* (2003)	222 (108; 114 controls) Chamber concentration, 0 (control) or 113 mg/m³ total suspended particulates; 6 h/d for 5 mo or 9.5 mo followed by 0 or 4.5 mo post-exposure recovery 9.5 mo	No recovery: NR; 17/30 (57%, 0.93 ± 0.18) With recovery: 5/26 (19%, 0.27 ± 0.10); 15/23 (65%, 0.74 ± 0.11)	Incidence: $P < 0.01$ Multiplicity: $P < 0.01$ Incidence: $P < 0.01$ Multiplicity: $P < 0.01$	
Wistar rats (M, F) Stinn *et al.* (2005b)	99 rats/group Nose-only exposure; concentration, 0 (controls) or low dose 3 mg/m³ or high dose 10 mg/m³; 6 h/d, 7 d/wk, 24 mo followed by 0 or 6 mo post-exposure recovery 30 mo	24 mo: controls–0/16 Low dose–0/16 High dose–0/16 30 mo: controls–2/99 (2%) Low dose–4/98 (4%) High dose–5/94 (5%)	NS	

[a] Simulated second-hand tobacco smoke: 89% sidestream and 11% mainstream smoke from Kentucky 1R4F or 2R1 reference cigarettes

d, day or days; F, female; h, hour or hours; M, male; mo, month or months; NR, not reported; NS, not significant; wk, week or weeks

PAHs with four and more rings (dose, 1.06 mg/rat) induced 5 lung carcinomas in 35 treated rats; fractions containing no PAHs or PAHs with two or three rings (16 mg/rat) had little or no carcinogenic effect (Grimmer *et al.*, 1988).

3.3 Observational studies of companion animals

In one study, sinonasal cancers occurred more frequently in pet dogs of long-nosed breeds which lived in homes with at least one smoker (Reif *et al.*, 1998), but no such excess risk was seen in a second study (Bukowski *et al.*, 1998). A marginal excess risk of lung cancer was observed in dogs aged 10 years or less and exposed to household tobacco smoke in one study (Reif *et al.*, 1992). Risk of bladder cancer in dogs was not related to exposure to household cigarette smoke in another study (Glickman *et al.*, 1989).

Risk of malignant lymphoma was increased in pet cats exposed to household tobacco smoke in one study (Bertone *et al.*, 2002), but the conclusion that this association was causal has been questioned (Denson, 2003). In another study by the same group (Bertone *et al.*, 2003), exposure of pet cats to household tobacco smoke was also associated with a non-significant 2-fold increase in risk of oral squamous cell carcinoma.

3.4 Synthesis

Several studies showed consistent increases in lung tumour multiplicity and often lung tumour incidence in inbred strain A/J mice and in transgenic mice with a dominant negative *p53* tumour suppressor gene exposed by inhalation. In addition, in one report, skin and mammary tumours were induced in NMRI mice exposed to sidestream cigarette smoke condensate applied topically to the skin.

4. Other Relevant Data

See Section 4 of the *Monograph* on Tobacco Smoking in this volume.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of second-hand tobacco smoke. Second-hand tobacco smoke causes cancer of the lung. Also, a positive association has been observed between exposure to second-hand tobacco smoke and cancers of the larynx and the pharynx.

There is *sufficient* 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 tobacco smoke condensates.

Second-hand tobacco smoke is *carcinogenic to humans (Group 1).*

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* Exceptionally, the most recent updates of well-established ongoing surveys and reports, published after the meeting, were included in this Monograph. The methodology and data available at the time of the meeting were reviewed by the Working Group; the updates reflect the most current estimates of prevalence of exposure and therefore have no influence on the final evaluation.