CHAPTER 21.

Analysis of tumour site concordance

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Introduction

Since its establishment in the early 1970s, the *IARC Monographs Programme* has evaluated more than 1000 agents with evidence of human exposure for which some suspicion exists of an increased cancer risk to humans. The *IARC Monographs Programme* has developed detailed criteria against which to evaluate the available scientific evidence on the carcinogenic potential of such agents. These criteria, which are described in the Preamble to the *IARC Monographs* (Cogliano et al., 2004; IARC, 2006), are used to evaluate and integrate the evidence provided by human epidemiological studies, animal cancer bioassays, and information on possible biological mechanisms of action, to classify agents into one of the following categories: *carcinogenic to humans* (Group 1), *probably carcinogenic to humans* (Group 2A), *possibly carcinogenic to humans* (Group 2B), *not classifiable as to its carcinogenicity to humans* (Group 3), and *probably not carcinogenic to humans* (Group 4). These evaluations involve classifying the data from both the human and the animal studies as providing *sufficient evidence of carcinogenicity*, *limited evidence of carcinogenicity*, *inadequate evidence of carcinogenicity*, or *evidence suggesting lack of carcinogenicity*. The information on biological mechanisms of action may be evaluated as *strong*, *moderate*, or *weak*, and is taken into consideration in the overall evaluation.

To date, IARC has developed 119 *Monographs* Volumes on more than 1000 agents for which there exists

some evidence of cancer risk to humans; of these, 120 agents met the criteria for Group 1. Volume 100 of the *IARC Monographs* provided a review and update of the 107 Group 1 agents identified as of 2009. Volume 100 is divided into six parts, focusing on pharmaceuticals (Volume 100A; IARC, 2012e); biological agents (Volume 100B; IARC, 2012b); arsenic, metals, fibres, and dusts (Volume 100C; IARC, 2012a); radiation (Volume 100D; IARC, 2012f); personal habits and indoor combustions (Volume 100E; IARC, 2012d); and chemical agents and related occupations (Volume 100F; IARC, 2012c). Since the publication of Volume 100, five additional agents had been added to Group 1 at the time the present analysis was undertaken: (i) diesel engine exhaust (reviewed in Volume 105; IARC, 2013), (ii) trichloroethylene (TCE) (evaluated in Volume 106; IARC, 2014), (iii) polychlorinated biphenyls (PCBs) and dioxin-like PCBs (reviewed in Volume 107; IARC, 2016b), and (iv) outdoor air pollution and (v) particulate matter in outdoor air pollution (both evaluated in Volume 109; IARC, 2016a). Had these five agents been evaluated within Volume 100, they would have been included in Volume 100F; for ease of reference, these agents are included in an expanded group of chemical agents and related occupations, denoted by Volume 100F*.

The 113 agents classified by IARC as known causes of cancer in humans up to and including Volume 109 of the *IARC Monographs* are listed in Table 21.1. Note that although 3,3′,4,4′,5-pentachlorobiphenyl (PCB 126) was evaluated as a separate Group 1 agent in Volume 100F, it is included within the group of agents consisting of PCBs and dioxin-like PCBs, which were determined to be Group 1 agents in Volume 107. For the purposes of the present analysis, PCBs and dioxin-like PCBs were considered as a single group of PCBs, resulting in 113 – 2 = 111 distinct agents for analysis. Including the five Group 1 agents identified since Volume 100, there are 23, 11, 10, 18, 12, and 37 Group 1 agents in Volumes 100A to 100F*, respectively.

Because both animal and human data are considered in evaluating the weight of evidence for human carcinogenicity, the degree of concordance between species for tumour induction by carcinogenic agents is important. A high degree of site concordance between species supports the ability of studies in experimental animals to predict not only a potential cancer risk to humans but also the specific sites of cancer induction expected from human exposure to carcinogenic agents. In contrast, lack of concordance may indicate the need for further research to make sure that all cancer sites have been identified in sensitive human subpopulations or in appropriate experimental animal models, and to identify the underlying mechanisms that different species may or may not have in common.

This chapter uses the data set assembled by Grosse et al. (Annex 1) derived from the available information on the agents classified by IARC as *carcinogenic to humans* (Group 1) in Volume 100 to Volume 109, the last *Monograph* for which final data were available at the time this analysis was conducted. This database includes all tumour sites identified in the *IARC Monographs* for which agents presented *sufficient evidence* of carcinogenicity in humans and/or animals, and includes internationally peer-reviewed and published data from studies in humans and experimental animals to support analyses of tumour sites seen in humans and animals. Although the database also includes human tumour sites for which there is *limited evidence* of carcinogenicity of the agent, such sites were not systematically identified in the *IARC Monographs*. Likewise, animal tumour sites were generally not identified in the case of *limited evidence* of carcinogenicity in animals.

The next section describes how information was retrieved and assembled from the data set compiled by Grosse et al., as well as the approach used to evaluate tumour site concordance between animals and humans. A detailed description of the results of the analysis of these data is then presented both in the text of this chapter and in online supplemental material (see below). A discussion of the results of these analyses and the conclusions drawn from this work are presented in the last two sections of this chapter.

Methods

Tumour nomenclature in animals and humans

Although human tumours can be coded in a standardized manner by use of the *International Classification of Diseases* coding system (WHO, 1977, 2011), a comparable nomenclature system does not exist for animal tumours. To render the animal and human tumours identified in the *IARC Monographs* comparable, a taxonomy of tumour sites was constructed (Table 21.2). As detailed in Supplemental Material I (online only; available from: http://publications.iarc.fr/578), this

Table 21.1. Group 1 agents included in Volumes 100A–F, 105, 106, 107, and 109[a]

Volume	Type of agent	Number of agents	Agents
100A	Pharmaceuticals	23	Aristolochic acid; Aristolochic acid, plants containing; Azathioprine; Busulfan; Chlorambucil; Chlornaphazine; Ciclosporin; Cyclophosphamide; Diethylstilbestrol; Estrogen-only menopausal therapy; Estrogen–progestogen menopausal therapy (combined); Estrogen–progestogen oral contraceptives (combined); Etoposide; Etoposide in combination with cisplatin and bleomycin; Melphalan; Methoxsalen in combination with UVA; MOPP; Phenacetin; Phenacetin, analgesic mixtures containing; 1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (Methyl-CCNU); Tamoxifen; Thiotepa; Treosulfan
100B	Biological agents	11	*Clonorchis sinensis* (infection with); Epstein–Barr virus; *Helicobacter pylori* (infection with); Hepatitis B virus; Hepatitis C virus; Human immunodeficiency virus type 1; Human papillomaviruses[b]; Human T-cell lymphotropic virus type 1; Kaposi sarcoma-associated herpesvirus; *Opisthorchis viverrini* (infection with); *Schistosoma haematobium* (infection with)
100C	Arsenic, metals, fibres, and dusts	10	Arsenic and inorganic arsenic compounds; Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite); Beryllium and beryllium compounds; Cadmium and cadmium compounds; Chromium(VI) compounds; Erionite; Leather dust; Nickel compounds; Silica dust, crystalline, in the form of quartz or cristobalite; Wood dust
100D	Radiation	18	Fission products including strontium-90; Haematite mining with exposure to radon (underground); Ionizing radiation (all types); Neutron radiation; Phosphorus-32, as phosphate; Plutonium-239; Radioiodines, including iodine-131; Internalized radionuclides that emit α-particles; Internalized radionuclides that emit β-particles; Radium-224 and its decay products; Radium-226 and its decay products; Radium-228 and its decay products; Radon-222 and its decay products; Solar radiation; Thorium-232 (as Thorotrast); UV radiation (bandwidth 100–400 nm, encompassing UVC, UVB, and UVA); UV-emitting tanning devices; X- and γ-radiation
100E	Personal habits and indoor combustions	12	Acetaldehyde associated with consumption of alcoholic beverages; Alcoholic beverages; Areca nut; Betel quid with tobacco; Betel quid without tobacco; Coal, indoor emissions from household combustion of; Ethanol in alcoholic beverages; *N*′-Nitrosonornicotine (NNN) and 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone NNK); Salted fish, Chinese-style; Second-hand tobacco smoke; Tobacco smoking; Tobacco, smokeless
100F	Chemical agents and related occupations	32	Acid mists, strong inorganic; Aflatoxins; Aluminium production; 4-Aminobiphenyl; Auramine production; Benzene; Benzidine; Benzidine, dyes metabolized to; Benzo[*a*]pyrene; Bis(chloromethyl)ether; Chloromethyl methyl ether (technical grade); 1,3-Butadiene; Coal gasification; Coal-tar distillation; Coal-tar pitch; Coke production; Ethylene oxide; Formaldehyde; Iron and steel founding, occupational exposure during; Isopropyl alcohol manufacture using strong acids; Magenta production; 4,4′-Methylenebis(2-chloroaniline) (MOCA); Mineral oils, untreated or mildly treated; 2-Naphthylamine; *ortho*-Toluidine; Painter, occupational exposure as a; 3,3′,4,4′,5-Pentachlorobiphenyl (PCB 126)[a]; 2,3,4,7,8-Pentachlorodibenzofuran (PeCDF); Rubber manufacturing industry, occupational exposures in the; Shale oils; Soot (as found in occupational exposure of chimney sweeps); Sulfur mustard; 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin; Vinyl chloride

Table 21.1. Group 1 agents included in Volumes 100A–F, 105, 106, 107, and 109[a] (continued)

Volume	Type of agent	Number of agents	Agents
105[c]	Diesel and gasoline engine exhausts and some nitroarenes	1	Engine exhaust, diesel
106[c]	Trichloroethylene and some chlorinated agents	1	Trichloroethylene
107[c]	Polychlorinated biphenyls and polybrominated biphenyls	1	Polychlorinated biphenyls (PCBs) and dioxin-like PCBs[a]
109[c]	Outdoor air pollution	2	Outdoor air pollution; Particulate matter in outdoor air pollution

UV, ultraviolet.

[a] Although 113 Group 1 agents have been identified up to and including *Monographs* Volume 109, the present analysis is based on 111 distinct agents remaining after considering PCBs and dioxin-like PCBs within the broader category of PCBs, and including PCB 126 within the broader category of PCBs.

[b] Human papillomavirus (HPV) types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 were evaluated as *carcinogenic to humans*.

[c] During the concordance analyses, the Group 1 agents in these Volumes were included with “chemical agents and related occupations” in Volume 100F*.

Table 21.2. Anatomically based taxonomy of tumour sites/organ systems in animals and humans

Organ system	Sites coded from Volume 100 (A, B, C, D, E, and F*)[a]
Upper aerodigestive tract	Nasal cavity and paranasal sinuses Nasopharynx Oral cavity Pharynx Tongue Tonsil Salivary gland
Respiratory system	Larynx Lung Lower respiratory tract
Mesothelium	Mesothelium
Digestive tract	Oesophagus Stomach Intestine (including colon and rectum)
Digestive organs	Liver parenchyma and bile ducts Pancreas NOS Gallbladder
Nervous system and eye	Brain and spinal cord (CNS) Eye
Endocrine system	Thyroid, follicular epithelium Adrenal gland (medulla, cortex, NOS) Pituitary gland
Kidney	Kidney (renal cortex, renal medulla, kidney NOS)
Urothelium	Urothelium (renal pelvis, ureter, or bladder)
Lymphoid and haematopoietic tissues	Haematopoietic tissue Lymphoid tissue
Skin	Skin and adnexae Cutaneous melanocytes
Connective tissues	Soft connective tissue Blood vasculature (endothelium) Hard connective tissue (bone, cartilage)
Female breast, female reproductive organs, and female reproductive tract	Breast Ovary Uterine cervix Uterus Vulva/vagina
Other groupings	All cancers combined All solid cancers Exocrine glands NOS

CNS, central nervous system; NOS, not otherwise specified.
[a] These sites are derived from all site descriptors used in *IARC Monographs* to describe human and experimental animal cancer data (see Supplemental Table 1. Animal and human tumour sites for 111 Group 1 agents identified up to and including Volume 109 of the *IARC Monographs*).

taxonomy is anatomically based and includes 47 tumour sites grouped within 15 organ and tissue systems. There are 39 distinct animal and human tumour sites specified for Group 1 agents in Volume 100A–F*, and eight additional tumour sites were considered to be important, even though they did not appear in the tumour site concordance data set developed by Grosse et al. (Annex 1). The individual tumour sites seen in either animals or humans up to and including Volume 109 of the *IARC Monographs* are listed in Table 21.2. The category "other groupings" includes the three sites ("all cancers combined", "all solid cancers", and "exocrine glands not otherwise specified") that do not fit into any of the other 14 groupings of organ and tissue systems. All analyses reported in this chapter are based on the 39 individual tumour sites within the 14 organ and tissue systems listed in Table 21.2 (excluding tumours of the male reproductive tract, for which the data do not show *sufficient evidence* in both humans and animals).

Aggregation of tumour sites within an organ and tissue system was guided by several factors, including anatomical and functional relatedness. The specialized epithelia of the upper aerodigestive tract, respiratory system, digestive tract, and digestive organs are found for the most part in a single or a few anatomical sites, which are precisely captured by the available epidemiological and experimental data. In contrast, both the kidney and the urothelium are data-rich sites, and carcinogenic agents for either site display little or no overlap in target organ. Accordingly, the kidney and the urothelium were analysed separately rather than being aggregated as "urinary tract". Cancers of soft connective tissues, lymphoid and haematopoietic tissues, and bone and cartilage can arise wherever in the body their progenitor tissues occur, and are aggregated according to tissue of origin without regard to anatomical location. Likewise, skin cancers are aggregated irrespective of anatomical location, with the exception that malignant melanoma as it occurs in humans is unknown in rats or mice; cutaneous melanocytes are thus included separately in Table 21.2 as a human tumour site only for the sake of completeness. Estrogen-producing and estrogen-responsive tissues are aggregated in the organ system "female breast, female reproductive organs, and female reproductive tract". In contrast to the female reproductive system, no carcinogens are known with *sufficient evidence* for the male reproductive system in humans, despite the high prevalence in humans of prostate and testicular germ cell cancers.

Retrieval of data on tumour occurrence from the IARC Monographs

Grosse et al. (Annex 1) extracted data from Volumes 100, 105, 106, 107, and 109 on tumour sites reported in humans or animals for the 111 distinct Group 1 agents considered here. This information is illustrated in Table 21.3, with one compound from each of Volumes 100A–F, as well as diesel engine exhaust (Volume 105), TCE (Volume 106), PCBs (Volume 107), and particulate matter in outdoor air pollution (Volume 109). Table 21.3 gives the tumour sites for which the agents provide *sufficient evidence* of carcinogenicity in humans, as well as sites for which there is *limited evidence.* Tumour sites for which *sufficient evidence* of carcinogenicity exists in specific animal species are also noted. Information on the histology of animal lesions, when available, is also recorded in Table 21.3; however, because this information is not generally available in the *IARC Monographs* for human studies, it was not considered in the comparative analyses reported here.

Although tumour sites for which agents show *limited evidence* of carcinogenicity in humans are included in Table 21.3, this information is not considered in the present analysis. In fact, although the original intent was to consider tumour sites with *sufficient* or *limited evidence* in humans when evaluating concordance with animal tumour sites with *sufficient evidence*, there are only two Group 1 agents with *limited*, but not *sufficient*, evidence of carcinogenicity in humans.

Effects of sex, strain, and route of administration

The last column in Table 21.3 provides details on animal studies relevant to the evaluation of the agent of interest, including the sex and strain of the test animals and the route of administration of the test agent. Although this information has been recorded where available, it is difficult to examine concordance with respect to these important factors for a variety of reasons, as outlined below.

Because many epidemiological studies are based on predominantly male occupational cohorts, men tend to be over-represented in the human studies on Group 1 agents. Other agents, such as hormonal oral contraceptives, are evaluated only in women. Certain lesions, notably breast cancer and prostate cancer, are largely sex-specific. Also, some animal studies use only one sex, and others do not specify whether male

Table 21.3. Information on animal and human tumours and tumour sites for Group 1 agents in the *IARC Monographs* (adapted from Annex 1, by Grosse et al.)

Volume Agent number	Agent	Sites with *sufficient evidence* in humans	Site with *limited evidence* in humans	Agent tested in experimental animals	Species Site	Histology	Study/sex/strain/ exposure route	Comments
100A 3	Azathioprine	Non-Hodgkin lymphoma, skin (squamous cell carcinoma)		Azathioprine	Mouse Lymphoid tissue	Lymphoma	Mitrou et al. (1979a) (Volume 26), F, New Zealand Black and New Zealand White, s.c.; Mitrou et al. (1979b) (Volume 26), F, New Zealand Black and New Zealand White, s.c.; Ito et al. (1989), F, B6C3F1, p.o.; Brambilla et al. (1971), MF, Swiss, i.p.	
100B 25	Epstein–Barr virus	Burkitt lymphoma, immunosuppression-related non-Hodgkin lymphoma, extranodal NK/T-cell lymphoma (nasal type), Hodgkin lymphoma, nasopharyngeal carcinoma	Lymphoepithelioma-like carcinoma, gastric carcinoma					No data on animal studies listed; humans are the only natural hosts for Epstein–Barr virus
100C 35	Arsenic and inorganic arsenic compounds	Lung, bladder, skin	Kidney, liver, prostate	Dimethylarsinic acid [DMA(V)], Monomethylarsinous acid [MMA(III)], Sodium arsenite	Mouse Lung	Bronchiolo-alveolar carcinoma	DMA(V): Tokar et al. (2012a), M, CD1, d.w.; Sodium arsenite: Waalkes et al. (2003), F, C3H/HeNCr, in utero; Waalkes et al. (2006), M, CD1, in utero; Tokar et al. (2011), MF, CD1, in utero + p.o.; Tokar et al. (2012a), M, CD1, in utero; MMA(III): Tokar et al. (2012b), M, CD1, in utero	

Table 21.3. Information on animal and human tumours and tumour sites for Group 1 agents in the *IARC Monographs* (adapted from Annex 1, by Grosse et al.) (continued)

Volume Agent number	Agent	Sites with *sufficient evidence* in humans	Site with *limited evidence* in humans	Agent tested in experimental animals	Species Site	Histology	Study/sex/strain/ exposure route	Comments
100D 45	Fission products including strontium-90	Solid cancers, leukaemia		Strontium-90	Mouse Bone	Osteosarcoma	Nilsson (1970, 1971), M, CBA, i.p.; Nilsson et al. (1980), F, CBA, i.p.	
100E 68	Coal, indoor emissions from household combustion of	Lung		Coal smoke	Mouse Lung	Bronchiolo-alveolar carcinoma	Liang et al. (1988), MF, Kunming, inh.; Lin et al. (1995), MF, Kunming, inh.	
100F 80	Benzene	Acute myeloid leukaemia, acute non-lymphoblastic leukaemia	Acute lymphoblastic leukaemia, chronic lymphocytic leukaemia, multiple myeloma, non-Hodgkin lymphoma	Benzene	Mouse Thymus	Lymphoma	Snyder et al. (1980), M, C57Bl/6J, inh.; Cronkite et al. (1984), F, C57Bl/6 BNL, inh.	
105 107	Engine exhaust, diesel	Lung	Bladder	Whole diesel engine exhaust	Rat Lung	Bronchiolo-alveolar carcinoma	Ishinishi et al. (1986),MF, F344, inh.: Mauderly et al. (1986, 1987), MF F344, inh.: Iwai et al. (1986), F, F344, inh.: Heinrich et al. (1995), F, Wistar, inh.: Nikula et al.. (1995), F, F344, inh.: Iwai et al. (2000), F, F344, inh.	
106 108	Trichloroethylene	Kidney	Non-Hodgkin lymphoma, liver	Trichloroethylene	Rat Kidney	Renal cell carcinoma	National Toxicology Program (1990), M, F344/N, g.; National Toxicology Program (1988), M, Osborne-Mendel, g.; National Toxicology Program (1988), F, ACI, g.	

Table 21.3. Information on animal and human tumours and tumour sites for Group 1 agents in the *IARC Monographs* (adapted from Annex 1, by Grosse et al.) (continued)

Volume Agent number	Agent	Sites with *sufficient evidence* in humans	Site with *limited evidence* in humans	Agent tested in experimental animals	Species Site	Histology	Study/sex/strain/ exposure route	Comments
107 109	Polychlorinated biphenyls	Skin (melanoma)	Non-Hodgkin lymphoma, breast	Aroclor 1260	Rat Liver	Hepatocellular carcinoma	Mayes et al. (1998), F, Sprague-Dawley, p.o.; Norback and Weltman (1985), F, Sprague-Dawley, p.o.; Kimbrough et al. (1975), F, Sherman, p.o.	
109 111	Particulate matter in outdoor air pollution	Lung						*Sufficient evidence* in experimental animals, but no organ sites identified due to the absence of two (or more) studies of adequate design and quality pointing at the same organ site (with a similar histological origin) in the same species

F, female; d.w., drinking-water; g., gavage; inh., inhalation; i.p., intraperitoneally; M, male; MF, male and female; NK, natural killer; p.o., orally; s.c., subcutaneously.

or female animals – or both – were used. For these reasons, separate analyses of species concordance across the spectrum of Group 1 agents are difficult to conduct. Separate concordance analyses by strain are also difficult, because of the sparseness of studies on specific strains of experimental animals. Indeed, in many cases information on strain is unavailable, precluding the possibility of strain-specific analyses.

Human exposure to carcinogens can occur by oral ingestion, inhalation, or dermal absorption, as well as via other routes, such as injection of pharmaceutical agents for therapeutic purposes. Animal studies may involve other routes of exposure, such as intraperitoneal injection or intratracheal instillation. In many cases, the route of exposure used in animal studies may not correspond to the predominant route by which humans are exposed; in such cases, the dose of the reactive metabolite reaching critical target tissues may be quite different, depending on the route of administration. Differences in routes of exposure between animals and humans could thus contribute to lack of concordance between tumour sites observed in animals and humans. However, because data on cancer outcomes for a given route of exposure are not available across the entire set of Group 1 agents, a systematic evaluation of concordance for specific exposure routes is not possible.

Species-specific tumour site profiles

Before the concordance analyses were conducted, the organ distribution was examined of the tumours caused by the 111 distinct Group 1 carcinogens identified by IARC to date, both in humans and in animal species. These distributions are of value in demonstrating the spectrum of tumours caused by these agents in different species, including the identification of the most common tumours caused in humans. Human tumours caused by the human tumour viruses reported in Volume 100B were included in these distributions, so that these results reflect the tumours caused by all 111 distinct Group 1 carcinogens considered here.

Organization of concordance analyses

Analytical results are presented first for the 39 tumour sites and then for the 14 organ and tissue systems. Because the present database involves only a moderate number of agents with comparable data in animals and humans, results aggregated by organ and tissue system may be expected to be more stable.

Results

The concordance data set assembled by Grosse et al. (Annex 1) and summarized in Table 21.1 includes 111 distinct Group 1 agents identified in the *IARC Monographs* up to and including Volume 109. Nine of these 111 agents were placed in Group 1 in the absence of *sufficient evidence* of carcinogenicity in humans (Table 21.4). These determinations were made on the basis of mechanistic upgrades according to the evaluation criteria outlined in the Preamble to the *IARC Monographs* (IARC, 2006). For example, benzo[*a*]pyrene (B[*a*]P) was placed in Group 1 on the basis of epidemiological data on exposure to mixtures of polycyclic aromatic hydrocarbons (PAHs) containing B[*a*]P that provided *sufficient evidence* for cancer of the lung or skin in humans, coupled with extensive mechanistic data on B[*a*]P, suggesting that the mechanisms by which this agent causes tumours in animals would also be expected to operate in humans; no data in humans on B[*a*]P alone were available for evaluation (IARC, 2010). An important aspect of such mechanistic upgrades for purposes of the present analysis is the general lack of identification of a human tumour site.

Of the nine agents in Table 21.4 placed in Group 1 on the basis of mechanistic upgrades, all but one – etoposide – demonstrated *sufficient evidence* of carcinogenicity in animals. In the assignment of etoposide to Group 1 in the absence of *sufficient evidence* in animals, the *Monograph* noted the *limited evidence* of carcinogenicity in humans on the basis of the induction of acute myeloid leukaemias with distinctive chromosomal translocations by drugs, including etoposide, that target topoisomerase II (IARC, 2012e). Of the nine mechanistic upgrades, three showed *limited evidence* in humans, and six had *inadequate evidence* in humans or no epidemiological data were available, for example for B[*a*]P and 2,3,4,7,8-pentachlorodibenzofuran (PeCDF).

Apart from the nine Group 1 mechanistic upgrades for which no human tumour sites were identified, there are four other agents for which the same is true (Table 21.5): ionizing radiation (all types), internalized radionuclides that emit α-particles, internalized radionuclides that emit β-particles, and ultraviolet (UV) radiation (bandwidth 100–400 nm, encompassing UVC, UVB, and UVA). These were generic evaluations across a range of agents falling in these categories. In addition, no human tumour site was specified for the agents areca nut and ethanol in

alcoholic beverages, because no epidemiological data were available for areca nut alone or for ethanol in alcoholic beverages alone (see Annex 1, by Grosse et al.).

No animal tumour sites were identified for 38 of the 111 agents considered here (Table 21.6). These included 20 agents with *inadequate evidence* in animals: seven agents representing occupational exposures that would be difficult to replicate in the laboratory; two pharmaceutical agents used in combination for which no animal data were available on the mixture; seven biological agents (all viruses) for which the selection of an appropriate animal model was problematic; two agents, etoposide and wood dust, for which the available animal tests were considered inadequate; and two agents, treosulfan and leather dust, for which no animal data were available. Although the two agents that lack any animal test data – treosulfan and leather dust – clearly do not permit an evaluation of concordance between animals and humans, the two agents for which inadequate animal data were available – etoposide and wood dust – warrant some further discussion to distinguish between the case in which well-conducted animal studies have failed to demonstrate carcinogenicity and the case in which the animal data are largely uninformative because of inadequate testing: Volume 76 (IARC, 2000) and Volume 100A (IARC, 2012e) of the *IARC Monographs* noted that etoposide was tested in only one experiment with wild-type and heterozygous neurofibromatosis type 1 (*Nf1*) knockout mice that were treated by gastric intubation for 6 weeks with etoposide at 100 mg/kg body weight/week (Mahgoub et al., 1999). This single short-duration study was judged as providing *inadequate evidence* of carcinogenicity in animals. The available studies with wood dust originally considered in Volume 62 (IARC, 1995) did not show significant carcinogenic or co-carcinogenic potential of beech wood dust, but these studies were subject to several limitations as well as inadequacies in data reporting. Upon re-evaluation of wood dust in Volume 100C (IARC, 2012a), it was concluded that most of the studies conducted with wood dust (nearly all with beech wood dust) had small numbers of animals or were of short duration, thus providing *inadequate evidence* of carcinogenicity in animals. These considerations suggest that neither etoposide nor wood dust have been subject to adequate animal testing, therefore precluding a determination of their carcinogenic potential in animals.

Ten agents, including six pharmaceutical products (busulfan, chlornaphazine, cyclosporine; combined estrogen–progestogen menopausal therapy, 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea [methyl-CCNU], and analgesic mixtures containing phenacetin), three biological agents (infections with *Clonorchis sinensis*, *Opisthorchis viverrini*, and *Schistosoma haematobium*), and one chemical agent (sulfur mustard), provided *limited*, but not *sufficient*, evidence of carcinogenicity in animals. As mentioned above, tumour sites are not specified in the *IARC Monographs* for agents that demonstrate only *limited evidence* in animals.

The reasons that these 10 agents were judged as providing only *limited evidence* of carcinogenicity in animals varied. For example, treatment with busulfan resulted in a significant increase in the incidence of thymic and ovarian tumours in BALB/c mice, which was found difficult to interpret, whereas in another study busulfan, when given to rats during gestation, affected the incidence of uterine adenocarcinomas in the offspring upon intrauterine treatment with *N*-ethyl-*N*′-nitro-*N*-nitrosoguanidine (IARC, 2012e). As a second example, sulfur mustard significantly increased the incidence of lung tumours (not otherwise specified) in mice after exposure by inhalation for 15 minutes, and of pulmonary tumours (not otherwise specified) after intravenous injection; a significant increase in the incidence of mammary tumours was seen after subcutaneous injection of sulfur mustard in rats, relative to an external control group, whereas forestomach tumours were numerically, but not significantly, elevated in rats treated by oral gavage (IARC, 2012c). The exposure by subcutaneous and intravascular injection was considered to be of limited relevance to the most common human routes of exposure. Although not meeting the stringent criterion for *sufficient evidence* of carcinogenicity in animals, the *limited evidence* provided by busulfan, as well as by the other six chemicals with only *limited evidence* of carcinogenicity in animals, does suggest that these agents have the potential to cause cancer in animals.

No tumour sites were specified for eight agents demonstrating *sufficient evidence* of carcinogenicity in animals, because reproducible results were unavailable in two or more studies of adequate design in the same species for any of these agents. Although melphalan showed evidence of a statistically significant increase in the incidence of tumours of the forestomach, skin, and lung in mice, as well as lymphosarcoma, these results were not replicated in a second, independent study (IARC,

Table 21.4. Agents placed in Group 1 on the basis of mechanistic upgrades[a]

Agent	Level of evidence in humans/ animals	Human tumour site	Basis for mechanistic upgrade
Aristolochic acid	*Limited*/ *Sufficient*	Not specified	Herbal remedies containing aristolochic acid provide *sufficient evidence* for upper urinary tract cancer in humans; genotoxic mechanistic data
Benzo[*a*]pyrene (B[*a*]P)	[No epidemiological data]/ *Sufficient*	Not specified	PAH mixtures containing B[*a*]P provide *sufficient evidence* for lung or skin cancer in humans; extensive mechanistic data on B[*a*]P linking animal and human biology
Dyes metabolized to benzidine	*Inadequate*/ *Sufficient*	Not specified	Benzidine provides *sufficient evidence* of being a human bladder carcinogen
Ethylene oxide	*Limited*/ *Sufficient*	Not specified	*Limited evidence* for non-Hodgkin lymphoma, breast cancer in humans; genotoxic mechanistic data
Etoposide	*Limited*/ *Inadequate*	Not specified	*Limited evidence* of acute myeloid leukaemia in humans, with distinctive chromosomal translocations
4,4′-Methylenebis(2-chloroaniline) (MOCA)	*Inadequate*/ *Sufficient*	Not specified	Bladder cancer expected in humans, based on mechanistic data and human case report
Neutron radiation	*Inadequate*/ *Sufficient*	Not specified	Biophysics of radiation damage induction similar across different types of radiation
N′-Nitrosonornicotine (NNN) and 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	*Inadequate*/ *Sufficient*	Not specified	Target sites correspond to those of smokeless tobacco; mechanistic data on tobacco smoke
2,3,4,7,8-Pentachlorodibenzofuran (PeCDF)	[No epidemiological data]/ *Sufficient*	Not specified	*Sufficient evidence* in experimental animals combined with strong mechanistic support for receptor-mediated mechanism, with biological activity identical to that of 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD) for every mechanistic step

PAH, polycyclic aromatic hydrocarbon.

[a] Although dioxin-like PCBs evaluated in Volume 107 were also upgraded to Group 1 on the basis of support for receptor-mediated mechanisms and analogies with TCDD (IARC, 2016b), dioxin-like PCBs have been subsumed within the broader category of PCBs for the purposes of the present analysis of 111 distinct Group 1 agents, and are therefore not included in this table.

Table 21.5. Group 1 agents with no human tumour sites specified (15 agents)

Nature of evidence in humans (number of agents)	Volume: Agent(s)
Mechanistic upgrades	
Mechanistic upgrade with no human tumour site specified (9 agents)	**Volume 100A:** Aristolochic acid; Etoposide. **Volume 100D:** Neutron radiation. **Volume 100E:** *N′*-Nitrosonornicotine (NNN) and 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). **Volume 100F:** Benzo[*a*]pyrene (B[*a*]P); Dyes metabolized to benzidine; Ethylene oxide; 4,4′-Methylenebis(2-chloroaniline) (MOCA); 2,3,4,7,8-Pentachlorodibenzofuran (PeCDF)
Generic evaluations	
Generic evaluation, of all types of ionizing radiation; internalized radionuclides that emit α-particles; internalized radionuclides that emit β-particles; and the UV region (100–400 nm) of the electromagnetic spectrum (4 agents)	**Volume 100D:** Ionizing radiation (all types); Internalized radionuclides that emit α-particles; Internalized radionuclides that emit β-particles; UV radiation (bandwidth 100–400 nm, encompassing UVC, UVB, and UVA)
Absence of epidemiological data on the agent alone	
No epidemiological data available for agent alone (2 agents)	**Volume 100E:** Areca nut; Ethanol in alcoholic beverages

2012c). In rats, melphalan also produced mammary gland tumours and peritoneal sarcoma, but these findings were again not replicated in independent studies. Phosphorous-32 caused leukaemia in mice and osteogenic sarcomas in rats in single studies. Similarly, acetaldehyde in drinking-water induced pancreatic adenomas, combined lymphomas and leukaemias, uterine and mammary gland adenocarcinomas, and head osteosarcomas in rats, but without replication. Betel quid with tobacco produced malignant forestomach and cheek pouch tumours in a single study in hamsters. *Sufficient evidence* of carcinogenicity in animals of aluminium refining was based on a single limited skin application study in mice with PAH-containing particulates from aluminium production plants, in conjunction with *sufficient evidence* of carcinogenicity in experimental animals for many of the PAHs detected in air samples from such plants, and previously evaluated in Volume 92 (IARC, 2010). Had the animal evidence for the agents mentioned above been eligible for inclusion in the tumour site concordance database, additional concordant results would have been noted, including concordance between lymphoid and haematopoietic tissues in mice and humans for both melphalan and phosphorous-32, and concordance between tumours of the upper aerodigestive tract in hamsters and humans for betel quid with tobacco.

Although PeCDF provided *sufficient evidence* of carcinogenicity in animals, no animal site was identified. PeCDF was tested by the United States National Toxicology Program in a 2-year animal bioassay (female rats only) with exposure by oral gavage (National Toxicology Program, 2006). There was some evidence of carcinogenic activity of PeCDF, based on increased incidences of hepatocellular adenoma and cholangiocarcinoma of the liver and gingival squamous cell carcinoma of the oral mucosa. The occurrence of cystic keratinizing epithelioma of the lung, neoplasms of the pancreatic acinus, and carcinoma of the uterus may have been related to administration of PeCDF. There were also three rat studies of PeCDF in combination with *N*-methyl-*N′*-nitro-*N*-nitrosoguanidine (MNNG) and *N*-nitrosodiethylamine (NDEA), where increased tumour multiplicity was observed in each case (IARC, 2012c). These observations led to the conclusion that there is *sufficient evidence* for the carcinogenicity of PeCDF in animals, although there is no specific organ site that can be designated as responsible for this *sufficient evidence*. Because of the absence of a specific tumour site in

Table 21.6. Group 1 agents with no animal tumour sites specified (38 agents)

Nature of evidence in animals (number of agents)	Volume: Agent(s)
Agents with inadequate evidence in animals	
Occupational exposures are complex and probably could not be reliably replicated in the laboratory (7 agents)	**Volume 100F:** Acid mists, strong inorganic; Auramine production; Iron and steel founding, occupational exposure during; Isopropyl alcohol manufacture using strong acids; Magenta production; Painter, occupational exposure as a; Rubber manufacturing industry, occupational exposures in the.
Used in combination; no animal data available on mixture (2 agents)	**Volume 100A:** Etoposide in combination with cisplatin and bleomycin; MOPP.
Use of animal models problematic because of species specificity and other limitations (7 agents)	**Volume 100B:** Infection with Epstein–Barr virus; Hepatitis B virus; Hepatitis C virus; Human immunodeficiency virus type 1; Human papillomaviruses; Human T-cell lymphotropic virus type 1; Kaposi sarcoma-associated herpesvirus.
Animal tests conducted but considered inadequate (2 agents)	**Volume 100A:** Etoposide. **Volume 100C:** Wood dust.
No animal data available (2 agents)	**Volume 100A:** Treosulfan. **Volume 100C:** Leather dust.
Agents with limited evidence in animals	
Evidence of carcinogenicity in animals judged as *limited* for various reasons (10 agents)	**Volume 100A:** Busulfan; Chlornaphazine; Ciclosporin; Estrogen–progestogen menopausal therapy (combined); 1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (Methyl-CCNU); Phenacetin, analgesic mixtures containing. **Volume 100B:** *Clonorchis sinensis* (infection with); *Opisthorchis viverrini* (infection with); *Schistosoma haematobium* (infection with). **Volume 100F:** Sulfur mustard.
Agents with sufficient evidence in animals	
Sufficient evidence in animals, but no tumour sites specified[a] (8 agents)	**Volume 100A:** Melphalan. **Volume 100D:** Phosphorus-32, as phosphate. **Volume 100E:** Acetaldehyde associated with the consumption of alcoholic beverages; Betel quid with tobacco. **Volume 100F:** Aluminium production; 2,3,4,7,8-pentachlorodibenzofuran (PeCDF); **Volume 109:** Outdoor air pollution; Particulate matter in outdoor air pollution.

[a] *Sufficient evidence* in experimental animals, but no organ sites identified due to the absence of at least two studies of adequate design and quality showing tumours at the same organ site with a similar histological origin in the same species.

animals, PeCDF is not included in the concordance analyses.

A component of four Group 1 agents, but not the agents themselves, demonstrated *sufficient evidence* of carcinogenicity in animals. These are: fission products including strontium-90, where strontium-90 demonstrated *sufficient evidence* of carcinogenicity in animals (IARC, 2012f); haematite mining with exposure to radon (underground), where radon demonstrated *sufficient evidence* of carcinogenicity in animals (IARC, 2012f); acetaldehyde associated with consumption of alcoholic beverages, where acetaldehyde demonstrated *sufficient evidence* of carcinogenicity in animals (IARC, 2012d); and occupational exposures during aluminium production, where airborne particulate polynuclear organic matter from aluminium production plants demonstrated *sufficient evidence* of carcinogenicity in animals (IARC, 2012c). Although this animal evidence is consistent with the *sufficient evidence* for the carcinogenicity of these four agents in humans, the animal evidence represents only a component of these agents.

Excluding the 20 agents in Table 21.5 that lack appropriate animal data, i.e. seven occupational exposures not reproducible in the laboratory, two agents used in combination with no animal data available on the mixture, seven agents where the use of animal models is problematic because of species specificity or other limitations, and four agents for which animal tests were inadequate (two agents) or unavailable (two agents), all 91 distinct Group 1 agents identified by IARC up to and including Volume 109 of the *IARC Monographs* provided either *sufficient evidence* (82 agents) or *limited evidence* (nine agents) of carcinogenicity in animals. This observation provides support for the use of animal data in human cancer risk assessment.

To further explore the correspondence between sites where tumours are seen in animals and humans among the 111 distinct Group 1 agents considered here, descriptive statistics are presented on tumour site profiles by species, followed by an evaluation of concordance between tumour sites seen in animals and humans. Results are presented first for the 39 tumour sites included in the anatomically based tumour nomenclature system seen in either animals or humans, followed by the data for the 14 organ and tissue systems.

Tumour site profiles by species

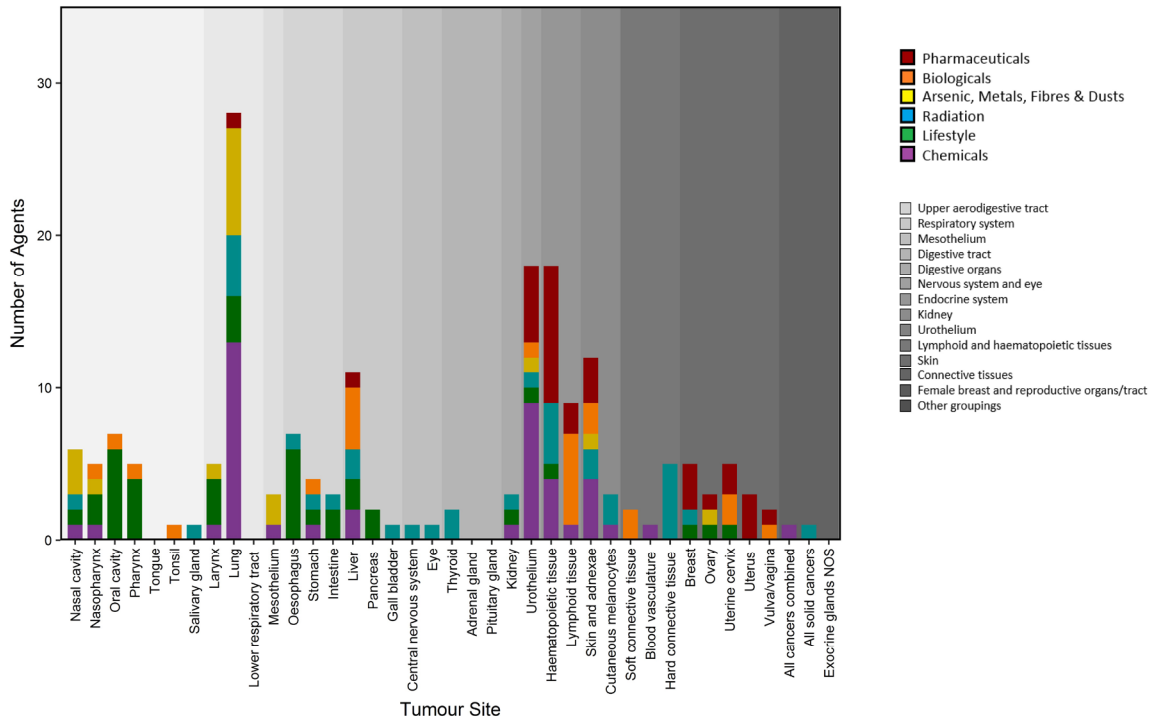
The number of agents that induce tumours in humans at each of the 39 tumour sites is shown in Fig. 21.1 by type of agent (pharmaceuticals; biological agents; arsenic, metals, fibres, and dusts; radiation; personal habits and indoor combustions; and chemical agents and related occupations). Lung tumours are the most common tumour seen in humans, with 28 of the 111 known human carcinogens inducing lesions at this site; of these, 13 are associated with exposure to chemical agents and related occupations and seven are in the category of arsenic, metals, fibres, and dusts. Tumours of the haematopoietic tissues are associated with exposure to 18 agents, urothelial tumours with 18 agents, skin tumours with 12 agents, and liver and bile duct tumours with 11 agents. The category chemical agents and related occupations accounts for half (9 of 18) of the agents that cause urothelial tumours, and pharmaceuticals account for half (9 of 18) of the agents that cause tumours in haematopoietic tissues.

The number of agents that induce tumours in one or more animal species at each of the 39 tumour sites is shown in Fig. 21.2 by type of agent. As in humans, lung tumours are the most common tumour in animals, with 29 of the 111 known human carcinogens inducing lesions at this site, mostly from the categories of chemical agents and related occupations (10 agents), arsenic, metals, fibres, and dusts (7 agents), and radiation (7 agents). After the lung, the animal sites associated with the largest number of carcinogenic agents are the liver parenchyma and bile ducts (19 agents), the skin and adnexae (18 agents), lymphoid tissue (14 agents), the breast (12 agents), and soft connective tissue (11 agents). Separate tumour profiles are shown for agents that cause tumours in mice (48 agents) and rats (49 agents) in Fig. 21.3 and Fig. 21.4, respectively. In rodents (mice and rats combined), the lung is the site associated with the largest number of carcinogens.

Organ and tissue system profiles by species

The number of agents that induce tumours in humans in each of the 14 aggregate organ and tissue systems is shown in Fig. 21.5 by type of agent. Tumours of the respiratory system are caused by 31 of the 111 human carcinogens, mostly from the categories of chemical agents and related occupations (14 agents), arsenic, metals, fibres, and dusts (7 agents), and personal habits and indoor combustions (5 agents). After the respiratory system, the organ and tissue systems associated with the largest number of agents are lymphoid and haematopoietic tissues (26 agents),

Fig. 21.1. Number of agents that induce tumours in humans in each of 39 tumour sites, by type of agent.



the urothelium (18 agents), and the upper aerodigestive tract (16 agents). Pharmaceuticals are the largest group of agents associated with tumours of the lymphoid and haematopoietic tissues (11 of 26 agents), and chemical agents and related occupations are most often associated with tumours of the urothelium (9 of 18 agents). Personal habits and indoor combustions are most commonly associated with tumours of the upper aerodigestive tract (7 of 16 agents).

The number of agents that induce tumours in one or more animal species at each of the 14 organ and tissue systems is given in Fig. 21.6 by type of agent. Tumours of the respiratory system are caused by 29 of the 111 agents, mostly from the categories of chemical agents and related occupations (10 agents), arsenic, metals, fibres, and dusts (7 agents), and radiation (7 agents). Tumours of the digestive organs are caused by 19 agents, mostly from the categories of chemical agents and related occupations (12 agents) and radiation (4 agents). Skin tumours are caused by 18 agents, mostly from the category of chemical agents and related occupations (12 agents). Connective tissue tumours are associated with 17 agents, mostly from the categories of radiation (8 agents) and chemical agents and related occupations (5 agents).

In mice (Fig. 21.7), tumours of the skin and connective tissues are caused by 29 agents, consisting mostly of tumours caused by chemical agents and related occupations (14) and radiation (10). In rats (Fig. 21.8), tumours of the respiratory system are caused by 19 agents, including those in the categories of arsenic, metals, fibres, and dusts (6 agents), radiation (6 agents), and chemical agents and related occupations (5 agents).

Qualitative assessment of concordance

Of the 111 distinct Group 1 agents identified up to and including Volume 109 (see Table 21.1), for 60 agents both a human tumour site and an animal tumour site have been identified, 15 agents had no human tumour site specified (Table 21.5), and 38 agents had no animal tumour site identified (Table 21.6). Because two agents – etoposide and PeCDF – have neither a human nor an animal tumour site specified, there are 111 − 15 − 38 + 2 = 60 agents with at least one tumour site identified in both humans and animals. These 60 agents have been used to evaluate concordance between tumour sites seen in animals and humans, because at least one tumour site has been identified in both.

Fig. 21.2. Number of agents that induce tumours in animals in each of 39 tumour sites, by type of agent.

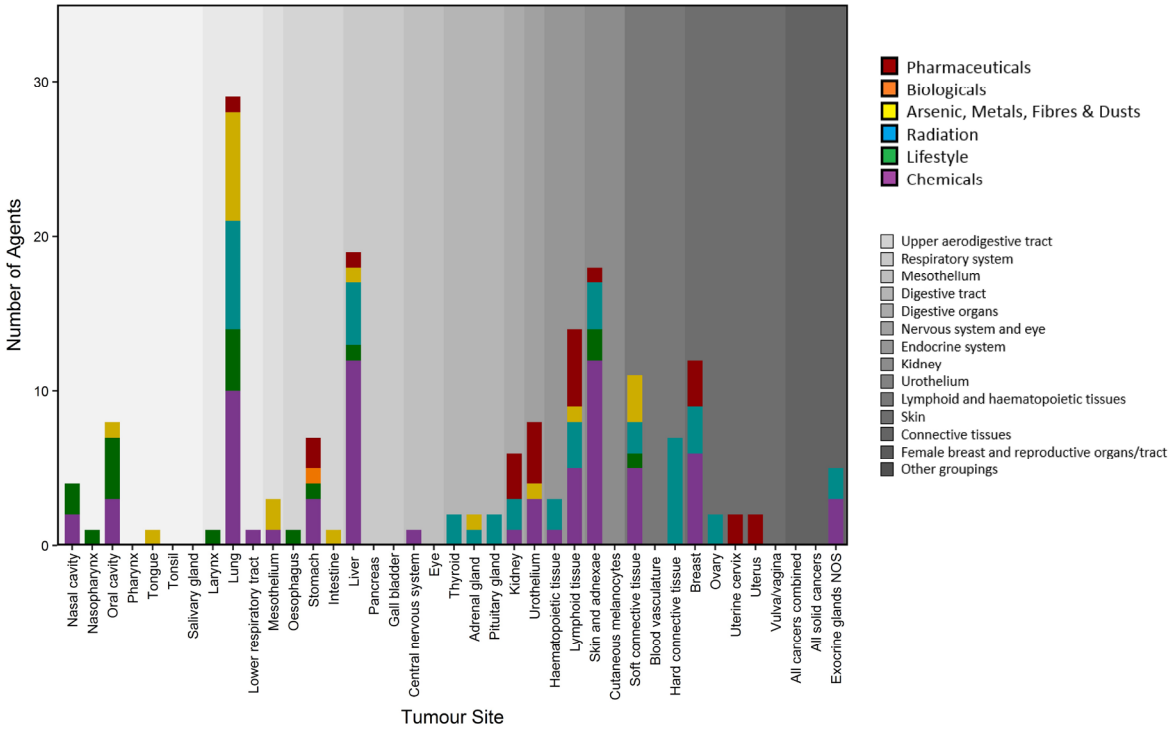


Fig. 21.3. Number of agents that induce tumours in mice in each of 39 tumour sites, by type of agent.

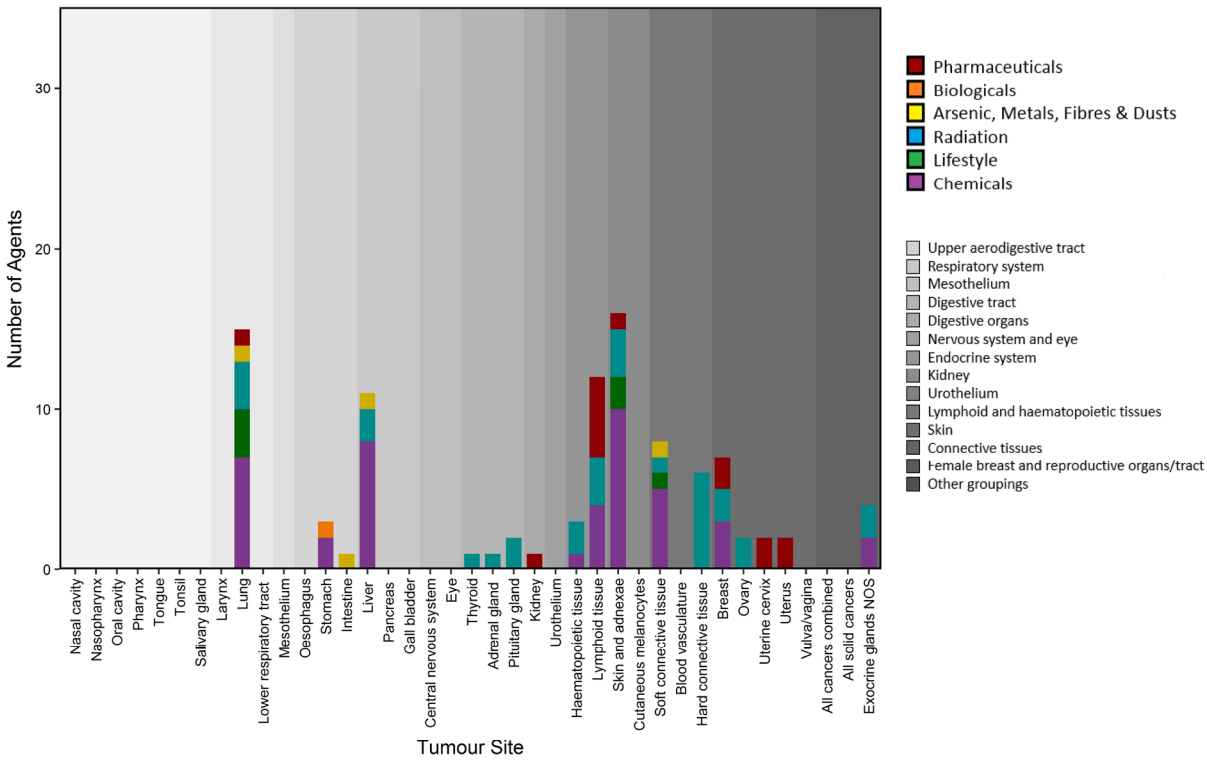
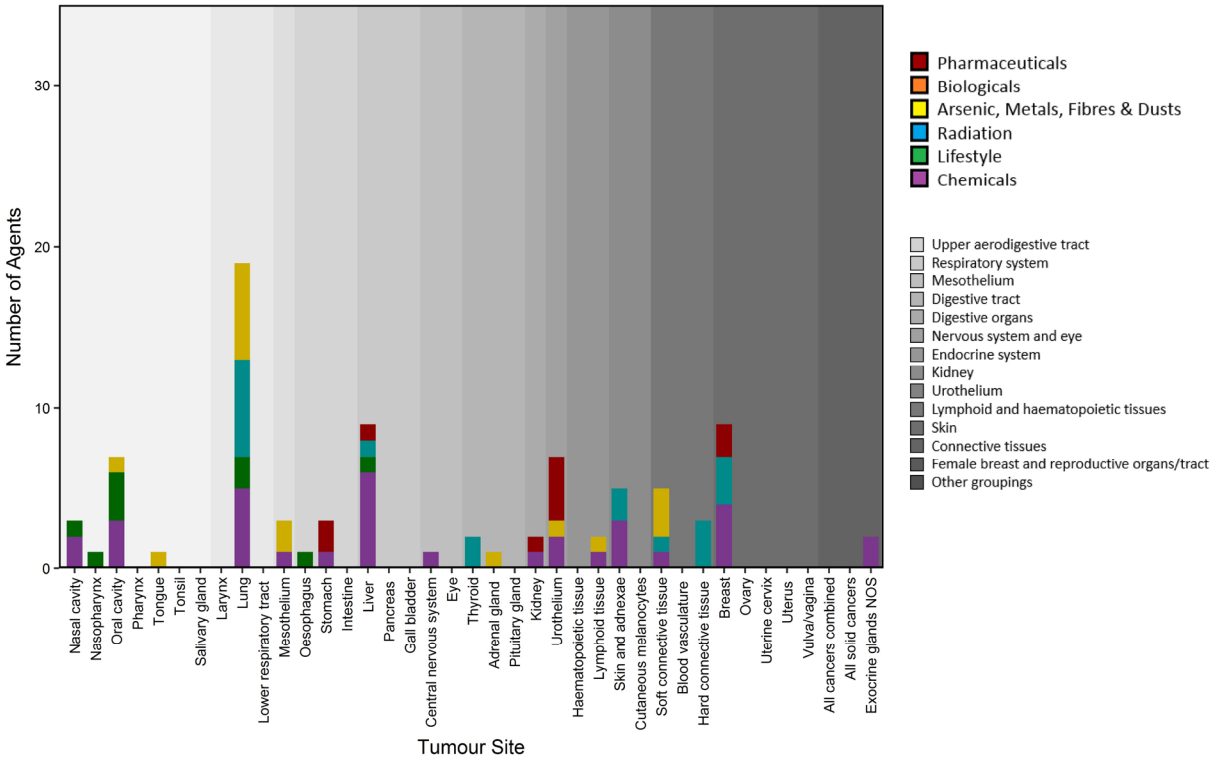


Fig. 21.4. Number of agents that induce tumours in rats in each of 39 tumour sites, by type of agent.



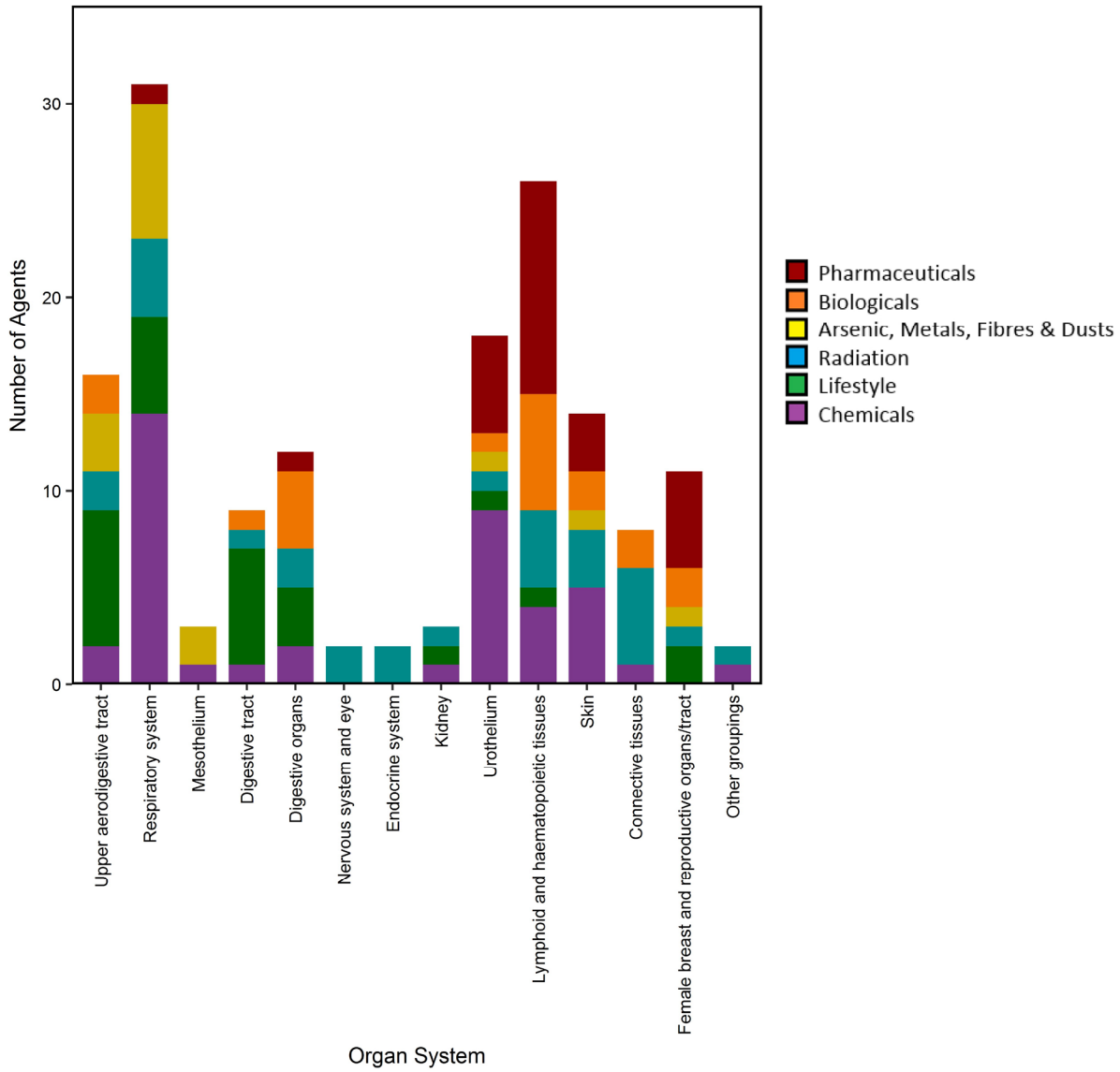
The overlap between human and animal tumour sites targeted by these 60 agents is summarized in Table 21.7 by organ and tissue system and tumour site. The category "other groupings" of tumours – which comprises "all cancers combined", "all solid cancers", and "exocrine glands not otherwise specified" – was created to accommodate tumour sites reported in the *IARC Monographs* that did not fall into any of the other categories in Table 21.2. The only human site identified for 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD) is "all cancers combined"; fission products including strontium-90 are associated with "all solid cancers" in humans, but also with tumours in haematopoietic tissue. Because this category lacks biological cohesiveness, "other groupings" of tumours were not considered in the concordance analysis.

Nine agents cause tumours of the upper aerodigestive tract in humans, and nine agents cause tumours in this organ and tissue system in animals; four agents cause tumours in this system in both humans and animals. There are 9 + 9 − 4 = 14 distinct agents that cause tumours in this system in either humans or animals, for an overlap of 4 of 14, or 29%. Within the upper aerodigestive tract, there are three agents that cause tumours in the nasal cavity and paranasal sinuses in humans and three agents that cause tumours at this site in animals, with no overlap. Of the three agents that induce tumours in the nasopharynx, one agent causes tumours in both humans and animals, for an overlap of 33%. In the oral cavity, overlap is 25%. Overlap is not calculated when there are no agents that cause tumours in either humans or animals, as in the pharynx, tongue, and salivary gland.

The lung is the most common site at which tumours are observed, with 62% overlap among the 26 agents that cause lung tumours in humans or animals. Among the 10 agents that cause tumours in the urothelium (renal pelvis, ureter, or bladder), there is 70% overlap between agents that cause tumours in humans or animals.

Because results for individual tumour sites are often based on small numbers, emphasis is placed on interpretation of results at the organ and tissue system level, where the sample size is generally larger than for individual tumour sites within organ and tissue systems. Overlap varies among the organ and tissue systems, ranging from 20% (based on 10 agents) in the digestive tract

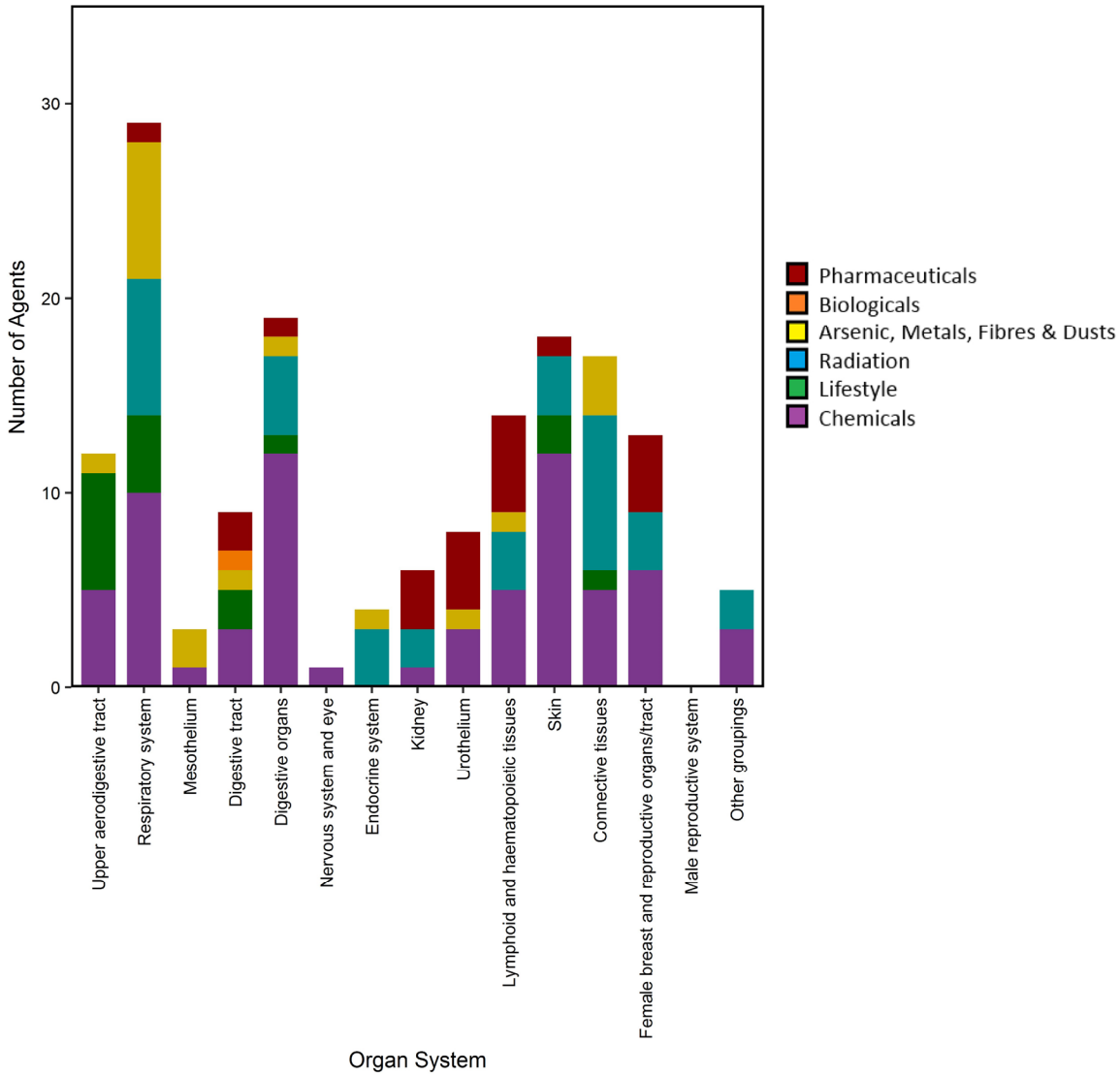
Fig. 21.5. Number of agents that induce tumours in humans in each of 14 organ and tissue systems, by type of agent.



to 100% in the mesothelium. Overall, high overlap is seen for some organ and tissue systems but not for others. Some caution is needed in interpreting concordance at sites where the sample size is particularly small: although 100% concordance was noted for agents that cause tumours of the mesothelium, only two Group 1 agents – asbestos and erionite – meeting the criteria for inclusion in the concordance analysis caused tumours at this site.

The results in Table 21.7 are depicted in graphical form in Fig. 21.9. As noted above, of the 14 Group 1 agents that cause tumours of the upper aerodigestive tract in either humans or animals, nine agents cause tumours in the upper aerodigestive tract in humans (and not in animals), nine agents cause tumours in this system in animals (and not in humans), and four agents cause tumours in this system in both humans and animals, for an overlap of 29%. Of the 27 agents that cause tumours of the respiratory system in either humans or animals, 21 agents cause respiratory tumours in humans, 22 agents cause respiratory tumours in animals, and 16 agents cause respiratory tumours in both humans

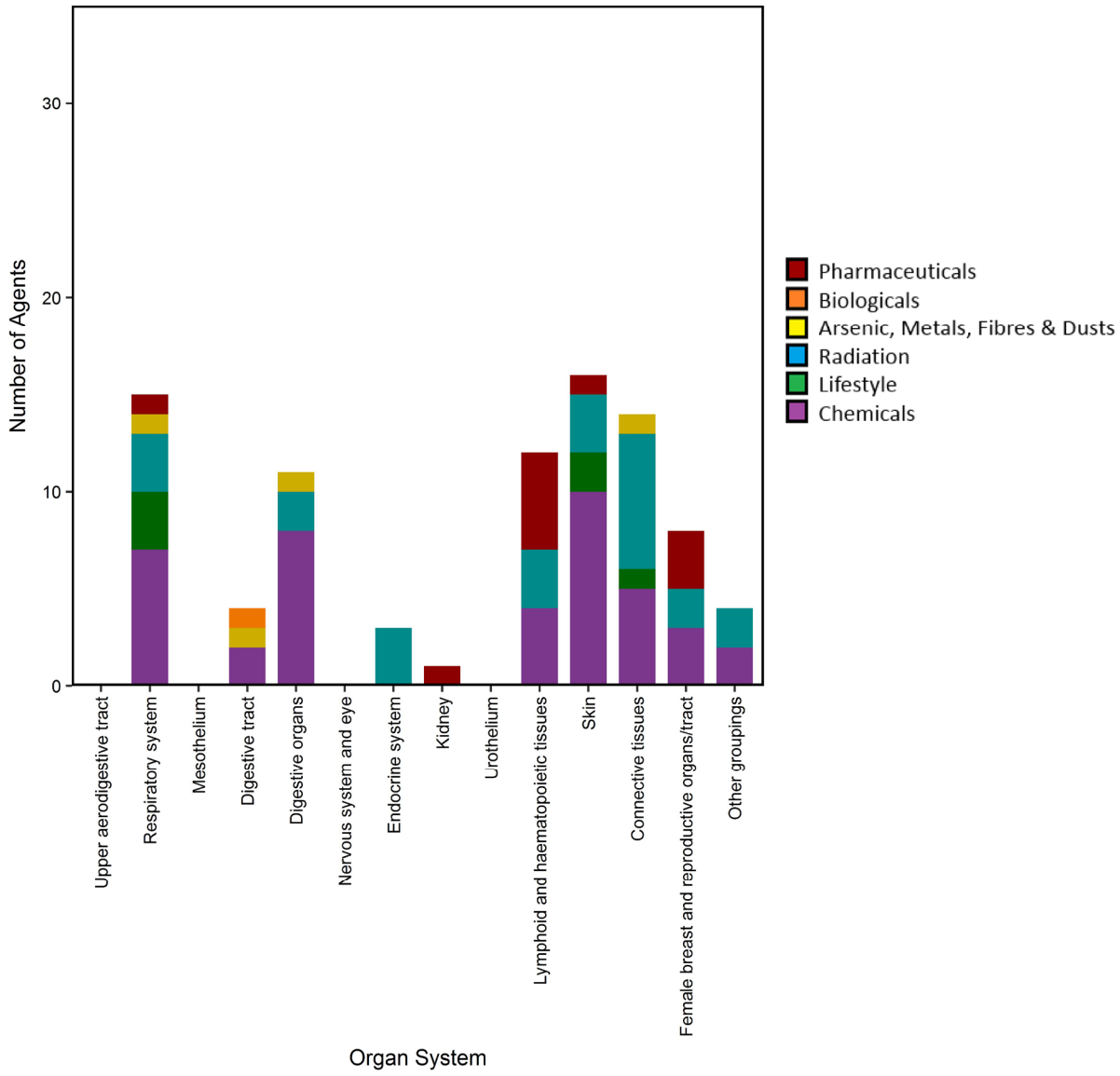
Fig. 21.6. Number of agents that induce tumours in animals in each of 14 organ and tissue systems, by type of agent.



and animals, for an overlap of 59%. Although they present the same data as shown in Table 21.7, the graphical representations of these results in Fig. 21.9 for all organ and tissue systems also illustrate the large variation in sample size among the organ and tissue systems; the area of the circles is proportional to sample size.

The results presented in Table 21.7 are based on concordance between tumour sites seen in humans and all animal species tested, reflecting the interest in evaluating the extent to which tumours caused by Group 1 agents occur in similar organ and tissue systems in humans and in animals. The animal data included in this analysis are dominated by results obtained in studies with rats and mice: of the 60 Group 1 agents included in the analysis, 40, 38, 8, 7, and 3 agents cause tumours in mice, rats, hamsters, dogs, and monkeys, respectively. Therefore, including only mice and rats in the analysis yielded results similar to those in Table 21.7 (see details in Supplemental Material II [online only; available from: http://publications.iarc.fr/578], where Supplemental Table 6 presents results for all animal species tested

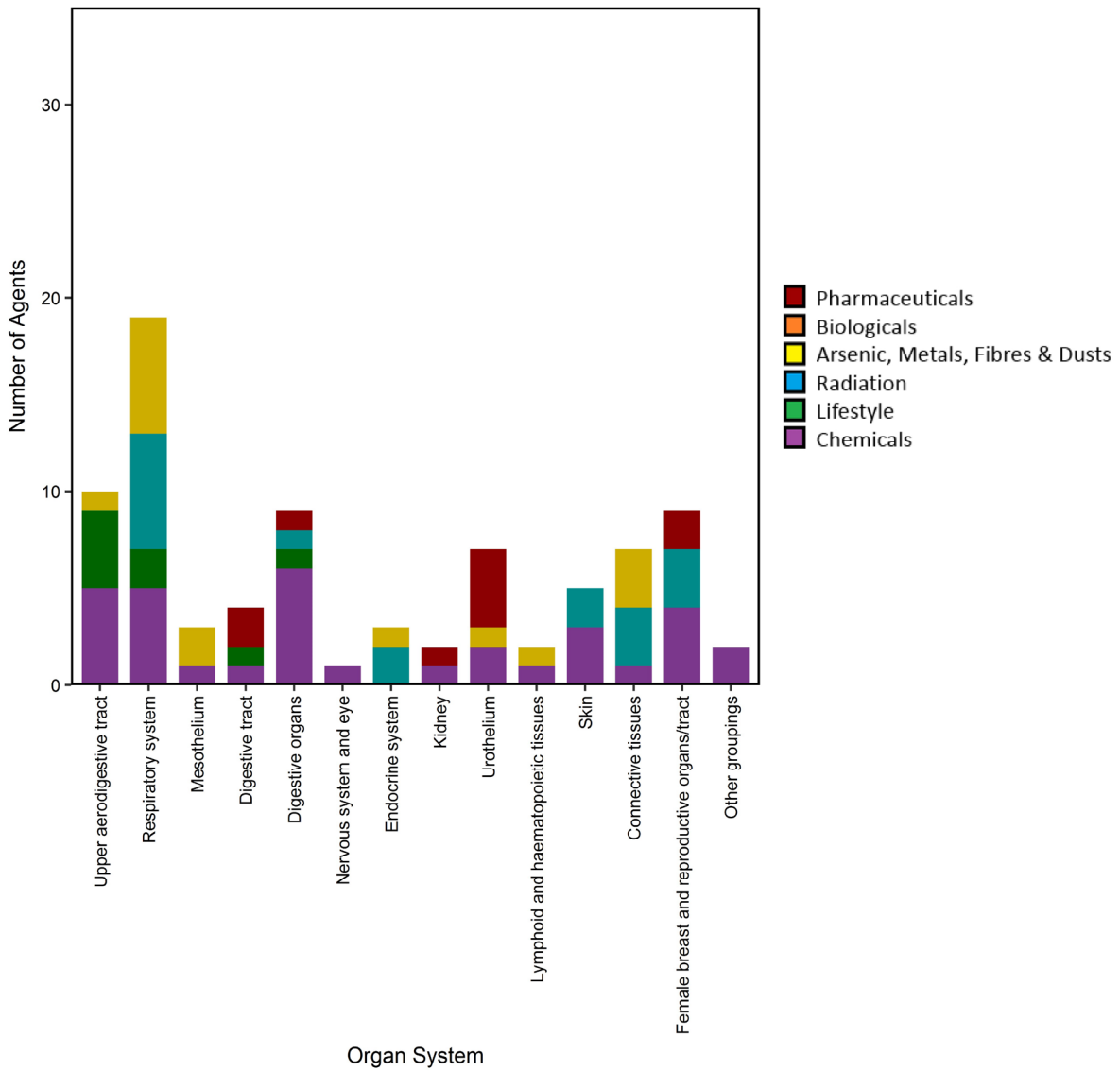
Fig. 21.7. Number of agents that induce tumours in mice in each of 14 organ and tissue systems, by type of agent.



and Supplemental Table 7 presents results for mice and rats only).

Fig. 21.10 shows the percentage of Group 1 agents that cause tumours in specific organ and tissue systems in humans that are also associated with tumours in animals (panel A), as well as the percentage of agents that cause tumours in specific organ and tissue systems in animals that are also associated with tumours in humans (panel B). As detailed in Supplemental Material II (online only; available from: http://publications.iarc.fr/578), it is important to note that the measures of concordance presented in Fig. 21.10 differ from those in Table 21.7. The percentage overlap in Table 21.7 (and Fig. 21.9) reflects the number of agents that cause tumours in a specific organ and tissue system in *both* humans *and* animals, relative to the number of agents that cause tumours in that system in *either* humans *or* animals, providing an overall measure of overlap between animal and human carcinogens in a specific organ and tissue system. The percentage overlap in panel A of Fig. 21.10 provides a measure of the overlap between agents that cause tumours in a specific organ and tissue system in animals with agents that cause tumours in that system in humans. Conversely, the percentage

Fig. 21.8. Number of agents that induce tumours in rats in each of 14 organ and tissue systems, by type of agent.



overlap in panel B of Fig. 21.10 provides a measure of the overlap between agents that cause tumours in a specific organ and tissue system in humans with agents that cause tumours in that system in animals. Note that unless the numbers of agents that cause tumours in humans and animals in a specific organ and tissue system are the same (as is the case for tumours of the upper aerodigestive tract), the results in panel A, where human carcinogens constitute the reference set against which animal carcinogens are compared, will differ from those in panel B, where animal carcinogens constitute the reference set for comparison with human carcinogens.

As indicated in panel A of Fig. 21.10, all agents (100%) that cause tumours of the mesothelium, endocrine system, and connective tissues in humans also cause tumours in those organ and tissue systems in animals. Overlap of at least 50% is observed for all other organ and tissue systems, with the exception of the upper aerodigestive tract (44%) and the digestive tract (33%). Conversely, there is less overlap between agents that cause tumours in specific organ and tissue systems in animals with results in humans (Fig. 21.10, panel B), possibly reflecting the larger number of studies

Table 21.7. Concordance between tumours seen in humans and animals for 60 Group 1 agents by organ and tissue system and tumour site

Organ and tissue system[a] *Tumour site*[a]	Number of agents			Overlap[b] (%)
	Humans	Animals	Both	
Upper aerodigestive tract	9	9	4	29
Nasal cavity and paranasal sinuses	*3*	*3*	*0*	*0*
Nasopharynx	*3*	*1*	*1*	*33*
Oral cavity	*4*	*6*	*2*	*25*
Pharynx	*2*	*0*	*0*	*N/A*
Tongue	*0*	*1*	*0*	*N/A*
Salivary gland	*1*	*0*	*0*	*N/A*
Respiratory system	21	22	16	59
Larynx	*3*	*1*	*1*	*33*
Lung	*20*	*22*	*16*	*62*
Mesothelium	2	2	2	100
Mesothelium	*2*	*2*	*2*	*100*
Digestive tract	6	6	2	20
Oesophagus	*5*	*0*	*0*	*N/A*
Stomach	*3*	*5*	*1*	*14*
Intestine (including colon and rectum)	*3*	*1*	*0*	*0*
Digestive organs	8	14	4	22
Liver parenchyma and bile ducts	*7*	*14*	*4*	*24*
Pancreas NOS	*2*	*0*	*0*	*N/A*
Gall bladder	*1*	*0*	*0*	*N/A*
Nervous system and eye	2	0	0	N/A
Brain and spinal cord (CNS)	*1*	*0*	*0*	*N/A*
Eye	*1*	*0*	*0*	*N/A*
Endocrine system	2	3	2	67
Thyroid, follicular epithelium	*2*	*2*	*2*	*100*
Adrenal gland (medulla, cortex, NOS)	*0*	*1*	*0*	*N/A*
Pituitary gland	*0*	*1*	*0*	*N/A*
Kidney	3	5	2	33
Kidney (renal cortex, renal medulla, kidney NOS)	*3*	*5*	*2*	*33*
Urothelium	10	7	7	70
Urothelium (renal pelvis, ureter, or bladder)	*10*	*7*	*7*	*70*

Table 21.7. Concordance between tumours seen in humans and animals for 60 Group 1 agents by organ and tissue system and tumour site (continued)

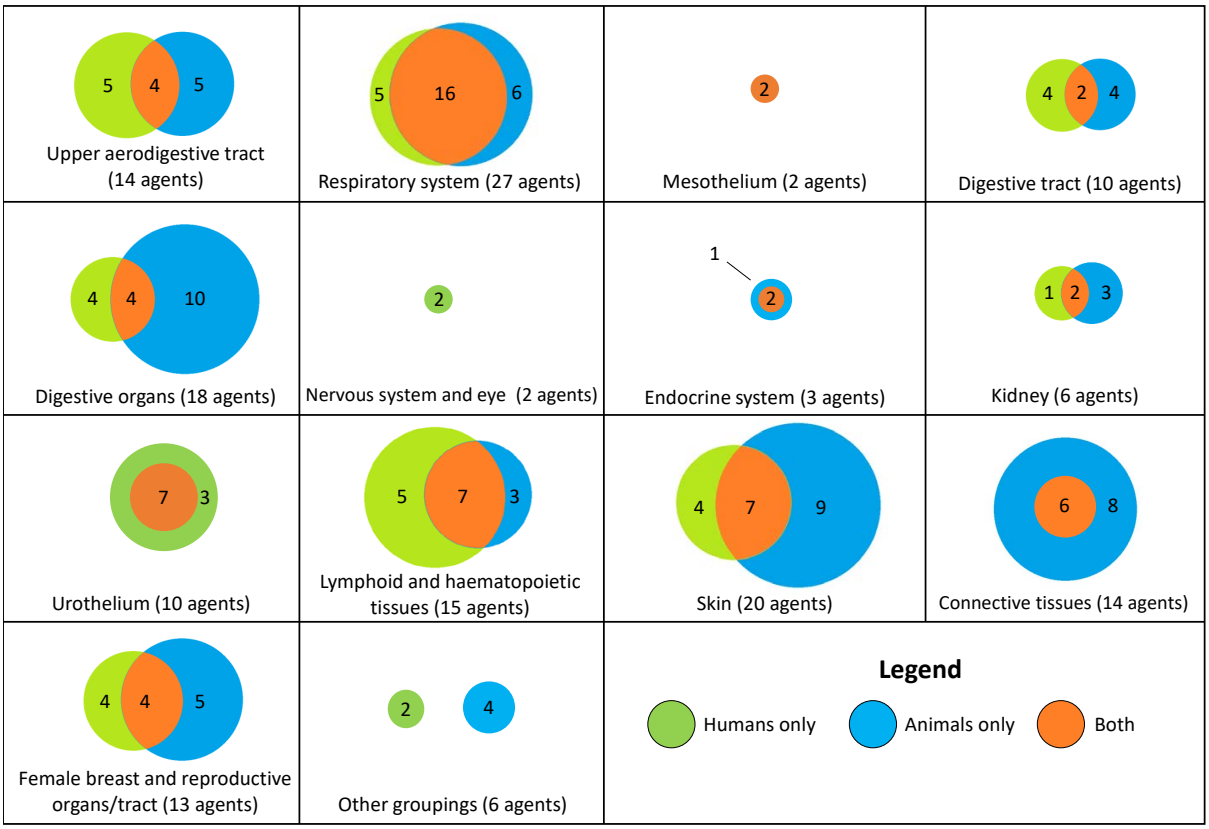
Organ and tissue system[a] *Tumour site*[a]	Number of agents			Overlap[b] (%)
	Humans	Animals	Both	
Lymphoid and haematopoietic tissues	12	10	7	47
Haematopoietic tissues	*10*	*2*	*2*	*20*
Lymphoid tissue	*2*	*10*	*1*	*9*
Skin	11	16	7	35
Skin and adnexae	*9*	*16*	*6*	*32*
Cutaneous melanocytes	*3*	*0*	*0*	*N/A*
Connective tissues	6	14	6	43
Soft connective tissue	*0*	*9*	*0*	*N/A*
Blood vasculature (endothelium)	*1*	*0*	*0*	*N/A*
Hard connective tissue (bone, cartilage)	*5*	*5*	*4*	*67*
Female breast, female reproductive organs, and female reproductive tract	8	9	4	31
Breast	*4*	*8*	*2*	*20*
Ovary	*3*	*1*	*0*	*0*
Uterine cervix	*3*	*2*	*1*	*25*
Uterus	*2*	*2*	*1*	*33*
Vulva/vagina	*1*	*0*	*0*	*N/A*
Other groupings	2	4	0	0
All cancers combined	*1*	*0*	*0*	*N/A*
All solid cancers	*1*	*0*	*0*	*N/A*
Exocrine glands NOS	*0*	*4*	*0*	*N/A*

CNS, central nervous system; N/A, not applicable: assigned to sites/systems when overlap is not possible (positive data are available in either humans or animals, but not in both); NOS, not otherwise specified.

[a] Systems/sites in the anatomically based tumour nomenclature system (see Table 21.2) that lack *sufficient evidence* in both humans and animals not shown. For example, there were insufficient data on tumours of the male reproductive tract in both humans and animals.

[b] Percentage overlap calculated as $[N_b/(N_h + N_a - N_b)] \times 100\%$, where N_h, N_a, and N_b denote the number of agents with *sufficient evidence* of carcinogenicity in humans, animals, or both humans and animals, respectively.

Fig. 21.9. Concordance between tumour sites seen in humans and animals for 60 Group 1 agents by organ and tissue system.



conducted in animals compared with humans, the broader spectrum of tissues (potential tumour sites) examined in animal studies than in human studies, or the limitations associated with the conduct of human studies at environmental exposure levels. As is the case with the concordance results focusing on overall overlap, as presented in Table 21.7, caution is needed in interpreting results where there are few agents for comparison in Fig. 21.10 (both panels A and B).

The 60 agents included in the present concordance analysis are listed in Table 21.8. This table presents the tumour site data for humans and animals at the organ and tissue system level only, because results for individual tumour sites are too sparse to support meaningful comparisons. The human data are presented in the column on the left, the animal data in the column on the right, and the overlap in the middle column. With this display, potential relationships among agents that cause tumours within the same organ and tissue system can be examined. Overlap between human and animal carcinogens acting within the same organ and tissue system can also be examined both for individual agents and for groups of agents. Of the 60 agents for which there is *sufficient evidence* of carcinogenicity in at least one tumour site in both humans and animals, 52 (87%) cause tumours within at least one of the same organ and tissue systems in Table 21.8.

To permit a more complete comparison between animal and human tumour sites, tumour sites with only *limited evidence* in humans are included in Table 21.8 (in *italics*). For agents such as diethylstilbestrol (a synthetic non-steroidal estrogen that was widely prescribed in the USA between the 1940s and the 1970s but is rarely used now), there is difficulty in generating newer data on human exposure. Because men exposed to diethylstilbestrol in utero

Fig. 21.10. Overlap between Group 1 agents with *sufficient evidence* of carcinogenicity in humans and animals that cause tumours in specific organ and tissue systems. (A) Overlap between animals and humans; the number of Group 1 agents that cause tumours in specific organ and tissue systems in humans is shown. (B) Overlap between humans and animals; the number of Group 1 agents that cause tumours in specific organ and tissue systems in animals is shown.

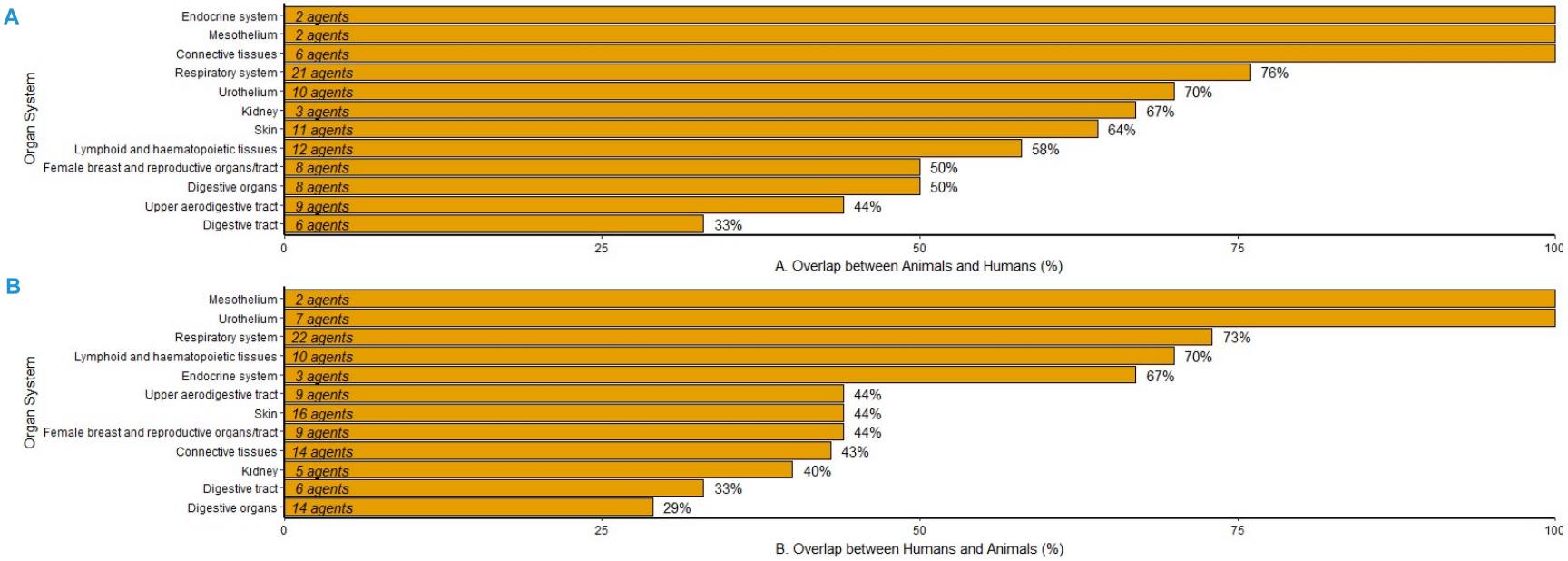


Table 21.8. Comparison of 60 Group 1 agents with *sufficient* or *limited evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in animals in specific organ and tissue systems[a]

Humans[b] **Agent (*Monographs* Volume[c])**	**Humans and animals[b]** **Agent (*Monographs* Volume)**	**Animals[b]** **Agent (*Monographs* Volume)**
Upper aerodigestive tract (29% overlap[d])		
Chromium(VI) compounds (100C) Nickel compounds (100C) Radium-226 and decay products (100D) X- and γ-radiation (100D) *Radioiodines, including iodine-131(100D)* Betel quid without tobacco (100E) Alcoholic beverages (100E) Salted fish, Chinese-style (100E) *Second-hand tobacco smoke (100E)* Tobacco, smokeless (100E) Tobacco smoking (100E) Formaldehyde (100F)	Alcoholic beverages (100E) Salted fish, Chinese-style (100E) Tobacco, smokeless (100E) Formaldehyde (100F) *Chromium(VI) compounds (100C)*	Chromium(VI) (100C) Alcoholic beverages (100E) Salted fish, Chinese-style (100E) Tobacco, smokeless (100E) Formaldehyde (100F) Benzene (100F) 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (100F) Polychlorinated biphenyls (100F) Bis(chloromethyl)ether; Chloromethyl methyl ether (100F)

Table 21.8. Comparison of 60 Group 1 agents with *sufficient* or *limited evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in animals in specific organ and tissue systems[a] (continued)

Humans[b] **Agent (*Monographs* Volume[c])**	**Humans and animals[b]** **Agent (*Monographs* Volume)**	**Animals[b]** **Agent (*Monographs* Volume)**
Respiratory system (59% overlap)		
Arsenic and inorganic arsenic compounds (100C) Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite) (100C) Beryllium and beryllium compounds (100C) Cadmium and cadmium compounds (100C) Chromium(VI) compounds (100C) Nickel compounds (100C) Silica dust, crystalline, in the form of quartz or cristobalite (100C) Haematite mining with exposure to radon (underground) (100D) Plutonium-239 (100D) Radon-222 and its decay products (100D) X- and γ-radiation (100D) Alcoholic beverages (100E) Coal, indoor emissions from household combustion of (100E) Second-hand tobacco smoke (100E) Tobacco smoking (100E) Bis(chloromethyl)ether; Chloromethyl methyl ether (technical grade) (100F) Coal gasification (100F) Coal-tar pitch (100F) Coke production (100F) Soot (as found in occupational exposure of chimney sweeps) (100F) 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (100F) Engine exhaust, diesel (100F)	Arsenic and inorganic arsenic compounds (100C) Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite) (100C) Beryllium and beryllium compounds (100C) Cadmium and cadmium compounds (100C) Chromium(VI) compounds (100C) Nickel compounds (100C) Silica dust, crystalline, in the form of quartz or cristobalite (100C) Haematite mining with exposure to radon (underground) (100D) Plutonium-239 (100D) Radon-222 and its decay products (100D) X- and γ-radiation (100D) Coal, indoor emissions from household combustion of (100E) Second-hand tobacco smoke (100E) Tobacco smoking (100E) Coke production (100F) Engine exhaust, diesel (100F) 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (100F)	Cyclophosphamide (100A) Arsenic and inorganic arsenic compounds (100C) Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite) (100C) Beryllium and beryllium compounds (100C) Cadmium and cadmium compounds (100C) Chromium(VI) compounds (100C) Nickel compounds (100C) Silica dust, crystalline, in the form of quartz or cristobalite (100C) Haematite mining with exposure to radon (underground) (100D) Plutonium-239 (100D) Radon-222 and its decay products (100D) X- and γ-radiation (100D) Coal, indoor emissions from household combustion of (100E) Second-hand tobacco smoke (100E) Tobacco smoking (100E) Benzene (100F) 1,3-Butadiene (100F) Coke production (100F) Vinyl chloride (100F) Engine exhaust, diesel (100F*) 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (100F*) Trichloroethylene (100F*)

Table 21.8. Comparison of 60 Group 1 agents with *sufficient* or *limited evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in animals in specific organ and tissue systems[a] (continued)

Humans[b] **Agent (*Monographs* Volume[c])**	**Humans and animals[b]** **Agent (*Monographs* Volume)**	**Animals[b]** **Agent (*Monographs* Volume)**
Mesothelium (100% overlap)		
Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite) (100C) Erionite (100C)	Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite) (100C) Erionite (100C)	Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite) (100C) Erionite (100C)
Digestive tract (20% overlap)		
Helicobacter pylori (infection with) (100B) X- and γ-radiation (100D) *Radioiodines, including iodine-131 (100D)* Alcoholic beverages (100E) Betel quid without tobacco (100E) *Salted fish, Chinese-style (100E)* Tobacco smoking (100E) Tobacco, smokeless (100E)	*Helicobacter pylori* (infection with) (100B) Betel quid without tobacco (100E)	Aristolochic acid, plants containing (100A) *Helicobacter pylori* (infection with) (100B) Chromium(VI) compounds (100C) Betel quid without tobacco (100E) Benzene (100F) 1,3-Butadiene (100F)
Digestive organs (22% overlap)		
Estrogen–progestogen oral contraceptives (combined) (100A) *Arsenic and inorganic arsenic compounds (100C)* *Cadmium and cadmium compounds (100C)* Thorium-232 (as Thorotrast) (100D) Plutonium-239 (100D) *X- and γ-radiation (100D)* Alcoholic beverages (100E) *Betel quid without tobacco (100E)* Tobacco smoking (100E) Tobacco, smokeless (100E) Aflatoxins (100F) Vinyl chloride (100F) *Trichloroethylene (100F*)*	Arsenic and inorganic arsenic compounds (100C) Plutonium-239 (100D) Thorium-232 (as Thorotrast) (100D) X- and γ-radiation (100D) Aflatoxins (100F) Vinyl chloride (100F) Trichloroethylene (100F*)	Tamoxifen (100A) Arsenic and inorganic arsenic compounds (100C) Thorium-232 (as Thorotrast) (100D) Plutonium-239 (100D) X- and γ-radiation (100D) Aflatoxins (100F) 4-Aminobiphenyl (100F) Benzidine (100F) 1,3-Butadiene (100F) 2-Naphthylamine (100F) 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (100F) Vinyl chloride (100F) Trichloroethylene (100F*) Polychlorinated biphenyls (100F)

Table 21.8. Comparison of 60 Group 1 agents with *sufficient* or *limited evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in animals in specific organ and tissue systems[a] (continued)

Humans[b] **Agent (*Monographs* Volume[c])**	**Humans and animals[b]** **Agent (*Monographs* Volume)**	**Animals[b]** **Agent (*Monographs* Volume)**
Nervous system and eye (N/A)		
UV-emitting tanning devices (100D) **X- and γ-radiation (100D)** *Solar radiation (100D)*		
Endocrine system (67% overlap)		
Radioiodines, including iodine-131 (100D) X- and γ-radiation (100D)	Radioiodines, including iodine-131 (100D) X- and γ-radiation (100D)	Nickel compounds (100C) Radioiodines, including iodine-131 (100D) X- and γ-radiation (100D)
Kidney (33% overlap)		
Arsenic and inorganic arsenic (100C) *Cadmium and cadmium compounds (100C)* X- and γ-radiation (100D) Tobacco smoking (100E) Trichloroethylene (100F*)	X- and γ-radiation (100D) Trichloroethylene (100F*)	Diethylstilbestrol (100A) Estrogen-only menopausal therapy (100A) Phenacetin (100A) X- and γ-radiation (100D) Trichloroethylene (100F*)
Urothelium (70% overlap)		
Aristolochic acid, plants containing (100A) Cyclophosphamide (100A) Phenacetin (100A) Arsenic and inorganic arsenic compounds (100C) X- and γ-radiation (100D) Tobacco smoking (100E) *Coal-tar pitch (100F)* *Soot (as found in occupational exposure of chimney sweeps) (100F)* 4-Aminobiphenyl (100F) Benzidine (100F) 2-Naphthylamine (100F) *ortho*-Toluidine (100F) *Engine exhaust, diesel (100F*)*	Aristolochic acid, plants containing (100A) Cyclophosphamide (100A) Phenacetin (100A) Arsenic and inorganic arsenic compounds (100C) 4-Aminobiphenyl (100F) 2-Naphthylamine (100F) *ortho*-Toluidine (100F)	Aristolochic acid, plants containing (100A) Cyclophosphamide (100A) Phenacetin (100A) Arsenic and inorganic arsenic compounds (100C) 2-Naphthylamine (100F) 4-Aminobiphenyl (100F) *ortho*-Toluidine (100F)

Table 21.8. Comparison of 60 Group 1 agents with *sufficient* or *limited evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in animals in specific organ and tissue systems[a] (continued)

Humans[b] **Agent (*Monographs* Volume[c])**	**Humans and animals[b]** **Agent (*Monographs* Volume)**	**Animals[b]** **Agent (*Monographs* Volume)**
Lymphoid and haematopoietic tissues (47% overlap)		
Azathioprine (100A) Chlorambucil (100A) Cyclophosphamide (100A) Thiotepa (100A) *Helicobacter pylori* (infection with) (100B) Fission products including strontium-90 (100D) Thorium-232 (as Thorotrast) (100D) X- and γ-radiation (100D) *Radioiodines, including iodine-131(100D)* *Radon-222 and its decay products (100D)* Tobacco smoking (100E) *Ethylene oxide (100F)* Benzene (100F) 1,3-Butadiene (100F) Formaldehyde (100F) *Trichloroethylene (100F*)* *2,3,7,8-Tetrachlorodibenzo*-para-*dioxin (100F)* *Polychlorinated biphenyls (100F*)*	Azathioprine (100A) Chlorambucil (100A) Cyclophosphamide (100A) Thiotepa (100A) X- and γ-radiation (100D) Benzene (100F) 1,3-Butadiene (100F) 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (100F)	Azathioprine (100A) Chlorambucil (100A) Cyclophosphamide (100A) Estrogen-only menopausal therapy (100A) Thiotepa (100A) Silica dust, crystalline, in the form of quartz or cristobalite (100C) X- and γ-radiation (100D) Ethylene oxide (100F) Benzene (100F) 1,3-Butadiene (100F) 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (100F)

Table 21.8. Comparison of 60 Group 1 agents with *sufficient* or *limited evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in animals in specific organ and tissue systems[a] (continued)

Humans[b] **Agent (*Monographs* Volume[c])**	**Humans and animals[b]** **Agent (*Monographs* Volume)**	**Animals[b]** **Agent (*Monographs* Volume)**
Skin (35% overlap)		
Azathioprine (100A) Methoxsalen in combination with UVA (100A) Arsenic and inorganic arsenic compounds (100C) Solar radiation (100D) UV-emitting tanning devices (100D) X- and γ-radiation (100D) Coal-tar distillation (100F) Mineral oils, untreated or mildly treated (100F) Shale oils (100F) Soot (as found in occupational exposure of chimney sweeps) (100F) Polychlorinated biphenyls (100F*)	Methoxsalen in combination with UVA (100A) Solar radiation (100D) UV-emitting tanning devices (100D) Coal-tar distillation (100F) Mineral oils, untreated or mildly treated (100F) Shale oils (100F) Soot (as found in occupational exposure of chimney sweeps) (100F)	Methoxsalen in combination with UVA (100A) Solar radiation (100D) UV-emitting tanning devices (100D) Coal, indoor emissions from household combustion of (100E) Tobacco smoking (100E) Benzene (100F) Bis(chloromethyl)ether; Chloromethyl methyl ether (technical grade) (100F) Coal gasification (100F) Coal-tar distillation (100F) Coal-tar pitch (100F) Coke production (100F) Mineral oils, untreated or mildly treated (100F) Shale oils (100F) Soot (as found in occupational exposure of chimney sweeps) (100F) 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (100F) *ortho*-Toluidine (100F)

Table 21.8. Comparison of 60 Group 1 agents with *sufficient* or *limited evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in animals in specific organ and tissue systems[a] (continued)

Humans[b] **Agent (*Monographs* Volume[c])**	**Humans and animals[b]** **Agent (*Monographs* Volume)**	**Animals[b]** **Agent (*Monographs* Volume)**
Connective tissues (43% overlap)		
Plutonium-239 (100D) Radium-224 and its decay products (100D) Radium-226 and its decay products (100D) Radium-228 and its decay products (100D) X- and γ-radiation (100D) *Radioiodines, including iodine-131 (100D)* Vinyl chloride (100F) *2,3,7,8-Tetrachlorodibenzo*-para-*dioxin (100F)*	Plutonium-239 (100D) Radium-224 and its decay products (100D) Radium-226 and its decay products (100D) Radium-228 and its decay products (100D) X- and γ-radiation (100D) Vinyl chloride (100F)	Cadmium and cadmium compounds (100C) Chromium(VI) compounds (100C) Nickel compounds (100C) Fission products including strontium-90 (100D) Plutonium-239 (100D) Radium-224 and its decay products (100D) Radium-226 and its decay products (100D) Radium-228 and its decay products (100D) X- and γ-radiation (100D) 4-Aminobiphenyl (100F) Bis(chloromethyl)ether; Chloromethyl methyl ether (technical grade) (100F) 1,3-Butadiene (100F) *ortho*-Toluidine (100F) Vinyl chloride (100F)
Female breast, female reproductive organs, and female reproductive tract (31% overlap)		
Diethylstilbestrol (100A) Estrogen-only menopausal therapy (100A) Estrogen–progestogen oral contraceptives (combined) (100A) Tamoxifen (100A) Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite) (100C) X- and γ-radiation (100D) Alcoholic beverages (100E) Tobacco smoking (100E) *Ethylene oxide (100F)* *Polychlorinated biphenyls (100F*)*	Diethylstilbestrol (100A) Estrogen-only menopausal therapy (100A) Estrogen–progestogen oral contraceptives (combined) (100A) X- and γ-radiation (100D)	Cyclophosphamide (100A) Diethylstilbestrol (100A) Estrogen-only menopausal therapy (100A) Estrogen–progestogen oral contraceptives (combined) (100A) X- and γ-radiation (100D) Benzene (100F) Benzidine (100F) 1,3-Butadiene (100F) Vinyl chloride (100F)

Table 21.8. Comparison of 60 Group 1 agents with *sufficient* or *limited evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in animals in specific organ and tissue systems[a] (continued)

Humans[b] **Agent (*Monographs* Volume[c])**	**Humans and animals[b]** **Agent (*Monographs* Volume)**	**Animals[b]** **Agent (*Monographs* Volume)**
Male reproductive organs including prostate and testes (overlap N/A)		
Diethylstilbestrol (100A) *Arsenic and inorganic arsenic compounds (100C)* *Cadmium and cadmium compounds (100C)* *Thorium-232 (as Thorotrast) (100D)* *X- and γ-radiation (100D)*		
Other groupings (0%)		
2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (100F) [all cancers combined] Fission products including strontium-90 (100D) [all solid cancers] *Plutonium-239 (100D)*		X- and γ-radiation (100D) [exocrine glands NOS] Benzene (100F) [exocrine glands NOS] 1,3-Butadiene (100F) [exocrine glands NOS] Vinyl chloride (100F) [exocrine glands NOS]

N/A, not applicable: denotes organ and tissue systems when overlap is not possible (positive data are available in either humans or animals, but not in both); UV, ultraviolet.

[a] Organ and tissue systems in the anatomically based tumour nomenclature system (see Supplemental Table 1. Animal and human tumour sites for 111 Group 1 agents identified up to and including Volume 109 of the *IARC Monographs*). Data inputs for human and animal data with *sufficient evidence* of carcinogenicity are from Supplemental Table 2. Database of animal and human tumour sites for 111 distinct Group 1 agents up to and including Volume 109 of the *IARC Monographs*. Agents that lack *sufficient evidence* in both humans and animals are not shown, with the exception of limited additional data inputs for *limited evidence* of human sites from Volumes 100A–F, Volume 107, and Volume 109 (in *italics*) and included data for ethylene oxide, estrogen–progestogen oral contraceptives, and diethylstilbestrol. Data for male reproductive organs are also included, although they are not part of the concordance analyses. 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin is included, but its designation of "all cancers combined" for human data precludes specific site analyses between species.

[b] Agents with *sufficient evidence* in humans, animals, and both humans and animals.

[c] Part A, B, C, D, E, or F in Volume 100 of the *IARC Monographs* in which the agent is included. Volume 100F* denotes chemical agents and related occupations identified as Group 1 agents after the publication of Volume 100.

[d] Number of agents with *sufficient evidence* in both humans and animals, as a percentage of the total number of agents that cause tumours in either humans or animals (or both) in the specified organ and tissue system (see Table 21.7).

have passed the age of highest risk for testicular cancer, further study cannot clarify the association between this exposure and this type of cancer (IARC, 2012e). Human data for this agent will remain limited for this end-point, although supported by the induction of testicular tumours in rodents.

With ongoing studies, more evidence can be gathered that provides increasing certainty about potential cancer risks to humans. Although IARC had previously evaluated TCE in 1979, 1987, and 1995, this substance was not declared to be *carcinogenic to humans* – causing kidney cancer – until 2012, after the emergence of new data (IARC, 2014). Although it was noted that a positive association had been observed between liver cancer and exposure to TCE, the lack of data was cited as the rationale for its designation as demonstrating only *limited evidence* of carcinogenicity in humans in the previous evaluations. In 2013, an updated pooled analysis of three Nordic studies with 10–15 years of additional follow-up demonstrated that human exposure to TCE was associated with a possibly increased risk of liver cancer (Hansen et al., 2013). Inclusion of the limited data for TCE-induced liver cancer in humans allows for the observation of overlap between animals and humans for this end-point.

This example illustrates that the inclusion of agents with *limited evidence* of carcinogenicity in humans enhances the ability to identify concordant relationships. Comparison between Table 21.7, which mentions only sites with *sufficient evidence* in humans, and Table 21.8, which also lists sites with *limited evidence* in humans, illustrates increased coherence, when limited human data are considered, among agents that have similar chemical and mechanistic characteristics. For example, if the *limited evidence* of tumours of the upper aerodigestive tract for chromium(VI) compounds in humans noted in Table 21.8 were admitted as evidence of carcinogenicity in humans, concordance between animals and humans would be established within this organ and tissue system.

Concordance may also be increased if less stringent criteria are applied than are used by IARC for determining *sufficient evidence* of carcinogenicity in animals. In evaluating the available animal data on estrogen–progestogen oral contraceptives (IARC, 2012e), it was concluded that "the data evaluated showed a consistent carcinogenic effect of several estrogen–progestogen combinations across different animal models in several organs." Similarly, the synthesis statement in the evaluation of diethylstilbestrol (IARC, 2012e) notes: "The oral administration of diethylstilbestrol induced tumours of the ovary, endometrium, and cervix, and mammary adenocarcinomas in female mice. Osteosarcomas and Leydig cell tumours were induced in rasH2 [transgenic] and Xpa/p53 [knockout] male mice, respectively. Subcutaneous implantation of diethylstilbestrol induced mammary tumours in female Wistar rats. Perinatal exposure to diethylstilbestrol induces lymphoma, uterine sarcomas, adenocarcinomas, and pituitary, vaginal, and ovarian tumours in female mice. Uterine adenocarcinomas and mammary and vaginal tumours were also induced in female rats. In hamsters, diethylstilbestrol perinatal exposure induced kidney tumours."

Although agents affecting male reproductive organs are included in Table 21.8, they are not part of the concordance analyses in Table 21.7, because of a lack of *sufficient evidence* in either humans or animals. TCDD is included in Table 21.8, but its designation as an agent affecting "all cancers combined" in humans precludes site-specific tumour concordance analyses. Nevertheless, the *limited evidence* of carcinogenicity of TCDD in humans in the respiratory system and lymphoid and hematopoietic tissues is consistent with the *sufficient evidence* of carcinogenicity in animals in these two organ and tissue systems. These examples illustrate increased site concordance by applying less stringent criteria than those applied for the concordance analysis presented in Table 21.7.

Table 21.8 shows human data indicating biological plausibility for the upper aerodigestive tract and lung to be targets for agents for which the portal of entry is the lung (as with dusts, particles, and particles that serve as a vehicle for a mixture of other carcinogens, such as during tobacco smoking and coke production). Lymphohaematopoietic cancers are a consistent end-point for antineoplastic alkylating agents that induce these cancers after their use in chemotherapy to eradicate other neoplasms (IARC, 2012e), for radioactive materials (IARC, 2012f), and for several chemical agents and related compounds that are metabolized to or are in themselves agents that are reactive with DNA (IARC, 2012c).

Table 21.8 also illustrates some of the potential relationships between agents that may act in a similar fashion in humans. Tobacco smoke and its related agents (smokeless tobacco and second-hand tobacco smoke) affect several similar organ

and tissue systems. For radioactive materials, almost all organs and sites are affected by ionizing radiation; these agents affect multiple target tissues because they are able to reach the nucleus and cause a variety of DNA lesions and other effects reflected by the key characteristics of human carcinogens (see Chapter 10, by Smith, and Chapter 22, by Krewski et al.; see also Smith et al., 2016).

Radioactive materials also do not require metabolism in order to induce cancer. Several dyes are associated with urothelial cancer in humans and act through a similar mechanism (IARC, 2012c). Agents that disrupt the endocrine system and related organs (e.g. PCBs, diethylstilbestrol, estrogen-only menopausal therapy, combined estrogen–progestogen oral contraceptives, and tamoxifen) induce cancer at similar sites, including the female reproductive organs and the breast. Metals appear to have many target sites in common, including the upper aerodigestive tract, the respiratory system, the kidney, and the prostate.

As noted previously, the animal database is predominantly populated by results from studies in rodents. Respiratory tract tumours are induced in rodents by many of the same agents that cause such tumours in humans. For the mesothelium, where tumour formation in humans or animals is rare and is specifically induced by a small number of agents, there is good agreement between the human and animal databases. Many agents metabolized in the liver to reactive compounds induce liver cancer in animal models, with less apparent overlap with the human data (see digestive organs, Table 21.8). Susceptibility of the liver in rodents to cancer induction is species-, sex-, and strain-specific and varies widely. Nonetheless, all agents that induce liver cancer in rodents induce cancer at some other site in humans. In some instances the apparent lack of overlap between the animal and human databases can still reflect mechanistic concordance for similar agents. Dyes such as magenta, 4-aminobiphenyl, benzidine, and 2-naphthylamine all cause liver cancer in rodents and urothelial cancer in humans. TCDD and PCBs are both associated with liver cancer in rodents and tumours of the lymphoid and haematopoietic tissues in humans.

Human exposures to diethylstilbestrol, estrogen-only menopausal therapy, and combined estrogen–progestogen oral contraceptives are all associated with cancers of the female breast, female reproductive organs, and female reproductive tract. Kidney cancer is induced in male hamsters upon exposure to either diethylstilbestrol or estrogens used in menopausal therapy. Data from a control group that received only estrogen, presented in the *Monograph* on combined estrogen–progestogen oral contraceptives, indicate a similar result (IARC, 2012e). Although there appears to be concordance in rodents for the tumours induced by these agents, there does not appear to be overlap with humans: rodent kidney versus female breast and reproductive organs. However, there may be mechanistic concordance between these two end-points, because both diethylstilbestrol and estrogen may damage DNA through oxidative damage, formation of unstable adducts, and induction of apurinic sites. In male Syrian hamsters the major metabolites of diethylstilbestrol are catechols that easily oxidize to catechol *o*-quinones, which are DNA-reactive. Implantation of estrone or estradiol in castrated male hamsters results in the induction of renal carcinomas exclusively (Li et al., 1983). Metabolic activation of estrogens by cytochrome P450 may also be related to a mechanism similar to that for PAHs (Cavalieri and Rogan, 2014). Thus, diethylstilbestrol and estrogen may have mechanistic similarities that result in an apparent lack of organ and tissue system overlap, with the hamster kidney being indicative of human risk.

Discussion

Since the early 1970s, the *IARC Monographs Programme* has been evaluating potential cancer risks to humans (Saracci and Wild, 2015). Separate evaluations of the available animal and human evidence are made, and these are then combined to make an overall evaluation of the strength of evidence of carcinogenicity to humans. At the time of this analysis, 120 distinct agents have met the IARC criteria for determining causality and for designation of these agents as *carcinogenic to humans* (Group 1). Of these, 111 distinct Group 1 agents were included in the data set of tumours and tumour sites in animals and humans developed by Grosse et al. (Annex 1).

The well-established weight-of-evidence criteria for the evaluation of the available human, animal, mechanistic, and exposure data used by IARC are detailed in the Preamble to the *IARC Monographs* (IARC, 2006) and provide clear guidance to the Working Groups convened to review agents. If the criteria for *sufficient evidence* of carcinogenicity in both animals and humans are satisfied, then causality can be reasonably inferred, and this can be strengthened by mechanistic considerations.

However, an immediate challenge in making comparisons for tumour site concordance between species was how to compare tumours in animals and in humans. A detailed historical discussion of approaches to the coding of human tumours was provided by Muir and Percy (1991), considering the topographical, morphological, and histological characteristics of the lesion to be classified. In the absence of a common coding system for animal and human tumours, an anatomically based tumour taxonomy system was developed during the course of the work presented here.

Although this system worked well for the purposes of the present concordance analysis, there are some animal sites that do not have a human counterpart, including the Harderian gland and the Zymbal gland. Tumours at these unique sites occurred rarely and were included within the category of "other groupings" in the anatomically based tumour nomenclature system used here. Other sites that are unique to animals but are, however, closely related to a similar human site were aligned with the corresponding human tumour site; for example, the forestomach was considered as part of the stomach in the anatomically based taxonomy system.

This tool, developed for tumour comparisons across and within species, included 39 individual tumour sites for which agents showed *sufficient evidence* of carcinogenicity in humans and/or animals, which were further aggregated into 14 organ and tissue systems. This aggregation allows comparisons to be made at a higher level of organization, reflecting anatomical and physiological similarities among certain tumour sites; for example, the lung and lower respiratory tract are considered together as the respiratory system. Aggregation also allows more data to be considered for analysis, which increases the robustness of the ensuing conclusions. For the concordance analyses, data at both the individual tumour site level and the organ and tissue system level were examined.

Although the present analysis demonstrates generally good agreement between tumour sites in animals and in humans after exposure to Group 1 carcinogens, concordance was not demonstrated with every agent and tumour site. There are several factors and important limitations that may result in lack of tumour concordance based on these data. For many of the 111 agents, relevant and reliable data to support a complete analysis of concordance are unavailable for either animals or humans. For some agents, notably the human tumour viruses, relevant animal models are lacking, thereby precluding the possibility of obtaining results on concordance. There may also be little motivation for conducting animal tests for other agents, such as leather dust in occupational environments or acetaldehyde associated with consumption of alcoholic beverages. Mixtures such as those in combined estrogen–progestogen menopausal therapy may also not have been evaluated in animals, particularly if the components of the mixture had been previously evaluated separately. Relevant animal tests may still provide only *limited* or *inadequate* evidence of carcinogenicity through limitations in study design or conduct, or if the mechanism of action of the agent of interest was specific to humans and not easily replicated in an experimental animal model. Animal studies may also show tumours that are species- and/or sex-specific.

As part of the determination of weight of evidence, agents that induce tumours at multiple sites and across multiple species are considered to present a more robust cancer hazard to humans. However, the experimental animal database used for the analysis consists primarily of rodent data. It is notable that of the 111 Group 1 agents examined here, three agents caused tumours in humans and in four animal species (mice, rats, hamsters, and non-human primates): asbestos, which causes lung tumours in all five species; plutonium-239, which causes skin tumours in these species; and 2-naphthylamine, which causes urinary tract/uroendothelial tumours in these species. These agents are examples of carcinogens that cause the same type of tumour in multiple species, thereby demonstrating a high degree of interspecies tumour site concordance.

The present analyses exclude the human tumour viruses evaluated in Volume 100B, because, with the possible exception of human T-cell lymphotropic virus type 1 (HTLV-1), the use of animals to assess the potential cancer risks of human tumour viruses is problematic (IARC, 2012b). The best animal models to study human viruses are non-human primates, which are difficult to use experimentally both because of the time and expense involved in conducting studies with long-lived species and because the incidence of cancer is low in non-human primates. Although transgenic mouse models have been developed for evaluating human cancer viruses, such models are considered more informative for understanding cancer

mechanisms than for human cancer risk assessment (see Chapter 9, by Lambert and Banks).

The criteria for *sufficient evidence* of carcinogenicity in animals as outlined in the Preamble to the *IARC Monographs* (IARC, 2006) generally require independent replication in two different animal species, or particularly strong results in a single species. The *IARC Monographs* generally do not identify animal tumour sites for agents with only *limited evidence* of carcinogenicity in animals. The criteria developed by Grosse et al. (Annex 1) further restrict the use of tumour data for agents with *sufficient evidence* in experimental animals (e.g. tumour sites were not identified in the absence of two or more animal studies of adequate design and quality pointing at the same tumour site with a similar histological origin in the same species). Although melphalan produced tumours of the forestomach, skin, and lung as well as lymphosarcomas in mice and mammary gland tumours and peritoneal sarcomas in rats (IARC, 2012c), none of these tumour sites were replicated in a second animal species, and hence are not included in the data set of Grosse et al. (Annex 1).

Human evidence is also subject to limitations. As noted above, the opportunity may no longer be available to conduct further informative studies in humans of a substance like diethylstilbestrol. The absence of *sufficient evidence* in humans may be due to a lack of evidence in appropriate epidemiological or clinical studies, or to the inability of existing studies to detect an association between exposure to the agent of interest (including exposures early or later in life) and a tumour outcome. Study limitations may also include inadequate power as a result of small sample size. If human exposures to the agent of interest are extremely low, a particularly large, well-conducted study would be required to achieve reasonable sensitivity.

Failure of human studies to identify tumour sites can occur when these studies do not consider all possible sites. Most case–control studies focus on only one or a limited number of tumour sites. Human studies that fail to identify a relevant tumour site may have low sensitivity, possibly because they do not focus on the most appropriate study population. As noted above for TCE, evidence on specific tumour sites may not yet have accrued at the time of an evaluation. After the first evaluation of tobacco smoking in Volume 38 of the *IARC Monographs* (IARC, 1986), cigarette smoking was subsequently shown – in Volume 83 – to cause cancer at a much larger number of tumour sites, including cancers of the nasal cavities and nasal sinuses, oesophagus, stomach, liver, kidney, and uterine cervix, and myeloid leukaemia (IARC, 2004). Thus, the potential for underestimation of interspecies tumour site concordance may result from missing tumour sites for agents for which *sufficient evidence* of carcinogenicity in humans already exists.

How human study data are reported in the *Monographs* may also affect the ability to conduct analyses to establish tumour site concordance. A specific example of this constraint is ionizing radiation. No specific human tumour sites were identified for ionizing radiation (all types), internalized radionuclides that emit α-particles, internalized radionuclides that emit β-particles, and UV radiation (bandwidth 100–400 nm, encompassing UVC, UVB, and UVA). Although the skin was not explicitly mentioned as a human tumour site for UV radiation in Volume 100D, the skin is implicitly suggested as being a human tumour site for this agent. In the present analysis, the lack of explicit designation of the skin as a human tumour site for UV radiation precluded its use. A similar situation occurred for areca nut, for which the oral cavity might have been considered as a human tumour site, although this site was not explicitly designated in the *Monograph*.

An agent can be categorized by IARC as a Group 1 carcinogen in the absence of *sufficient evidence* for carcinogenicity in humans when it is clear that the mechanisms by which the agent causes cancer in animals also operate in humans. Such "mechanistic upgrades" have occurred with various levels of human evidence, including for aristolochic acid (*limited evidence* of carcinogenicity in humans; IARC, 2012e), B[*a*]P (*inadequate evidence* in humans; IARC, 2012c), ethylene oxide (*limited evidence* in humans; IARC, 2012c), 4,4′-methylenebis(2-chloroaniline) (MOCA) (*inadequate evidence* in humans; IARC, 2012c); and neutron radiation (*inadequate evidence* in humans; IARC, 2012f).

For further discussion of mechanistic upgrades and key characteristics of Group 1 agents developed for this analysis, see Chapter 10, by Smith, Chapter 22, by Krewski et al., Smith et al. (2016), and Birkett et al. (2019). Ten key characteristics of human carcinogens described by Smith et al. (2016) focus on whether the agent (1) is electrophilic or can be metabolically activated to electrophiles, (2) is genotoxic, (3) alters DNA repair or causes genomic instability, (4) induces epigenetic alterations, (5) induces oxidative

stress, (6) induces chronic inflammation, (7) is immunosuppressive, (8) modulates receptor-mediated effects, (9) causes immortalization, and/or (10) alters cell proliferation, cell death, or nutrient supply. These considerations will be relevant in planned future analyses of coherence between tumours in animals and humans, taking into account key characteristics of carcinogens. However, mechanistic upgrades limit the ability to identify tumour site concordance when human tumour sites are not identified.

Exposure assessment is one of the most difficult aspects of epidemiological investigations (Nieuwenhuijsen, 2003). In some cases, such as ecological studies that compare two population groups subject to notably different exposure circumstances, exposure may not be measured at all. In other cases, however, exposures may be very well determined, as with the use of personal dosimeters to measure exposures to agents such as ambient air pollution or ionizing radiation, or in the dose regimens of pharmaceutical drugs or medical radiation. In the future, enhanced exposure assessment methodologies may serve to strengthen the ability of epidemiological studies to identify Group 1 agents (Cohen-Hubal et al., 2010; National Research Council, 2012). Biomarkers of exposure are expected to play an important part in the future of exposure science (Gurusankar et al., 2017).

The data set assembled and evaluated by Grosse et al. (Annex 1) was retrieved from the *IARC Monographs*. Thus, these agents do not represent a "random sample" of all potential human carcinogens, and the data set is populated by the available animal and human evidence that was the focus of the *Monographs* from which they were drawn. The ability to determine concordance may change as additional Group 1 agents are identified, or as additional animal or human evidence on current Group 1 agents becomes available. New mechanistic data could affect IARC evaluations of agents currently classified in Group 2A (*probably carcinogenic to humans*) and Group 2B (*possibly carcinogenic to humans*), and hence affect the concordance estimates reported here. Birkett et al. (2019) noted that additional information on the 10 mechanistic key characteristics of human carcinogens described by Smith et al. (2016) is available in the general scientific literature, beyond what is summarized in the *IARC Monographs*.

In addition to the restrictions used by Grosse et al. (Annex 1) for inclusion of certain experimental animal data, other limitations of the database affect the ability to determine tumour site concordance, including incomplete information on tumour histology, limited information on the effects of sex, strain, and route of exposure, and limited information on dose-dependent effects. These and other limitations are discussed briefly below.

Incomplete information on tumour histology

Because of incomplete information on the histology of lesions in both animal and human studies, it was not possible to conduct concordance analyses for specific histological subtypes of cancers at a given site (such as adenocarcinoma or squamous cell carcinoma of the lung). The concordance analyses reported here are necessarily restricted to tumours occurring in a given organ or tissue (such as lung cancer) or in a more broadly defined organ and tissue system (such as the upper aerodigestive tract and the respiratory system). The concordance analyses reported here are based either on 39 tumour sites or on the broader classification of 14 organ and tissue systems.

Effects of sex, strain, and route of exposure

Risks of cancer can differ between male and female animals, among different strains of the same animal species, and by route of exposure. Because of incomplete information on these three factors in the database used in the present analysis, it was not possible to evaluate how concordance might vary by sex, strain, or exposure route.

Effects of dose

Because the primary objective of the *IARC Monographs Programme* is to identify agents with the potential to cause cancer in humans in qualitative terms, rather than to quantify the level of risk at a given dose, information on dose dependence in cancer risk is not systematically collected in the *Monographs*, although this is currently under review by IARC (IARC Advisory Group to Recommend on Quantitative Risk Characterization, 2013). Therefore, analyses of concordance considering dose–response relationships seen in animals and humans were not attempted at this time.

Multisite/multiorgan carcinogenicity

Several agents, notably radiation and tobacco smoke, induce malignant lesions at multiple sites or in multiple organ and tissue systems. Volume 100F (IARC, 2012c) summarizes the evidence that 1,3-butadiene induces haemangiosarcomas of the heart, malignant lymphomas, bronchiolo-alveolar neoplasms, and squamous cell neoplasms of

the forestomach in male and female B6C3F1 mice, and acinar cell carcinomas of the mammary gland, granulosa cell neoplasms of the ovary, and hepatocellular neoplasms in female mice. Assessing species concordance with multisite carcinogens is inherently more difficult than with carcinogens that affect a single organ or tissue. Understanding the mechanistic and other attributes of such multisite carcinogens will be useful in translating results in experimental animals to humans.

Measures of concordance

For simplicity of presentation, concordance was evaluated here in terms of the "overlap" between tumour sites seen in animals and humans. Although more formal statistical analyses of concordance as described in Supplemental Material II (online only; available from: http://publications.iarc.fr/578) were considered during the course of this work, the consensus of the Working Group was to represent concordance in terms of the simpler, more directly interpretable, indicators of "overlap" in Table 21.7 and Fig. 21.10.

Small sample size

After the 111 Group 1 agents tabulated by Grosse et al. (Annex 1) up to and including Volume 109 of the *IARC Monographs* were filtered to include only agents that provided *sufficient evidence* of carcinogenicity in at least one tumour site in humans and at least one tumour site in animals, 60 agents remained eligible for concordance analysis. Because the sample size for some tumour sites is small (only two agents – asbestos and erionite – caused tumours of the mesothelium), caution is needed in interpreting the concordance results presented in this chapter for these sites.

Predictive value of animal tests for carcinogenicity

Using a database comprising 150 agents tested for toxicity in animals and humans, Olson et al. (2000) estimated the positive predictive value (PPV) and the negative predictive value (NPV) for human toxicity (excluding cancer). In this context, the PPV is defined as the probability of observing human toxicity in clinical testing, given that toxicity has been observed in animal tests. The PPV for human toxicity was estimated to be 71% for rodent and non-rodent species combined, 63% for non-rodents alone, and 43% for rodents alone. Although a statement of the PPV and the NPV of animal cancer tests for human carcinogenicity may be desirable, this cannot be done on the basis of the IARC concordance database considered in this chapter. This is because both the PPV and the NPV depend on the prevalence of true positives in the database (Altman and Bland, 1994). Because the IARC concordance database comprises Group 1 agents that are known causes of cancer in humans, the PPV of animal cancer tests will artificially be calculated as 100%, whereas a lower PPV would be obtained with a more representative database that includes agents that do not cause cancer in humans. However, identifying agents that do not cause cancer in humans is not the focus of the *IARC Monographs Programme*; at present, only one agent – caprolactam – is classified as *probably not carcinogenic to humans* (Group 4).

In considering the relevance of animal data in the context of the *IARC Monographs*, it is important to keep in mind how animal data are used in the identification of Group 1 agents, according to the criteria outlined in the Preamble to the *IARC Monographs* (IARC, 2006). Most Group 1 agents are identified on the basis of *sufficient evidence* in humans, and for the purpose of the overall evaluation, there is no immediate recourse to animal data. Of the 111 Group 1 agents considered in this chapter, 102 demonstrated *sufficient evidence* of carcinogenicity in humans; the remaining nine agents were placed in Group 1 because the mechanisms by which tumours occurred in animals were considered to be directly relevant to humans, or on the basis of other relevant mechanistic considerations. For example, neutron radiation was placed in Group 1 despite *inadequate evidence* in humans, because the biophysics of radiation damage is similar for different types of ionizing radiation.

Bearing in mind the contribution of animal data to the identification of Group 1 agents in the *IARC Monographs*, it is possible with the present IARC concordance database to make a statement about the likelihood of positive results in animals among the Group 1 agents that have been shown to cause cancer in humans. Excluding mechanistic upgrades (nine agents) and Group 1 agents that lack appropriate animal data (20 agents), *all* Group 1 agents with *sufficient evidence* of carcinogenicity in humans have also provided *sufficient* or *limited evidence* of carcinogenicity in one or more animal species.

Conclusions

The *IARC Monographs Programme* is widely recognized as one of the most authoritative sources of information on the identification of agents that may be carcinogenic to humans. The *Monographs* are prepared with the involvement of

leading scientific experts worldwide, who apply the guidance provided in the Preamble to the *IARC Monographs* (IARC, 2006) to evaluate the weight of evidence that an agent may present a cancer risk to humans. Up to and including Volume 109, more than 2000 scientists have contributed to the development of the *IARC Monographs*; nearly 200 scientists were involved in Volume 100 alone. Since its beginning in 1971–1972 (Saracci and Wild, 2015), the *IARC Monographs Programme* has evaluated more than 1000 agents for their potential to cause cancer in humans, with 120 of these agents assigned to Group 1, indicating that the weight of evidence supports the conclusion that the agent is *carcinogenic to humans*.

A noteworthy aspect of the process used by IARC to identify the causes of cancer in humans is the reliance on leading experts in the Working Groups that conduct the evaluations documented in the *Monographs* to interpret the data according to the weight-of-evidence guidelines provided in the Preamble to the *IARC Monographs* (IARC, 2006). With the trend towards greater reliance on systematic review (National Research Council, 2014) and structured weight-of-evidence approaches to the evaluation of toxic substances (Rhomberg et al., 2013), the continued involvement of international experts in the *IARC Monographs* to interpret the often extensive human, animal, and mechanistic data is a major strength of the *IARC Monographs Programme*.

Collectively, the *IARC Monographs* provide a rich source of information on the causes of cancer in humans. In particular, Volume 100 presents a review and update of 107 Group 1 agents identified in the previous 99 Volumes of the *IARC Monographs*, providing a veritable "encyclopaedia of carcinogens". This information, supplemented with data on Group 1 agents identified in Volumes 101 to 109, formed the basis for the analyses included in this chapter. After both PCB 126 and dioxin-like PCBs were subsumed within the broader category of PCBs, 113 – 2 = 111 district Group 1 agents were included in the concordance analyses presented in this chapter. The importance of human data in the IARC carcinogen evaluation process is highlighted by the observation that 102 of the 111 distinct Group 1 agents identified at the time this analysis was done demonstrated *sufficient evidence* of carcinogenicity in humans.

Analysis of concordance between tumour sites in animals and humans was restricted to 60 Group 1 agents demonstrating *sufficient evidence* for at least one tumour site in animals and in humans. Substantial overlap between animal and human tumours was seen in some organ and tissue systems but not in others. This analysis focused on tumours seen in the 14 organ and tissue systems in the anatomically based tumour classification system rather than 39 individual tumour sites, because of the sparseness of data at the individual tumour site level.

The principle that agents that are carcinogenic in experimental animals should be regarded as presenting a carcinogenic risk to humans was further confirmed in the course of this investigation. Excluding agents for which animal data are lacking or otherwise uninformative, all agents that cause cancer in humans also cause cancer in one more animal species, a finding consistent with an earlier evaluation of results from the *IARC Monographs Programme* (Wilbourn et al., 1986) and commented upon by other authors (Tomatis et al., 1989; Huff, 1994; Maronpot et al., 2004). However, it is important to note that the present database cannot be used to estimate the predictive value of animal cancer tests for humans, because it comprised by design only Group 1 agents; the PPV and the NPV of the animal data for humans would be 100% and 0%, respectively (an artefact of a database that comprises human carcinogens only).

Despite the challenges in evaluating concordance between tumour sites in animals and humans, the IARC concordance database is a useful source of information for comparing animal and human data with respect to the tumours caused in different species by the 111 distinct Group 1 agents identified by IARC up to and including Volume 109 of the *IARC Monographs*. Future *Monographs* may benefit from a more systematic summary of the animal and human data on agents evaluated within the *IARC Monographs Programme*, including data on the types of tumours seen in animal and human studies, possibly using the anatomically based tumour nomenclature system introduced in this chapter to facilitate comparisons between animals and humans. Data on route of exposure, sex, and animal strain would also support comparisons of animal and human tumours at a finer level of biological resolution. Data on the exposure or dose levels at which tumours are seen in animals and humans would further support evaluation of the relative carcinogenic potency of agents evaluated in animals and humans. Information on tumour sites affected by agents evaluated within the *IARC Monographs Programme* should be

recorded in as much detail as possible to facilitate future evaluations of the concordance between tumours seen in animals and humans on a site-specific basis.

Summary

Since its inception in the early 1970s, the *IARC Monographs Programme* has developed 119 *Monographs* Volumes on more than 1000 agents for which there exists some evidence of cancer risk to humans; of these, 120 agents met the criteria for classification as *carcinogenic to humans* (Group 1). Volume 100 of the *IARC Monographs*, compiled in 2008–2009 and published in 2012, provided a review and update of the 107 Group 1 agents identified as of 2009. These agents were divided into six broad categories: pharmaceuticals; biological agents; arsenic, metals, fibres, and dusts; radiation; personal habits and indoor combustions; and chemical agents and related occupations. The data set developed by Grosse et al. (Annex 1) for human and animal tumours and tumour sites associated with exposure to these agents, as well as five additional Group 1 agents defined in subsequent Volumes of the *Monographs*, were used to analyse the degree of concordance between sites where tumours arise in humans and in experimental animals (mice, rats, hamsters, dogs, and non-human primates). An anatomically based tumour nomenclature system, representing 39 tumour sites and 14 organ and tissue systems for which agents presented *sufficient evidence* of carcinogenicity in humans and/or in experimental animals, was developed and used as the basis for interspecies comparison. The present analysis identified 91 Group 1 agents with *sufficient evidence* (82 agents) or *limited evidence* (9 agents) of carcinogenicity in animals. The most common tumours observed in both humans and animals were those of the respiratory system (including larynx, lung, and lower respiratory tract). In humans, such tumours were observed for 31 of the 111 distinct Group 1 carcinogens identified up to and including Volume 109 of the *IARC Monographs*, comprising mostly chemical agents and related occupations (14 agents), arsenic, metals, fibres, and dusts (7 agents), and personal habits and indoor combustions (5 agents). After tumours in the respiratory system, those in lymphoid and haematopoietic tissues (26 agents), the urothelium (18 agents), and the upper aerodigestive tract (16 agents) were most often seen in humans, and tumours in digestive organs (19 agents), the skin (18 agents), and connective tissues (17 agents) were most often seen in animals. Exposures to radiation (particularly X- and γ-radiation) and tobacco smoke were associated with tumours at multiple sites in humans. Although the *IARC Monographs* do not emphasize tumour site concordance between animals and humans, substantial concordance was observed for several organ and tissue systems, even under the stringent criteria for *sufficient evidence* of carcinogenicity used by IARC. Of the 60 agents for which at least one tumour site had been identified in both humans and animals, 52 (87%) cause tumours in at least one of the same organ and tissue systems in humans and animals. It should be noted that some caution is needed in interpreting concordance at sites where the sample size is particularly small: although perfect (100%) concordance was noted for agents that cause tumours of the mesothelium, only two Group 1 agents meeting the criteria for inclusion in the concordance analysis caused tumours at this site. Although the present analysis demonstrates good concordance between animals and humans for many, but not all, tumour sites, limitations of the available data may result in underestimation of concordance.

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