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Concordance between sites of tumor development in humans and in experimental animals for 111 agents that are carcinogenic to humans

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ABSTRACT

Since the inception of the *IARC Monographs Programme* in the early 1970s, this *Programme* has developed 119 *Monograph* Volumes on more than 1000 agents for which there exists some evidence of cancer risk to humans. Of these, 120 agents were found to meet 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: (I) pharmaceuticals; (II) biological agents; (III) arsenic, metals, fibers and dusts; (IV) radiation; (V) personal habits and indoor combustions; and (VI) chemical agents and related occupations. The Group I agents reviewed in Volume 100, as well as five additional Group 1 agents defined in subsequent Volumes of the *Monographs*, were used to assess the degree of concordance between sites where tumors originate in humans and experimental animals including mice, rats, hamsters, dogs, and non-human primates using an anatomically based tumor nomenclature system, representing 39 tumor sites and 14 organ and tissue systems. This evaluation identified 91 Group 1 agents with *sufficient evidence* (82 agents) or *limited evidence* (9 agents) of carcinogenicity in animals. The most common tumors observed in both humans and animals were those of the respiratory system including larynx, lung, and lower respiratory tract. In humans, respiratory system tumors were noted for 31 of the 111 distinct Group 1 carcinogens identified up to and including Volume 109 of the *IARC Monographs*, comprising predominantly 14 chemical agents and related occupations in category VI; seven arsenic, metals, fibers, and dusts in category III, and five personal habits and indoor combustions in category V. Subsequent to respiratory system tumors, those in lymphoid and hematopoietic tissues (26 agents), the urothelium (18 agents), and the upper aerodigestive tract (16 agents) were most often seen in humans, while tumors in digestive organs (19 agents), skin (18 agents), and connective tissues (17 agents) were frequently seen in animals. Exposures to radiation, particularly X- and γ-radiation, and tobacco smoke were associated with tumors at multiple sites in humans. Although the *IARC Monographs* did not emphasize tumor site concordance between animals and humans, substantial concordance was detected 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 tumor site was identified in both humans and animals, 52 (87%) exhibited tumors 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 sample size is particularly small. Although perfect (100%) concordance was noted for agents that induce tumors of the mesothelium, only two Group 1 agents that met the criteria for inclusion in the concordance analysis caused tumors at this site. Although the present analysis demonstrates good concordance between animals and humans for many, but not all, tumor sites, limitations of available data may result in underestimation of concordance.

KEYWORDS

human tumor sites; animal tumor sites; tumor classification; concordance; overlap

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Introduction

Since its establishment in the early 1970s, the *IARC Monographs Programme* has evaluated more than 1000 agents for which some evidence exists of a possibly increased cancer risk to humans. The *IARC Monographs Programme* has established detailed criteria for which to assess 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 weigh the evidence provided by human epidemiological studies, animal cancer bioassays, and information on possible biological mechanisms of action, to classify agents as follows.

Group 1: *carcinogenic to humans*
Group 2A: *probably carcinogenic to humans*
Group 2B: *possibly carcinogenic to humans*
Group 3: *not classifiable as to its carcinogenicity to humans*
Group 4: *probably not carcinogenic to humans*

These assessments involve classifying data derived from both human and animal investigations as providing either *sufficient evidence of carcinogenicity; limited evidence of carcinogenicity; inadequate evidence of carcinogenicity*, or *evidence suggesting lack of carcinogenicity*. The information derived from biological mechanisms of action may be designated as *strong, moderate*, or *weak*, and is taken into consideration in the overall evaluation.

To date, IARC has produced 119 *Monograph* Volumes on more than 1000 agents for which there exists some evidence of increased 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 (I) pharmaceuticals (Volume 100A; IARC 2012e), (II) biological agents (Volume 100B; IARC 2012b), (III) arsenic, metals, fibers, and dusts (Volume 100C; IARC 2012a), (IV) radiation (Volume 100D; IARC 2012f), (V) personal habits and indoor combustions (Volume 100E; IARC 2012d), and (VI) 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 this current analysis was undertaken including (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), (iv) outdoor air pollution and (v) particulate matter (PM) in outdoor air pollution (both evaluated in Volume 109; IARC 2016a). 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 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 (WOE) for human carcinogenicity, the degree of concordance between species for tumor induction by carcinogenic agents is important. A high degree of site concordance between species supports the ability of investigations 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 (1) ensure that all cancer sites have been identified in sensitive human subpopulations or in appropriate experimental animal models, and (2) identify the underlying mechanisms of action (MOA) that different species may or may not have in common.

This evaluation used the dataset assembled by Grosse et al. (2019) derived from the available information on agents classified by IARC as *carcinogenic to humans* (Group 1) in Volume 100 to Volume 109. This database includes all tumor sites identified in the *IARC Monographs* for which

Table 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
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 *Monograph* 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*.

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 tumor sites observed in humans and animals. Although the database also includes human tumor sites for which there is *limited evidence* of carcinogenicity for the agent,

these sites were not systematically identified in the *IARC Monographs*. Similarly, animal tumor sites were generally not identified in the case of *limited evidence* of carcinogenicity in animals.

Tumor nomenclature in animals and humans

Although human tumors can be coded in a standardized manner by employment of the *International Classification of Diseases* coding system (WHO 1977, 2011), a comparable nomenclature system does not exist for animal tumors. To render animal and human tumors identified in the *IARC Monographs* comparable, a taxonomy of tumor sites was constructed by Krewski et al. (2019a). As shown in Table 2, this taxonomy is anatomically based and includes 47 tumor sites grouped within 15 organ and tissue systems. There are 39 distinct animal and human tumor sites specified for Group 1 agents in Volume 100A–F*; 8 additional tumor sites were considered to be important, even though they did not appear in the tumor site concordance dataset developed by Grosse et al. (2019). The individual tumor sites noted in either animals or humans up to and including Volume 109 of the *IARC Monographs* are listed in Table 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 review are based upon the 39 individual tumor sites within the 14 organ and tissue systems presented in Table 2 (excluding tumors of the male reproductive tract, for which the data do not show *sufficient evidence* in both humans and animals).

Retrieval of data on tumor occurrence from the IARC monographs

Grosse et al. (2019) extracted data from Volumes 100, 105, 106, 107, and 109 on tumor sites reported in humans or animals for the 111 distinct Group 1 agents considered here as illustrated in Table 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 PM in outdoor air pollution (Volume 109). Table 3 provides the tumor sites for which the agents provide *sufficient evidence* of carcinogenicity in humans, as well as sites for which there is *limited evidence*. Tumor 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 noted in Table 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.

Effects of gender, strain, and route of administration

The last column in Table 3 provides details on animal studies relevant to the evaluation of the agent of interest, including gender and strain of the test animals and 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 upon predominantly male occupational cohorts, men tend to be over-represented in human investigations on Group 1 agents. Other agents, such as hormonal oral contraceptives, are assessed only in women. Certain lesions, notably breast cancer and prostate cancer, are largely gender-specific. In addition, some animal studies use only one gender, and others do not specify whether male 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 may occur following 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 or subcutaneous injection or intratracheal instillation. In many cases, the route of exposure used

Table 2. Anatomically based taxonomy of tumor 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 hematopoietic tissues	Hmatopoietic 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 tumor sites for 111 Group 1 agents identified up to and including Volume 109 of the *IARC Monographs*).

in animal investigations 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 upon the route of administration. Differences in routes of exposure between animals and humans might thus contribute to lack of concordance between tumor sites detected 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.

Attributes of the concordance database

The concordance dataset assembled by Grosse et al. (2019) and summarized in Table 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 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 derived from B[*a*]P exposure, suggesting that the MOA by which this agent induces tumors in animals would also be expected to operate in humans. It should be noted that no data obtained from humans regarding 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 tumor site.

Of the nine agents in Table 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 drug-induced acute myeloid leukemias with distinctive chromosomal translocations attributed to etoposide which targets topoisomerase II (IARC 2012e). Of

Table 3. Information on animal and human tumors and tumor 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, Mori, and Naito (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, Diwan, and Waalkes (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, Diwan, and Waalkes (2012a), M, CD1, in utero; MMA(III): Tokar et al. (2012b), M, CD1, in utero	
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, Dai, and Sun (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.	

(*Continued*)

Table 3. (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
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. National Toxicology Program (1990), M, F344/N, g.; National Toxicology Program (1988), M, Osborne-Mendel, g.; National Toxicology Program (1988), F, ACI, g. 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.	
106	108	Trichloroethylene	Kidney	Non-Hodgkin lymphoma, liver	Trichloroethylene	Rat	Kidney	Renal cell carcinoma		
107	109	Polychlorinated biphenyls	Skin (melanoma)	Non-Hodgkin lymphoma, breast	Aroclor 1260	Rat	Liver	Hepatocellular carcinoma		
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; NK, natural killer; p.o., orally; s.c., subcutaneously.

Table 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, 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.

these nine mechanistic upgrades, three showed *limited evidence* in humans and six had inadequate *evidence* in humans or no epidemiological data were available as for example B[*a*]P and for 2,3,4,7,8-pentachlorodibenzofuran (PeCDF).

Apart from the nine Group 1 mechanistic upgrades for which no human tumor sites were identified, there are four other agents for which this the case (Table 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 assessments across a range of agents falling in these categories. In addition, no human tumor 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 (Grosse et al. 2019).

No animal tumor sites were identified for 38 of the 111 agents considered here (Table 6). These included 20 agents with *inadequate evidence* in animals: seven agents representing occupational exposures that would be difficult to replicate in the lab; two pharmaceutical agents employed 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 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

Table 5. Group 1 agents with no human tumor sites specified (15 agents).

Nature of evidence in humans (number of agents)	Volume: Agent(s)
Mechanistic upgrades	
Mechanistic upgrade with no human tumor 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

Table 6. Group 1 agents with no animal tumor 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 tumor 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 tumors at the same organ site with a similar histological origin in the same species.

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 failed to demonstrate carcinogenicity and the case in which 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 six 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 investigations 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 were subjected 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, tumor sites are not specified in the *IARC Monographs* for agents that demonstrate only *limited evidence* in animals.

No tumor sites were specified for eight agents demonstrating *sufficient evidence* of carcinogenicity in animals, because reproducible results were unavailable in two or more investigations of adequate design in the same species for any of these agents. Although melphalan displayed evidence of a significant increase in the incidence of tumors of the forestomach, skin, and lung in mice, as well as lymphosarcoma, these observations were not replicated in a second, independent study (IARC 2012c). In rats, melphalan also produced mammary gland tumors and peritoneal sarcoma, but these findings were again not replicated in independent studies. Phosphorous-32 produced leukemia in mice and osteogenic sarcomas in rats in single studies. Similarly, acetaldehyde in drinking-water induced pancreatic adenomas, combined lymphomas and leukemias, uterine and mammary gland adenocarcinomas, and head osteosarcomas in rats, but without replication. Betel quid with tobacco-produced malignant forestomach and cheek pouch tumors in a single experiment in hamsters. *Sufficient evidence* of carcinogenicity in animals of aluminum refining was based upon a single-limited skin application study in mice with PAH-containing particulates from aluminum 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 tumor site concordance database, additional concordant results would have been noted, including concordance between lymphoid and hematopoietic tissues in mice and humans for both melphalan and phosphorous-32, and concordance between tumors 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 upon elevated 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 experiments with PeCDF in combination with *N*-methyl-*N*-nitro-*N*-nitrosoguanidine (MNNG) and *N*-nitrosodiethylamine (NDEA), where increased tumor multiplicity was found in each case (IARC 2012c). These observations led to the conclusion that there is *sufficient evidence* for carcinogenicity of PeCDF in animals, although there was no specific organ site that might be designated as responsible for this *sufficient evidence*. Because of the absence of a specific tumor site in animals, PeCDF is not included in the concordance analyses.

A component of four Group 1 agents, but not the agents themselves, exhibited *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 displayed *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 aluminum production, where airborne particulate polynuclear organic matter from aluminum production plants exhibited *sufficient evidence* of carcinogenicity in animals (IARC 2012c). Although this animal evidence is consistent with *sufficient evidence* for carcinogenicity of these four agents in humans, animal evidence represents only a component of these agents.

Excluding the 20 agents in Table 5 that lack appropriate animal data where seven occupational exposures were not reproducible in the lab, 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* (9 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 tumors are seen in animals and humans among the 111 distinct Group 1 agents considered here, descriptive statistics are presented on tumor site profiles by species, followed by an evaluation of concordance between tumor sites noted in animals and humans. Results are presented first for the 39 tumor sites included in the anatomically based tumor nomenclature system detected in either animals or humans, followed by data for the 14 organ and tissue systems.

Tumor site profiles by species

The number of agents that induce tumors in humans at each of the 39 tumor sites is illustrated in Figure 1 by type of agent in the six categories (pharmaceuticals; biological agents; arsenic, metals, fibers, and dusts; radiation; personal habits and indoor combustions; and chemical agents and related occupations). Lung tumors are the most common seen in humans, with 28 of the 111 known human carcinogens inducing lesions at this

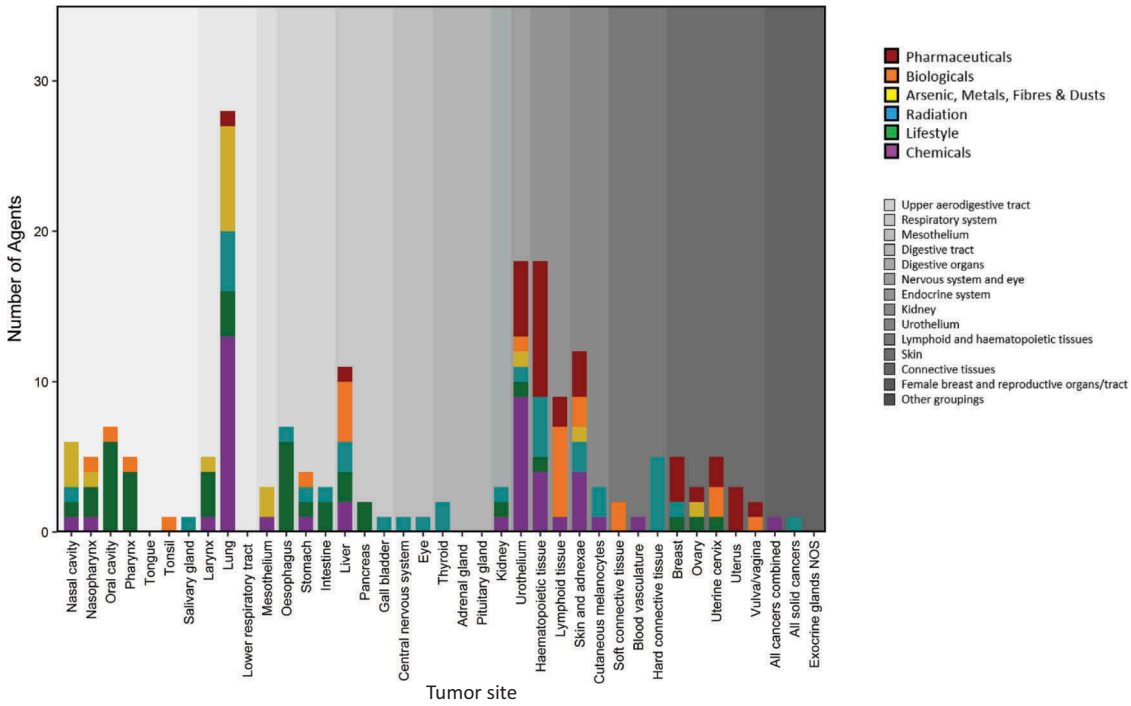

Figure 1. Number of agents that induce tumors in humans in each of 39 tumor sites, by type of agent.

site; of these, 13 are associated with exposure to chemical agents and related occupations and seven are in the category of arsenic, metals, fibers, and dusts. Tumors of the hematopoietic tissues are associated with exposure to 18 agents, urothelial with 18 agents, skin with 12 agents, and liver and bile duct with 11 agents. The category chemical agents and related occupations accounts for half (9 of 18) of the agents that induce urothelial tumors, and pharmaceuticals account for half (9 of 18) of the agents that produce tumors in hematopoietic tissues.

The number of agents that induce tumors in one or more animal species at each of the 39 tumor sites is presented in Figure 2 by type of agent. As in humans, lung tumors are the most common 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, fibers, and dusts (7 agents); and radiation (7 agents). After lung, the animal sites associated with the largest number of carcinogenic agents are liver parenchyma and bile ducts (19 agents), skin and adnexa (18 agents), lymphoid tissue (14 agents), breast (12 agents), and soft connective tissue (11 agents). Separate tumor profiles are shown for agents that initiate tumors in mice (48 agents) and rats (49 agents) in Figures 3 and 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 tumors in humans in each of the 14 aggregate organ and tissue systems is presented in Figure 5 by type of agent. Tumors of the respiratory system were induced by 31 of the 111 human carcinogens, predominantly from the categories of chemical agents and related occupations (14 agents) arsenic, metals, fibers, 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 compounds are lymphoid and hematopoietic tissues (26), the urothelium (18), and upper aerodigestive tract (16). Pharmaceuticals are the largest group of substances associated with tumors of the lymphoid and hematopoietic tissues (11 of 26 agents), and chemical agents and related occupations are most often associated with tumors of the urothelium (9 of 18 agents). Personal habits and indoor

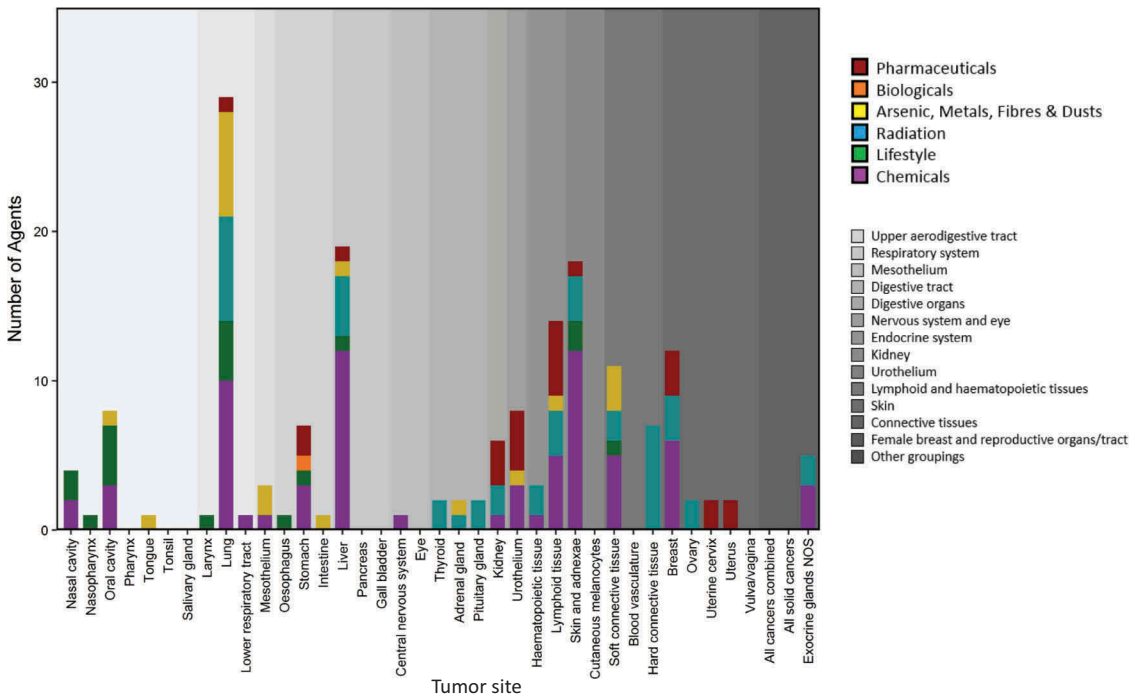

Figure 2. Number of agents that induce tumors in animals in each of 39 tumor sites, by type of agent.

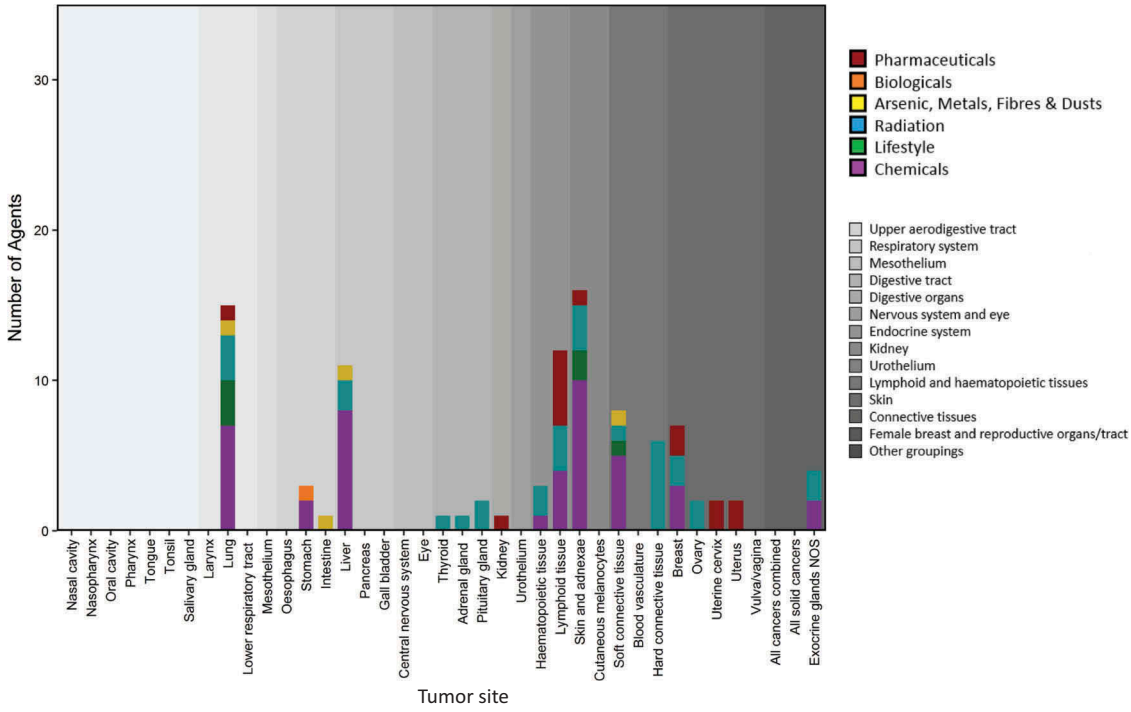

Figure 3. Number of agents that induce tumors in mice in each of 39 tumor sites, by type of agent.

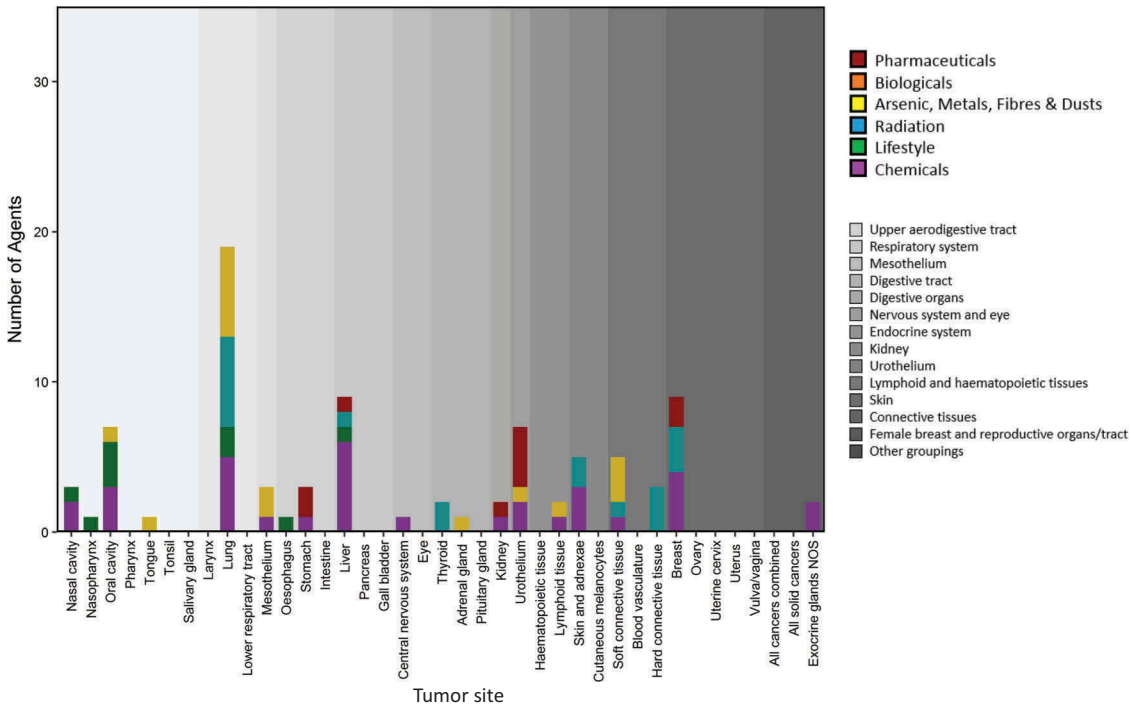

Figure 4. Number of agents that induce tumors in rats in each of 39 tumor sites, by type of agent.

combustions are most frequently associated with tumors of the upper aerodigestive tract (7 of 16 agents).

The number of agents that induce tumors in one or more animal species at each of the 14 organ and tissue systems is given in Figure 6 by type of agent. Tumors of the respiratory system are initiated by 29 of the 111 agents, mostly from the categories of chemical agents and related occupations (10 agents); arsenic, metals, fibers, and dusts

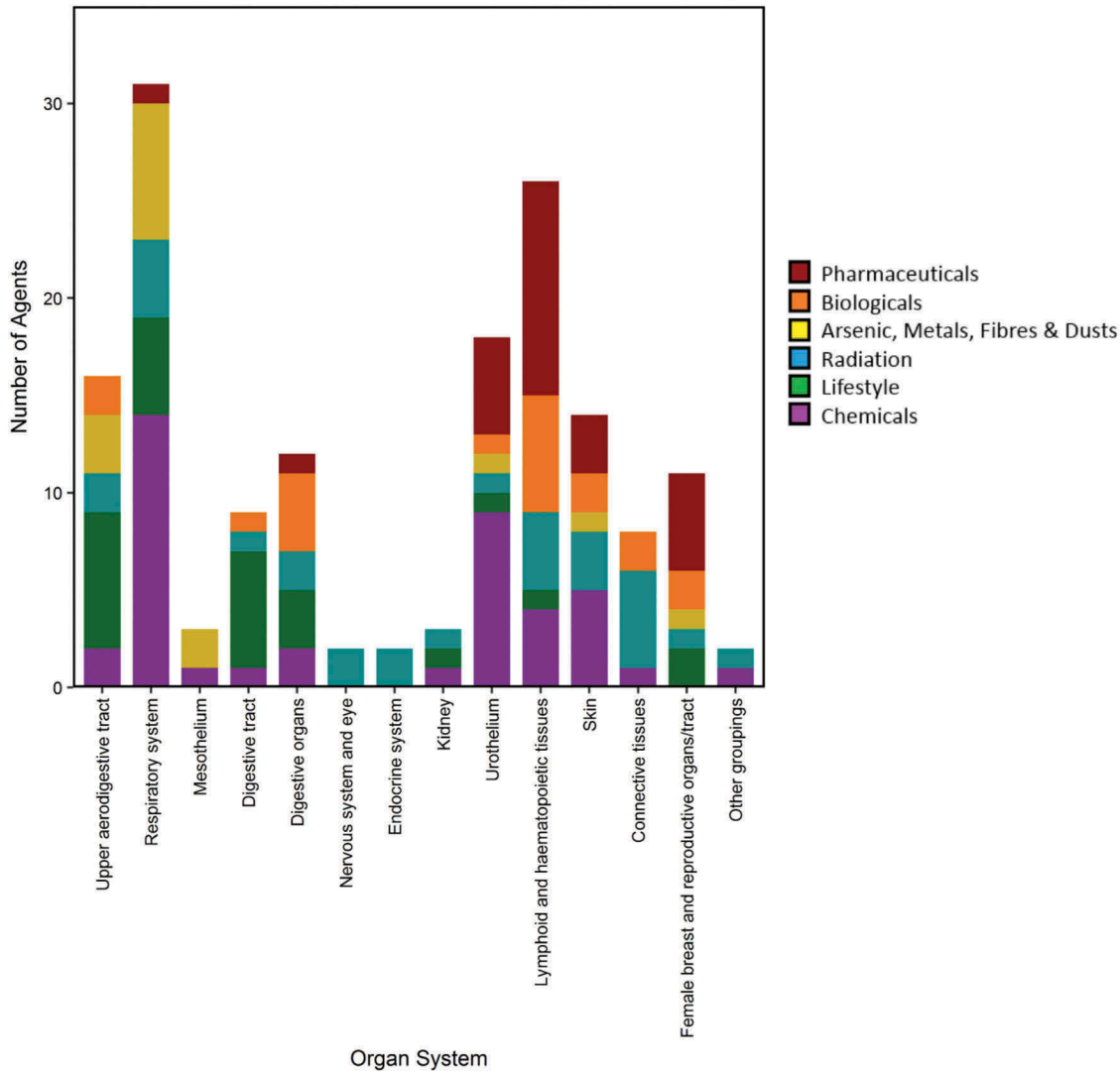

Figure 5. Number of agents that induce tumors in humans in each of 14 organ and tissue systems, by type of agent.

(7 agents), and radiation (7 agents). Tumors of the digestive organs are attributed to 19 agents, predominantly from the categories of chemical agents and related occupations (12 agents) and radiation (4 agents). Skin tumors are produced by 18 agents, mostly from the category of chemical agents and related occupations (12 agents). Connective tissue tumors are associated with 17 agents, predominantly from the categories of radiation (8 agents) and chemical agents and related occupations (5 agents).

In mice (Figure 7), tumors of the skin and connective tissues were attributed to 29 agents, consisting mostly of tumors induced by chemical agents and related occupations (14) and radiation (10). In rats (Figure 8), tumors of the respiratory system were initiated by 19 agents, including those in the categories of arsenic, metals, fibers, 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 1), for 60 agents both a human tumor site and an animal neoplastic site were identified, 15 agents displayed no human tumor site specified (Table 5), while 38 agents exhibited no animal tumor site identified (Table 6). Because two agents – etoposide and

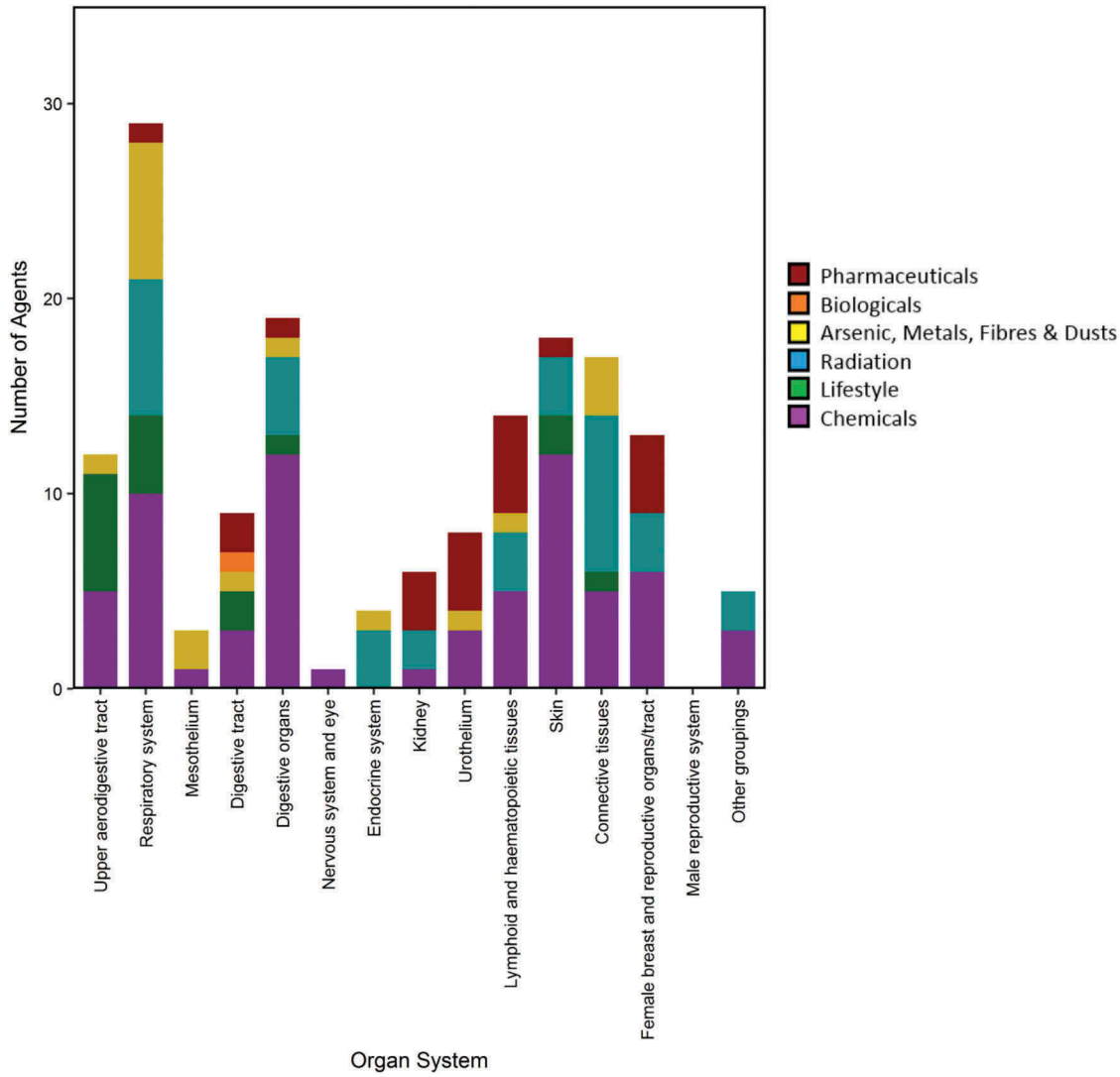

Figure 6. Number of agents that induce tumors in animals in each of 14 organ and tissue systems, by type of agent.

PeCDF – showed neither a human nor an animal tumor site specified, there are 111 − 15 − 38 + 2 = 60 agents with at least one tumor site identified in both humans and animals. These 60 agents were utilized to evaluate concordance between tumor sites seen in animals and humans because at least one tumor site was identified in both.

The overlap between human and animal tumor sites targeted by these 60 agents is summarized in Table 7 by organ and tissue system and tumor site. The category "other groupings" of tumors – which comprises "all cancers combined", "all solid cancers", and "exocrine glands not otherwise specified" – was created to accommodate tumor sites reported in the *IARC Monographs* that did not fall into any of the other categories in Table 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 tumors in hematopoietic tissue. Because this category lacks biological cohesiveness, "other groupings" of tumors were not considered in the concordance analysis.

Nine agents produced tumors of the upper aerodigestive tract in humans, and nine substances induced tumors in this organ and tissue system in animals; four compounds initiated tumors in this system in both humans and animals. There are 9 + 9 − 4 = 14 distinct agents that induce tumors in this system in either humans or animals, for an overlap of four of 14, or 29%. Within the upper aerodigestive tract, there are three agents that produced tumors in the nasal cavity and

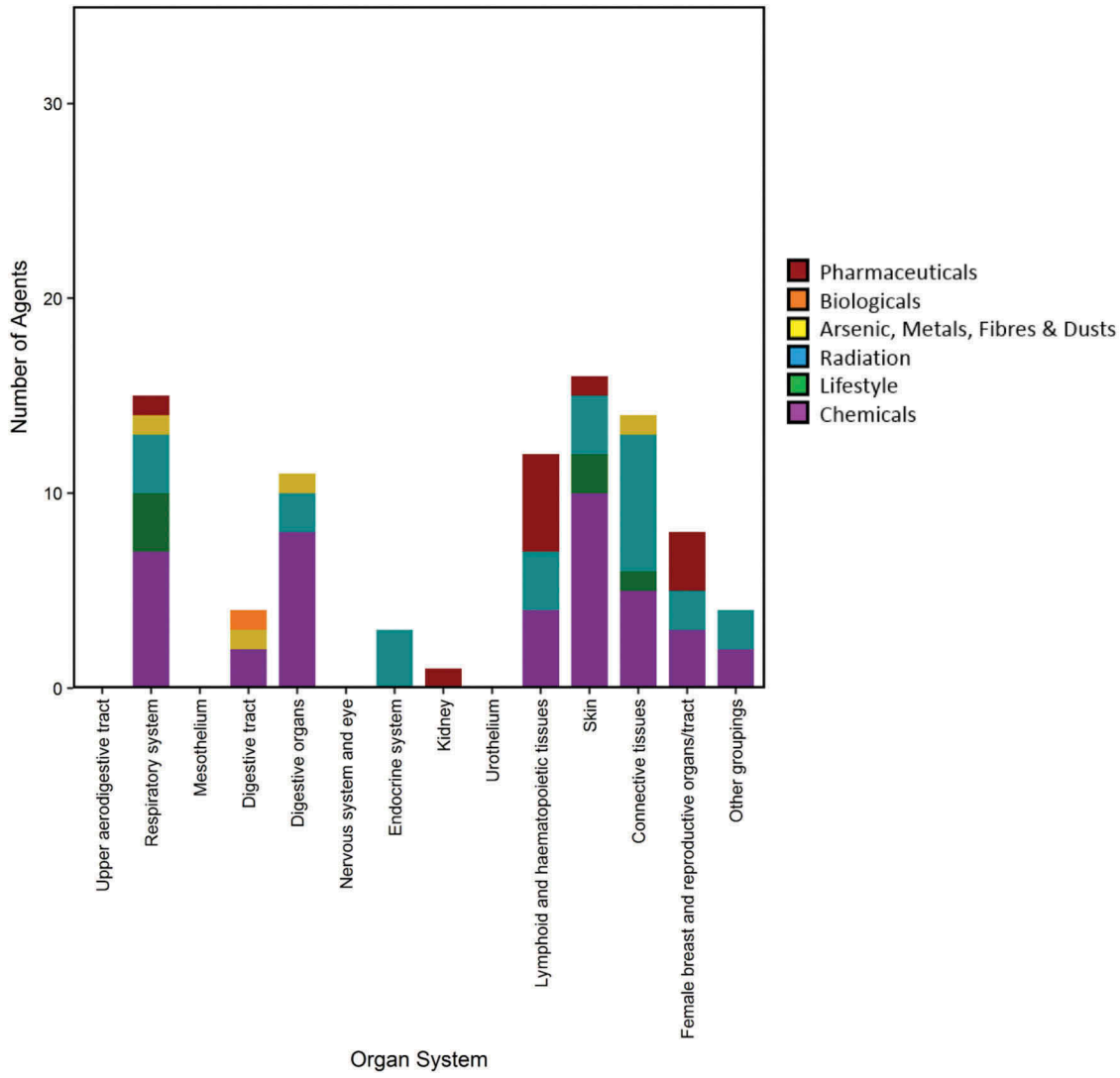

Figure 7. Number of agents that induce tumors in mice in each of 14 organ and tissue systems, by type of agent.

paranasal sinuses in humans and three agents that induced tumors at this site in animals, with no overlap. Of the three substances that induce tumors in the nasopharynx, one agent produced tumors in both humans and animals, for an overlap of 33%. In the oral cavity, overlap was 25%. Overlap is not calculated when there are no agents that initiate tumors in either humans or animals, as in the pharynx, tongue, and salivary gland.

The lung is the most frequent site at which tumors are observed, with 62% overlap among the 26 agents that are attributed to produce lung tumors in humans or animals. Among the ten compounds that induce urothelium neoplasms (renal pelvis, ureter, or bladder), there is 70% overlap between agents that initiate tumors in humans or animals.

Because results for individual tumor sites are often based upon small numbers, emphasis is placed upon interpretation of findings at the organ and tissue system level, where sample size is generally larger than for individual tumor sites within organ and tissue systems. Overlap varies among organ and tissue systems, ranging from 20% (based upon ten agents) in the digestive tract to 100% in the mesothelium. Overall, high overlap was noted for some organ and tissue systems but not for others. Some caution is needed in interpreting concordance at sites where sample size is particularly small. Although 100% concordance was noted for agents that induce mesothelial

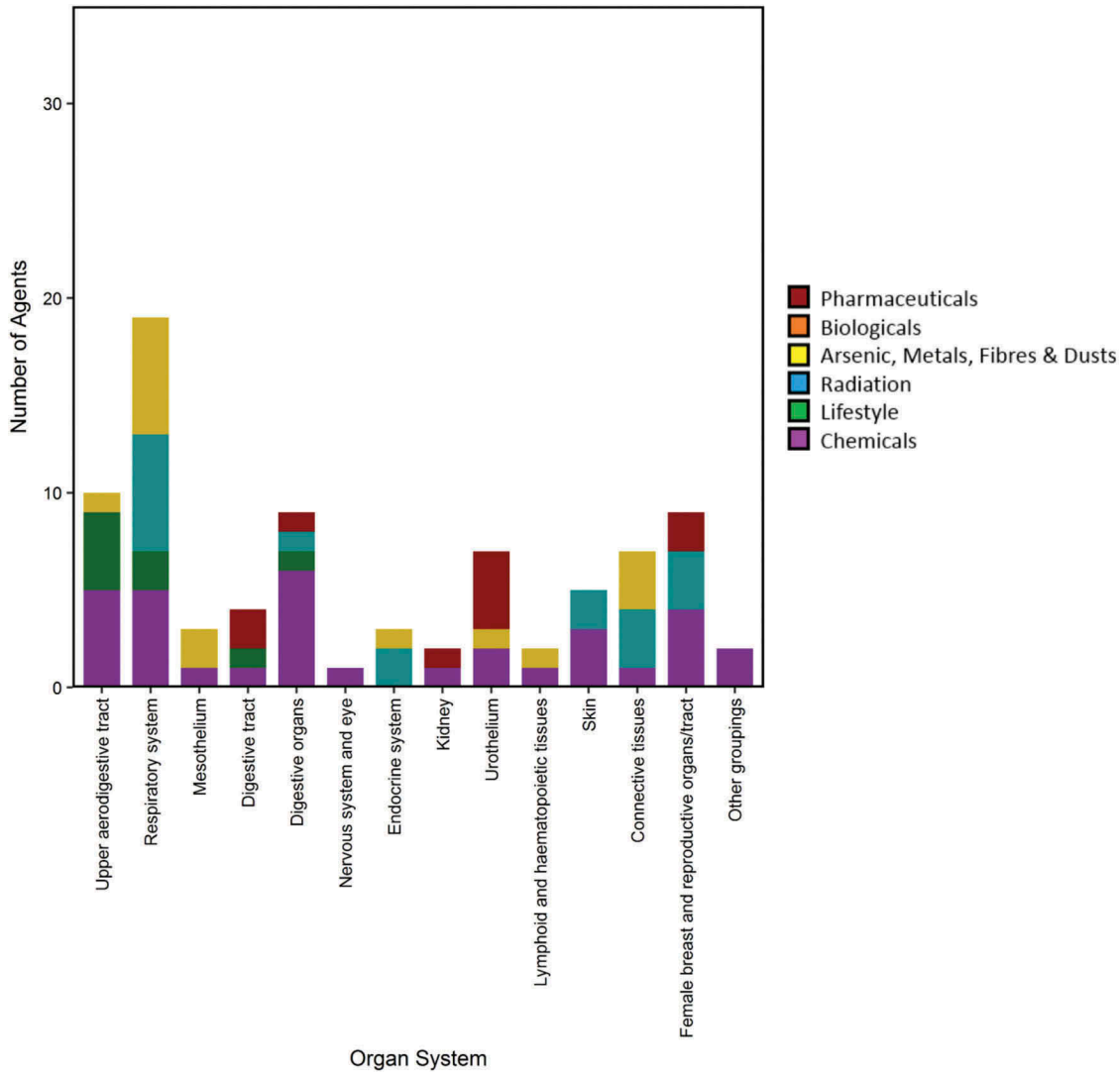

Figure 8. Number of agents that induce tumors in rats in each of 14 organ and tissue systems, by type of agent.

neoplasms, only two Group 1 agents – asbestos and erionite – met the criteria for inclusion in the concordance analysis caused tumors at this site.

The results in Table 7 are depicted in graphical form in Figure 9. As noted above, of the 14 Group 1 agents that induce tumors of the upper aerodigestive tract in either humans or animals, nine produced tumors in the upper aerodigestive tract in humans (and not in animals) and nine in this system in animals (and not in humans), while four induced tumors in this system in both humans and animals, for an overlap of 29%. Of the 27 agents that initiated respiratory system neoplasms in either humans or animals, 21 tumors occurred in humans, 22 in animals, and 16 in both humans and animals, for an overlap of 59%. Although the same data are presented in Table 7, the graphical representations of these results in Figure 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 7 are based upon concordance between tumor sites reported in humans and all animal species tested, reflecting the interest in evaluating the extent to which tumors induced by Group 1 agents occur in similar organ and tissue systems in humans and animals. The animal data included in this analysis are dominated by findings obtained in investigations with rats and mice: of the 60 Group 1 substances included in the

Table 7. Concordance between tumors seen in humans and animals for 60 Group 1 agents by organ and tissue system and tumor site.

Organ and tissue system[a] *Tumor site*[a]	Number of agents			
	Humans	Animals	Both	Overlap[b] (%)
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*
Lymphoid and hematopoietic tissues	12	10	7	47
Hematopoietic tissues	*10*	*2*	*2*	*20*
Lymphoid tissue	*2*	*10*	*1*	*9*
Skin	11	16	7	35
Skin and adnexa	*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 (38)	*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 tumor nomenclature system (see Table 2) that lack *sufficient evidence* in both humans and animals not shown. For example, there were insufficient data on tumors 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.

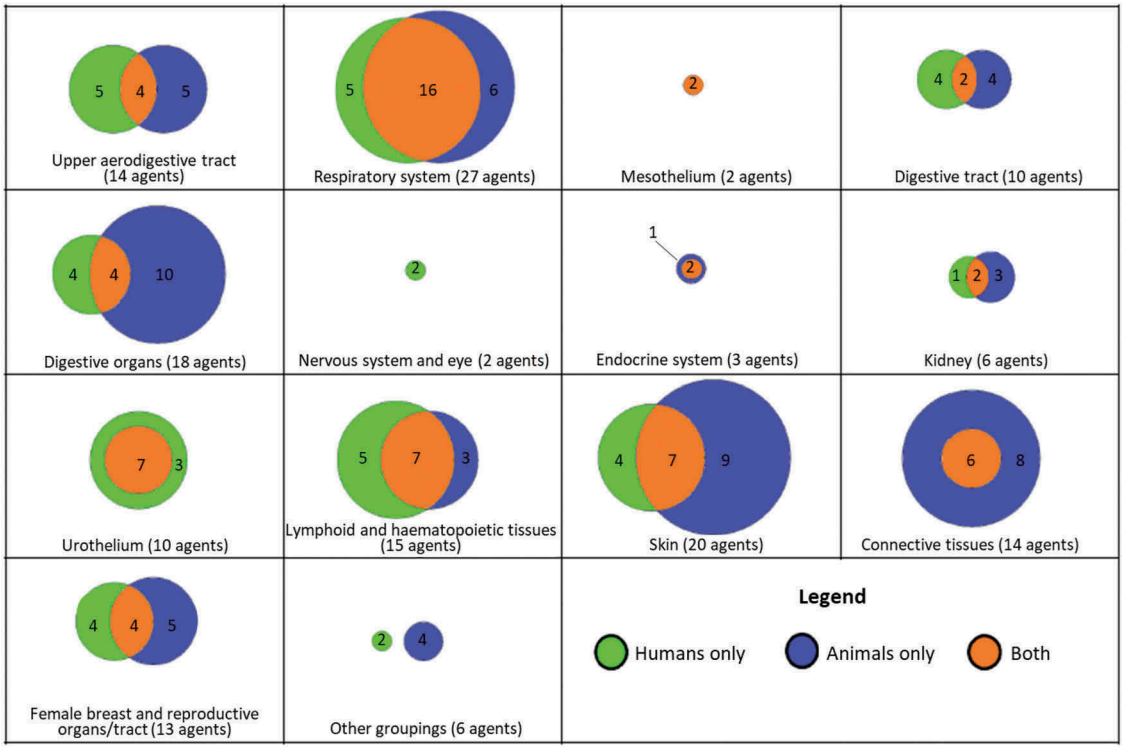

Figure 9. Concordance between tumor sites seen in humans and animals for 60 Group 1 agents by organ and tissue system.

analysis, 40, 38, 8, 7, and 3 compounds attributed to produce neoplasms in mice, rats, hamsters, dogs, and monkeys, respectively. Therefore, including only mice and rats in the analysis yielded observations similar to those in Table 7 (for further details, see Krewski et al. 2019a, Supplemental Material II, where Supplemental Table 6 presents results for all animal species tested and Supplemental Table 7 provides information for mice and rats only).

Figure 10 shows the % of Group 1 agents that induce tumors in specific organ and tissue systems in humans that are also associated with neoplasms in animals (panel A), as well as % substances agents that produce tumors in specific organ and tissue systems in animals that are also associated with carcinoma in humans (panel B). As explained in Krewski et al. (2019a, Supplemental Material II), it is important to note that the measures of

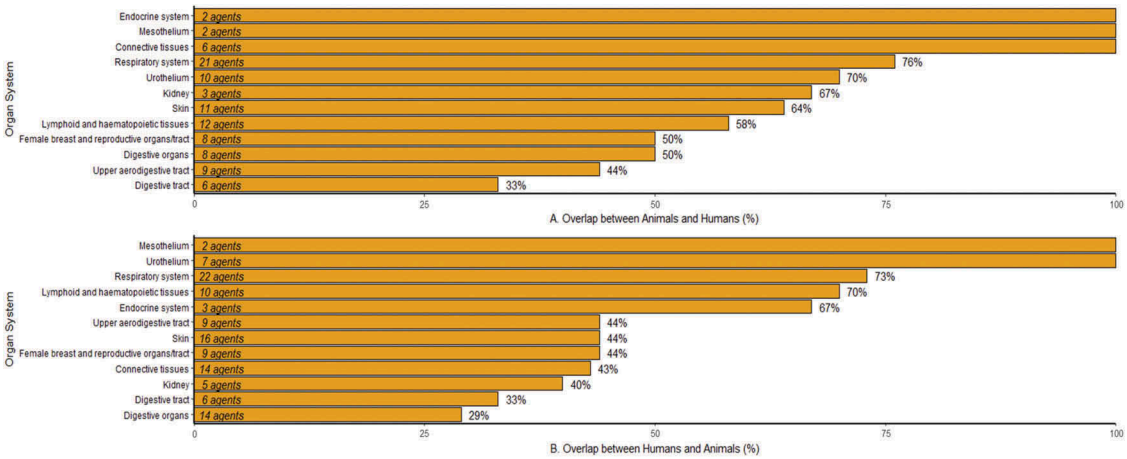

Figure 10. Overlap between Group 1 agents with *sufficient evidence* of carcinogenicity in humans and animals that cause tumors in specific organ and tissue systems. (A) Overlap between animals and humans; the number of Group 1 agents that cause tumors in specific organ and tissue systems in humans is shown. (B) Overlap between humans and animals; the number of Group 1 agents that cause tumors in specific organ and tissue systems in animals is shown.

concordance presented in Figure 10 differ from those in Table 7. The % overlap in Table 7 (and Figure 9) reflects the number of agents that initiate tumors in a specific organ and tissue system in *both* humans *and* animals, relative to the number of substances that induce neoplasms 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 % overlap in panel A of Figure 10 provides a measure of the overlap between agents that induce neoplasms in a specific organ and tissue system in animals with agents that produce tumors in that system in humans. Conversely, the % overlap in panel B of Figure 10 provides a measure of the overlap between agents that initiate neoplasms in a specific organ and tissue system in humans with agents that produce carcinoma in that system in animals. Note that unless the numbers of substances that induce tumors in humans and animals in a specific organ and tissue system are the same (as is the case for carcinoma of the upper aerodigestive tract), the results in panel A, where human carcinogens constitute the reference set against which animal carcinogens are compared, might differ from those in panel B, where animal carcinogens constitute the reference set for comparison with human carcinogens.

As indicated in panel A of Figure 10, all agents (100%) that induce tumors of the mesothelium, endocrine system, and connective tissues in humans also produce carcinoma 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 digestive tract (33%). Conversely, there is less overlap between substances that produce carcinoma in specific organ and tissue systems in animals with observations in humans (Figure 10, panel B), possibly reflecting the larger number of studies conducted in animals compared with humans, the broader spectrum of tissues (potential tumor sites) examined in animal experiments than in human investigations, or limitations associated with conduct of human studies at environmental exposure levels. As is the case with the concordance results focusing on overall overlap, as presented in Table 7, caution is needed in interpreting findings where there are few agents for comparison as in Figure 10 (both panels A and B).

The 60 agents included in the present concordance analysis are listed in Table 8. This table presents the tumor site data for humans and animals at the organ and tissue system level only, because data for individual tumor sites are too sparse to support meaningful comparisons. The human data are presented in the column on the left, animal data on the right, and overlap in the middle. With this display, potential relationships among agents that induce carcinoma 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 seen both for individual and for groups of substances. Of the 60 agents for which there is *sufficient evidence* of carcinogenicity in at least one tumor site in both humans and animals, 52 (87%) produced tumors within at least one of the same organ and tissue systems in Table 8.

To permit a more complete comparison between animal and human tumor sites, tumor sites with only *limited evidence* in humans are included in Table 8 (in *italics*). For agents such as diethylstilbestrol (DES) (a synthetic nonsteroidal 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. Since men exposed to DES *in utero* 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 remains limited for this end-point, although supported by induction of testicular carcinoma in rodents.

With ongoing studies, more evidence can be gathered that provides increasing certainty regarding potential cancer risks to humans. Although IARC previously evaluated TCE in 1979, 1987, and 1995, this substance was not declared to be *carcinogenic to humans* – producing kidney cancer – until 2012, after the emergence of new data (IARC 2014). Although it was noted that a positive association was observed between liver cancer and exposure to TCE, 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

Table 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)	Alcoholic beverages (100E)	Chromium(VI) (100C)
Nickel compounds (100C)	Salted fish, Chinese-style (100E)	Alcoholic beverages (100E)
Radium-226 and decay products (100D)	Tobacco, smokeless (100E)	Salted fish, Chinese-style (100E)
X- and γ-radiation (100D)	Formaldehyde (100F)	Tobacco, smokeless (100E)
Radioiodines, including iodine-131(100D)	*Chromium(VI) compounds (100C)*	Formaldehyde (100F)
Betel quid without tobacco (100E)		Benzene (100F)
Alcoholic beverages (100E)		2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (100F)
Salted fish, Chinese-style (100E)		Polychlorinated biphenyls (100F)
Second-hand tobacco smoke (100E)		Bis(chloromethyl)ether; Chloromethyl methyl ether (100F)
Tobacco, smokeless (100E)		
Tobacco smoking (100E)		
Formaldehyde (100F)		
Respiratory system (59% overlap)		
Arsenic and inorganic arsenic compounds (100C)	Arsenic and inorganic arsenic compounds (100C)	Cyclophosphamide (100A)
Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite) (100C)	Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite) (100C)	Arsenic and inorganic arsenic compounds (100C) Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite) (100C)
Beryllium and beryllium compounds (100C)	Beryllium and beryllium compounds (100C)	Beryllium and beryllium compounds (100C)
Cadmium and cadmium compounds (100C)	Cadmium and cadmium compounds (100C)	Cadmium and cadmium compounds (100C)
Chromium(VI) compounds (100C)	Chromium(VI) compounds (100C)	Chromium(VI) compounds (100C)
Nickel compounds (100C)	Nickel compounds (100C)	Nickel compounds (100C)
Silica dust, crystalline, in the form of quartz or cristobalite (100C)	Silica dust, crystalline, in the form of quartz or cristobalite (100C)	Silica dust, crystalline, in the form of quartz or cristobalite (100C)
Haematite mining with exposure to radon (underground) (100D)	Haematite mining with exposure to radon (underground) (100D)	Haematite mining with exposure to radon (underground) (100D)
Plutonium-239 (100D)	Plutonium-239 (100D)	Plutonium-239 (100D)
Radon-222 and its decay products (100D)	Radon-222 and its decay products (100D)	Radon-222 and its decay products (100D)
X- and γ-radiation (100D)	X- and γ-radiation (100D)	X- and γ-radiation (100D)
Alcoholic beverages (100E)	Coal, indoor emissions from household combustion of (100E)	Coal, indoor emissions from household combustion of (100E)
Coal, indoor emissions from household combustion of (100E)	Second-hand tobacco smoke (100E)	Second-hand tobacco smoke (100E)
Second-hand tobacco smoke (100E)	Tobacco smoking (100E)	Tobacco smoking (100E)
Tobacco smoking (100E)	Coke production (100F)	Benzene (100F)
Bis(chloromethyl)ether; Chloromethyl methyl ether (technical grade) (100F)	Engine exhaust, diesel (100F)	1,3-Butadiene (100F)
Coal gasification (100F)	2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (100F)	Coke production (100F)
Coal-tar pitch (100F)		Vinyl chloride (100F)
Coke production (100F)		Engine exhaust, diesel (100F*)
Soot (as found in occupational exposure of chimney sweeps) (100F)		2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (100F*)
2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (100F)		Trichloroethylene (100F*)
Engine exhaust, diesel (100F)		
Mesothelium (100% overlap)		
Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite) (100C)	Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite) (100C)	Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite) (100C)
Erionite (100C)	Erionite (100C)	Erionite (100C)
Digestive tract (20% overlap)		

(*Continued*)

Table 8. (Continued).

Humans[b] Agent (*Monographs* Volume[c])	Humans and animals[b] Agent (*Monographs* Volume)	Animals[b] Agent (*Monographs* Volume)
Helicobacter pylori (infection with) (100B)	*Helicobacter pylori* (infection with) (100B)	Aristolochic acid, plants containing (100A)
X- and γ-radiation (100D)	Betel quid without tobacco (100E)	*Helicobacter pylori* (infection with) (100B)
Radioiodines, including iodine-131 (100D)		Chromium(VI) compounds (100C)
Alcoholic beverages (100E)		Betel quid without tobacco (100E)
Betel quid without tobacco (100E)		Benzene (100F)
Salted fish, Chinese-style (100E)		1,3-Butadiene (100F)
Tobacco smoking (100E)		
Tobacco, smokeless (100E)		
Digestive organs (22% overlap)		
Estrogen–progestogen oral contraceptives (combined) (100A)	Arsenic and inorganic arsenic compounds (100C)	Tamoxifen (100A)
Arsenic and inorganic arsenic compounds (100C)	Plutonium-239 (100D)	Arsenic and inorganic arsenic compounds (100C)
Thorium-232 (as Thorotrast) (100D)	Thorium-232 (as Thorotrast) (100D)	Thorium-232 (as Thorotrast) (100D)
Plutonium-239 (100D)	X- and γ-radiation (100D)	Plutonium-239 (100D)
X- and γ-radiation (100D)	Aflatoxins (100F)	X- and γ-radiation (100D)
Alcoholic beverages (100E)	Vinyl chloride (100F)	Aflatoxins (100F)
Betel quid without tobacco (100E)	Trichloroethylene (100F*)	4-Aminobiphenyl (100F)
Tobacco smoking (100E)		Benzidine (100F)
Tobacco, smokeless (100E)		1,3-Butadiene (100F)
Aflatoxins (100F)		2-Naphthylamine (100F)
Vinyl chloride (100F)		2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (100F)
Trichloroethylene (100F)*		Vinyl chloride (100F)
		Trichloroethylene (100F*)
		Polychlorinated biphenyls (100F)
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)	Radioiodines, including iodine-131 (100D)	Nickel compounds (100C)
X- and γ-radiation (100D)	X- and γ-radiation (100D)	Radioiodines, including iodine-131 (100D)
		X- and γ-radiation (100D)
Kidney (33% overlap)		
Arsenic and inorganic arsenic (100C)	X- and γ-radiation (100D)	Diethylstilbestrol (100A)
Cadmium and cadmium compounds (100C)	Trichloroethylene (100F*)	Estrogen-only menopausal therapy (100A)
X- and γ-radiation (100D)		Phenacetin (100A)
Tobacco smoking (100E)		X- and γ-radiation (100D)
Trichloroethylene (100F*)		Trichloroethylene (100F*)
Urothelium (70% overlap)		
Aristolochic acid, plants containing (100A)	Aristolochic acid, plants containing (100A)	Aristolochic acid, plants containing (100A)
Cyclophosphamide (100A)	Cyclophosphamide (100A)	Cyclophosphamide (100A)
Phenacetin (100A)	Phenacetin (100A)	Phenacetin (100A)
Arsenic and inorganic arsenic compounds (100C)	Arsenic and inorganic arsenic compounds (100C)	Arsenic and inorganic arsenic compounds (100C)
X- and γ-radiation (100D)	4-Aminobiphenyl (100F)	2-Naphthylamine (100F)
Tobacco smoking (100E)	2-Naphthylamine (100F)	4-Aminobiphenyl (100F)
Coal-tar pitch (100F)	*ortho*-Toluidine (100F)	*ortho*-Toluidine (100F)

(*Continued*)

Table 8. (Continued).

Humans[b] Agent (*Monographs* Volume[c])	Humans and animals[b] Agent (*Monographs* Volume)	Animals[b] Agent (*Monographs* Volume)
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)*		
Lymphoid and hematopoietic tissues (47% overlap)		
Azathioprine (100A)	Azathioprine (100A)	Azathioprine (100A)
Chlorambucil (100A)	Chlorambucil (100A)	Chlorambucil (100A)
Cyclophosphamide (100A)	Cyclophosphamide (100A)	Cyclophosphamide (100A)
Thiotepa (100A)	Thiotepa (100A)	Estrogen-only menopausal therapy (100A)
Helicobacter pylori (infection with) (100B)	X- and γ-radiation (100D)	Thiotepa (100A)
Fission products including strontium-90 (100D)	Benzene (100F)	Silica dust, crystalline, in the form of quartz or cristobalite (100C)
Thorium-232 (as Thorotrast) (100D)	1,3-Butadiene (100F)	X- and γ-radiation (100D)
X- and γ-radiation (100D)	2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (100F)	Ethylene oxide (100F)
		Benzene (100F)
		1,3-Butadiene (100F)
		2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (100F)
Skin (35% overlap)		
Azathioprine (100A)	Methoxsalen in combination with UVA (100A)	Methoxsalen in combination with UVA (100A)
Methoxsalen in combination with UVA (100A)	Solar radiation (100D)	Solar radiation (100D)
Arsenic and inorganic arsenic compounds (100C)	UV-emitting tanning devices (100D)	UV-emitting tanning devices (100D)
Solar radiation (100D)	Coal-tar distillation (100F)	Coal, indoor emissions from household combustion of (100E)
UV-emitting tanning devices (100D)	Mineral oils, untreated or mildly treated (100F)	Tobacco smoking (100E)
X- and γ-radiation (100D)	Shale oils (100F)	Benzene (100F)
Coal-tar distillation (100F)	Soot (as found in occupational exposure of chimney sweeps) (100F)	Bis(chloromethyl)ether; Chloromethyl methyl ether (technical grade) (100F)
Mineral oils, untreated or mildly treated (100F)		Coal gasification (100F)
Shale oils (100F)		Coal-tar distillation (100F)
Soot (as found in occupational exposure of chimney sweeps) (100F)		Coal-tar pitch (100F)
Polychlorinated biphenyls (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)
Connective tissues (43% overlap)		
Plutonium-239 (100D)	Plutonium-239 (100D)	Cadmium and cadmium compounds (100C)
Radium-224 and its decay products (100D)	Radium-224 and its decay products (100D)	Chromium(VI) compounds (100C)
Radium-226 and its decay products (100D)	Radium-226 and its decay products (100D)	Nickel compounds (100C)
Radium-228 and its decay products (100D)		Fission products including strontium-90 (100D)
		Plutonium-239 (100D)

(*Continued*)

Table 8. (Continued).

Humans[b] Agent (*Monographs* Volume[c])	Humans and animals[b] Agent (*Monographs* Volume)	Animals[b] Agent (*Monographs* Volume)
X- and γ-radiation (100D)	Radium-228 and its decay products (100D)	Radium-224 and its decay products (100D)
Radioiodines, including iodine-131 (100D)	X- and γ-radiation (100D)	Radium-226 and its decay products (100D)
Vinyl chloride (100F)	Vinyl chloride (100F)	Radium-228 and its decay products (100D)
2,3,7,8-Tetrachlorodibenzo-para-*dioxin (100F)*		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)	Diethylstilbestrol (100A)	Cyclophosphamide (100A)
Estrogen-only menopausal therapy (100A)	Estrogen-only menopausal therapy (100A)	Diethylstilbestrol (100A)
Estrogen–progestogen oral contraceptives (combined) (100A)	Estrogen–progestogen oral contraceptives (combined) (100A)	Estrogen-only menopausal therapy (100A)
Tamoxifen (100A)	X- and γ-radiation (100D)	Estrogen–progestogen oral contraceptives (combined) (100A)
Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite) (100C)		X- and γ-radiation (100D)
		Benzene (100F)
X- and γ-radiation (100D)		Benzidine (100F)
Alcoholic beverages (100E)		1,3-Butadiene (100F)
Tobacco smoking (100E)		Vinyl chloride (100F)
Ethylene oxide (100F)		
Polychlorinated biphenyls (100F)*		
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]		X- and γ-radiation (100D) [exocrine glands NOS]
		Benzene (100F) [exocrine glands NOS]
Fission products including strontium-90 (100D) [all solid cancers]		1,3-Butadiene (100F) [exocrine glands NOS]
		Vinyl chloride (100F) [exocrine glands NOS]
Plutonium-239 (100D)		

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 tumor nomenclature system (see Supplemental Table 1. Animal and human tumor site 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 tumor 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 tumors in either humans or animals (or both) in the specified organ and tissue system (see Table 7).

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 limited data for TCE-induced liver cancer in humans enables the observation of overlap between animals and humans for this end-point.

This example illustrates that inclusion of agents with *limited evidence* of carcinogenicity in humans enhances the ability to identify concordant relationships. Comparison between Table 7, which mentions only sites with sufficient evidence in humans, and Table 8, which also lists sites with *limited evidence* in humans, illustrates increased coherence, when limited human data are considered, among substances that exhibit similar chemical and mechanistic characteristics. For example, if the *limited evidence* of tumors of the upper aerodigestive tract for chromium(VI) compounds in humans noted in Table 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 elevated if less stringent criteria are applied than those used by IARC for determining *sufficient evidence* of carcinogenicity in animals. For example, in evaluating 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 DES (IARC 2012e) notes: "The oral administration of diethylstilbestrol induced tumors of the ovary, endometrium, and cervix, and mammary adenocarcinomas in female mice. Osteosarcomas and Leydig cell tumors were induced in rasH2 [transgenic] and Xpa/p53 [knockout] male mice, respectively. Subcutaneous implantation of DES induced mammary tumors in female Wistar rats. Perinatal exposure to DES initiated lymphoma, uterine sarcomas, adenocarcinomas, and pituitary, vaginal, and ovarian tumors in female mice. Uterine adenocarcinomas and mammary and vaginal tumors were also induced in female rats. In hamsters, DES perinatal exposure induced kidney tumors.

Although agents affecting male reproductive organs are included in Table 8, these are not part of the concordance analyses in Table 7, because of a lack of *sufficient evidence* in either humans or animals. TCDD is included in Table 8, but its designation as a chemical affecting "all cancers combined" in humans precludes site-specific tumor 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 enhanced site concordance by applying less stringent criteria than those utilized for concordance analysis presented in Table 7.

Table 8 shows human data indicating biological plausibility for 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). Lymphohematopoietic cancers are a consistent end-point for antineoplastic alkylating compounds that induce these cancers after their use in chemotherapy to eradicate other neoplasms (IARC 2012e), for radioactive materials (IARC 2012f), and for several chemical and related compounds that are metabolized to or are in themselves agents that are reactive with DNA (IARC 2012c).

Table 8 also illustrates some of the potential relationships between agents that may act in a similar fashion in humans. Tobacco smoke and its related substances (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 initiate a variety of DNA lesions and other effects reflected by the key characteristics of human carcinogens (Krewski et al. 2019b; 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 including PCBs, DES, estrogen-

only menopausal therapy, combined estrogen–progestogen oral contraceptives, and tamoxifen induce cancer at similar sites, including the female reproductive organs and mammary tissue. Metals appear to have many target sites in common, including upper aerodigestive tract, respiratory system, kidney, and prostate.

As noted previously, the animal database is predominantly populated by results from studies in rodents. Respiratory tract tumors are induced in rodents by many of the same substances that produce carcinoma in humans. For the mesothelium, where tumor 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 chemicals metabolized in the liver to reactive compounds induce liver cancer in animal models, with less apparent overlap with human data (see digestive organs, Table 8). Susceptibility of the liver in rodents to cancer induction is species-, gender-, and strain-specific and varies widely. Nonetheless, all compounds that induce liver cancer in rodents produce carcinoma at some other site in humans. In some instances, the apparent lack of overlap between animal and human databases may still reflect mechanistic concordance for similar agents. Dyes such as magenta, 4-aminobiphenyl, benzidine, and 2-naphthylamine all produce liver cancer in rodents and urothelial carcinomas in humans. TCDD and PCBs are both associated with liver neoplasms in rodents and with tumors of the lymphoid and hematopoietic tissues in humans.

Human exposures to DES, 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 DES 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 finding (IARC 2012e). Although there appears to be concordance in rodents for tumors induced by these agents, there does not appear to be overlap with humans with respect to rodent kidney versus female breast and reproductive organs. However, there may be mechanistic concordance between these two endpoints, because both DES 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 DES are catechols that readily 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, DES and estrogen may display MOA 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 met the IARC criteria for determining causality and for designation of these substances as *carcinogenic to humans* (Group 1). Of these, 111 distinct Group 1 agents were included in the dataset of tumors and tumor sites in animals and humans developed by Grosse et al. (2019).

The well-established WOE criteria for assessment of available human, animal, MOA, 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 may be reasonably inferred, and this might be strengthened by MOA considerations.

However, an immediate challenge in making comparisons for tumor site concordance between species was how to compare tumors in animals and humans. A detailed historical discussion of approaches to the coding of human tumors 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 tumors, an anatomically based tumor taxonomy system was developed during the course of the review 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 Zymbal gland. Tumors at these unique sites occurred rarely and were included within the category of "other groupings" in the anatomically based tumor 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 tumor site; for example, the forestomach was considered as part of the stomach in the anatomically based taxonomy system.

This system includes 39 individual tumor 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 enabled comparisons to be made at a higher level of organization, reflecting anatomical and physiological similarities among certain tumor sites; for example, the lung and lower respiratory tract are considered together as the respiratory system. Aggregation also enables more data to be considered for analysis, which increases the robustness of the ensuing conclusions. For the concordance analyses, data at both the individual tumor site level and organ and tissue system level were examined.

Although the present analysis demonstrates generally good agreement between tumor sites in animals and in humans after exposure to Group 1 carcinogens, concordance was not demonstrated with every agent and tumor site. There are several factors and important limitations that may result in lack of tumor concordance based upon 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 substances, notably human tumor 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 MOA of the chemical of interest was specific to humans and not easily replicated in an experimental animal model. Animal studies may also show tumors that are species- and/or gender-specific.

As part of the determination of WOE, agents that induce tumors 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 induced tumors in humans and in four animal species (mice, rats, hamsters, and non-human primates): asbestos, which produces lung carcinoma in all five species; plutonium-239, which initiates skin tumors in these species; and 2-naphthylamine, which induces urinary tract/uroendothelial neoplasms in these species. These substances are examples of carcinogens that induce the same type of tumor in multiple species, thereby demonstrating a high degree of interspecies tumor site concordance.

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

cancer mechanisms than for human cancer risk assessment.

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 tumor sites for agents with only *limited evidence* of carcinogenicity in animals. The criteria developed by Grosse et al. (2019) (Annex, 1) further restrict the use of tumor data for agents with *sufficient evidence* in experimental animals (e.g., tumor sites were not identified in the absence of two or more animal studies of adequate design and quality indicative of the same tumor site with a similar histological origin in the same species). Although melphalan produced tumors of the forestomach, skin, and lung as well as lymphosarcomas in mice and mammary gland tumors and peritoneal sarcomas in rats (IARC 2012c), none of these tumor sites were replicated in a second animal species, and hence are not included in the dataset of Grosse et al. (2019).

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 DES. The absence of *sufficient evidence* in humans may be due to a lack of evidence in appropriate epidemiological or clinical investigations, or to the inability of existing studies to detect an association between exposure to the compound of interest (including exposures early or later in life) and a tumor 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 investigation would be required to achieve reasonable sensitivity.

Failure of human studies to identify tumor sites might occur when these investigations do not consider all possible sites. Most case–control studies focus on only one or a limited number of tumor sites. Human investigations that fail to identify a relevant tumor site may exhibit low sensitivity, possibly because they do not focus on the most appropriate study population. As noted above for TCE, evidence on specific tumor 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 produce cancer at a larger number of tumor sites, including cancers of nasal cavities and nasal sinuses, esophagus, stomach, liver, kidneys, and uterine cervix, and myeloid leukemia (IARC 2004). Thus, the potential for underestimation of interspecies tumor site concordance may result from missing tumor sites for substances 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 tumor site concordance. A specific example of this constraint is ionizing radiation. No specific human tumor 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 tumor site for UV radiation in Volume 100D, skin is implicitly suggested as being a human tumor site for this agent. In the present analysis, the lack of explicit designation of skin as a human tumor 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 tumor 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 MOA by which the substance induces cancer in animals also operates in humans. Such "mechanistic upgrades" 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).

Exposure assessment is one of the most difficult aspects of epidemiological investigations (Nieuwe nhuijsen et al., 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 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 investigations 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 dataset assembled and evaluated by Grosse et al. (2019) was retrieved from the *IARC Monographs*. Thus, these agents do not represent a "random sample" of all potential human carcinogens, and the dataset is populated by 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 might 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.

In addition to the restrictions used by Grosse et al. (2019) for inclusion of certain experimental animal data, other limitations of the database affect the ability to determine tumor site concordance, including incomplete information on tumor histology, limited information on the effects of gender, strain, and route of exposure, and limited information on dose-dependent effects. These and other limitations are discussed briefly below.

Incomplete information on tumor 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 tumors 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 upon 39 tumor sites or on the broader classification of 14 organ and tissue systems.

Effects of gender, strain, and route of exposure

Risks of cancer may 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 employed in the present analysis, it was not possible to evaluate how concordance might vary by gender, strain, or exposure route.

Effects of dose

Because the primary objective of the *IARC Monographs Programme* is to identify agents with potential to induce 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 hemangiosarcomas of the heart, malignant lymphomas, bronchiol-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 MOA 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 tumor sites seen in animals and humans. Although more formal statistical analyses of concordance as described in Krewski et al. (2019a, Supplemental Material II) were considered during the course of this investigation, the consensus of the Working Group was to represent concordance in terms of the simpler, more directly interpretable, indicators of "overlap" in Table 7 and Figure 10.

Small sample size

After the 111 Group 1 agents tabulated by Grosse et al. (2019). (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 tumor site in humans and at least one tumor site in animals, 60 agents remained eligible for concordance analysis. Because the sample size for some tumor sites is small (only two agents – asbestos and erionite – produced mesothelial tumors), caution is needed in interpreting the concordance results presented in this review 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 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 review. This is because both PPV and NPV depend upon prevalence of true positives in the database (Altman and Bland 1994). Since the IARC concordance database comprises Group 1 agents that are attributed to initiate cancer in humans, the PPV of animal cancer tests might artificially be calculated as 100%, whereas a lower PPV may be obtained with a more representative database that includes substances that do not produce cancer in humans. However, identifying agents that do not induce 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 substances were placed in Group 1 because the MOA by which tumors 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 regarding the likelihood of positive results in animals among the Group 1 agents that were found to induce cancer in humans. Excluding mechanistic

upgrades (nine agents) and Group 1 agents that lack appropriate animal data (20 substances), *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

Despite the challenges in evaluating concordance between tumor sites in animals and humans, the IARC concordance database is a useful source of information for comparing animal and human data with respect to tumors induced 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 tumors detected in animal and human studies, possibly using the anatomically based tumor nomenclature system introduced in this review to facilitate comparisons between animals and humans. Data on route of exposure, gender, and animal strain would also support comparisons of animal and human tumors at a finer level of biological resolution. Data on the exposure or dose levels at which tumors are observed in animals and humans would further support evaluation of the relative carcinogenic potency of agents evaluated in animals and humans. Information on tumor sites affected by agents evaluated within the *IARC Monographs Programme* needs to be recorded in as much detail as possible to facilitate future evaluations of concordance between tumors identified in animals and humans on a site-specific basis.

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