Animal and Human Tumour Site Concordance

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Research Triangle Park, North Carolina
January 7, 2014

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IARC Group 1 Agents

Group 1 Agents Identified by the International Agency for Research on Cancer

V100	Class of Agent	No of Agents	Additional Volumes V105	V106	V107	V109	Total
A	Pharmaceuticals	23					23
B	Biological agents	11					11
C	Arsenic, metals, fibres and dusts	10					10
D	Radiation	18					18
E	Personal habits and indoor combustions	12					12
F	Chemical agents and related occupations	33	1[a]	1[b]	2[c]	2[d]	39
Total		**107**					**113**

[a]Trichloroethylene

[b]Diesel Exhaust

[c]Polychlorinated biphenyls (PCBs) and Dioxin-like PCBs

[d]Outdoor air pollution and particulate matter from outdoor air pollution

Tumour Site Concordance Database

- Currently includes 95 Group 1 agents identified through Volume 106, excluding 11 biological agents and ‘all radiation’

- Includes tumour sites for which there is *sufficient evidence of carcinogenicity* in humans (12 agents placed in Group 1 without sufficient evidence in humans through ‘mechanistic upgrades’)

- Includes tumour sites for which there is *sufficient evidence of carcinogenicity* in animals (25 agents do not have sufficient evidence in animals according to IARC weight of evidence criteria)

Coding of Tumours Occurring in Animals and Humans

Coding of Tumours Occurring in Animals and Humans (1 of 2)

Organ System	Sites Coded from Volume 100 (A,B,C,D,E and F*)
Upper aerodigestive tract and respiratory system	Larynx
	Lip
	Lower respiratory tract (larynx& trachea& lung)
	Lung
	Mesothelium
	Nose
	Oral cavity
	Pharynx
	Tongue
Digestive system	Bile ducts (intrahepatic & extrahepatic)
	Digestive tract
	Gallbladder
	Liver
	Pancreas
	Salivary gland
Nervous and endocrine systems	Adrenal gland NOS
	Adrenal medulla
	CNS
	Eye
	Pituitary gland
	Thyroid
Urinary system	Kidney
	Urinary tract/urothelium

Coding of Tumours Occurring in Animals and Humans (2 of 2)

Organ System	Sites Coded from Volume 100 (A,B,C,D,E and F*)
Lymphoid and hematopoietic systems	Haematopoietic tissue Leukaemia NOS Lymphoid tissue
Skin and connective tissues	Hard connective tissue Skin Soft connective tissue
Female breast, and female reproductive organs and reproductive tract	Breast Endometrium Lower reproductive tract Ovary Uterus
Male reproductive system	Prostate Testis
Other groupings	All cancers combined Solid cancers Solid tumours aside from lung

39 tumour sites
9 organ and tissue systems

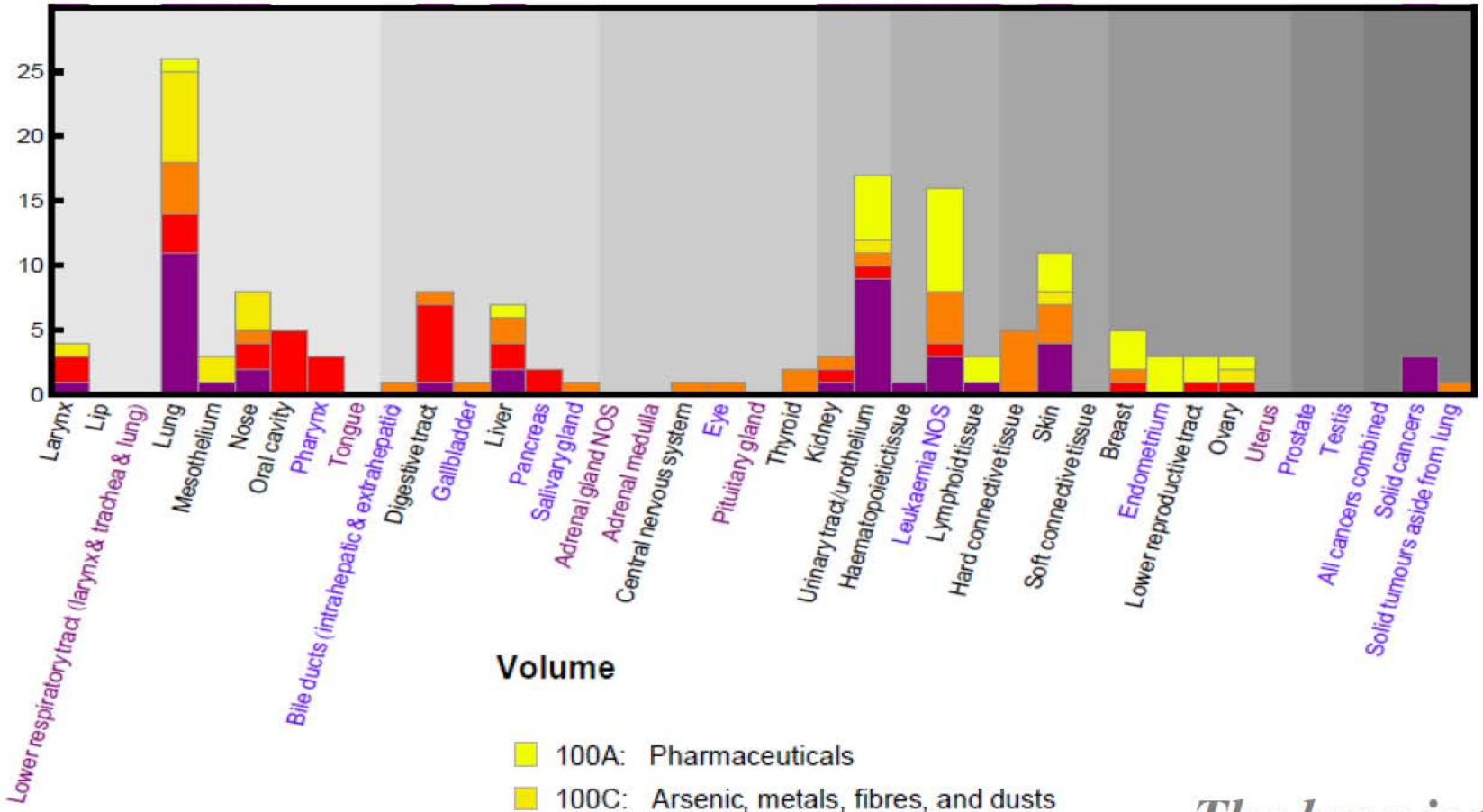
Tumour Site Concordance Database

Table 3. Abstraction of Information on Animal and Human Tumours for Group 1 Agents in the IARC Monographs (adapted from Lajoie et al., 2012)

Volume	Agent No	Agent	Sites with sufficient evidence in humans	Sites with limited evidence in humans	Agent tested in experimental animals	Species	Site	Histology	Study/Gender/Strain/Exposure route
100A	3	Azathioprine	Non Hodgkin lymphoma, skin (squamous cell carcinoma)		Azathioprine	Mouse	thymus	lymphoma	Imamura et al. (1973) (Vol 26 p. 51), MF, C57BL, s.c.; Casey et al. (1968b) (Vol 26 p. 52), M, New Zealand Black, i.m.; Casey et al. (1968a), (Vol 26 p.52),M, New Zealand Black, i.m.
100B	25	Epstein-Barr virus	Burkitt lymphoma, immune-suppression-related non Hodgkin lymphoma, estranodal NK/T-cell lymphoma (nasal type), Hodgkin lymphoma, nasopharyngeal carcinoma	lympho-epithelioma-like carcinoma, gastric carcinoma					
100C	35	Arsenic and inorganic arsenic compounds	lung, urinary bladder, skin	kidney, liver, prostate	Dimethylarsinic acid (DMAv), Monomethylarsonous acid (MMAIII), Sodium arsenite	Mouse	lung	bronchiolo-alveolar carcinoma	DMAv: Tokar et al. (2012a), M, CD1, d.w.; Sodium arsenite: Waalkes et al. (2003), F, C3H/HeNCr, in utero; Waalkes et al. (2006a), M, CD1, in utero; Tokar et al. (2011), MF, CD1, in utero + p.o.; Tokar et al. (2012), M, CD1, in utero; MMAIII: Tokar et al. (2012b), M, CD1, in utero
100D	45	Fission products including Sr-90	Solid cancers, leukaemia						
100E	68	coal, indoor emissions from household combusion of	lung		coal soot extract	Mouse	lung	bronchiolo-alveolar carcinoma	Yin et al. (1984), NR, Kunming, i.t.; Liang et al. (1983), M, Kunming, s.c.; Liang et al. (1984), M, Kunming, s.c.
100F	80	Benzene	Acute myeloid leukaemia/ acute non-lymphocytic leukemia	acute lymphocytic 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.
V105	108	Engine Exhaust, diesel	Lung	Urinary 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.
V106	109	Trichloroethylene	Kidney	non-Hodgkin's lymphoma, liver	Trichloroethylene	Rat	Kidney	renal-cell carcinoma	NTP (1990), M, F344/N, g.; NTP (1988), M, Osborne-Mendel, g.; NTP (1988), F, ACI, g.

Distribution of Tumour Sites in Animals and Humans

Number of Group 1 Agents Inducing Tumours in Humans



Volume

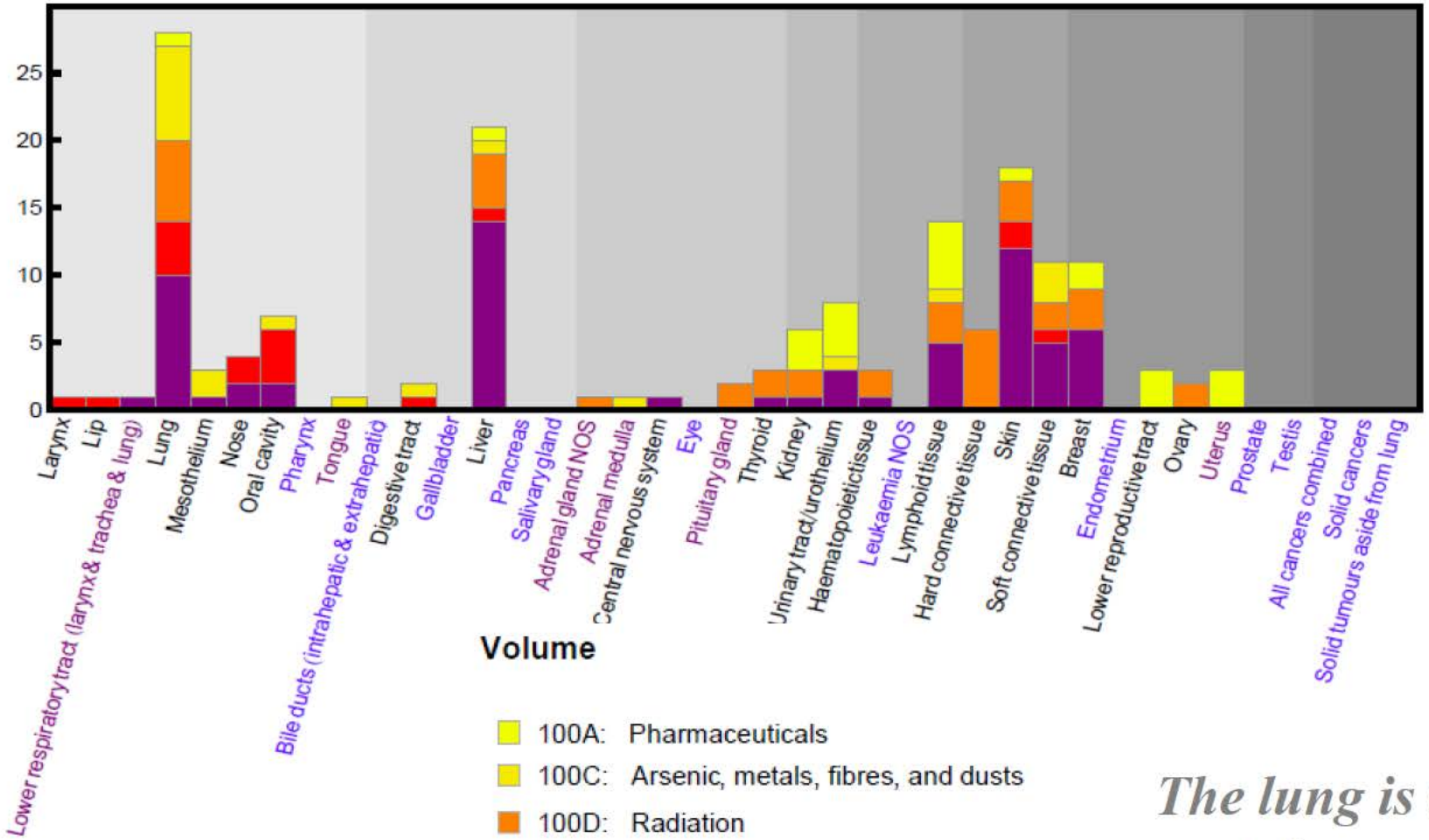
- 100A: Pharmaceuticals
- 100C: Arsenic, metals, fibres, and dusts
- 100D: Radiation
- 100E: Personal habits and indoor combustions
- 100F*: Chemical agents and related occupations (including diesel and exhaust, and some chlorinated agents)

Cancer sites reported in

- Both humans and animals
- Humans only
- Animals only

The lung is the most frequently affected site in humans

Number of Group 1 Agents Inducing Tumours in Animals



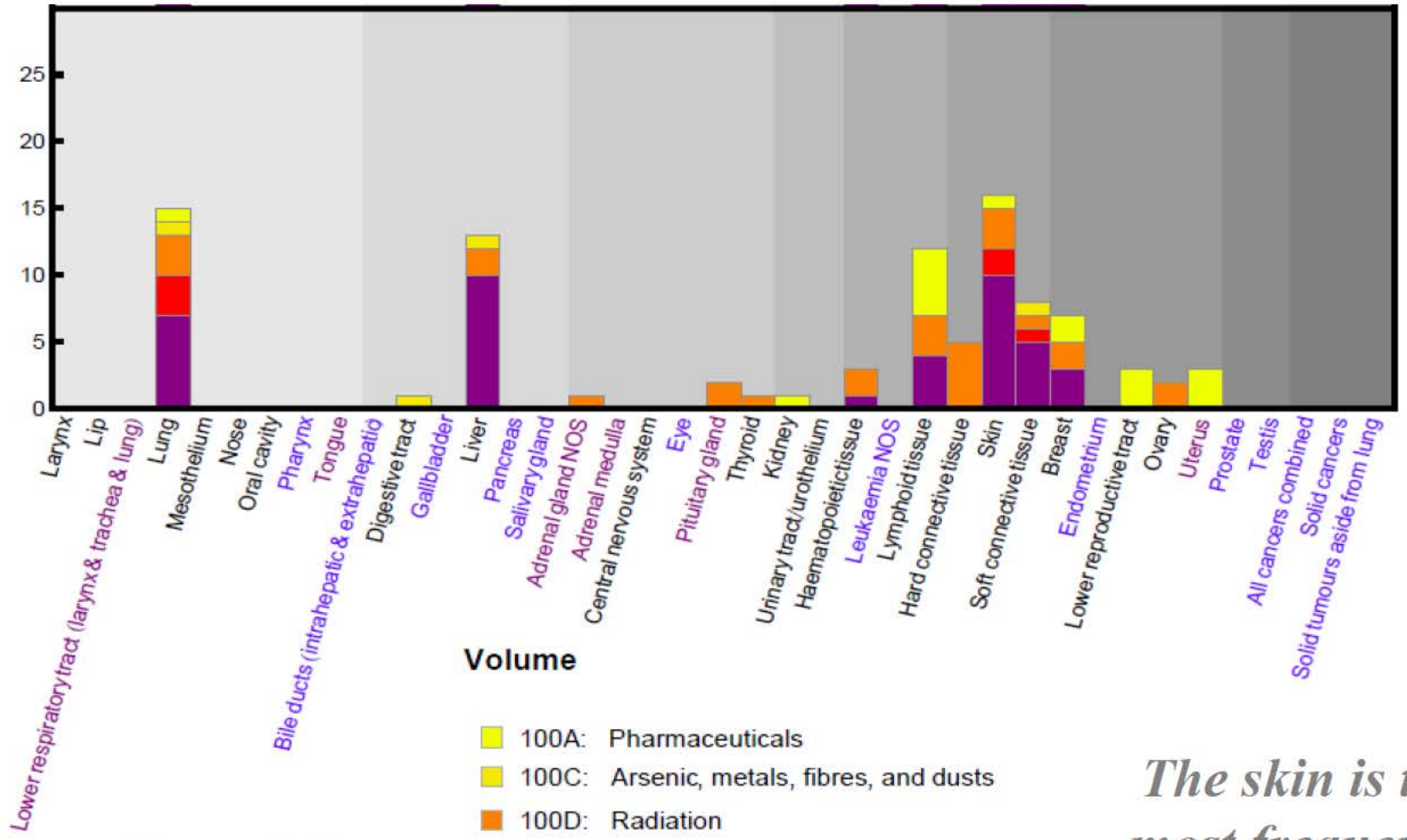
Cancer sites reported in

- Both humans and animals
- Humans only
- Animals only

- 100A: Pharmaceuticals
- 100C: Arsenic, metals, fibres, and dusts
- 100D: Radiation
- 100E: Personal habits and indoor combustions
- 100F*: Chemical agents and related occupations (including diesel and exhaust, and some chlorinated agents)

The lung is the most frequently affected site in animals

Number of Group 1 Agents Inducing Tumours in Mice



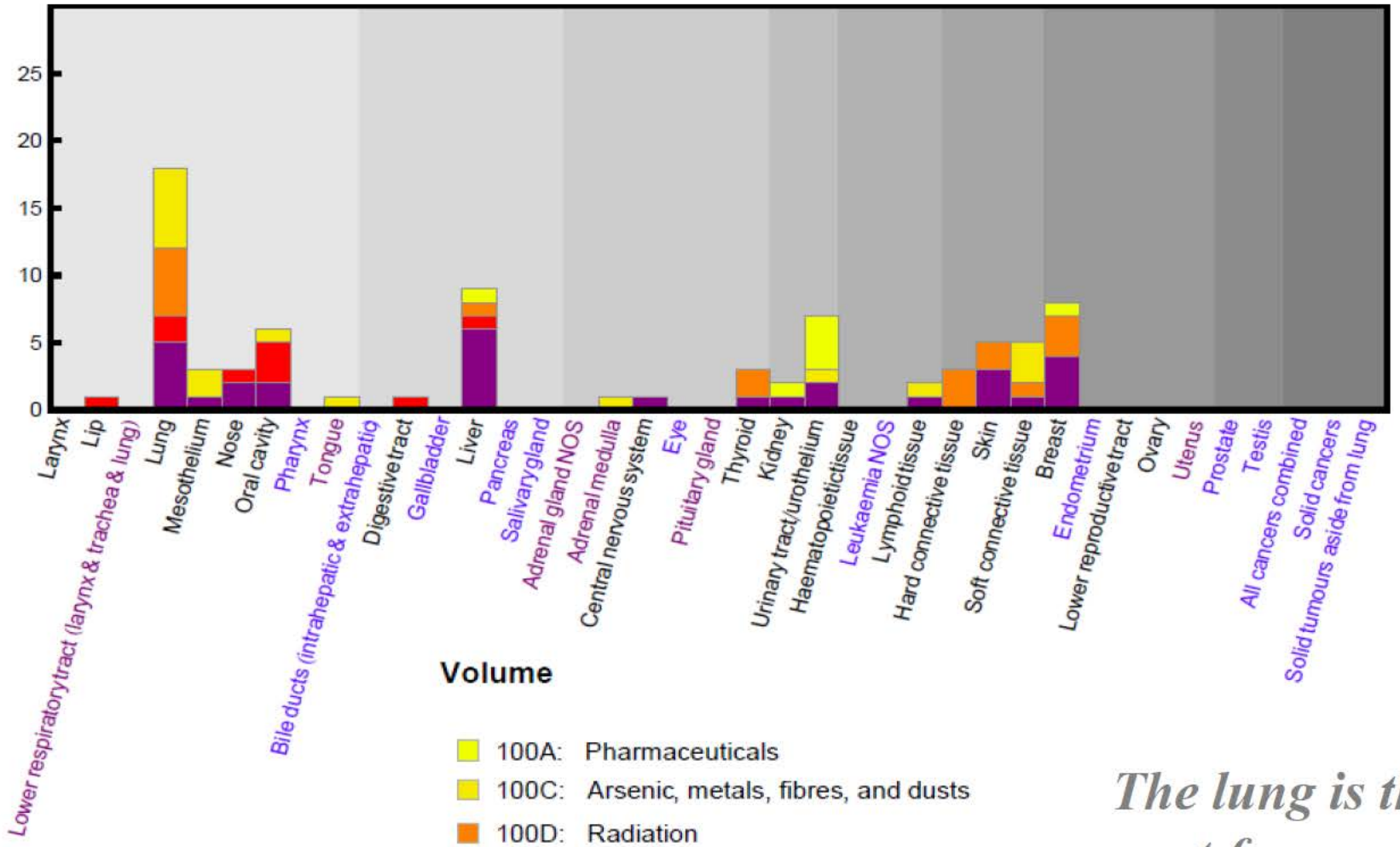
Cancer sites reported in

- Both humans and animals
- Humans only
- Animals only

- 100A: Pharmaceuticals
- 100C: Arsenic, metals, fibres, and dusts
- 100D: Radiation
- 100E: Personal habits and indoor combustions
- 100F*: Chemical agents and related occupations (including diesel and exhaust, and some chlorinated agents)

The skin is the most frequently affected site in mice

Number of Group 1 Agents Inducing Tumours in Rats



Volume

- 100A: Pharmaceuticals
- 100C: Arsenic, metals, fibres, and dusts
- 100D: Radiation
- 100E: Personal habits and indoor combustions
- 100F*: Chemical agents and related occupations (including diesel and exhaust, and some chlorinated agents)

Cancer sites reported in

- Both humans and animals
- Humans only
- Animals only

The lung is the most frequently affected site in rats

‘Heat Maps’ of Tumour Concordance in Animals and Humans

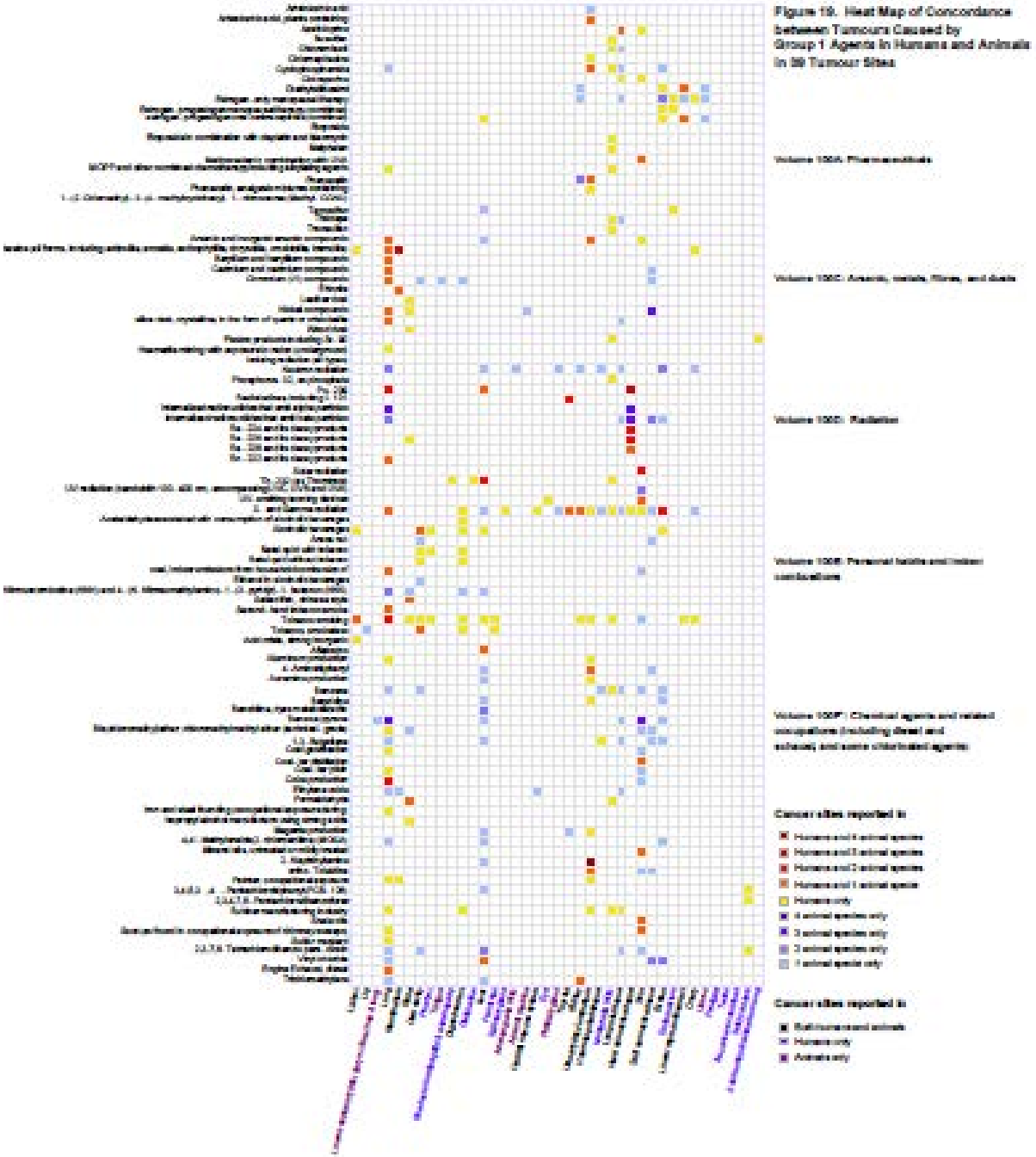


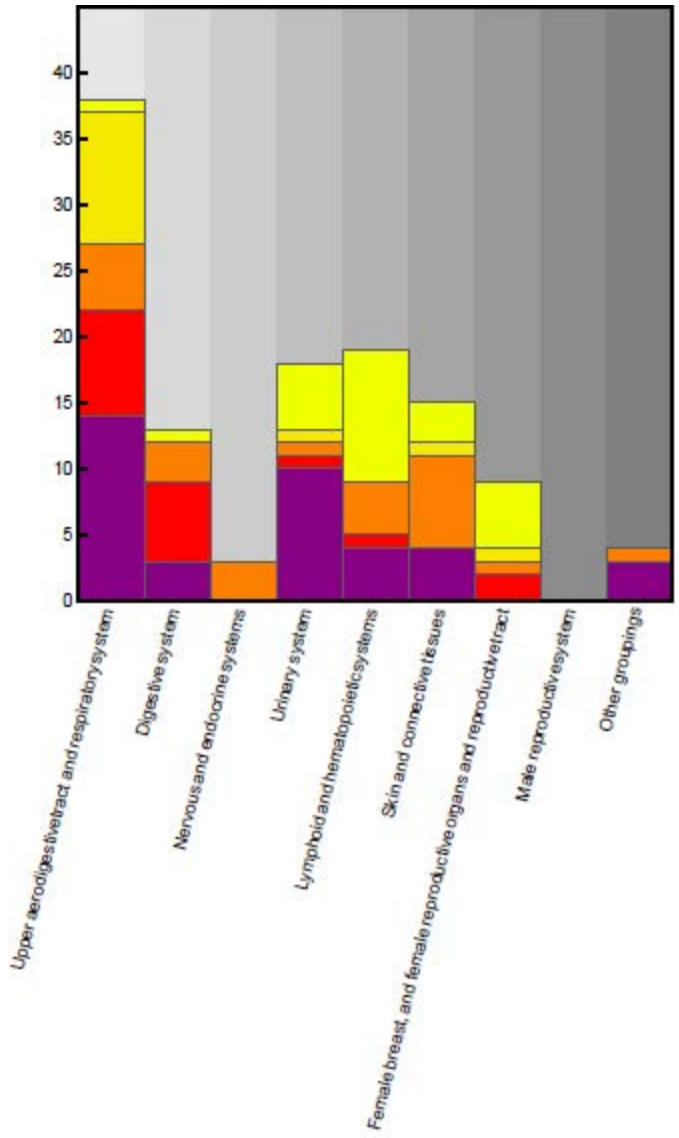
Figure 19. Heat Map of Concordance between Tumours Caused by Group 1 Agents in Humans and Animals in 39 Tumour Sites

Strong Associations Visually Apparent in Heat Maps

Heat maps linking the strength of the association between Group 1 agents and different tumor sites identified particularly strong associations between ***asbestos and lung tumours****, between* ***Pu-239 and skin tumours****, and between* ***2-napthylamine and urinary tract/uroendothelial tumours****, where in each case the same tumours are induced in humans and in four animal species.*

Animal and Human Concordance based on Organ and Tissue Systems

Number of Group 1 Agents Inducing Tumours in Humans

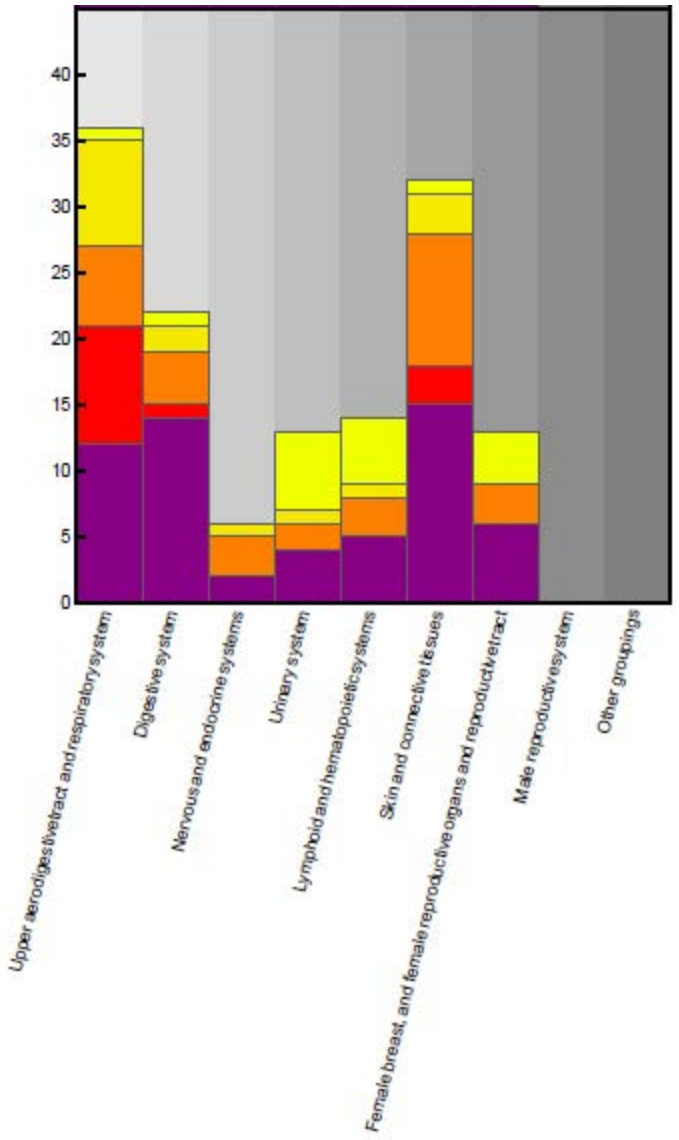


Volume

- 100A: Pharmaceuticals
- 100C: Arsenic, metals, fibres, and dusts
- 100D: Radiation
- 100E: Personal habits and indoor combustions
- 100F*: Chemical agents and related occupations (including diesel and exhaust, and some chlorinated agents)

Tumours of the upper aerodigestive tract and respiratory system are most frequently seen in humans

Number of Group 1 Agents Inducing Tumours in Animals

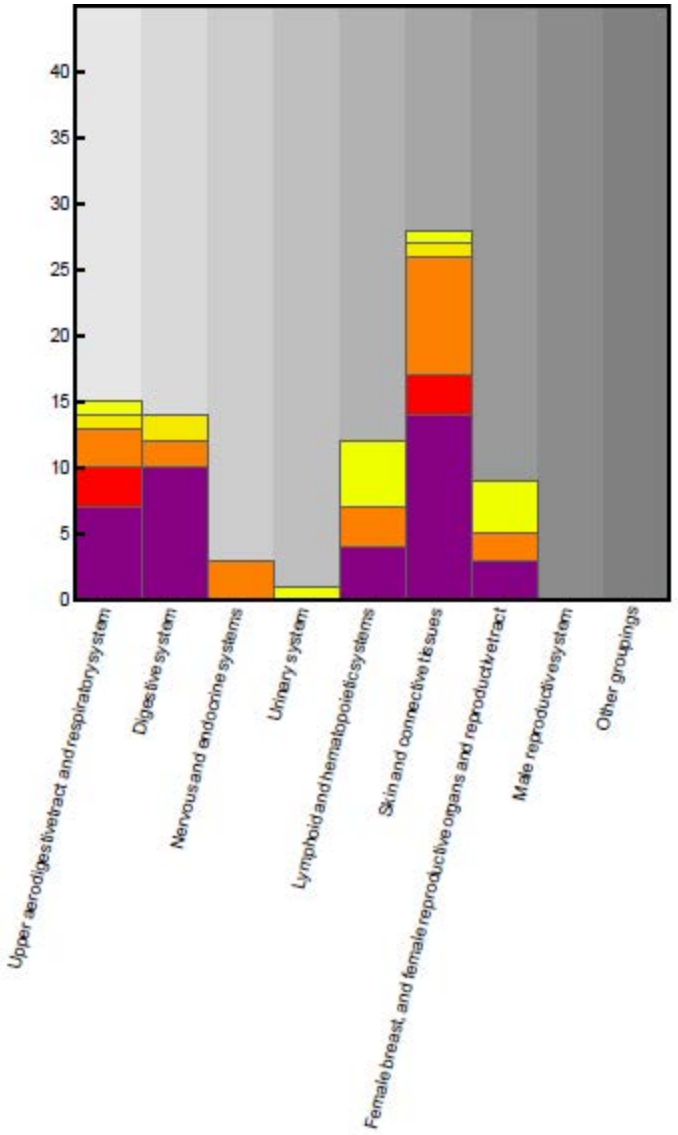


Volume

- 100A: Pharmaceuticals
- 100C: Arsenic, metals, fibres, and dusts
- 100D: Radiation
- 100E: Personal habits and indoor combustions
- 100F*: Chemical agents and related occupations (including diesel and exhaust, and some chlorinated agents)

Tumours of the upper aerodigestive tract and respiratory system are most frequently seen in animals

Number of Group 1 Agents Inducing Tumours in Mice

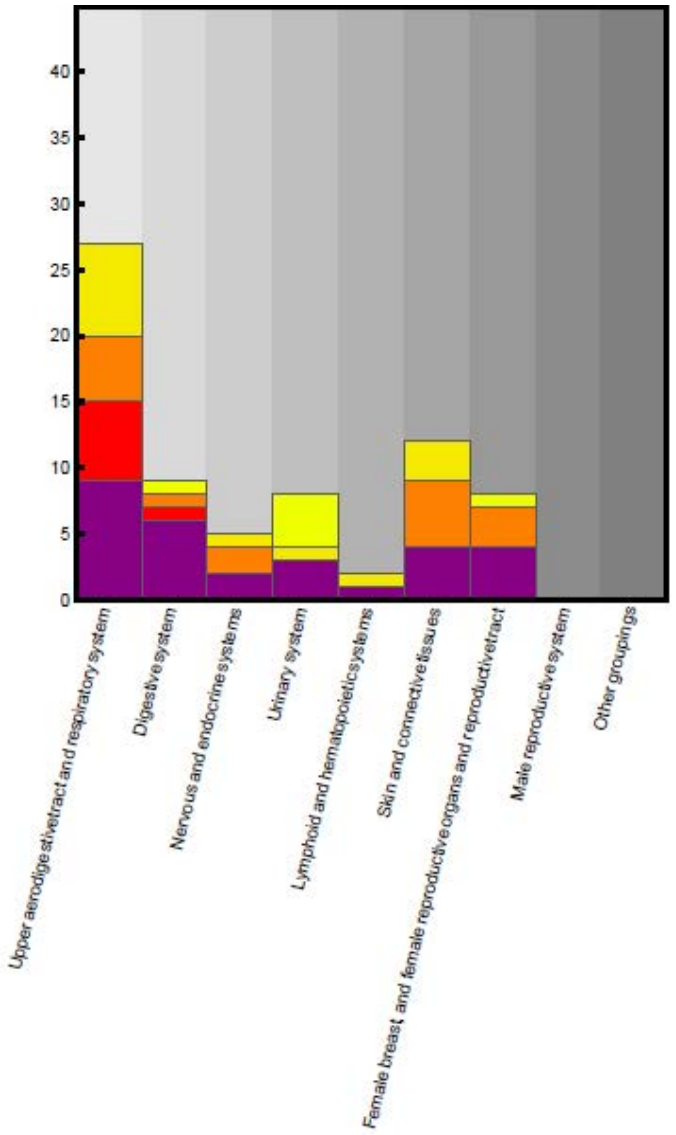


Volume

- 100A: Pharmaceuticals
- 100C: Arsenic, metals, fibres, and dusts
- 100D: Radiation
- 100E: Personal habits and indoor combustions
- 100F*: Chemical agents and related occupations (including diesel and exhaust, and some chlorinated agents)

Tumours of the skin and connective tissue are most frequently seen in mice

Number of Group 1 Agents Inducing Tumours in Rats



Volume

- 100A: Pharmaceuticals
- 100C: Arsenic, metals, fibres, and dusts
- 100D: Radiation
- 100E: Personal habits and indoor combustions
- 100F*: Chemical agents and related occupations (including diesel and exhaust, and some chlorinated agents)

Tumours of the upper aerodigestive tract and respiratory system are most frequently seen in rats

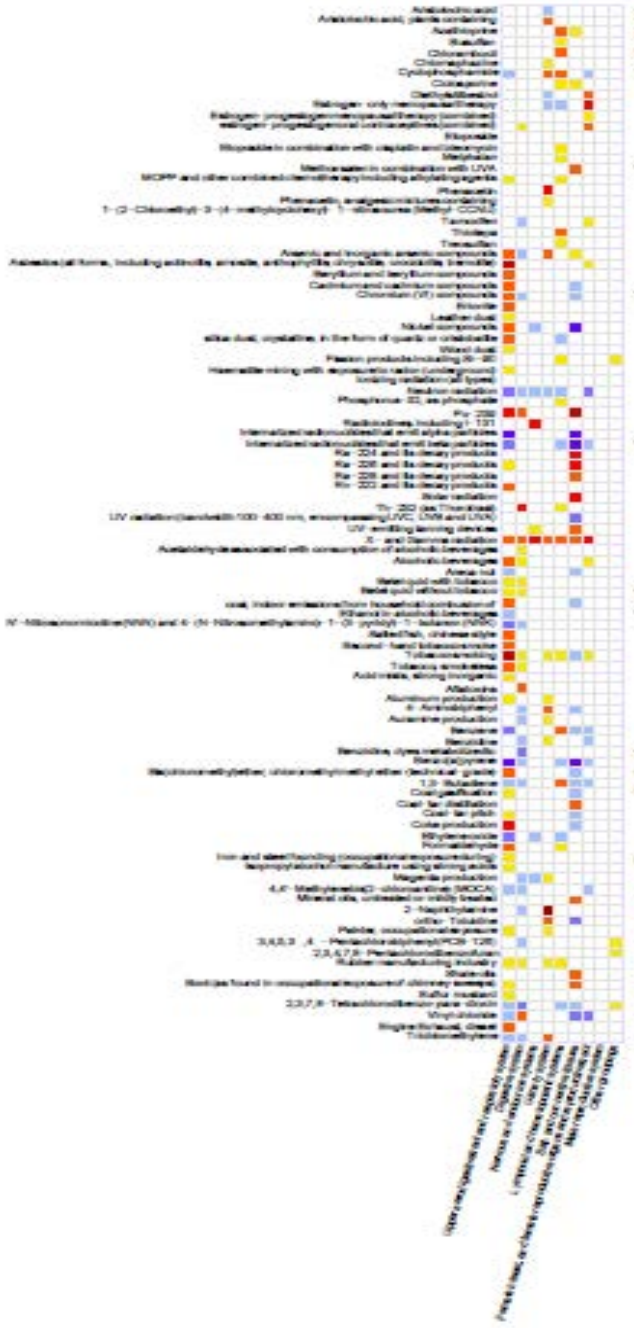


Figure 24. Heat Map of Concordance between Tumours Caused by Group 1 Agents in Humans and Animals in 9 Organ Systems

Volume 100A: Pharmaceuticals

Volume 100C: Arsenic, metals, fibres, and dusts

Volume 100D: Radiation

Volume 100E: Personal habits and indoor combustions

Volume 100F*: Chemical agents and related occupations (including diesel and exhaust, and some chlorinated agents)

Cancer sites reported in

- Humans and 4 animal species
- Humans and 3 animal species
- Humans and 2 animal species
- Humans and 1 animal specie
- Humans only
- 4 animal species only
- 3 animal species only
- 2 animal species only
- 1 animal specie only

Visual Patterns Apparent in Heat Maps

Heat maps linking the strength of the association between Group 1 agents and organ tissue systems identified the ***upper aerodigestive tract and respiratory system*** *as the system in which tumours were induced by Group 1 agents most often in both humans and animals.*

X-rays and gamma radiation *affected 7 of the 9 tissue and organ systems in both animals and humans.*

Tobacco smoking *affected multiple organ and tissue systems in humans.*

Selected Quantitative Measures of Concordance

Table 8. Kappa Statistics with 90% Confidence Intervals for Concordance Analyses 1 and 2: Humans and Individual Animal Species

Analysis 1: Concordance by Site

Site	Mouse	Rat	Hamster	Dog	Primate
Lung	0.2 (−0.17, .56)	0.54 (0.14, 0.78)	−0.38 (NE, 0.42)	0.6 (−0.18, NE)	
Mesothelium		0.79 (0.10, 0.99)	1. (−0.06, NE)		−0.33 (NE, 0.77)
Nose		0.54 (0.01, 0.88)	−0.14 (NE, 0.62)		
Thyroid	0.66 (−0.01, NE)	0.79 (0.1, 0.99)			
Hard connective tissue	0.63 (0.09, 0.9)	0.37 (−0.05, 0.84)		0.5 (−0.28, NE)	
Skin	0.38 (0, 0.68)	0.19 (−0.9, 0.68)			
Lower reproductive tract	0.64 (0.05, 0.94)				

Group	Kappa
Slight	0.01-0.20

Fair	0.21-0.40
Moderate	0.41-0.60

Substantial	0.61-0.80
Almost Perfect	0.81-0.99

Concordance for lung tumours between humans and any animal species highest for Group 1 agents in Volumes 100 C,D and E (data not shown)

Table 8. Kappa Statistics with 90% Confidence Intervals for Concordance Analyses 1 and 2: Humans and Individual Animal Species

Analysis 2: Concordance by Organ System

Organ System	Mouse	Rat	Hamster	Dog	Primate
Upper aerodigestive tract and respiratory system	0.17 (–0.2, 0.53)	0.51 (0.15, 0.71)	0.13 (–0.45, 0.51)	0.33 (–0.32, 0.89)	0.5 (–0.43, NE)
Nervous and endocrine system	0.64 (0.05, 0.94)	0.54 (0.04, NE)			
Urinary system	0.12 (–0.05, 0.12)	0.67 (0.23, 0.89)	0.23 (–0.29, 0.76)	1. (–0.03, NE)	0.5 (–0.43, NE)
Lymphoid and haemopoetic system	0.63 (0.2, 0.84)	–0.07 (NE, 0.45)			
Female breast reproductive organs and tract	0.51 (0.07, 0.75)	0.17 (–0.14, 0.6)			

Group	Kappa
Slight	0.01-0.20

Fair	0.21-0.40
Moderate	0.41-0.60

Substantial	0.61-0.80
Almost Perfect	0.81-0.99

Concordance Between Mice and Rats

- Overall concordance between mice and rats in 266 NTP bioassays was 74% (Haseman et al., 1986)
- Gold et al. (1989) reported a similar overall concordance between mice and rats of 76% in 392 experiments in their Carcinogenic Potency Databases
- Piegorsch et al. (1992) determined that, considering experimental error, the maximum observable concordance is limited to about 80% under the NCI/NTP bioassay protocol

Concordance Analysis . . . a Work in Progress

Draft of December 18, 2013

Concordance between Animal and Human Tumours:

An Analysis of 109 Agents Known to Cause Cancer in Humans

Daniel Krewski[1,2,3], Brian Collins[2], Jerry Rice[4], Pascal Lajoie[1,5], Yann Grosse[6], Robert Baan[6], Vincent Cogliano[7], Kurt Straif[6], Christopher Portier[6], Michael Bird[1,2], Julian Little[3] & Jan M. Zielinski[1,3,7]
on behalf of the IARC Working Group on 'Tumour-site Concordance and Mechanisms of Carcinogenesis' which convened in Lyon April/November 2012

Tumour Mechanisms Database

- Similar database of tumour mechanisms currently being finalized (database includes information from outside Volume 100)
- Analysis of 24 mechanistic endpoints derived from in vitro and in vivo animal and human studies underway
- Analysis of 10 major mechanisms also underway