encompass a range of non-cancer toxicities, "top-down" broad literature searches aimed at comprehensively identifying studies on all potential toxic effects of an agent are employed (EPA 2014; NRC 2014). These comprehensive searches of peer-reviewed literature are supplemented by examining past IARC Monographs or other authoritative reviews; databases (e.g., PubChem); and, peer-reviewed government reports can also be systematically searched. The search terms used and literature retrieved can be documented (e.g., using MyNCBI, which saves searches of the National Center for Biotechnology database, or https://hawcproject.org).

Step 2: Screening and organizing the results

Based on title and abstract review, studies identified initially are excluded if no data on the chemical or a metabolite are reported, or if no data on toxicological or other cancer-related effects of the chemical is provided. For example, a study on levels of a chemical, but not effects of the chemical, would be excluded. Included studies are then organized by the population (human or experimental systems) and by the endpoints associated with the 10 key characteristics (see Table 1). Studies relevant to toxicokinetics (covering absorption, distribution, metabolism and excretion) are also identified. Additionally, authoritative, comprehensive review articles are identified, as are studies reporting toxicological endpoints in cancer target and non-target tissues. These may include morphological evaluations pertaining to the dysfunction of organs, tissues, and cells. Importantly, studies reporting endpoints that are relevant to multiple characteristics may fall under several categories.

To illustrate these two steps, targeted literature searches were conducted to identify endpoints for the effects of benzene pertinent to the 10 key characteristics, in populations comprising humans or experimental systems. The literature searches were conducted using the Health Assessment

Workplace Collaborative (HAWC) Literature Search tool (https://hawcproject.org/), documenting the search terms, sources, and articles retrieved. Following title and abstract review, studies were excluded if they were not about benzene or its metabolites, or if they reported no data on toxicological endpoints. Included studies were further sorted into categories representing the 10 key characteristics based on the mechanistic endpoints and species evaluated (i.e. human in vivo, human in vitro, mammalian in vivo, mammalian in vitro, non-mammalian; see Figure 1). The figure also identifies reviews, gene expression studies, and articles relevant to toxicokinetics, toxicity, or susceptibility.

Step 3: Using the key characteristics to synthesize mechanistic information and to develop adverse-outcome networks

It is increasingly evident that multiple biological alterations or sets of different perturbations are necessary to convert a normal cell to a transformed cell and ultimately a tumor (Hanahan and Weinberg 2011). Carcinogens appear to impact this complex process in various ways and can act through multiple mechanisms to induce cancer and other adverse health outcomes (Goodson et al. 2015; Guyton et al. 2009). Using the 10 key characteristics as a basis, the collected information can be organized to form hypotheses and evaluate the evidentiary support for mechanistic events as a function of relevant aspects (e.g. dose, species, temporality, etc) (Guyton et al. 2009). The diverse and complex mechanistic endpoints elicited by benzene can then be organized into an overview inclusive of multiple alterations and any linkages thereof (Figure 2). The resulting overview can provide guidance for further assessments of the literature, including dose relevance, species relevance, and temporality of events. This additional detailed information can then be used to produce proposed mechanisms or adverse outcome pathway networks as

described in (McHale et al. 2012) and the EPA's NexGen Risk Assessment Report (EPA2014). We note that there is evidence that benzene is associated with 8 of the 10 key characteristics we have described.

Figure 3 presents a similar overview for PCBs based on data from IARC Monograph Volume 107 (IARC 2015). In summarizing the mechanistic evidence, this Monograph Working Group indicated that PCBs may induce up to 7 of the 10 key characteristics in producing carcinogenicity (Lauby-Secretan et al. 2013). We note that the less chlorinated PCBs are associated with key characteristics similar to benzene (metabolic activation, DNA damage, cellular proliferation), whereas the dioxin-like PCBs are associated primarily with receptor-mediated activities.

Recently, using this same approach, the Working Groups of IARC Monograph Volume 112 and Volume 113 concluded that strong mechanistic evidence exists for 5 key characteristics being involved in malathion carcinogenicity (i.e. genotoxicity, oxidative stress, inflammation, receptor-mediated effects and cell proliferation or death), 3 in DDT carcinogenicity (i.e. immunosuppression, receptor-mediated effects and oxidative stress) and 2 each for diazinon and glyphosate (i.e. genotoxicity and oxidative stress), providing evidence to support their classification as probable human carcinogens in Group 2A (Guyton et al. 2015; Loomis et al. 2015).

Discussion and Conclusions

Identification and incorporation of important, novel scientific findings providing insights into cancer mechanisms is an increasingly essential aspect of carcinogen hazard identification and

risk assessment. Systematic approaches are needed to organize the available mechanistic data relevant to the overall evaluation of the carcinogenic hazard of an agent. Information to support the identification of 10 key characteristics of human carcinogens was obtained during the Volume 100 Monographs and two subsequent expert workshops. These characteristics, although not necessarily representing mechanisms themselves, provide the rationale for an objective approach to identifying and organizing relevant mechanistic data. Using literature collected previously by others as well as by us, we have categorized the literature data according to the 10 characteristics for benzene and PCBs. This approach identified pertinent positive literature for 8 of the 10 key characteristics on benzene and 7 for PCBs, thereby providing a practical, objective method for organizing the large mechanistic literature associated with these chemicals.

This approach also lays the groundwork for a structured evaluation of the strength of the mechanistic evidence base, and therefore its utility in supporting hazard classifications. In the IARC Monographs the strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated using the terms 'weak', 'moderate' or 'strong' (http://monographs.iarc.fr/ENG/Preamble/index.php). In general, the strongest indications that a particular mechanism operates in humans derive from data obtained in exposed humans or in human cells in vitro. Data from experimental animals can support a mechanism by findings of consistent results and from studies that challenge the hypothesized mechanism experimentally. Other considerations include whether multiple mechanisms might contribute to tumor development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental animals and whether a unique mechanism might operate in a susceptible group. The possible contribution of alternative mechanisms must be considered before concluding that tumors observed in experimental animals

are not relevant to humans. An uneven level of experimental support for different mechanisms may reflect that disproportionate resources have been focused on investigating a favored mechanism. All of these factors make assignment of descriptors such as "strong" to the mechanistic evidence challenging, but recent experience with two IARC Monograph meetings suggest that the weighing of the evidence on the basis of the 10 key characteristics focuses the group discussion on the available science and allows rapid consensus to be reached regardless of the strength of the evidence base (Guyton et al. 2015; Loomis et al. 2015).

Because the literature search and categorization approach described herein is comprehensive, it may aid consideration of the overall strength of the mechanistic database according to these principles. In particular, it is inclusive of diverse mechanistic evidence, enabling support for divergent or related mechanisms from human and experimental systems to be identified. Moreover, the literature support for endpoints relevant to specific mechanisms can be evaluated in an integrated fashion when the mechanism is complex. Additionally, comparisons across agents will be facilitated, including evaluation of any similarities or differences in the pattern of key characteristics with agents that are currently classified.

As this approach is carried forward, we hope it will facilitate the objective identification of mechanistic data for consideration in the context of epidemiology, animal bioassay, or other types of evidence (e.g., studies in model organisms or *in vitro* assays) when classifying agents with regard to carcinogenic hazard. Equally important is to consider whether key characteristics of carcinogens are apparent upon exposures that are relevant to human health (Thomas et al. 2013). Overall, these developments will aid advancement of future evaluations of newly

introduced chemicals, including those for which mechanistic data provide the primary evidence of carcinogenicity.

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Table 1. Key characteristics of carcinogens.

Characteristic	Examples of relevant evidence
1. Is Electrophilic or Can Be Metabolically Activated	Parent compound or metabolite with an electrophilic structure (e.g., epoxide, quinone, etc), formation of DNA and protein adducts.
2. Is Genotoxic	DNA damage (DNA strand breaks, DNA-protein cross-links, unscheduled DNA synthesis), intercalation, gene mutations, cytogenetic changes (e.g., chromosome aberrations, micronuclei).
3. Alters DNA repair or causes genomic instability	Alterations of DNA replication or repair (e.g., topoisomerase II, base-excision or double-strand break repair)
4. Induces Epigenetic Alterations	DNA methylation, histone modification, microRNA expression
5. Induces Oxidative Stress	Oxygen radicals, oxidative stress, oxidative damage to macromolecules (e.g., DNA, lipids)
6. Induces chronic inflammation	Elevated white blood cells, myeloperoxidase activity, altered cytokine and/or chemokine production
7. Is Immunosuppressive	Decreased immunosurveillance, immune system dysfunction
8. Modulates receptor-mediated effects	Receptor in/activation (e.g., ER, PPAR, AhR) or modulation of exogenous ligands (including hormones)
9. Causes Immortalization	Inhibition of senescence, cell transformation
10. Alters cell proliferation, cell death or nutrient supply	Increased proliferation, decreased apoptosis, changes in growth factors, energetics and signaling pathways related to cellular replication or cell cycle control, angiogenesis

Any of the 10 characteristics in this table could interact with any other (e.g. oxidative stress, DNA damage and chronic inflammation, which when combined provides stronger evidence for a cancer mechanism than would oxidative stress alone).

Figure Legends

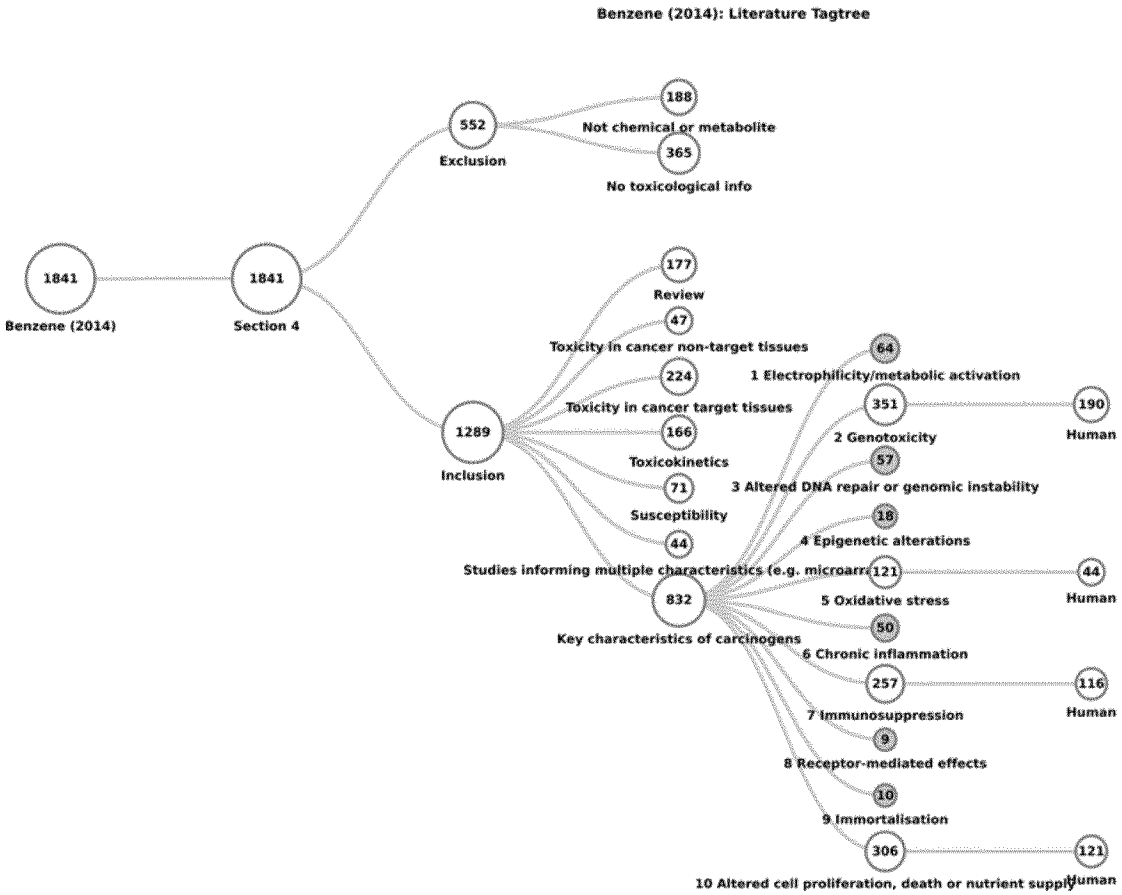
Figure 1: Literature flow diagram, illustrating the systematic identification and categorization process for benzene mechanistic studies. Using appropriate MeSH terms and key words, targeted literature searches were conducted for the 10 key characteristics using online tools available from the HAWC Project (https://hawcproject.org/). Section 4 refers to the location of the discussion of mechanistic data within the IARC Monograph structure (http://monographs.iarc.fr/ENG/Preamble/currentb4studiesother0706.php). All inclusion categories were expanded to document the number of studies attributed to each, down to the individual key characteristic level, which were expanded to illustrate human information when >100 total studies were identified. Less frequently encountered key characteristic categories (grey circles) were left unexpanded for clarity. Human refers to both humans exposed in vivo and human cells exposed in vitro.

Figure 2: An overview of how benzene induces 8 of the key characteristics in a probable mechanism of carcinogenicity. A full review of these mechanistic data is given in (McHale et al. 2012), from which this Figure was adapted.

Figure 3: An overview of how polychlorinated biphenyls (PCBs) may induce 7 key characteristics in their carcinogenicity (Lauby-Secretan et al. 2013). Highly chlorinated PCBs act as ligands for the aryl hydrocarbon receptor (AhR) and other receptors activating a large number of genes in a tissue- and cell-specific manner that can lead to cell proliferation, apoptosis and other effects that influence cancer risk. Less chlorinated PCBs can be activated to electrophilic metabolites, such as arene oxides and quinones, which can cause genotoxic effects and induce oxidative stress. Receptor binding to CAR and AhR (a key characteristic) leads

xenobiotic metabolism induction (not a key characteristic, brown not blue box) that in turn leads to genotoxicity and other key characteristics.

Figure ¶


Benzene (2014): Literature Tagtree
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Benzene (2014)
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Section 4
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Exclusion
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Not chemical or metabolite
365
No toxicological info
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Inclusion
177
Review
47
Toxicity in cancer non-target tissues
224
Toxicity in cancer target tissues
166
Toxicokinetics
71
Susceptibility
44
Studies informing multiple characteristics (e.g. microarr
832
Key characteristics of carcinogens
64
1 Electrophilicity/metabolic activation
351
2 Genotoxicity
190
Human
57
3 Altered DNA repair or genomic instability
18
4 Epigenetic alterations
121
5 Oxidative stress
44
Human
50
6 Chronic inflammation
257
7 Immunosuppression
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Human
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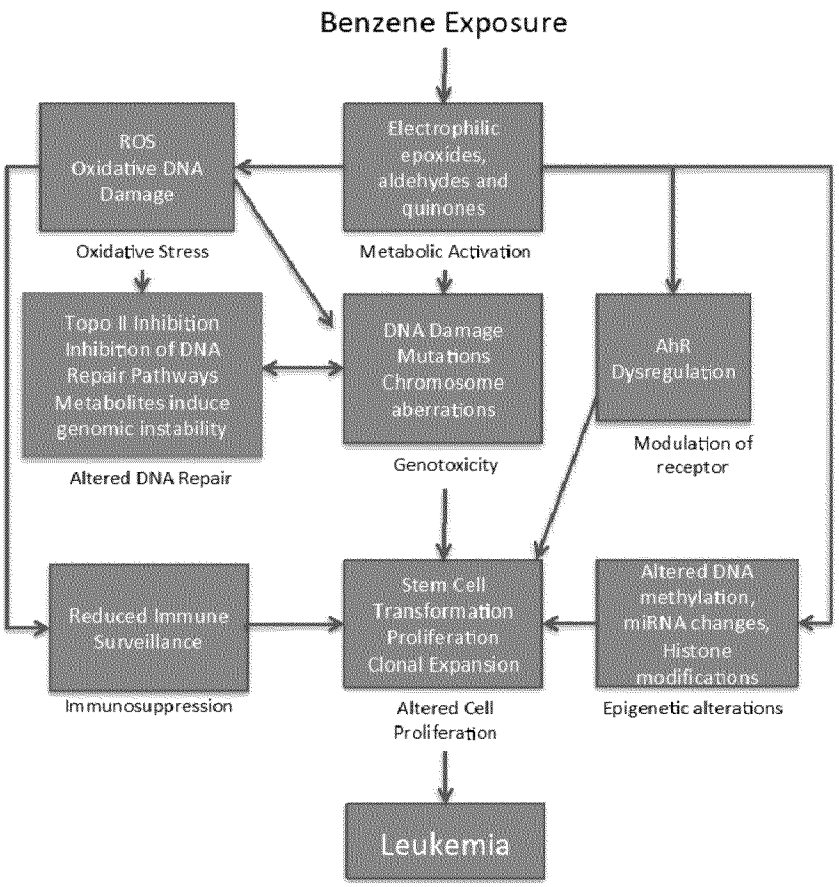
8 Receptor-mediated effects
10
9 Immortalisation
306
10 Altered cell proliferation, death or nutrient supply
121
Human

Figure └ Ó


Benzene Exposure
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Oxidative DNA
Damage
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Electrophilic
epoxides,
aldehydes and
quinones
Metabolic Activation
Topo II Inhibition
Inhibition of DNA
Repair Pathways
Metabolites induce
genomic instability
Altered DNA Repair
DNA Damage
Mutations
Chromosome
aberrations
Genotoxicity
AhR
Dysregulation
Modulation of
receptor
Reduced Immune
Surveillance
Immunosuppression
Stem Cell
Transformation
Proliferation
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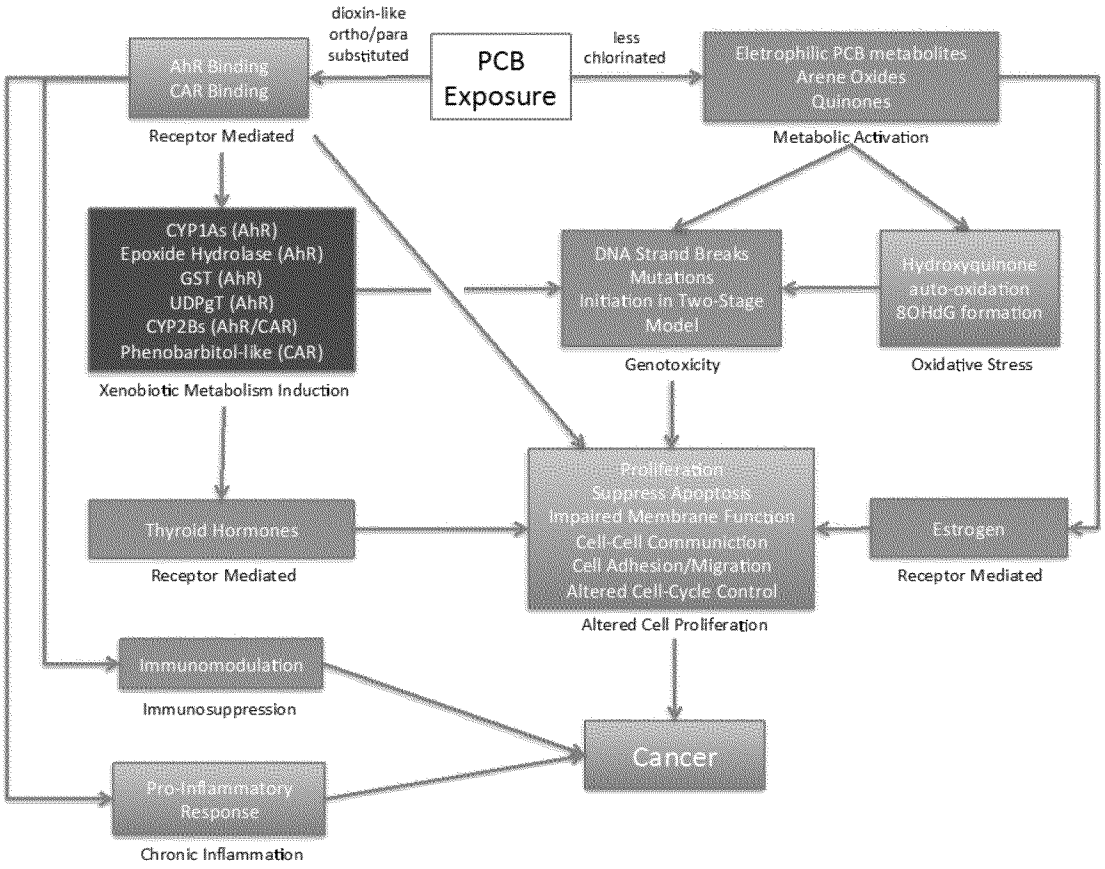
Figure └ Ô


dioxin-like
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CAR Binding
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Eletrophilic PCB metabolites
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Quinones
Metabolic Activation
CYP1As (AhR)
Epoxide Hydrolase (AhR)
GST (AhR)
UDPgT (AhR)
CYP2Bs (AhR/CAR)
Phenobarbitol-like (CAR)
Xenobiotic Metabolism Induction
DNA Strand Breaks
Mutations
Initiation in Two-Stage
Model
Genotoxicity
Hydroxyquinone
auto-oxidation
8OHdG formation
Oxidative Stress
Proliferation
Suppress Apoptosis
Impaired Membrane Function
Cell-Cell Communiction
Cell Adhesion/Migration
Altered Cell-Cycle Control
Altered Cell Proliferation
Thyroid Hormones
Receptor Mediated
Estrogen
Receptor Mediated
Immunomodulation
Immunosuppression
Cancer
Pro-Inflammatory
Response
Chronic Inflammation

To: Cogliano, Vincent[cogliano.vincent@epa.gov]
From: Kathryn Guyton
Sent: Fri 11/13/2015 12:45:17 PM
Subject: Re: Glyphosate: EFSA updates toxicological profile
circVSefsa.pdf

Hi Vince,
Don't know if you this may make you homesick for Lyon, but here is the latest from Le Monde and BBC:
http://www.bbc.co.uk/programmes/b06nrzqm starting from around 7 min.
Hope you are well,
Kate

From: "Cogliano, Vincent" <cogliano.vincent@epa.gov>
Date: Thursday 12 November 2015 at 12:39
To: Kate Guyton <guytonk@iarc.fr>
Subject: Fwd: Glyphosate: EFSA updates toxicological profile

Begin forwarded message:

From: "Cogliano, Vincent" <cogliano.vincent@epa.gov>
To: "Kurt Straif" <StraifK@iarc.fr>, "Guha Neela" <GuhaN@iarc.fr>, "Gaudin Nicolas" <**Ex. 6 - Personal Privacy**>
Subject: Fwd: Glyphosate: EFSA updates toxicological profile

Begin forwarded message:

From: "Bahadori, Tina" <Bahadori.Tina@epa.gov>
To: "Fegley, Robert" <Fegley.Robert@epa.gov>, "McQueen, Jacqueline" <McQueen.Jacqueline@epa.gov>, "Cogliano, Vincent" <cogliano.vincent@epa.gov>, "Wood, Charles" <Wood.Charles@epa.gov>, "Lobdell, Danelle" <Lobdell.Danelle@epa.gov>, "Egeghy, Peter" <Egeghy.Peter@epa.gov>
Cc: "Birchfield, Norman" <Birchfield.Norman@epa.gov>
Subject: Glyphosate: EFSA updates toxicological profile

In case you had not seen this announcement yet – full assessment and additional information can be found: http://www.efsa.europa.eu/en/efsajournal/pub/4302.

Tina

From: LIEM Djien [mailto:Djien.LIEM@efsa.europa.eu]
Sent: Thursday, November 12, 2015 2:57 AM
To: Taveau, Daniella <Taveau.Daniella@epa.gov>; Dix, David <Dix.David@epa.gov>; Miller, David <Miller.DavidJ@epa.gov>; Cowles, James <Cowles.James@epa.gov>;

Robbins, Jane <Robbins.Jane@epa.gov>; Rowland, Jess <Rowland.Jess@epa.gov>; Mary Ko Manibusan (manibusan.mary@epa.gov) <manibusan.mary@epa.gov>; Thomas, Russell <Thomas.Russell@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Villeneuve, Dan <Villeneuve.Dan@epa.gov>
Subject: UNDER EMBARGO - Glyphosate: EFSA updates toxicological profile

Dear Colleagues,

Today 12 November at 12:00 CET, EFSA will publish a Conclusion on the Peer review on glyphosate and a complementary technical document.

It will be accompanied by a News Story and a non technical summary.

The documents are under embargo until **12:00 CET** when they will be published on our website.

For any further information on the Conclusion, please contact Jose Tarazona (Jose.Tarazona@efsa.europa.eu).

For any further information on the News Story, please contact Simon Terry (simon.terry@efsa.europa.eu).

Best regards,

Djien

Djien Liem, PhD

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Pour les experts européens, le glyphosate est sans danger

L'Autorité européenne de sécurité des aliments juge « improbable » le risque cancérogène de l'herbicide

Sauf surprise, le glyphosate devrait être de nouveau autorisé pour dix ans en Europe. L'Autorité européenne de sécurité des aliments (EFSA) a rendu, jeudi 12 novembre, un avis favorable au maintien sur le marché de cette molécule herbicide, principe actif du célèbre désherbant Roundup. L'avis de l'EFSA servira de base à la décision de la Commission européenne d'accorder, ou non, une nouvelle autorisation décennale au produit. Il estime *« improbable »* que *« le glyphosate soit génotoxique* [toxique pour l'ADN] *ou qu'il constitue une menace cancérogène pour l'homme ».*

L'opinion de l'EFSA tranche avec l'avis, rendu en mars, du Centre international de recherche sur le cancer (CIRC). Au contraire de l'EFSA, l'agence de l'Organisation mondiale de la santé (OMS) estimait en effet disposer *« de preuves fortes de la génotoxicité du glyphosate »* et classait la substance comme *« cancérogène probable »*

L'avis de l'EFSA a été accueilli avec colère par un grand nombre d'organisations non gouvernementales (ONG). *« La loi européenne dispose qu'un lien "présumé" avec le cancer signifie qu'un pesticide ne peut pas être utilisé, sauf si l'exposition humaine est démontrablement "négligeable"* , déclare Greenpeace dans un communiqué. *Or, le glyphosate est tant utilisé que l'exposition humaine est inévitable. On le retrouvé fréquemment dans l'air, dans l'eau, dans les jardins publics, sur les terres agricoles et dans la nourriture.»*

La substance la plus utilisée

Aux côtés d'ONG engagées contre l'agrochimie comme Greenpeace, Pesticide Action Network, Générations futures, etc., la Ligue contre le cancer s'est également manifestée. *« C'est la première fois que nous nous mobilisons à travers une campagne publique pour obtenir le retrait d'un pesticide* , explique-t-on à la Ligue. *Nous regrettons vivement l'avis de l'EFSA. »*

Le retrait pur et simple de la molécule semble peu probable. Le glyphosate est la substance active la plus utilisée au monde, en raison de l'adoption rapide des cultures transgéniques tolérantes au Roundup, qui facilite son usage. Au niveau mondial, sa production est passée de 600 000 tonnes en 2008 à 720 000 tonnes en 2012. En France, le glyphosate est aussi la molécule active la plus utilisée : environ 8 000 tonnes par an pour les usages professionnels.

Comment expliquer les divergences de vue entre l'EFSA et le CIRC ? *« Notre évaluation a pris en compte un certain nombre d'études non évaluées par le CIRC, ce qui explique en partie pourquoi les deux évaluations ont abouti à des conclusions différentes »* dit-on à l'agence européenne basée à Parme (Italie). Ce qui est formulé quelque peu différemment au siège lyonnais de l'agence de l'OMS. *« Notre méthodologie consiste à ne tenir compte d'études que dans la mesure où elles sont publiques, publiées dans des revues scientifiques avec révision par les pairs* [c'est-à-dire une expertise préalable à la publication], précise-t-on au CIRC. *Alors que l'EFSA examine aussi des résultats d'études industrielles non publiées. »* Vérité en deçà des Alpes, erreur au-delà.

Les divergences entre les deux expertises sont considérables, notamment sur la génotoxicité du glyphosate. Car, outre des études in vitro et sur l'animal, des travaux menés sur les humains sont également disponibles dans la littérature scientifique. *« Il existe des études suggérant la génotoxicité de produits commerciaux à base de glyphosate sur des sujets humains, conduites après des opérations de pulvérisations aériennes,* indique Christopher Portier, ancien directeur du National Center for Environmental Health des Centres de contrôle et de prévention des maladies d'Atlanta (Etats-Unis) et autorité mondiale dans le domaine de la cancérogénèse. *Ces études n'ont pas été prises en compte par l'EFSA au motif que ce n'est pas du glyphosate pur qui a été utilisé, mais du glyphosate avec des co-formulants. D'un point de vue de santé publique, cela n'a aucun sens. »*

Le Centre international de recherche sur le cancer (OMS) estimait, en mars, disposer « de preuves fortes de la génotoxicité du glyphosate »

« C'est très perturbant »

Sur la cancérogénicité, la polémique n'est pas moins forte. *« L'EFSA disposait de cinq études sur la souris, toutes montrant des excès de plusieurs types de tumeurs. Dans chaque expérience, ces excès sont statistiquement significatifs, mais l'EFSA ne les a pas considérés comme tels : les experts européens ont utilisé une base de données historique de groupes témoins pour comparer les excès de tumeurs obtenus,* ajoute M. Portier, qui fait partie des scientifiques consultés par le CIRC. *Faire cela n'est pas autorisé par les règles internationales de bonnes pratiques toxicologiques. »*

Une « base de données historique de groupes témoins » rassemble les données issues des groupes témoins de nombreuses expériences précédentes : elle donne la fréquence de certaines pathologies chez des animaux de laboratoire non exposés à des toxiques. Mais son utilisation doit être justifiée.

Interrogée, l'EFSA rétorque être restée *« en ligne avec les règles internationales »* Cependant, le document-guide des bonnes pratiques toxicologiques édité par l'Organisation de coopération et le développement économiques et cité par l'EFSA donne raison au CIRC : *« Il doit être souligné que le groupe témoin de l'expérience est toujours le plus important à considérer pour évaluer l'augmentation des taux de cancers. »* Ce qui, en l'occurrence, n'a pas été le cas.

Ce n'est pas tout. *« Non seulement la comparaison avec les données historiques de groupes témoins n'est pas autorisée quand le groupe témoin de l'expérience est suffisant,* confirme-t-on au CIRC, *mais la base de données historique de témoins utilisée par l'EFSA regroupe plusieurs souches de souris de laboratoire, ce qui rend invalide toute comparaison avec une souche unique. Nous sommes curieux de savoir comment l'EFSA va justifier cela. »*

La virulence des critiques rompt avec l'entre-soi du monde de l'expertise sanitaire. *« Il m'est très difficile de comprendre comment des toxicologues peuvent endosser un tel avis, dont les auteurs avaient, semble-t-il, déjà la réponse avant que la question ne soit posée,* fulmine M. Portier. *C'est très perturbant. »*

stéphane foucart

LES CHIFFRES

750

produits

Le glyphosateentre dans la composition de plus de 750 produits utilisés dans l'agriculture, la foresterie, pour des usages urbains et domestiques, et commercialisés par plus de 90 fabricants répartis dans une vingtaine de pays.Synthétisé par Monsanto dans les années 1970, le glyphosate est le principal ingrédient du désherbant Roundup, l'herbicide le plus utilisé du monde.

720 000 TONNES

production mondiale

Elle est passée de 600 000 tonnes en 2008 à 650 000 en 2011 pour atteindre 720 000 tonnes en 2012.

8 000 TONNES

épandues en France en 2011

C'est le pesticide de synthèse le plus utilisé en France. C'est aussi le principal responsable du déclassement des eaux. A cela s'ajoutent 2 000 tonnes utilisées par les particuliers (jardinage, etc.)

L'usine chimique Synthron, pollueuse multirécidiviste

Site Seveso « haut », l'entreprise et son PDG, 401e fortune de France, sont accusés d'infractions répétées au code de l'environnement

Etait-ce l'ultime procès de Robert Moor, le PDG de l'entreprise chimique Synthron, ou seulement un de plus pour cet homme de 85 ans, déjà condamné quatre fois ? M. Moor a comparu devant le tribunal correctionnel de Tours, jeudi 12 novembre, en son nom propre et comme représentant de cette usine de fabrication de produits chimiques qui cumule, depuis des années, une série d'infractions aux codes de l'environnement et du travail.

Au dossier, sept arrêtés de mise en demeure pour non-respect des règles de sécurité de cette installation, classée site Seveso « haut » et installée à Auzouer-en-Touraine (Indre-et-Loire), où sont manipulées des centaines de substances chimiques dont certaines sont cancérogènes, toxiques ou inflammables. Et les reproches pleuvent : stockage anarchique, non-étiquetage des produits, rejets dans la rivière de la Brenne et dans l'atmosphère, absence de formation du personnel aux risques chimiques, recours abusifs aux intérimaires, etc.

« Quand on arrive dans cet établissement pour la première fois, on a l'impression d'un site à l'abandon, témoigne à la barre Christophe Simbelie, inspecteur de l'environnement à la direction régionale de l'environnement (Dreal), chargé de suivre Synthron entre 2012 et 2015. *Tout est plus ou moins rouillé, des murs en partie écroulés, des carreaux cassés, des peintures dégradées, des anciennes cuves déposées ci et là…»* En octobre 2014, un contrôle de la Dreal relève quelque 57 non-conformités sur le site.

Lors de son précédent procès, en 2014, M. Moor avait déjà répondu des faits similaires : stockages dangereux, absence de politique de formation, fuites et rejets… Neuf incidents avaient alors été versés au dossier, dont une explosion dans un atelier. L'affaire avait fait l'objet d'une vaste instruction, avec une perquisition de l'usine et du siège de la maison mère, Protex International, par une soixantaine d'enquêteurs, et avait été dépaysée au pôle santé public du tribunal de grande instance de Paris. M. Moor avait été condamné à six mois d'emprisonnement avec sursis et 40 500 euros d'amende.

Mais la saga judiciaire de Synthron remonte plus loin encore. En 1988, une explosion fait flamber l'usine. *« On s'est retrouvés saupoudrés de cendres, on ne savait pas ce qu'on respirait, on ne savait pas si on pouvait manger nos légumes,* se souvient Mireille Hagel, une riveraine, qui se bat depuis plus de vingt-cinq ans sur ce dossier avec des associations de protection de l'environnement. *La Brenne est devenue marron-rouge, tous les poissons sont morts. »* La ville de Tours, privée d'eau pendant plusieurs jours, est ravitaillée par camions-citernes.

Depuis, les incidents se suivent, les procédures administratives et judiciaires aussi. En 2004, nouvelle pollution grave de la Brenne. Lors du procès, quatre ans plus tard, se dessine une nouvelle façon d'évaluer le préjudice environnemental, non plus en se contentant de compter les quantités de poissons morts, mais en prenant en compte toute la faune aquatique, et, selon les juges, le paysage est l'*« âme du territoire ».*

« Quand on arrive dans cet établissement, on a l'impression d'un site à l'abandon »

CHRISTOPHE SIMBELIE
inspecteur de l'environnement à la Dreal

La répétition des infractions est telle que, d'après Serge Atico, du Bureau national du suivi des installations classées, cité à l'audience, Synthron est au premier rang du nombre de procédures engagées contre des sites Seveso en France. La deuxième place étant occupée par Protelor, autre usine du groupe Protex International. Niant toute responsabilité, M. Moor se dit assailli par *« les demandes de la Dreal, ridicules et irréalistes ». « Il y a un nouveau texte par semaine pour la protection environnementale, on n'arrive pas à suivre. »*

L'octogénaire, 401e fortune de France, à la tête d'un groupe familial affichant 160 millions d'euros de chiffre d'affaires, a été décrit à l'audience comme un patron tout-puissant et omniprésent, qui n'investit dans la sécurité qu'en tout dernier recours. *« Payer 395 000 euros d'amendes en dix ans, ou investir quelques millions d'euros pour se mettre en conformité… N'avez-vous pas pris finalement une décision rationnelle d'un point de vue économique ? »* interroge l'avocat des parties civiles. Le procureur a requis une amende de 491 000 euros pour Synthron et de 216 500 euros pour M. Moor, avec une interdiction de gérer une société pendant cinq ans. Le jugement a été mis en délibéré.

angela bolis

To: MSteph14@jhu.edu[MSteph14@jhu.edu]
Cc: Cogliano, Vincent[cogliano.vincent@epa.gov]
From: VJ Cogliano
Sent: Fri 11/13/2015 5:09:45 AM
Subject: Fwd: FW: ACTION NEEDED: Final sign-off on the systematic review manuscript

Hello Marty--Here are the references you requested:

1. The IARC Monographs' Instructions to Authors (http://monographs.iarc.fr/ENG/Preamble/instructions.php) and the NTP Report on Carcinogens Handbook (http://ntp.niehs.nih.gov/pubhealth/roc/handbook/index.html)

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3. To relate the IRIS "stopping rules" to systematic review, replace the text you highlighted with:

Systematic reviews typically include a literature-search cutoff date, after which "late-breaking" studies are not considered. Because IRIS evaluations are expected to consider late-breaking studies if they would change major conclusions, the EPA has developed a process for considering pivotal studies that are published after the literature search has closed (http://www2.epa.gov/sites/production/files/2014-06/documents/iris_stoppingrules.pdf).

I'll send you another message very soon if I have any comments on the manuscript.

Thank you for coordinating this work.

With best regards,
Vince

From: Martin Stephens [mailto:msteph14@jhu.edu]
Sent: Tuesday, November 03, 2015 12:32 PM
To: Cogliano, Vincent <cogliano.vincent@epa.gov>
Subject: Re: ACTION NEEDED: Final sign-off on the systematic review manuscript
Importance: High

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passages, which I've cut and pasted from the manuscript?

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Groups of scientists in both the US and EU are collaborating to advance systematic review approaches in toxicology. Guidance for conducting systematic reviews in toxicology has been published.[i],[ii],[MS1] [iii]

Can you supply the two citations that you reference? The NTP reference is different from the cited Rooney et al. reference?

The second passage:

The US Environmental Protection Agency's Integrated Risk Information System (IRIS) program has also embraced systematic review methods, and the agency is developing its own procedures for implementing them. [MS2]

[MS2] Vince: plz provide reference(s).

Third, and final, passage:

Because IRIS evaluations can last up to 2 years and because of the need to consider "late-breaking" studies that would change major conclusions, the agency has developed a process for considering critical, pivotal studies that would make a substantial contribution to the outcome even after the literature search has been closed.[MS3]

[MS3] Nancy Beck writes: This seems sort of out of place here. Perhaps Vince can say more about how the stopping rules relate to a Systematic review?

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Thanks Vince. Your prompt response would be appreciated.

All the best,

Marty

Martin L. Stephens, Ph.D.

Senior Research Associate

Johns Hopkins Center for Alternatives to Animal Testing

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msteph14@jhu.edu

From: <Cogliano>, Vincent Cogliano <cogliano.vincent@epa.gov>
Date: Monday, October 5, 2015 5:34 PM
To: Martin Stephens <msteph14@jhu.edu>
Subject: RE: ACTION NEEDED: Final sign-off on the systematic review manuscript

Hello Martin—Thank you for having this manuscript drafted. It reads quite well and will make a good contribution to the field. Attached are my edits.

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Thanks and best regards,

Vince

From: Martin Stephens [mailto:msteph14@jhu.edu]
Sent: Thursday, September 17, 2015 7:10 PM
To: Thomas Hartung; Roberta Scherer; Andrew Rooney; Cogliano, Vincent; Didier Verloo; Nancy_Beck@americanchemistry.com; Kay Dickersin; Suzanne Fitzpatrick; George Gray; jmcpartland@edf.org; Sebastian Hoffmann; James Freeman
Cc: k_betts@nasw.org; Martin Stephens
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Dear All,

Attached is the draft manuscript based on our November workshop, revised in light of the your comments. Please make a final review of the manuscript and send any last-minute comments to the full group. Notice that in some cases, tracked comments in the manuscript call upon specific co-authors (Andy, Vince, Didier, and Bobbi) to provide information or clarification. Please send me any final edits by **Oct. 5th**. If I haven't heard from you by then, I will assume you are okay with the manuscript.

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We are considering sending the manuscript to *Toxicological Sciences, Systematic Reviews, or Risk Analysis*. We welcome your thoughts on these and related options. Please let us know if you have any connection to the editorial team of any of these journals and whether you might thereby be in a position to check with the editors regarding how they might view the suitability of the manuscript for their journal.

Thanks for your efforts!

Regards,

Marty

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From: Martin Stephens <msteph14@jhu.edu>
Date: Tuesday, June 9, 2015 10:02 AM
To: Thomas Hartung <thartun1@jhu.edu>, Roberta Scherer <rscherer@jhsph.edu>, Andrew Rooney <Andrew.Rooney@nih.gov>, Vincent Cogliano <cogliano.vincent@epa.gov>, Didier Verloo <Didier.VERLOO@efsa.europa.eu>, Nancy Beck <nancy_beck@americanchemistry.com>, Kay Dickersin <kdicker3@jhu.edu>, Suzanne Fitzpatrick <suzanne.fitzpatrick@fda.hhs.gov>, George Gray <gmgray@gwu.edu>, Jennifer McPartland <jmcpartland@edf.org>, Sebastian Hoffmann <sebastian.hoffmann@seh-cs.com>, James Freeman <james.j.freeman@exxonmobil.com>
Cc: Martin Stephens <msteph14@jhu.edu>, Kellyn Betts <k_betts@nasw.org>
Subject: draft manuscript from our Nov. workshop

Dear All,

It's been approximately six months since our Nov. 21st workshop on "The Emergence of Systematic Review and Related Evidence-based Approaches in Toxicology." At the time, a few of us talked privately about the possibility of having a paper come out of the workshop. What we were envisioning was not a bland workshop summary but a paper that used the workshop as a spring-board to talk about where we are now with systematic review in toxicology, where we've come from (historical antecedents), where we like to head, and what the challenges might be. With the help of science writer Kellyn Betts, we've produced a draft of this paper.

The paper (attached) no doubt still needs a fair amount of work. What we'd like from you at this point is three things:

1. The first is your edits/comments on the current draft. You'll see several places in the manuscript where we ask for input from the presenters. We'd especially like feedback for these sections.
2. Second, we'd like to get your agreement to be a co-author on the paper. If you need to make your agreement conditional on agency approval, or conditional on certain changes to be made in the manuscript, just let us know. You'll get an opportunity to sign off on the final version.
3. And finally, we'd like to get your thoughts on which journal to eventually submit the manuscript to. Possibilities that have been floated so far amongst the Evidence-based Toxicology Collaboration folks include Environmental Health Perspectives, Toxicological Sciences, Archives of Toxicology, and Critical Reviews in Toxicology.

We think the paper will help facilitate the uptake of systematic review in toxicology, as well as help to harmonize approaches in a way that will still leave room for adaptations to individual agency needs.

May I hear from you by **June 22nd**?

Best,

Marty

Martin L. Stephens, Ph.D.

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[i] Rooney AA, Boyles AL, Wolfe MS, Bucher JR, Thayer KA. 2014. Systematic review and evidence integration for literature-based environmental health science assessments. *Environ Health Perspect* 122:711–718; http://dx.doi.org/10.1289/ehp.1307972

[ii] European Food Safety Authority; Application of systematic review methodology to food and feed safety assessments to support decision making. EFSA Journal 2010; 8(6):1637. [90 pp.]. doi:10.2903/j.efsa.2010.1637. Available online: www.efsa.europa.eu

[iii] Woodruff, T.J. and Sutton, P. 2014 The Navigation Guide Systematic Review Methodology: A Rigorous and Transparent Method for Translating Environmental Health Science into Better Health Outcomes. *Environ Health Perspect 122: 1007-1014.* DOI:10.1289/ehp.1307175

[MS1]Vince says: Add IARC and NTP, or call these three "exploratory," as they have not had the breadth of application of IARC and NTP.

[MS2]

[MS3]

To: Cogliano, Vincent[cogliano.vincent@epa.gov]
From: VJ Cogliano
Sent: Fri 11/13/2015 5:05:01 AM
Subject: Re: FW: ACTION NEEDED: Final sign-off on the systematic review manuscript

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On Tue, Nov 10, 2015 at 5:18 PM, Cogliano, Vincent <cogliano.vincent@epa.gov> wrote:

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443-742-1189 (mobile), 410-614-4989 (office)

msteph14@jhu.edu

From: Martin Stephens <msteph14@jhu.edu>
Date: Tuesday, June 9, 2015 10:02 AM
To: Thomas Hartung <thartun1@jhu.edu>, Roberta Scherer <rscherer@jhsph.edu>, Andrew Rooney <Andrew.Rooney@nih.gov>, Vincent Cogliano <cogliano.vincent@epa.gov>, Didier Verloo <Didier.VERLOO@efsa.europa.eu>, Nancy Beck <nancy_beck@americanchemistry.com>, Kay Dickersin <kdicker3@jhu.edu>, Suzanne Fitzpatrick <suzanne.fitzpatrick@fda.hhs.gov>, George Gray <gmgray@gwu.edu>, Jennifer McPartland <jmcpartland@edf.org>, Sebastian Hoffmann <sebastian.hoffmann@seh-cs.com>, James Freeman <james.j.freeman@exxonmobil.com>
Cc: Martin Stephens <msteph14@jhu.edu>, Kellyn Betts <k_betts@nasw.org>
Subject: draft manuscript from our Nov. workshop

Dear All,

It's been approximately six months since our Nov. 21st workshop on "The Emergence of Systematic Review and Related Evidence-based Approaches in Toxicology." At the time, a few of us talked privately about the possibility of having a paper come out of the workshop. What we were envisioning was not a bland workshop summary but a paper that used the workshop as a spring-board to talk about where we are now with systematic review in toxicology, where we've come from (historical antecedents), where we like to head, and what the challenges might be. With the help of science writer Kellyn Betts, we've produced a draft of this paper.

The paper (attached) no doubt still needs a fair amount of work. What we'd like from you at this point is three things:

1. The first is your edits/comments on the current draft. You'll see several places in the manuscript where we ask for input from the presenters. We'd especially like feedback for these sections.
2. Second, we'd like to get your agreement to be a co-author on the paper. If you need to make your agreement conditional on agency approval, or conditional on certain changes to be made in the manuscript, just let us know. You'll get an opportunity to sign off on the final version.
3. And finally, we'd like to get your thoughts on which journal to eventually submit the manuscript to. Possibilities that have been floated so far amongst the Evidence-based Toxicology Collaboration folks include Environmental Health Perspectives, Toxicological Sciences, Archives of Toxicology, and Critical Reviews in Toxicology.

We think the paper will help facilitate the uptake of systematic review in toxicology, as well as help to harmonize approaches in a way that will still leave room for adaptations to individual agency needs.

May I hear from you by **June 22nd**?

Best,

Marty

Martin L. Stephens, Ph.D.

Johns Hopkins Center for Alternatives to Animal Testing

Director, Evidence-based Toxicology

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msteph14@jhu.edu

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[i] Rooney AA, Boyles AL, Wolfe MS, Bucher JR, Thayer KA. 2014. Systematic review and evidence integration for literature-based environmental health science assessments. *Environ Health Perspect* 122:711–718; http://dx.doi.org/10.1289/ehp.1307972

[ii] European Food Safety Authority; Application of systematic review methodology to food and feed safety assessments to support decision making. EFSA Journal 2010; 8(6):1637. [90 pp.]. doi:10.2903/j.efsa.2010.1637. Available online: www.efsa.europa.eu

[iii] Woodruff, T.J. and Sutton, P. 2014 The Navigation Guide Systematic Review Methodology: A Rigorous and Transparent Method for Translating Environmental Health Science into Better Health Outcomes. *Environ Health Perspect 122: 1007-1014.* DOI:10.1289/ehp.1307175

[MS1]Vince says: Add IARC and NTP, or call these three "exploratory," as they have not had the breadth of application of IARC and NTP.

[MS2]

[MS3]

To: Cogliano, Vincent[cogliano.vincent@epa.gov]
From: Kurt Straif
Sent: Thur 11/12/2015 12:15:15 PM
Subject: RE: Glyphosate: EFSA updates toxicological profile

Thx, vincent,

We started receiving interview requests already yesterday…

Kurt

From: Cogliano, Vincent [mailto:cogliano.vincent@epa.gov]
Sent: 12 November 2015 12:38
To: Kurt Straif <StraifK@iarc.fr>; Neela Guha <guhan@iarc.fr>; Gaudin Nicolas <NicholasGaudin@hotmail.com>
Subject: Fwd: Glyphosate: EFSA updates toxicological profile

Begin forwarded message:

From: "Bahadori, Tina" <Bahadori.Tina@epa.gov>
To: "Fegley, Robert" <Fegley.Robert@epa.gov>, "McQueen, Jacqueline" <McQueen.Jacqueline@epa.gov>, "Cogliano, Vincent" <cogliano.vincent@epa.gov>, "Wood, Charles" <Wood.Charles@epa.gov>, "Lobdell, Danelle" <Lobdell.Danelle@epa.gov>, "Egeghy, Peter" <Egeghy.Peter@epa.gov>
Cc: "Birchfield, Norman" <Birchfield.Norman@epa.gov>
Subject: Glyphosate: EFSA updates toxicological profile

In case you had not seen this announcement yet – full assessment and additional information can be found: http://www.efsa.europa.eu/en/efsajournal/pub/4302.

Tina

From: LIEM Djien [mailto:Djien.LIEM@efsa.europa.eu]
Sent: Thursday, November 12, 2015 2:57 AM
To: Taveau, Daniella <Taveau.Daniella@epa.gov>; Dix, David <Dix.David@epa.gov>; Miller, David <Miller.DavidJ@epa.gov>; Cowles, James <Cowles.James@epa.gov>; Robbins, Jane <Robbins.Jane@epa.gov>; Rowland, Jess <Rowland.Jess@epa.gov>; Mary Ko Manibusan (manibusan.mary@epa.gov) <manibusan.mary@epa.gov>; Thomas, Russell

<Thomas.Russell@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Villeneuve, Dan <Villeneuve.Dan@epa.gov>
Subject: UNDER EMBARGO - Glyphosate: EFSA updates toxicological profile

Dear Colleagues,

Today 12 November at 12:00 CET, EFSA will publish a Conclusion on the Peer review on glyphosate and a complementary technical document.

It will be accompanied by a News Story and a non technical summary.

The documents are under embargo until **12:00 CET** when they will be published on our website.

For any further information on the Conclusion, please contact Jose Tarazona (Jose.Tarazona@efsa.europa.eu).

For any further information on the News Story, please contact Simon Terry (simon.terry@efsa.europa.eu).

Best regards,

Djien

Djien Liem, PhD

Lead Expert in International Scientific Cooperation

Advisory Forum and Scientific Cooperation Unit

European Food Safety Authority

Via Carlo Magno 1A

43126 Parma (Italy)

Tel. +39 0521 036225

www.efsa.europa.eu

The documents are scheduled for publication on **12 November 2015 at 12:00 CET. They are shared under embargo in advance for your information and not for wider distribution.** The documents are shared on a confidential basis in advance of final publication and are therefore not intended to be shared beyond recipients identified in the distribution list above until the final documents are actually published. There is always a possibility that there will be additional changes before the final version is published and that the actual date and/or time of publication, indicated by the embargo, may change. Please note that only the final, published version remains the reference document. The EFSA website should be checked for confirmation of final content and publication. Only documents which are published on EFSA's website can be cited/used.

To: Kurt Straif[StraifK@iarc.fr]; Dana Loomis[LoomisD@iarc.fr]; Véronique Terrasse[TerrasseV@iarc.fr]; Cogliano, Vincent[cogliano.vincent@epa.gov]
From: Nicolas Gaudin
Sent: Tue 11/10/2015 10:01:56 PM
Subject: EPA Used Monsanto¹s Research to Give Roundup a Pass

Fyi
Nicolas

https://theintercept.com/2015/11/03/epa-used-monsanto-funded-research/

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Intercept Privacy

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Photo: Seth Perlman/AP

 Sharon Lerner

Sharon Lerner

Nov. 3 2015, 9:32 p.m.

THE ENVIRONMENTAL PROTECTION AGENCY concluded in June that there was "no convincing evidence" that glyphosate, the most widely used herbicide in the U.S. and the world, is an endocrine disruptor.

On the face of it, this was great news, given that some 300 million pounds of the chemical were used on U.S. crops in 2012, the most recent year measured, and endocrine disruption has been linked to a range of serious health effects, including cancer, infertility, and diabetes. Monsanto, which sells glyphosate under the name Roundup, certainly felt good about it. "I was happy to see that the safety profile of one of our products was upheld by an independent regulatory agency," wrote Steve Levine on Monsanto's blog.

But the EPA's exoneration — which means that the agency will not require additional tests of the chemical's effects on the hormonal system — is undercut by the fact that the decision was based almost entirely on pesticide industry studies. Only five independently funded studies were considered in the review of whether glyphosate interferes with the endocrine system. Twenty-seven out of 32 studies that looked at glyphosate's effect on hormones and were cited in the June review — most of which are not publicly available and were obtained by

The Intercept through a Freedom of Information Act request — were either conducted or funded by industry. Most of the studies were sponsored by Monsanto or an industry group called the Joint Glyphosate Task Force. One study was by Syngenta, which sells its own glyphosate-containing herbicide, Touchdown.

Findings of Harm Were Dismissed

Who pays for studies matters, according to *The Intercept*'s review of the evidence used in the EPA's decision. Of the small minority of independently funded studies that the agency considered in determining whether the chemical poses a danger to the endocrine system, three of five found that it did. One, for instance, found that exposure to glyphosate-Roundup "may induce significant adverse effects on the reproductive system of male Wistar rats at puberty and during adulthood." Another concluded that "low and environmentally relevant concentrations of glyphosate possessed estrogenic activity." And a review of the literature turns up many more peer-reviewed studies finding glyphosate can interfere with hormones, affecting such things as hormonal activity in human liver cells, functioning of rat sperm, and the sex ratio of exposed tadpoles.

Yet, of the 27 industry studies, none concluded that glyphosate caused harm. Only one admitted that the pesticide might have had a role in causing the health problems observed in lab animals exposed to it. Some rats that consumed it were more likely to have to have soft stools, reduced body weight, and smaller litters. But because that evidence didn't meet a test of statistical significance, the authors of the Monsanto study deemed it "equivocal."

Indeed, many of the industry-funded studies contained data that suggested that exposure to glyphosate had serious effects, including a decrease in the number of viable fetuses and fetal body weight in rats; inflammation of hormone-producing cells in the pancreas of rats; and increases in the number of pancreatic cancers in rats. Each is an endocrine-related outcome. Yet in each case, sometimes even after animals died, the scientists found reasons to discount the findings — or to simply dismiss them.

When rats exposed to glyphosate had a decreased number of pregnancies that implanted, for instance, the authors of a 1980 Monsanto-sponsored study explained that "since ovulation and implantation occurred prior to treatment, the decreases … were not considered to be treatment related." Although they noted

that the decrease in implantations and viable fetuses was "statistically significant," the authors nonetheless concluded that the decrease in implantations was a random occurrence.

While recent research has shown that very low doses of endocrine disruptors can not only have health effects but effects that are more dramatic than those caused by higher doses, some of the studies dismiss clear examples of harm because they occur in animals given relatively low doses of the substance. A study prepared by Monsanto in 1990, for instance, noted a statistically significant increase in pancreatic cancers among rats exposed to a relatively low dose of Roundup. The rats had a 14 percent chance of cancer, compared to a 2 percent chance in the control group. But since some rats exposed to higher amounts of the chemical had lower cancer rates, the scientists concluded the elevation was "unrelated to glyphosate administration."

A Flawed System

Independent scientists may come up with different results than industry-funded ones for a variety of reasons, including how a study is designed or carried out. But Michelle Boone, a biologist who served on an EPA panel that evaluated the safety of atrazine, another pesticide, told *The Intercept* that analysis of those results is an area particularly ripe for bias. "Once you have industry intimately involved in interpreting the data and how it's written up, it's problematic."

Having companies fund and perform studies that affect them financially would seem to be an obvious conflict of interest, but that's the standard practice at EPA. The glyphosate review, which was completed in June, was one of 52 reporting on the endocrine disrupting potential of pesticides, all of which relied heavily on industry-funded research and most of which concluded, as the one of glyphosate did, that there was no cause for further testing. (Though marketed as a weed killer, or herbicide, glyphosate is considered to be a pesticide by the EPA.)

Asking chemical companies to do their own testing makes financial — if not scientific — sense for the cash-strapped federal agency. Monsanto, which had more than $15.8 billion in net sales last year (roughly twice the EPA's annual budget), can easily foot the research bill. Companies like Monsanto, Syngenta, or Dow can either do the research themselves or hire contract research labs, such as Wildlife International or CeeTox, Inc., which supplied much of the

research for the glyphosate review.

But the fact that these labs depend upon the large corporations that employ them as evaluators can't help but skew their findings, according to critics of the system. "They know who's buttering their toast," said Doug Gurian Sherman, a senior scientist at the Center for Food Safety and former staff scientist at the EPA Office of Pesticide Programs. "It's not that people are going to necessarily do something clearly fraudulent. It's more that it puts a pressure to shave things in a direction to whoever's paying the bills."

The process can be distorted beginning with the very first step, when a company chooses which lab will perform its tests. "Industry is very aware of companies they can hire that have never found an estrogen positive chemical," said Laura Vandenberg, a professor of biology at University of Massachusetts, Amherst, who specializes in endocrine disruption and hazard assessment. "Just like you know which mechanic in your neighborhood is more likely to be dishonest. They know who is more likely to give them a favorable finding."

The EPA defended its process in a statement. "We want to make clear that EPA maintains a transparent, public process for assessing potential risks to human health when evaluating pesticide products," it began. The agency statement also pointed out that the law requires pesticide companies to provide studies supporting their products. "Once studies are submitted to the agency, EPA scientists analyze the data to ensure that the design of the study is appropriate and that the data have been collected and analyzed accurately."

Syngenta responded in a statement that pointed out that pesticide companies have to provide data to the EPA: "The law requires manufacturers do extensive scientific studies to prove a new compound is safe. EPA controls and documents the studies' strict adherence to its guidelines. This provides the highest level of transparency to the agency, fellow scientists and the public."

A spokesperson for Monsanto wrote in an email that "the government requires many, many studies to make sure herbicides can be used safely. While some of these studies are required to come from us, many of these studies are conducted by third-party scientists and labs. The EPA looked at 11 different validated assays assessing the potential for effect of glyphosate on endocrine pathways in humans and wildlife. Based on its review of the data, EPA concluded 'there was no convincing evidence of potential interaction with the estrogen, androgen or thyroid pathways' and this conclusion is consistent with the results from other

safety studies conducted in accordance with international and assessment guidelines." Dow, Wildlife International, and CeeTox, Inc. did not respond to *The Intercept*'s requests for comment.

A False Sense of Security

The dependence on industry is just one of several limitations of the EPA's effort to screen pesticides for their potential to interfere with the way androgen, estrogen, and thyroid hormones work. The effort has also been dogged by delays. Congress mandated that the agency begin screening to see whether pesticides were endocrine disruptors back in 1996. Yet the screenings of the 52 pesticides in June were the first to emerge from the program in almost 20 years since the testing was required.

In the intervening time, our knowledge about endocrine disruptors has exploded, leaving many of the tests on them out of date. Indeed, many of the studies submitted for the glyphosate review dated back to the 1970s. One was 40 years old. In all, 15 of the 27 industry studies predated the term "endocrine disruption," which was coined in 1991.

Perhaps the most important discovery in the area of endocrine research in the decades since those studies were performed is that even small amounts of hormonally active chemicals can have powerful effects. Yet the cutoffs used in the EPA's screening program were far higher than the lowest levels shown to have effects in the latest research.

"We see effects at levels that are 1,000 times lower" than the cutoff EPA uses, said Vandenberg, who warned of the false sense of security given by such insensitive screenings. "It's like putting your deaf grandfather in front of a TV and asking him if he can hear it and when he says no, you conclude the TV is off."

Almost as problematic as the industry-provided data, some critics say, is the research the agency doesn't consider. "They exclude studies that others in the field would consider to be perfectly good," said Sherman, of the Center for Food Safety. Or, as was the case in the glyphosate review, findings of harm by independently conducted studies may be considered but discounted.

While independent scientists have complained about the role of the pesticide industry in its own regulation for years — and suggested ways to fix it, including discounting any studies that have a conflict of interest — there's little progress on that front.

In fact, having cleared this review, glyphosate is now about to face another regulatory hurdle that, while bigger, is similarly flawed. Every 15 years, the EPA must review pesticides on the market in light of the latest science. Glyphosate's review, which will include research on its health effects on humans and is expected to be completed in the next few months, is the first to come after the International Agency for Research on Cancer labeled glyphosate a probable carcinogen in March. If the EPA doesn't reregister glyphosate, it could be essentially banned, as it already is in France and Sri Lanka.

Monsanto seems optimistic its product will survive the coming EPA review, noting in the blog post about the recent EPA review that "glyphosate's safety is supported by one of the most extensive worldwide human health databases ever compiled on an agricultural product."

Unfortunately, Monsanto has supplied most of that data.

Contact the author:

Sharon Lerner fastlerner@gmail.com

To: Cogliano, Vincent[cogliano.vincent@epa.gov]
From: onbehalfof+ehpmanuscripts+niehs.nih.gov@manuscriptcentral.com
Sent: Mon 11/2/2015 2:46:01 PM
Subject: Invitation to Review 15-10909-ART for EHP

02-Nov-2015

Dear Dr. Cogliano:

Manuscript ID 15-10909-ART titled "Prioritizing Chemicals for Risk Assessment Using Chemoinformatics: Examples from the IARC Monographs on Pesticides" by Guha, Neela; Guyton, Kathryn; Loomis, Dana; Barupal, Dinesh has been submitted to Environmental Health Perspectives.

I invite you to review this manuscript. The abstract appears at the end of this letter. Please let me know as soon as possible if you will be able to accept my invitation to review. We prefer to receive review comments within two weeks of accepting the invitation, but if you need extra time please let us know and we can adjust the due date.

If you are unable to review at this time, I would appreciate you recommending another expert reviewer. Recommendations for alternate reviewers should be e-mailed to EHPManuscripts@niehs.nih.gov. Please be sure to reference the correct manuscript number in the subject field of your e-mail.

By clicking the appropriate link at the bottom of the page, your reply will be automatically registered with our online manuscript submission and review system.

If you accept my invitation to review this manuscript, you will be notified via e-mail about how to access Manuscript Central, our online manuscript submission and review system. You will then have access to the manuscript and reviewer instructions in your Reviewer Center.

I realize that our expert reviewers greatly contribute to the high standards of the Journal, and I thank you for your present and/or future participation.

Sincerely,

Dr. Manolis Kogevinas
Environmental Health Perspectives
ehpmanuscripts@niehs.nih.gov

Agreed: https://mc.manuscriptcentral.com/ehp?URL_MASK=6b426bb4defa4c1cb6d3a2cc64b8a3a0

Declined: https://mc.manuscriptcentral.com/ehp?URL_MASK=72cd7aa6780c41f98902beee67670fe1

Unavailable: https://mc.manuscriptcentral.com/ehp?URL_MASK=3bb2a561fe53437e9976f4bb753be49b

MANUSCRIPT DETAILS

TITLE: Prioritizing Chemicals for Risk Assessment Using Chemoinformatics: Examples from the IARC Monographs on Pesticides

ABSTRACT: Identifying cancer hazards is the first step towards cancer prevention. The IARC Monographs Programme, which has evaluated nearly 1000 agents for carcinogenic potential since 1971, typically selects agents for hazard identification on the basis of public nominations, expert advice, published data on carcinogenicity, and public health importance. Here we present a novel and complementary strategy for identifying agents for hazard evaluation using chemoinformatics, database integration and automated text mining. To inform selection among a broad range of pesticides nominated

for evaluation, we identified and screened nearly 6000 relevant chemical structures, thereafter systematically compiled information on 980 pesticides, creating chemical similarity network maps that allowed cluster visualization by chemical similarity, class, and the number of publications concerning epidemiology, cancer bioassays, and carcinogenic mechanisms. For the IARC Monograph meetings that took place in March and June 2015, this approach supported high priority evaluation of glyphosate, malathion, parathion, tetrachlorvinphos, diazinon, DDT, lindane, and 2,4-D. This systematic approach, accounting for chemical similarity and overlaying multiple data sources, can be used by risk assessors as well as researchers to systematize, inform and increase efficiency in selecting and prioritizing agents for hazard identification, risk assessment, regulation or further investigation. This approach could be extended to an array of outcomes and agents, including occupational carcinogens, drugs, and foods.

To: Cogliano, Vincent[cogliano.vincent@epa.gov]; cportier@mac.com[cportier@mac.com]; straifk@iarc.fr[straifk@iarc.fr]
From: Ivan Rusyn
Sent: Mon 10/26/2015 7:20:12 PM
Subject: Fwd: Krewski et al manuscript

Dear Vince,
please see below a conversation that Chris and I had off line regarding one of the manuscripts that were sent around by Robert. I believe this is an issue that requires further consideration. Your opinion would be much appreciated.
Thank you,
Ivan

---------- Forwarded message ----------
From: **Chris Portier** <cportier@mac.com>
Date: Mon, Oct 26, 2015 at 9:35 AM
Subject: Re: Krewski et al manuscript
To: Ivan Rusyn <ivan.rusyn@gmail.com>
Cc: Kurt Straif <straifk@iarc.fr>, Robert Baan <BaanR@visitors.iarc.fr>

I am equally distressed about this paper. It seems that none of our discussions regarding what should and should not be in this paper were heeded by Dan. To give an idea of the disconnect, in the discussion he finally mentions the problem of the denominator in the concordance measures, but only suggests it could go in just one direction (it can go in both). And then, the discussion goes on to say the concordance between different animal species could not be done because of problems with the animal data. This makes zero sense. The whole quantitative concordance part of this paper needs to be completely removed and some of the text modified to strongly encourage people NOT to use this database in that way. The descriptive stats are fine, but I am even a bit uncomfortable with the heat maps as well. Finally, the whole thing is way too long for what it contributes.
If we cannot resolve these issues, my suggestion is for IARC not to publish this. Regardless, in its current form, I will ask to have my name removed from this.

C.

On Oct 25, 2015, at 9:13 PM, Ivan Rusyn <ivan.rusyn@gmail.com> wrote:

Chris and Kurt,

I am fine with Grosse et al manuscript as it is a database and can be of much use in the future.

The second one gives me great pause still. Tables 7 and 8 are difficult to interpret. It is not clear what “all species” columns are as it is neither in the legend nor in the text. Also, the legend says kappa lower bound has to be above 0 and for most numbers it is not. These tables don’t make it clear how many agents went into each comparison or the fact that some tumors are more common in rodents (i.e., liver) than in humans and vice versa… I can go on and on...

I am still not sure what benefit these analyses have vs the potential concern they will bring over the value of animal evidence. The “weight of evidence” crowd would be all over this and the Monographs program is booby trapping itself and the rest of hazard assessment community for decades to come...

Your names are on this manuscript, so I am appealing to you first as you are quite aware of the challenge we have been discussing with the strength of animal data for one of Vol 112 agents...

I hope you will weigh in on this.

Ivan

PS Robert, I cc-ing you on this too, so please take my considerations under advisement.

PPS All, please respond to this email, if you wish, to this GMAIL address, not my TAMU.EDU address...

To: Robert Baan[BaanR@visitors.iarc.fr]; Kurt Straif[StraifK@iarc.fr]; Yann Grosse[GrosseY@iarc.fr]
Cc: Jerry Rice[jr332@georgetown.edu]; Michael Bird[michaelgbird@gmail.com]; Brittany Milton[bmilton@risksciences.com]; Brian collins[brianandhelencollins@sympatico.ca]; Melissa Billard[melissabillard@me.com]; Cogliano, Vincent[cogliano.vincent@epa.gov]; Chris Portier[cportier@mac.com]; Julian Little[jlittle@uottawa.ca];
Ex. 6 - Personal Privacy
From: Daniel Krewski
Sent: Mon 10/5/2015 5:03:48 AM
Subject: Final Draft of Concordance Analysis Manuscript
2015 Krewski et al Concordance Analysis October 4.pdf
2015 Krewski et al Concordance Analaysis Supplement I October 4, 2015.pdf
2015 Krewski et al Concordance Analysis Supplement II October 4, 2015.pdf

Robert, I'm pleased to provide you with the final draft of the concordance analysis manuscript, along with two supplements that are intended for online publication only. This anlaysis is based on the final verison of the concordance databases that includes revisions to the database from last week.

The major changes incorporated since the last version include:

1) a revised tumour nomenclature system based on the comments provided by the WG at the last teleconference in August;

2) a discussion of the ten agents placed in Group-1 due to mechanistic upgrades;

3) an expanded discussion of agents with no tumour sites identified in animals (and the reasons for this);

4) an analysis showing that all Group-1 agents that have been appropriately tested in animals also provide sufficient or limited evidence in animals;

5) an discussion of why the concordance database does not support estimation of the predictive value (positive or negative) of animal evidence for humans;

6) a reference at the end of the discussion section to future joint analyses of the concordance and mechanisms databases.

The present manuscript retains the kappa statistics, but presents them in much less detail (the final analysis shows quite high kappa values in a number of cases). There is also a clear statement on what the kappa statistics measure, which may not have been clear in previous

discussions. While I find this analysis informative, I would appreciate your views on the current results.

Please let me know if you would like us to prepare an updated briefing for the WG; if not, we will look forward to your comments on our chapter.

Word and Excel files for your editorial use have been sent in a companion email . . .

With best regards.

Daniel Krewski, PhD, MHA

McLaughlin Chair in Risk Science

Professor and Director

McLaughlin Centre for Population Health Risk Assessment

University of Ottawa

Room 118, 850 Peter Morand Crescent, Ottawa, Ontario CANADA K1G 3Z7

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Administrative Assistant: Nicole Begnoche

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Project Coordinator: Shalu Darshan, PhD

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Email: sdarshan@uottawa.ca

Concordance between Animal and Human Tumours: An Analysis of 111 Agents Known to Cause Cancer in Humans

Supplemental Material I: Database of Anatomically-based Tumour Sites in Animals and Humans

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

[1]McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Canada
[2]Risk Sciences International, Ottawa, Canada
[3]School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa, Ottawa, Canada
[4]School of Medicine, Georgetown University, Washington, D.C., USA
[5]Department of Epidemiology, Queens University, Kingston, Canada
[6]*IARC Monographs Programme*, International Agency for Research on Cancer, Lyon, France
[7]Integrated Risk Information System, US Environmental Protection Agency, Washington, D.C., USA
[8]Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Canada

Krewski et al. (2015) conducted a comprehensive analysis of the concordance between tumours seen in animals and humans for 111 distinct Group-1 agents identified in the IARC Monographs programme through Volume 109, based on information abstracted from the IARC Monographs by Grosse et al. (2015). The format of data abstracted from the Monographs by Grosse et al. (2015) is illustrated in Figure 3 of Krewski et al. (2015), which includes histological information on animal and human tumours associated with these 111 agents, as well as information on the route of exposure and the gender and species of experimental animal models used.

Because there currently exists no common tumour nomenclature for animal and human tumours, Krewski et al. (2015, Table 2) developed an anatomically-based tumour nomenclature system that permits comparison of tumours seen in animals and humans on a site-specific basis, as well as on the basis of organ and tissue systems comprised of anatomically-related tumour sites. This system was developed by first identifying the anatomical tumour sites seen in both animals and humans for the 111 Group-1 agents based on the data abstracted from the Monographs by Grosse et al. (2015), as summarized in Supplemental Table 1. This was done by recording the individual tumour sites seen in humans and animals in columns 3 and 4 in Supplemental Table 1, respectively, organized by the organ and tissue systems in column 1; column 2 provides the common anatomically-based tumour site used for both animal and human tumours occurring at this site. It should be noted that although *sufficient evidence* for sites in italics in Supplementary Table 1 was not available in either animals or humans for any of the 111 Group-1 agents, these sites are included to record that they were considered, but not observed for various reasons noted in the footnotes to Supplementary Table 1, including the possibility that only *limited evidence* of carcinogenicity was available. This analysis formed the basis for the harmonized,

anatomically-based tumour nomenclature system used by Krewski et al. (2015) as the basis for evaluating concordance between animal and human tumours.

The IARC tumour site concordance database based on this anatomically-based tumour nomenclature system (Supplemental Table 2). A data dictionary describing the elements of Supplemental Table 2 is provided in Supplemental Table 3. Supplemental Table 4 provides the numerical codes assigned to the 47 individual tumour sites and 13 organ and tissue systems included in the database.

References

Gross et al. (2015). Database of Animal and Human Tumours Based on 111 Group-1 Distinct Agents Known to Cause Cancer in Humans. [This volume.]

Krewski et al. (2015). Concordance between Animal and Human Tumours: An Analysis of 111 Agents Known to Cause Cancer in Humans. [This volume.]

List of Tables

Supplemental Table 1. Animal and Human Tumour Sites for 111 Group-1 Agents Identified through Volume 109 of the IARC Monographs[i]

Organ and Tissue System	Tumour Site	Sites with *Sufficient Evidence* for Cancer in Humans	Sites with *Sufficient Evidence* for Cancer in Experimental Animals
Upper aerodigestive tract	Nasal cavity and paranasal sinuses Nasopharynx Oral cavity Pharynx Tongue Tonsil Salivary gland	Nasal cavity and paranasal sinuses Nasopharynx Oral cavity Pharynx (incl. oropharynx & hypopharynx) Tonsil Salivary gland	Nasal cavity Oral cavity Lip (inner) [ii] Tongue
Respiratory system	*Trachea* [iii] Larynx Lung Lower respiratory tract	*Trachea* Larynx Lung	*Trachea* Larynx Lung Lower respiratory tract (larynx, trachea, and lung)
Mesothelium	Mesothelium	Mesothelium	Pleural mesothelium Peritoneal mesothelium *Peritesticular mesothelium*
Digestive tract	Digestive tract (unspecified) Oesophagus Stomach Intestine, including colon and rectum	Digestive tract (unspecified) Oesophagus Stomach Colon and rectum	 Oesophagus Forestomach Glandular stomach Small and/or large intestine
Digestive organs	Liver parenchyma and bile ducts Pancreas NOS Gall bladder	Liver (parenchyma) and bile ducts Gall bladder Pancreas NOS	Liver parenchyma *Bile ducts* *Gall bladder* [iv] *Pancreas, exocrine*
Nervous system and eye	Brain and spinal cord (CNS) *Cranial and peripheral nerves* [v] Eye	Brain and spinal cord (CNS) *Cranial and peripheral nerves* Eye (melanoma)	Brain and spinal cord (CNS) *Cranial and spinal nerves*
Endocrine system	Thyroid, follicular epithelium	Thyroid	Thyroid, follicular epithelium

	Adrenal gland (medulla, cortex, NOS) Pituitary		Adrenal gland (medulla, cortex, NOS) Pituitary
Kidney	Kidney (renal cell carcinoma)	Kidney, unspecified	Kidney, unspecified
Urothelium	Urothelium (renal pelvis, ureter, urinary bladder)	Renal pelvis Ureter Urinary bladder	Renal pelvis Ureter Urinary bladder
Lymphoid and haematopoietic tissues	Haematopoietic tissue Lymphoid tissue	Haematopoietic tissue (AML, ANLL) [vi] Leukaemia, unspecified Lymphoid tissue (lymphoid leukaemia/lymphoma)	Haematopoietic tissue (granulocytic leukaemia) Lymphoid tissue including thymus (leukaemia/ lymphoma)
Skin	Skin and adnexae Cutaneous melanocytes	Skin and adnexae (general body surface including scrotum, penis, anus and conjunctivae) *Lip (outer)*[vii] Cutaneous melanocytes (malignant melanoma)	Skin and cutaneous sebaceous glands
Connective tissues	Soft connective tissue Blood vasculature (endothelium) Hard connective tissue (bone, cartilage)	Soft connective tissue Blood vasculature (endothelium) Angiosarcoma of the liver Hard connective tissue (bone, cartilage)	Soft connective tissue (incl. haemangiosarcoma) Hard connective tissue (bone, cartilage)
Female breast, female reproductive organs and reproductive tract	Breast Ovary Uterus Uterine cervix Vulva/vagina	Breast Ovary Uterus NOS Endometrium Uterine cervix Vulva/vagina	Mammary gland Ovary Uterus NOS
Male reproductive system [viii]	*Testis, germ cells* *Testis, specialized gonadal stroma*	*Testis, germ cells* *Testis, specialized gonadal stroma*	*Testis, specialized gonadal stroma (Leydig cells)*

	Prostate	*Prostate*	*Prostate*
Other groupings (not included in the concordance analysis)	All cancers combined All solid cancers *Solid cancers, aside from lung* *Multiple or unspecified sites* Exocrine glands NOS	All cancers combined All solid cancers *Solid cancers aside from lung* *Multiple or unspecified sites* *Exocrine glands NOS*	Non-digestive exocrine glands (including Harderian gland, Zymbal gland [ear duct], preputial gland)

[i] Although sites in italics were not in the concordance developed by Grosse et al. (2015) , they are included in the anatomically-based tumour taxonomy system for completeness.

[ii] The monographs do not distinguish between inner and outer lip; this was inferred to be lip inner because of the Group-1 agent it relates to 'smokeless tobacco'

[iii] Trachea was not found as a distinct site in the concordance database.

[iv] The rat has no gall bladder

[v] Cranial and peripheral nerves were not found as a distinct site in the current database.

[vi] AML: Acute myeloid leukemia; ANLL: Acute non-lymphocytic leukemia.

[vii] Lip (outer) provided only *limited evidence* in humans for solar radiation.

[viii] The male reproductive system provided on *limited evidence* in humans (in all three listed tumour sites).

Suplemental Table 2. Database of Animal and Human Tumour Sites for 111 Distinct Group-1 Agents through Volume 109 of the IARC Monographs

Volume	Agent Number	Agent Name	Species	Site	Anatomical Site	Anatomical Site Label	Anatomical Site Number	Organ System	Organ System Number	Animal Tumour Site Specified	Reason for Lack of Animal Data*	Mechanistic Upgrade	Human Tumour Site Specified
A	1	Aristolochic acid	Rat	Forestomach	Stomach	Stomach	15	Digestive tract	4	1		1	0
A	1	Aristolochic acid	Rat	Renal pelvis	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	1		1	0
A	1	Aristolochic acid	Human	Not specified						1		1	0
A	2	Aristolochic acid, plants containing	Rat	Forestomach	Stomach	Stomach	15	Digestive tract	4	1		0	1
A	2	Aristolochic acid, plants containing	Human	Renal pelvis	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	1		0	1
A	2	Aristolochic acid, plants containing	Rat	Renal pelvis	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	1		0	1
A	2	Aristolochic acid, plants containing	Human	Ureter	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	1		0	1
A	3	Azathioprine	Mouse	Lymphoid tissue	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	1		0	1
A	3	Azathioprine	Human	Non-Hodgkin lymphoma	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	1		0	1
A	3	Azathioprine	Mouse	Thymus	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	1		0	1
A	3	Azathioprine	Human	Skin (squamous cell carcinoma)	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1
A	4	Busulfan	Human	Acute myeloid leukaemia	Haematopoietic tissue	Haematopoietic tissue	28	Lymphoid and haematopoietic tissues	10	0	6	0	1
A	5	Chlorambucil	Human	Acute myeloid leukaemia	Haematopoietic tissue	Haematopoietic tissue	28	Lymphoid and haematopoietic tissues	10	1		0	1
A	5	Chlorambucil	Mouse	Lymphoid tissue	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	1		0	1
A	6	Chlornaphazine	Human	Bladder	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	0	6	0	1
A	7	Cyclophosphamide	Mouse	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
A	7	Cyclophosphamide	Human	Bladder	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	1		0	1
A	7	Cyclophosphamide	Rat	Urinary bladder	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	1		0	1
A	7	Cyclophosphamide	Human	Acute myeloid leukaemia	Haematopoietic tissue	Haematopoietic tissue	28	Lymphoid and haematopoietic tissues	10	1		0	1
A	7	Cyclophosphamide	Mouse	Lymphoid tissue	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	1		0	1
A	7	Cyclophosphamide	Mouse	Mammary gland	Breast	Breast	35	Female breast, female reproductive organs and reproductive tract	13	1		0	1
A	8	Ciclosporine	Human	Non-Hodgkin lymphoma	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	0	6	0	1
A	8	Ciclosporine	Human	Squamous cell carcinoma	Skin and adnexae	Skin and adnexae	30	Skin	11	0	6	0	1
A	9	Diethylstilbestrol	Hamster	Kidney	Kidney	Kidney	26	Kidney	8	1		0	1
A	9	Diethylstilbestrol	Human	Breast (exposure while pregnant)	Breast	Breast	35	Female breast, female reproductive organs and reproductive tract	13	1		0	1
A	9	Diethylstilbestrol	Human	Cervix (clear cell adenocarcinoma, exposure in utero)	Uterine cervix	Cervix	37	Female breast, female reproductive organs and reproductive tract	13	1		0	1
A	9	Diethylstilbestrol	Mouse	Uterine cervix	Uterine cervix	Cervix	37	Female breast, female reproductive organs and reproductive tract	13	1		0	1
A	9	Diethylstilbestrol	Mouse	Uterus	Uterus	Uterus	38	Female breast, female reproductive organs and reproductive tract	13	1		0	1
A	9	Diethylstilbestrol	Human	Vagina (clear cell adenocarcinoma, exposure in utero)	Vulva/vagina	Vulva/vagina	39	Female breast, female reproductive organs and reproductive tract	13	1		0	1
A	10	Estrogen-only menopausal therapy	Hamster	Kidney	Kidney	Kidney	26	Kidney	8	1		0	1
A	10	Estrogen-only menopausal therapy	Mouse	Lymphoid tissue	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	1		0	1
A	10	Estrogen-only menopausal therapy	Mouse	Mammary gland	Breast	Breast	35	Female breast, female reproductive organs and reproductive tract	13	1		0	1
A	10	Estrogen-only menopausal therapy	Rat	Mammary gland	Breast	Breast	35	Female breast, female reproductive organs and reproductive tract	13	1		0	1
A	10	Estrogen-only menopausal therapy	Human	Ovary	Ovary	Ovary	36	Female breast, female reproductive organs and reproductive tract	13	1		0	1
A	10	Estrogen-only menopausal therapy	Mouse	Uterine cervix	Uterine cervix	Cervix	37	Female breast, female reproductive organs and reproductive tract	13	1		0	1
A	10	Estrogen-only menopausal therapy	Human	Endometrium	Uterus	Uterus	38	Female breast, female reproductive organs and reproductive tract	13	1		0	1
A	10	Estrogen-only menopausal therapy	Mouse	Uterus	Uterus	Uterus	38	Female breast, female reproductive organs and reproductive tract	13	1		0	1
A	11	Estrogen-progestogen menopausal therapy (combined)	Human	Breast	Breast	Breast	35	Female breast, female reproductive organs and reproductive tract	13	0	6	0	1
A	11	Estrogen-progestogen menopausal therapy (combined)	Human	Endometrium (increased risk for estrogen-induced endometrial cancer decreases with the number of days per month that progestogens are used)	Uterus	Uterus	38	Female breast, female reproductive organs and reproductive tract	13	0	6	0	1
A	12	Estrogen-progestogen oral contraceptives (combined)	Human	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
A	12	Estrogen-progestogen oral contraceptives (combined)	Human	Breast	Breast	Breast	35	Female breast, female reproductive organs and reproductive tract	13	1		0	1
A	12	Estrogen-progestogen oral contraceptives (combined)	Human	Cervix	Uterine cervix	Cervix	37	Female breast, female reproductive organs and reproductive tract	13	1		0	1
A	12	Estrogen-progestogen oral contraceptives (combined)	Mouse	Uterine cervix	Uterine cervix	Cervix	37	Female breast, female reproductive organs and reproductive tract	13	1		0	1
A	12	Estrogen-progestogen oral contraceptives (combined)	Mouse	Uterus	Uterus	Uterus	38	Female breast, female reproductive organs and reproductive tract	13	1		0	1
A	13	Etoposide	Human	Not specified						0	4	1	0
A	14	Etoposide in combination with cisplatin and bleomycin	Human	Acute myeloid leukaemia	Haematopoietic tissue	Haematopoietic tissue	28	Lymphoid and haematopoietic tissues	10	0	2	0	1
A	15	Melphalan	Human	Acute myeloid leukaemia	Haematopoietic tissue	Haematopoietic tissue	28	Lymphoid and haematopoietic tissues	10	0	7	0	1
A	16	Methoxsalen in combination with UVA	Mouse	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1
A	16	Methoxsalen in combination with UVA	Human	Skin (squamous cell carcinoma)	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1

Suplemental Table 2. Database of Animal and Human Tumour Sites for 111 Distinct Group-1 Agents through Volume 109 of the IARC Monographs													
Volume	Agent Number	Agent Name	Species	Site	Anatomical Site	Anatomical Site Label	Anatomical Site Number	Organ System	Organ System Number	Animal Tumour Site Specified	Reason for Lack of Animal Data*	Mechanistic Upgrade	Human Tumour Site Specified
A	17	MOPP and other combined chemotherapy including alkylating agents	Human	Lung	Lung	Lung	10	Respiratory system	2	0	2	0	1
A	17	MOPP and other combined chemotherapy including alkylating agents	Human	Acute myeloid leukaemia	Haematopoietic tissue	Haematopoietic tissue	28	Lymphoid and haematopoietic tissues	10	0	2	0	1
A	18	Phenacetin	Mouse	Kidney	Kidney	Kidney	26	Kidney	8	1		1	1
A	18	Phenacetin	Rat	Kidney	Kidney	Kidney	26	Kidney	8	1		1	1
A	18	Phenacetin	Human	Renal pelvis	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	1		1	1
A	18	Phenacetin	Rat	Renal pelvis	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	1		1	1
A	18	Phenacetin	Human	Ureter	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	1		1	1
A	19	Phenacetin, analgesic mixtures containing	Human	Renal pelvis	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	0	6	0	1
A	19	Phenacetin, analgesic mixtures containing	Human	Ureter	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	0	6	0	1
A	20	1-(2-Chloroethyl)-3-(4-methylcyclohexyl)- 1-nitrosourea (Methyl-CCNU)	Human	Acute myeloid leukaemia	Haematopoietic tissue	Haematopoietic tissue	28	Lymphoid and haematopoietic tissues	10	1		0	1
A	21	Tamoxifen	Rat	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
A	21	Tamoxifen	Human	Endometrium	Uterus	Uterus	38	Female breast, female reproductive organs and reproductive tract	13	1		0	1
A	22	Thiotepa	Human	Leukaemia	Haematopoietic tissue	Haematopoietic tissue	28	Lymphoid and haematopoietic tissues	10	1		0	1
A	22	Thiotepa	Mouse	Lymphoid tissue	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	1		0	1
A	23	Treosulfan	Human	Acute myeloid leukaemia	Haematopoietic tissue	Haematopoietic tissue	28	Lymphoid and haematopoietic tissues	10	0	5	0	1
B	24	Clonorchis sinensis (infection with)	Human	Cholangiocarcinoma	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	0	6	0	1
B	25	Epstein-Barr virus	Human	Nasopharyngeal carcinoma	Nasopharynx	Nasopharynx	2	Upper aerodigestive tract	1	0	3	0	1
B	25	Epstein-Barr virus	Human	Hodgkin lymphoma	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	0	3	0	1
B	25	Epstein-Barr virus	Human	Immune-suppression-related non-Hodgkin lymphoma	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	0	3	0	1
B	25	Epstein-Barr virus	Human	Burkitt lymphoma	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	0	3	0	1
B	25	Epstein-Barr virus	Human	Estranodal NK/T-cell lymphoma (nasal type)	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	0	3	0	1
B	26	Helicobacter pylori (infection with)	Mouse	Glandular stomach	Stomach	Stomach	15	Digestive tract	4	1		0	1
B	26	Helicobacter pylori (infection with)	Human	Non-cardiac gastric carcinoma	Stomach	Stomach	15	Digestive tract	4	1		0	1
B	26	Helicobacter pylori (infection with)	Human	Low-grade B-cell MALT gastric lymphoma	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	1		0	1
B	27	Hepatitis B virus	Human	Hepatocellular carcinoma	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	0	3	0	1
B	28	Hepatitis C virus	Human	Hepatocellular carcinoma	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	0	3	0	1
B	28	Hepatitis C virus	Human	Non-Hodgkin lymphoma	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	0	3	0	1
B	29	Human immunodeficiency virus type 1	Human	Hodgkin lymphoma	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	0	3	0	1
B	29	Human immunodeficiency virus type 1	Human	Non-Hodgkin lymphoma	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	0	3	0	1
B	29	Human immunodeficiency virus type 1	Human	Anus	Skin and adnexae	Skin and adnexae	30	Skin	11	0	3	0	1
B	29	Human immunodeficiency virus type 1	Human	Conjuctiva	Skin and adnexae	Skin and adnexae	30	Skin	11	0	3	0	1
B	29	Human immunodeficiency virus type 1	Human	Kaposi sarcoma	Soft connective tissue	Soft connective tissue	32	Connective tissues	12	0	3	0	1
B	29	Human immunodeficiency virus type 1	Human	Cervix	Uterine cervix	Cervix	37	Female breast, female reproductive organs and reproductive tract	13	0	3	0	1
B	30	Human papillomavirus type 16	Human	Oral cavity	Oral cavity	Oral cavity	3	Upper aerodigestive tract	1	0	3	0	1
B	30	Human papillomavirus type 16	Human	Oropharynx	Pharynx	Pharynx	4	Upper aerodigestive tract	1	0	3	0	1
B	30	Human papillomavirus type 16	Human	Tonsil	Tonsil	Tonsil	6	Upper aerodigestive tract	1	0	3	0	1
B	30	Human papillomavirus type 16	Human	Anus	Skin and adnexae	Skin and adnexae	30	Skin	11	0	3	0	1
B	30	Human papillomavirus type 16	Human	Penis	Skin and adnexae	Skin and adnexae	30	Skin	11	0	3	0	1
B	30	Human papillomavirus type 16	Human	Cervix	Uterine cervix	Cervix	37	Female breast, female reproductive organs and reproductive tract	13	0	3	0	1
B	30	Human papillomavirus type 18	Human	Cervix	Uterine cervix	Cervix	37	Female breast, female reproductive organs and reproductive tract	13	0	3	0	1
B	30	Human papillomavirus type 31	Human	Cervix	Uterine cervix	Cervix	37	Female breast, female reproductive organs and reproductive tract	13	0	3	0	1
B	30	Human papillomavirus type 33	Human	Cervix	Uterine cervix	Cervix	37	Female breast, female reproductive organs and reproductive tract	13	0	3	0	1
B	30	Human papillomavirus type 35	Human	Cervix	Uterine cervix	Cervix	37	Female breast, female reproductive organs and reproductive tract	13	0	3	0	1
B	30	Human papillomavirus type 39	Human	Cervix	Uterine cervix	Cervix	37	Female breast, female reproductive organs and reproductive tract	13	0	3	0	1
B	30	Human papillomavirus type 45	Human	Cervix	Uterine cervix	Cervix	37	Female breast, female reproductive organs and reproductive tract	13	0	3	0	1
B	30	Human papillomavirus type 51	Human	Cervix	Uterine cervix	Cervix	37	Female breast, female reproductive organs and reproductive tract	13	0	3	0	1
B	30	Human papillomavirus type 52	Human	Cervix	Uterine cervix	Cervix	37	Female breast, female reproductive organs and reproductive tract	13	0	3	0	1
B	30	Human papillomavirus type 56	Human	Cervix	Uterine cervix	Cervix	37	Female breast, female reproductive organs and reproductive tract	13	0	3	0	1
B	30	Human papillomavirus type 58	Human	Cervix	Uterine cervix	Cervix	37	Female breast, female reproductive organs and reproductive tract	13	0	3	0	1
B	30	Human papillomavirus type 59	Human	Cervix	Uterine cervix	Cervix	37	Female breast, female reproductive organs and reproductive tract	13	0	3	0	1
B	30	Human papillomavirus type 16	Human	Vagina	Vulva/vagina	Vulva/vagina	39	Female breast, female reproductive organs and reproductive tract	13	0	3	0	1
B	30	Human papillomavirus type 16	Human	Vulva	Vulva/vagina	Vulva/vagina	39	Female breast, female reproductive organs and reproductive tract	13	0	3	0	1

Suplemental Table 2. Database of Animal and Human Tumour Sites for 111 Distinct Group-1 Agents through Volume 109 of the IARC Monographs

Volume	Agent Number	Agent Name	Species	Site	Anatomical Site	Anatomical Site Label	Anatomical Site Number	Organ System	Organ System Number	Animal Tumour Site Specified	Reason for Lack of Animal Data*	Mechanistic Upgrade	Human Tumour Site Specified
B	31	Human T-cell lymphotropic virus type 1	Human	Adult T-cell leukaemia/lymphoma	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	0	3	0	1
B	32	Kaposi sarcoma herpesvirus	Human	Primary effusion lymphoma	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	0	3	0	1
B	32	Kaposi sarcoma herpesvirus	Human	Kaposi sarcoma	Soft connective tissue	Soft connective tissue	32	Connective tissues	12	0	3	0	1
B	33	Opisthorchis viverrini (infection with)	Human	Cholangiocarcinoma	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	0	6	0	1
B	34	Schistosoma haematobium (infection with)	Human	Urinary bladder	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	0	6	0	1
C	35	Arsenic and inorganic arsenic compounds	Human	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
C	35	Arsenic and inorganic arsenic compounds	Mouse	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
C	35	Arsenic and inorganic arsenic compounds	Mouse	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
C	35	Arsenic and inorganic arsenic compounds	Human	Urinary bladder	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	1		0	1
C	35	Arsenic and inorganic arsenic compounds	Rat	Urinary bladder	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	1		0	1
C	35	Arsenic and inorganic arsenic compounds	Human	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1
C	36	Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite)	Human	Larynx	Larynx	Larynx	9	Respiratory system	2	1		0	1
C	36	Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite)	Human	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
C	36	Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite)	Rat	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
C	36	Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite)	Human	Mesothelioma	Mesothelium	Mesothelium	12	Mesothelium	3	1		0	1
C	36	Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite)	Baboon	Mesothelium	Mesothelium	Mesothelium	12	Mesothelium	3	1		0	1
C	36	Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite)	Hamster	Mesothelium	Mesothelium	Mesothelium	12	Mesothelium	3	1		0	1
C	36	Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite)	Rat	Mesothelium	Mesothelium	Mesothelium	12	Mesothelium	3	1		0	1
C	36	Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite)	Human	Ovary	Ovary	Ovary	36	Female breast, female reproductive organs and reproductive tract	13	1		0	1
C	37	Beryllium and beryllium compounds	Human	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
C	37	Beryllium and beryllium compounds	Rat	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
C	38	Cadmium and cadmium compounds	Human	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
C	38	Cadmium and cadmium compounds	Rat	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
C	38	Cadmium and cadmium compounds	Rat	Soft tissue	Soft connective tissue	Soft connective tissue	32	Connective tissues	12	1		0	1
C	39	Chromium (VI) compounds	Rat	Oral cavity	Oral cavity	Oral cavity	3	Upper aerodigestive tract	1	1		0	1
C	39	Chromium (VI) compounds	Rat	Tongue	Tongue	Tongue	5	Upper aerodigestive tract	1	1		0	1
C	39	Chromium (VI) compounds	Human	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
C	39	Chromium (VI) compounds	Rat	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
C	39	Chromium (VI) compounds	Mouse	Ileum	Intestine, including colon and rectum	Intestine	16	Digestive tract	4	1		0	1
C	39	Chromium (VI) compounds	Mouse	Jejunum	Intestine, including colon and rectum	Intestine	16	Digestive tract	4	1		0	1
C	39	Chromium (VI) compounds	Mouse	Small intestine	Intestine, including colon and rectum	Intestine	16	Digestive tract	4	1		0	1
C	39	Chromium (VI) compounds	Mouse	Duodenum	Intestine, including colon and rectum	Intestine	16	Digestive tract	4	1		0	1
C	39	Chromium (VI) compounds	Rat	Soft tissue	Soft connective tissue	Soft connective tissue	32	Connective tissues	12	1		0	1
C	40	Erionite	Human	Mesothelioma	Mesothelium	Mesothelium	12	Mesothelium	3	1		0	1
C	40	Erionite	Rat	Mesothelium	Mesothelium	Mesothelium	12	Mesothelium	3	1		0	1
C	41	Leather dust	Human	Nasal sinus	Nasal cavity and paranasal sinuses	Nasal cavity	1	Upper aerodigestive tract	1	0	5	0	1
C	42	Nickel compounds	Human	Nasal cavity and paranasal sinuses	Nasal cavity and paranasal sinuses	Nasal cavity	1	Upper aerodigestive tract	1	1		0	1
C	42	Nickel compounds	Human	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
C	42	Nickel compounds	Rat	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
C	42	Nickel compounds	Rat	Adrenal medulla	Adrenal gland	Adrenal gland	24	Endocrine system	7	1		0	1
C	42	Nickel compounds	Hamster	Soft tissue	Soft connective tissue	Soft connective tissue	32	Connective tissues	12	1		0	1
C	42	Nickel compounds	Mouse	Soft tissue	Soft connective tissue	Soft connective tissue	32	Connective tissues	12	1		0	1
C	42	Nickel compounds	Rat	Soft tissue	Soft connective tissue	Soft connective tissue	32	Connective tissues	12	1		0	1
C	43	Silica dust, crystalline, in the form of quartz or cristobalite	Human	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
C	43	Silica dust, crystalline, in the form of quartz or cristobalite	Rat	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
C	43	Silica dust, crystalline, in the form of quartz or cristobalite	Rat	Lymphoid tissue	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	1		0	1
C	44	Wood dust	Human	Nasal sinus	Nasal cavity and paranasal sinuses	Nasal cavity	1	Upper aerodigestive tract	1	0	4	0	1
C	44	Wood dust	Human	Nasopharynx	Nasopharynx	Nasopharynx	2	Upper aerodigestive tract	1	0	4	0	1
D	45	Fission products including Sr-90	Human	Leukaemia	Haematopoietic tissue	Haematopoietic tissue	28	Lymphoid and haematopoietic tissues	10	1		0	1
D	45	Fission products including Sr-90	Dog	Bone	Hard connective tissue (bone, cartilage)	Hard connective tissue	34	Connective tissues	12	1		0	1
D	45	Fission products including Sr-90	Mouse	Bone	Hard connective tissue (bone, cartilage)	Hard connective tissue	34	Connective tissues	12	1		0	1
D	45	Fission products including Sr-90	Human	Solid cancers	All solid cancers	All solid cancers	44	Other groupings	15	1		0	1
D	46	Haematite mining with exposure to radon (underground)	Human	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
D	46	Haematite mining with exposure to radon (underground)	Rat	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
D	47	Ionizing radiation (all types)	Human	Not specified						1		0	0
D	48	Neutron radiation	Mouse	Lung	Lung	Lung	10	Respiratory system	2	1		1	1
D	48	Neutron radiation	Rat	Lung	Lung	Lung	10	Respiratory system	2	1		1	1
D	48	Neutron radiation	Mouse	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		1	1
D	48	Neutron radiation	Mouse	Adrenal gland	Adrenal gland	Adrenal gland	24	Endocrine system	7	1		1	1
D	48	Neutron radiation	Mouse	Pituitary gland	Pituitary	Pituitary	25	Endocrine system	7	1		1	1

Suplemental Table 2. Database of Animal and Human Tumour Sites for 111 Distinct Group-1 Agents through Volume 109 of the IARC Monographs

Volume	Agent Number	Agent Name	Species	Site	Anatomical Site	Anatomical Site Label	Anatomical Site Number	Organ System	Organ System Number	Animal Tumour Site Specified	Reason for Lack of Animal Data*	Mechanistic Upgrade	Human Tumour Site Specified
D	48	Neutron radiation	Monkey (Rhesus)	Kidney	Kidney	Kidney	26	Kidney	8	1		1	1
D	48	Neutron radiation	Mouse	Haematopoietic tissue	Haematopoietic tissue	Haematopoietic tissue	28	Lymphoid and haematopoietic tissues	10	1		1	1
D	48	Neutron radiation	Mouse	Lymphoid tissue	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	1		1	1
D	48	Neutron radiation	Mouse	Thymus	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	1		1	1
D	48	Neutron radiation	Mouse	Mammary gland	Breast	Breast	35	Female breast, female reproductive organs and reproductive tract	13	1		1	1
D	48	Neutron radiation	Rat	Mammary gland	Breast	Breast	35	Female breast, female reproductive organs and reproductive tract	13	1		1	1
D	48	Neutron radiation	Mouse	Ovary	Ovary	Ovary	36	Female breast, female reproductive organs and reproductive tract	13	1		1	1
D	48	Neutron radiation	Mouse	Harderian gland	Exocrine glands NOS	Exocrine glands NOS	47	Other groupings	15	1		1	0
D	48	Neutron radiation	Human	Not specified						1		1	0
D	49	P-32, as phosphate	Human	Leukaemia	Haematopoietic tissue	Haematopoietic tissue	28	Lymphoid and haematopoietic tissues	10	0	7	0	1
D	50	Pu-239	Dog	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
D	50	Pu-239	Human	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
D	50	Pu-239	Rat	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
D	50	Pu-239	Dog	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
D	50	Pu-239	Human	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
D	50	Pu-239	Human	Bone	Hard connective tissue (bone, cartilage)	Hard connective tissue	34	Connective tissues	12	1		0	1
D	50	Pu-239	Dog	Skeletal system	Hard connective tissue (bone, cartilage)	Hard connective tissue	34	Connective tissues	12	1		0	1
D	50	Pu-239	Mouse	Skeletal system	Hard connective tissue (bone, cartilage)	Hard connective tissue	34	Connective tissues	12	1		0	1
D	50	Pu-239	Rat	Skeletal system	Hard connective tissue (bone, cartilage)	Hard connective tissue	34	Connective tissues	12	1		0	1
D	51	Radioiodines, including I-131	Human	Thyroid	Thyroid	Thyroid	23	Endocrine system	7	1		0	1
D	51	Radioiodines, including I-131	Mouse	Thyroid	Thyroid	Thyroid	23	Endocrine system	7	1		0	1
D	51	Radioiodines, including I-131	Rat	Thyroid	Thyroid	Thyroid	23	Endocrine system	7	1		0	1
D	52	Internalized radionuclides that emit alpha particles	Human	Not specified						1		0	0
D	52	Internalized radionuclides that emit alpha particles	Dog	Lung	Lung	Lung	10	Respiratory system	2	1		0	0
D	52	Internalized radionuclides that emit alpha particles	Hamster	Lung	Lung	Lung	10	Respiratory system	2	1		0	0
D	52	Internalized radionuclides that emit alpha particles	Rat	Lung	Lung	Lung	10	Respiratory system	2	1		0	0
D	52	Internalized radionuclides that emit alpha particles	Dog	Skeletal system	Hard connective tissue (bone, cartilage)	Hard connective tissue	34	Connective tissues	12	1		0	0
D	52	Internalized radionuclides that emit alpha particles	Mouse	Skeletal system	Hard connective tissue (bone, cartilage)	Hard connective tissue	34	Connective tissues	12	1		0	0
D	52	Internalized radionuclides that emit alpha particles	Rat	Skeletal system	Hard connective tissue (bone, cartilage)	Hard connective tissue	34	Connective tissues	12	1		0	0
D	53	Internalized radionuclides that emit beta particles	Human	Not specified						1		0	0
D	53	Internalized radionuclides that emit beta particles	Mouse	Lung	Lung	Lung	10	Respiratory system	2	1		0	0
D	53	Internalized radionuclides that emit beta particles	Rat	Lung	Lung	Lung	10	Respiratory system	2	1		0	0
D	53	Internalized radionuclides that emit beta particles	Mouse	Thymus	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	1		0	0
D	53	Internalized radionuclides that emit beta particles	Dog	Soft tissue	Soft connective tissue	Soft connective tissue	32	Connective tissues	12	1		0	0
D	53	Internalized radionuclides that emit beta particles	Rat	Soft tissue	Soft connective tissue	Soft connective tissue	32	Connective tissues	12	1		0	0
D	53	Internalized radionuclides that emit beta particles	Dog	Skeletal system	Hard connective tissue (bone, cartilage)	Hard connective tissue	34	Connective tissues	12	1		0	0
D	53	Internalized radionuclides that emit beta particles	Mouse	Skeletal system	Hard connective tissue (bone, cartilage)	Hard connective tissue	34	Connective tissues	12	1		0	0
D	53	Internalized radionuclides that emit beta particles	Rat	Skeletal system	Hard connective tissue (bone, cartilage)	Hard connective tissue	34	Connective tissues	12	1		0	0
D	53	Internalized radionuclides that emit beta particles	Rat	Mammary gland	Breast	Breast	35	Female breast, female reproductive organs and reproductive tract	13	1		0	0
D	54	Ra-224 and its decay products	Human	Bone	Hard connective tissue (bone, cartilage)	Hard connective tissue	34	Connective tissues	12	1		0	1
D	54	Ra-224 and its decay products	Dog	Skeletal system	Hard connective tissue (bone, cartilage)	Hard connective tissue	34	Connective tissues	12	1		0	1
D	54	Ra-224 and its decay products	Mouse	Skeletal system	Hard connective tissue (bone, cartilage)	Hard connective tissue	34	Connective tissues	12	1		0	1
D	55	Ra-226 and its decay products	Human	Paranasal sinus	Nasal cavity and paranasal sinuses	Nasal cavity	1	Upper aerodigestive tract	1	1		0	1
D	55	Ra-226 and its decay products	Human	Bone	Hard connective tissue (bone, cartilage)	Hard connective tissue	34	Connective tissues	12	1		0	1
D	55	Ra-226 and its decay products	Human	Mastoid process	Hard connective tissue (bone, cartilage)	Hard connective tissue	34	Connective tissues	12	1		0	1
D	55	Ra-226 and its decay products	Dog	Skeletal system	Hard connective tissue (bone, cartilage)	Hard connective tissue	34	Connective tissues	12	1		0	1
D	55	Ra-226 and its decay products	Mouse	Skeletal system	Hard connective tissue (bone, cartilage)	Hard connective tissue	34	Connective tissues	12	1		0	1
D	56	Ra-228 and its decay products	Human	Bone	Hard connective tissue (bone, cartilage)	Hard connective tissue	34	Connective tissues	12	1		0	1
D	56	Ra-228 and its decay products	Dog	Skeletal system	Hard connective tissue (bone, cartilage)	Hard connective tissue	34	Connective tissues	12	1		0	1
D	57	Rn-222 and its decay products	Human	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
D	57	Rn-222 and its decay products	Rat	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
D	58	Solar radiation	Mouse	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1
D	58	Solar radiation	Rat	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1
D	58	Solar radiation	Human	Skin (basal cell carcinoma, squamous cell carcinoma)	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1
D	58	Solar radiation	Human	Skin (malignant melanoma)	Cutaneous melanocytes	Cutaneous melanocytes	31	Skin	11	1		0	1
D	59	Th-232 (as Thorotrast)	Human	Extrahepatic bile ducts	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
D	59	Th-232 (as Thorotrast)	Hamster	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
D	59	Th-232 (as Thorotrast)	Human	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
D	59	Th-232 (as Thorotrast)	Rat	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
D	59	Th-232 (as Thorotrast)	Human	Gall bladder	Gall bladder	Gall bladder	19	Digestive organs	5	1		0	1
D	59	Th-232 (as Thorotrast)	Human	Leukaemia (excluding chronic lymphocytic leukaemia)	Haematopoietic tissue	Haematopoietic tissue	28	Lymphoid and haematopoietic tissues	10	1		0	1
D	60	UV radiation (bandwidth 100-400 nm, encompassing UVC, UVB and UVA)	Human	Not specified						1		0	0
D	60	UV radiation (bandwidth 100-400 nm, encompassing UVC, UVB and UVA)	Mouse	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	0

Suplemental Table 2. Database of Animal and Human Tumour Sites for 111 Distinct Group-1 Agents through Volume 109 of the IARC Monographs

Volume	Agent Number	Agent Name	Species	Site	Anatomical Site	Anatomical Site Label	Anatomical Site Number	Organ System	Organ System Number	Animal Tumour Site Specified	Reason for Lack of Animal Data*	Mechanistic Upgrade	Human Tumour Site Specified
D	60	UV radiation (bandwidth 100-400 nm, encompassing UVC, UVB and UVA)	Rat	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	0
D	61	UV-emitting tanning devices	Human	Eye (melanoma)	Eye	Eye	22	Nervous system and eye	6	1		0	1
D	61	UV-emitting tanning devices	Mouse	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1
D	61	UV-emitting tanning devices	Human	Skin (melanoma)	Cutaneous melanocytes	Cutaneous melanocytes	31	Skin	11	1		0	1
D	62	X- and Gamma radiation	Human	Salivary gland	Salivary gland	Salivary gland	7	Upper aerodigestive tract	1	1		0	1
D	62	X- and Gamma radiation	Human	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
D	62	X- and Gamma radiation	Mouse	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
D	62	X- and Gamma radiation	Human	Oesophagus	Oesophagus	Oesophagus	14	Digestive tract	4	1		0	1
D	62	X- and Gamma radiation	Human	Stomach	Stomach	Stomach	15	Digestive tract	4	1		0	1
D	62	X- and Gamma radiation	Human	Colon	Intestine, including colon and rectum	Intestine	16	Digestive tract	4	1		0	1
D	62	X- and Gamma radiation	Mouse	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
D	62	X- and Gamma radiation	Human	Brain and CNS	Brain and spinal cord (CNS)	CNS	20	Nervous system and eye	6	1		0	1
D	62	X- and Gamma radiation	Human	Thyroid	Thyroid	Thyroid	23	Endocrine system	7	1		0	1
D	62	X- and Gamma radiation	Rat	Thyroid	Thyroid	Thyroid	23	Endocrine system	7	1		0	1
D	62	X- and Gamma radiation	Mouse	Pituitary gland	Pituitary	Pituitary	25	Endocrine system	7	1		0	1
D	62	X- and Gamma radiation	Human	Kidney	Kidney	Kidney	26	Kidney	8	1		0	1
D	62	X- and Gamma radiation	Monkey (Rhesus)	Kidney	Kidney	Kidney	26	Kidney	8	1		0	1
D	62	X- and Gamma radiation	Human	Urinary bladder	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	1		0	1
D	62	X- and Gamma radiation	Mouse	Haematopoietic tissue	Haematopoietic tissue	Haematopoietic tissue	28	Lymphoid and haematopoietic tissues	10	1		0	1
D	62	X- and Gamma radiation	Human	Leukaemia (excl. chronic lymphocytic leukaemia)	Haematopoietic tissue	Haematopoietic tissue	28	Lymphoid and haematopoietic tissues	10	1		0	1
D	62	X- and Gamma radiation	Mouse	Lymphoid tissue	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	1		0	1
D	62	X- and Gamma radiation	Mouse	Thymus	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	1		0	1
D	62	X- and Gamma radiation	Human	Basal cell of the skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1
D	62	X- and Gamma radiation	Mouse	Soft tissue	Soft connective tissue	Soft connective tissue	32	Connective tissues	12	1		0	1
D	62	X- and Gamma radiation	Human	Bbone	Hard connective tissue (bone, cartilage)	Hard connective tissue	34	Connective tissues	12	1		0	1
D	62	X- and Gamma radiation	Human	Female breast	Breast	Breast	35	Female breast, female reproductive organs and reproductive tract	13	1		0	1
D	62	X- and Gamma radiation	Mouse	Mammary gland	Breast	Breast	35	Female breast, female reproductive organs and reproductive tract	13	1		0	1
D	62	X- and Gamma radiation	Rat	Mammary gland	Breast	Breast	35	Female breast, female reproductive organs and reproductive tract	13	1		0	1
D	62	X- and Gamma radiation	Mouse	Ovary	Ovary	Ovary	36	Female breast, female reproductive organs and reproductive tract	13	1		0	1
D	62	X- and Gamma radiation	Mouse	Harderian gland	Exocrine glands NOS	Exocrine glands NOS	47	Other groupings	15	1		0	1
E	63	Acetaldehyde associated with consumption of alcoholic beverages	Human	Oral cavity	Oral cavity	Oral cavity	3	Upper aerodigestive tract	1	0	7	0	1
E	63	Acetaldehyde associated with consumption of alcoholic beverages	Human	Pharynx	Pharynx	Pharynx	4	Upper aerodigestive tract	1	0	7	0	1
E	63	Acetaldehyde associated with consumption of alcoholic beverages	Human	Larynx	Larynx	Larynx	9	Respiratory system	2	0	7	0	1
E	63	Acetaldehyde associated with consumption of alcoholic beverages	Human	Oesophagus	Oesophagus	Oesophagus	14	Digestive tract	4	0	7	0	1
E	64	Alcoholic beverages	Human	Oral cavity	Oral cavity	Oral cavity	3	Upper aerodigestive tract	1	1		0	1
E	64	Alcoholic beverages	Rat	Oral cavity	Oral cavity	Oral cavity	3	Upper aerodigestive tract	1	1		0	1
E	64	Alcoholic beverages	Human	Pharynx	Pharynx	Pharynx	4	Upper aerodigestive tract	1	1		0	1
E	64	Alcoholic beverages	Human	Larynx	Larynx	Larynx	9	Respiratory system	2	1		0	1
E	64	Alcoholic beverages	Human	Oesophagus	Oesophagus	Oesophagus	14	Digestive tract	4	1		0	1
E	64	Alcoholic beverages	Human	Colorectum	Intestine, including colon and rectum	Intestine	16	Digestive tract	4	1		0	1
E	64	Alcoholic beverages	Human	Hepatocellular carcinoma	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
E	64	Alcoholic beverages	Human	breast	Breast	Breast	35	Female breast, female reproductive organs and reproductive tract	13	1		0	1
E	65	Areca nut	Human	Not specified						1		0	0
E	65	Areca nut	Hamster	Oral cavity	Oral cavity	Oral cavity	3	Upper aerodigestive tract	1	1		0	1
E	65	Areca nut	Mouse	Soft tissue	Soft connective tissue	Soft connective tissue	32	Connective tissues	12	1		0	1
E	66	Betel quid with tobacco	Human	Oral cavity	Oral cavity	Oral cavity	3	Upper aerodigestive tract	1	0	7	0	1
E	66	Betel quid with tobacco	Human	Pharynx	Pharynx	Pharynx	4	Upper aerodigestive tract	1	0	7	0	1
E	66	Betel quid with tobacco	Human	Oesophagus	Oesophagus	Oesophagus	14	Digestive tract	4	0	7	0	1
E	67	Betel quid without tobacco	Human	Oral cavity	Oral cavity	Oral cavity	3	Upper aerodigestive tract	1	1		0	1
E	67	Betel quid without tobacco	Human	Oesophagus	Oesophagus	Oesophagus	14	Digestive tract	4	1		0	1
E	67	Betel quid without tobacco	Hamster	Forestomach	Stomach	Stomach	15	Digestive tract	4	1		0	1
E	68	Coal, indoor emissions from household combusion of	Human	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
E	68	Coal, indoor emissions from household combusion of	Mouse	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
E	68	Coal, indoor emissions from household combusion of	Mouse	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1
E	69	Ethanol in alcoholic beverages	Human	Not specified						1		0	0
E	69	Ethanol in alcoholic beverages	Rat	Oral cavity	Oral cavity	Oral cavity	3	Upper aerodigestive tract	1	1		0	0
E	70	N'-Nitrosonornicotine (NNN) and 4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanon (NNK)	Hamster	Nasal cavity	Nasal cavity and paranasal sinuses	Nasal cavity	1	Upper aerodigestive tract	1	1		1	0
E	70	N'-Nitrosonornicotine (NNN) and 4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanon (NNK)	Hamster	Lung	Lung	Lung	10	Respiratory system	2	1		1	0
E	70	N'-Nitrosonornicotine (NNN) and 4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanon (NNK)	Rat	Lung	Lung	Lung	10	Respiratory system	2	1		1	0
E	70	N'-Nitrosonornicotine (NNN) and 4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanon (NNK)	Rat	Oesophagus	Oesophagus	Oesophagus	14	Digestive tract	4	1		1	0
E	70	N'-Nitrosonornicotine (NNN) and 4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanon (NNK)	Rat	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		1	0
E	70	N'-Nitrosonornicotine (NNN) and 4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanon (NNK)	Human	Not specified						1		1	0
E	71	Salted fish, chinese style	Rat	Nasal cavity	Nasal cavity and paranasal sinuses	Nasal cavity	1	Upper aerodigestive tract	1	1		0	1
E	71	Salted fish, chinese style	Rat	Paranasal sinus	Nasal cavity and paranasal sinuses	Nasal cavity	1	Upper aerodigestive tract	1	1		0	1
E	71	Salted fish, chinese style	Rat	Nasopharynx	Nasopharynx	Nasopharynx	2	Upper aerodigestive tract	1	1		0	1
E	71	Salted fish, chinese style	Human	Nasopharynx	Nasopharynx	Nasopharynx	2	Upper aerodigestive tract	1	1		0	1
E	72	Second-hand tobacco smoke	Human	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
E	72	Second-hand tobacco smoke	Mouse	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
E	73	Tobacco smoking	Human	Nasal cavity	Nasal cavity and paranasal sinuses	Nasal cavity	1	Upper aerodigestive tract	1	1		0	1

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E	73	Tobacco smoking	Human	Paranasal sinus	Nasal cavity and paranasal sinuses	Nasal cavity	1	Upper aerodigestive tract	1	1		0	1
E	73	Tobacco smoking	Human	Nasopharynx	Nasopharynx	Nasopharynx	2	Upper aerodigestive tract	1	1		0	1
E	73	Tobacco smoking	Human	Oral cavity	Oral cavity	Oral cavity	3	Upper aerodigestive tract	1	1		0	1
E	73	Tobacco smoking	Human	pharynx (incl. oropharynx & hypopharynx)	Pharynx	Pharynx	4	Upper aerodigestive tract	1	1		0	1
E	73	Tobacco smoking	Human	Larynx	Larynx	Larynx	9	Respiratory system	2	1		0	1
E	73	Tobacco smoking	Human	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
E	73	Tobacco smoking	Hamster	Larynx	Larynx	Larynx	9	Respiratory system	2	1		0	1
E	73	Tobacco smoking	Mouse	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
E	73	Tobacco smoking	Rat	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
E	73	Tobacco smoking	Human	Oesophagus	Oesophagus	Oesophagus	14	Digestive tract	4	1		0	1
E	73	Tobacco smoking	Human	Stomach	Stomach	Stomach	15	Digestive tract	4	1		0	1
E	73	Tobacco smoking	Human	Colorectum	Intestine, including colon and rectum	Intestine	16	Digestive tract	4	1		0	1
E	73	Tobacco smoking	Human	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
E	73	Tobacco smoking	Human	Hepatoblastoma in children (parental smoking)	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
E	73	Tobacco smoking	Human	Pancreas	Pancreas NOS	Pancreas	18	Digestive organs	5	1		0	1
E	73	Tobacco smoking	Human	Kidney	Kidney	Kidney	26	Kidney	8	1		0	1
E	73	Tobacco smoking	Human	Ureter	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	1		0	1
E	73	Tobacco smoking	Human	Urinary bladder	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	1		0	1
E	73	Tobacco smoking	Human	Myeloid leukaemia	Haematopoietic tissue	Haematopoietic tissue	28	Lymphoid and haematopoietic tissues	10	1		0	1
E	73	Tobacco smoking	Mouse	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1
E	73	Tobacco smoking	Human	ovary	Ovary	Ovary	36	Female breast, female reproductive organs and reproductive tract	13	1		0	1
E	73	Tobacco smoking	Human	Uterine cervix	Uterine cervix	Cervix	37	Female breast, female reproductive organs and reproductive tract	13	1		0	1
E	74	Tobacco, smokeless	Rat	Lip	Oral cavity	Oral cavity	3	Upper aerodigestive tract	1	1		0	1
E	74	Tobacco, smokeless	Human	Oral cavity	Oral cavity	Oral cavity	3	Upper aerodigestive tract	1	1		0	1
E	74	Tobacco, smokeless	Rat	Oral cavity	Oral cavity	Oral cavity	3	Upper aerodigestive tract	1	1		0	1
E	74	Tobacco, smokeless	Human	Oesophagus	Oesophagus	Oesophagus	14	Digestive tract	4	1		0	1
E	74	Tobacco, smokeless	Human	Pancreas	Pancreas NOS	Pancreas	18	Digestive organs	5	1		0	1
F	75	Acid mists, strong inorganic	Human	Larynx	Larynx	Larynx	9	Respiratory system	2	0	1	0	1
F	76	Aflatoxins	Human	Hepatocellular carcinoma	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
F	76	Aflatoxins	Rat	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
F	77	Aluminum production	Human	Lung	Lung	Lung	10	Respiratory system	2	0	7	0	1
F	77	Aluminum production	Human	Urinary bladder	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	0	7	0	1
F	78	4-Aminobiphenyl	Mouse	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
F	78	4-Aminobiphenyl	Dog	Urinary bladder	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	1		0	1
F	78	4-Aminobiphenyl	Human	Urinary bladder	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	1		0	1
F	78	4-Aminobiphenyl	Mouse	Soft tissue	Soft connective tissue	Soft connective tissue	32	Connective tissues	12	1		0	1
F	79	Auramine production	Human	Urinary bladder	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	0	1	0	1
F	80	Benzene	Rat	Oral cavity	Oral cavity	Oral cavity	3	Upper aerodigestive tract	1	1		0	1
F	80	Benzene	Mouse	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
F	80	Benzene	Rat	Forestomach	Stomach	Stomach	15	Digestive tract	4	1		0	1
F	80	Benzene	Human	Acute myeloid leukaemia/acute non-lymphocytic leukaemia	Haematopoietic tissue	Haematopoietic tissue	28	Lymphoid and haematopoietic tissues	10	1		0	1
F	80	Benzene	Mouse	Haematopoietic tissue	Haematopoietic tissue	Haematopoietic tissue	28	Lymphoid and haematopoietic tissues	10	1		0	1
F	80	Benzene	Mouse	Lymphoid tissue	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	1		0	1
F	80	Benzene	Mouse	Thymus	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	1		0	1
F	80	Benzene	Rat	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1
F	80	Benzene	Mouse	Mammary gland	Breast	Breast	35	Female breast, female reproductive organs and reproductive tract	13	1		0	1
F	80	Benzene	Mouse	Preputial gland	Exocrine glands NOS	Exocrine glands NOS	47	Other groupings	15	1		0	1
F	80	Benzene	Mouse	Zymbal gland	Exocrine glands NOS	Exocrine glands NOS	47	Other groupings	15	1		0	1
F	80	Benzene	Rat	Zymbal gland	Exocrine glands NOS	Exocrine glands NOS	47	Other groupings	15	1		0	1
F	81	Benzidine	Mouse	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
F	81	Benzidine	Human	Urinary bladder	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	1		0	1
F	81	Benzidine	Rat	Mammary gland	Breast	Breast	35	Female breast, female reproductive organs and reproductive tract	13	1		0	1
F	82	Benzidine, dyes metabolized to	Mouse	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		1	0
F	82	Benzidine, dyes metabolized to	Rat	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		1	0
F	82	Benzidine, dyes metabolized to	Human	Not specified						1		1	0
F	83	Benzo[*a*]pyrene	Hamster	Lung	Lung	Lung	10	Respiratory system	2	1		1	0
F	83	Benzo[*a*]pyrene	Mouse	Lung	Lung	Lung	10	Respiratory system	2	1		1	0
F	83	Benzo[*a*]pyrene	Rat	Lung	Lung	Lung	10	Respiratory system	2	1		1	0
F	83	Benzo[*a*]pyrene	Hamster	Lower respiratory tract (larynx, trachea, lung)	Lower respiratory tract	Lower respiratory tract	11	Respiratory system	2	1		1	0
F	83	Benzo[*a*]pyrene	Hamster	Forestomach	Stomach	Stomach	15	Digestive tract	4	1		1	0
F	83	Benzo[*a*]pyrene	Mouse	Forestomach	Stomach	Stomach	15	Digestive tract	4	1		1	0
F	83	Benzo[*a*]pyrene	Mouse	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		1	0
F	83	Benzo[*a*]pyrene	Mouse	Lymphoid tissue	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	1		1	0
F	83	Benzo[*a*]pyrene	Hamster	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		1	0
F	83	Benzo[*a*]pyrene	Mouse	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		1	0
F	83	Benzo[*a*]pyrene	Rat	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		1	0
F	83	Benzo[*a*]pyrene	Rat	Mammary gland	Breast	Breast	35	Female breast, female reproductive organs and reproductive tract	13	1		1	0
F	83	Benzo[*a*]pyrene	Human	Not specified						1		1	0
F	84	Bis(chloromethyl)ether; chloromethyl methyl ether (technical-grade)	Rat	Nasal cavity	Nasal cavity and paranasal sinuses	Nasal cavity	1	Upper aerodigestive tract	1	1		0	1
F	84	Bis(chloromethyl)ether; chloromethyl methyl ether (technical-grade)	Human	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
F	84	Bis(chloromethyl)ether; chloromethyl methyl ether (technical-grade)	Mouse	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1

Suplemental Table 2. Database of Animal and Human Tumour Sites for 111 Distinct Group-1 Agents through Volume 109 of the IARC Monographs

Volume	Agent Number	Agent Name	Species	Site	Anatomical Site	Anatomical Site Label	Anatomical Site Number	Organ System	Organ System Number	Animal Tumour Site Specified	Reason for Lack of Animal Data*	Mechanistic Upgrade	Human Tumour Site Specified
F	84	Bis(chloromethyl)ether; chloromethyl methyl ether (technical-grade)	Mouse	Soft tissue	Soft connective tissue	Soft connective tissue	32	Connective tissues	12	1		0	1
F	85	1,3-Butadiene	Mouse	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
F	85	1,3-Butadiene	Mouse	Forestomach	Stomach	Stomach	15	Digestive tract	4	1		0	1
F	85	1,3-Butadiene	Mouse	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
F	85	1,3-Butadiene	Human	Haematolymphatic organs	Haematopoietic tissue	Haematopoietic tissue	28	Lymphoid and haematopoietic tissues	10	1		0	1
F	85	1,3-Butadiene	Mouse	Lymphoid tissue	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	1		0	1
F	85	1,3-Butadiene	Mouse	Soft tissue	Soft connective tissue	Soft connective tissue	32	Connective tissues	12	1		0	1
F	85	1,3-Butadiene	Mouse	Mammary gland	Breast	Breast	35	Female breast, female reproductive organs and reproductive tract	13	1		0	1
F	85	1,3-Butadiene	Mouse	Harderian gland	Exocrine glands NOS	Exocrine glands NOS	47	Other groupings	15	1		0	1
F	85	1,3-Butadiene	Mouse	Preputial gland	Exocrine glands NOS	Exocrine glands NOS	47	Other groupings	15	1		0	1
F	86	Coal gasification	Human	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
F	86	Coal gasification	Mouse	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1
F	87	Coal-tar distillation	Human	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1
F	87	Coal-tar distillation	Mouse	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1
F	88	Coal-tar pitch	Human	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
F	88	Coal-tar pitch	Mouse	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1
F	89	Coke production	Human	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
F	89	Coke production	Mouse	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
F	89	Coke production	Rat	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
F	89	Coke production	Mouse	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1
F	90	Ethylene oxide	Mouse	Lung	Lung	Lung	10	Respiratory system	2	1		1	0
F	90	Ethylene oxide	Rat	Peritoneum	Mesothelium	Mesothelium	12	Mesothelium	3	1		1	0
F	90	Ethylene oxide	Rat	Brain	Brain and spinal cord (CNS)	CNS	20	Nervous system and eye	6	1		1	0
F	90	Ethylene oxide	Rat	Lymphoid tissue	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	1		1	0
F	90	Ethylene oxide	Human	Not specified						1		1	0
F	91	Formaldehyde	Rat	Nasal cavity	Nasal cavity and paranasal sinuses	Nasal cavity	1	Upper aerodigestive tract	1	1		0	1
F	91	Formaldehyde	Human	Nasopharynx	Nasopharynx	Nasopharynx	2	Upper aerodigestive tract	1	1		0	1
F	91	Formaldehyde	Human	Leukaemia	Haematopoietic tissue	Haematopoietic tissue	28	Lymphoid and haematopoietic tissues	10	1		0	1
F	92	Iron and steel founding (occupational exposure during)	Human	Lung	Lung	Lung	10	Respiratory system	2	0	1	0	1
F	93	Isopropyl alcohol manufacture using strong acids	Human	Nasal cavity	Nasal cavity and paranasal sinuses	Nasal cavity	1	Upper aerodigestive tract	1	0	1	0	1
F	94	Magenta production	Human	Urinary bladder	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	0	1	0	1
F	95	4,4'-Methylenebis(2-chloroaniline) (MOCA)	Rat	Lung	Lung	Lung	10	Respiratory system	2	1		1	0
F	95	4,4'-Methylenebis(2-chloroaniline) (MOCA)	Rat	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		1	0
F	95	4,4'-Methylenebis(2-chloroaniline) (MOCA)	Rat	Mammary gland	Breast	Breast	35	Female breast, female reproductive organs and reproductive tract	13	1		1	0
F	95	4,4'-Methylenebis(2-chloroaniline) (MOCA)	Human	Not specified						1		1	0
F	96	Mineral oils, untreated or mildly treated	Human	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1
F	96	Mineral oils, untreated or mildly treated	Mouse	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1
F	97	2-Naphthylamine	Mouse	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
F	97	2-Naphthylamine	Dog	Urinary bladder	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	1		0	1
F	97	2-Naphthylamine	Hamster	Urinary bladder	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	1		0	1
F	97	2-Naphthylamine	Human	Urinary bladder	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	1		0	1
F	97	2-Naphthylamine	Monkey	Urinary bladder	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	1		0	1
F	97	2-Naphthylamine	Rat	Urinary bladder	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	1		0	1
F	98	*ortho*-Toluidine	Human	Urinary bladder	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	1		0	1
F	98	*ortho*-Toluidine	Rat	Urinary bladder	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	1		0	1
F	98	*ortho*-Toluidine	Rat	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1
F	98	*ortho*-Toluidine	Mouse	Soft tissue	Soft connective tissue	Soft connective tissue	32	Connective tissues	12	1		0	1
F	99	Painter, occupational exposure	Human	Lung	Lung	Lung	10	Respiratory system	2	0	1	0	1
F	99	Painter, occupational exposure	Human	Mesothelioma	Mesothelium	Mesothelium	12	Mesothelium	3	0	1	0	1
F	99	Painter, occupational exposure	Human	Urinary bladder	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	0	1	0	1
F	100	2,3,4,7,8-Pentachlorodibenzofuran	Human	Not specified						0	7	1	0
F	101	Rubber manufacturing industry	Human	Lung	Lung	Lung	10	Respiratory system	2	0	1	0	1
F	101	Rubber manufacturing industry	Human	Stomach	Stomach	Stomach	15	Digestive tract	4	0	1	0	1
F	101	Rubber manufacturing industry	Human	Urinary bladder	Urothelium (renal pelvis, ureter, urinary bladder)	Urothelium	27	Urothelium	9	0	1	0	1
F	101	Rubber manufacturing industry	Human	Leukaemia	Haematopoietic tissue	Haematopoietic tissue	28	Lymphoid and haematopoietic tissues	10	0	1	0	1
F	101	Rubber manufacturing industry	Human	Lymphoma	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	0	1	0	1
F	102	Shale oils	Human	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1
F	102	Shale oils	Mouse	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1
F	103	Soot (as found in occupational exposure of chimney sweeps)	Human	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
F	103	Soot (as found in occupational exposure of chimney sweeps)	Human	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1
F	103	Soot (as found in occupational exposure of chimney sweeps)	Mouse	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1
F	104	Sulfur mustard	Human	Lung	Lung	Lung	10	Respiratory system	2	0	6	0	1
F	105	2,3,7,8-Tetrachlorodibenzo-para-dioxin	Rat	Oral cavity	Oral cavity	Oral cavity	3	Upper aerodigestive tract	1	1		0	1
F	105	2,3,7,8-Tetrachlorodibenzo-para-dioxin	Rat	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
F	105	2,3,7,8-Tetrachlorodibenzo-para-dioxin	Mouse	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
F	105	2,3,7,8-Tetrachlorodibenzo-para-dioxin	Rat	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
F	105	2,3,7,8-Tetrachlorodibenzo-para-dioxin	Mouse	Lymphoid tissue	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	1		0	1
F	105	2,3,7,8-Tetrachlorodibenzo-para-dioxin	Mouse	Thymus	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	1		0	1

Suplemental Table 2. Database of Animal and Human Tumour Sites for 111 Distinct Group-1 Agents through Volume 109 of the IARC Monographs													
Volume	Agent Number	Agent Name	Species	Site	Anatomical Site	Anatomical Site Label	Anatomical Site Number	Organ System	Organ System Number	Animal Tumour Site Specified	Reason for Lack of Animal Data*	Mechanistic Upgrade	Human Tumour Site Specified
F	105	2,3,7,8-Tetrachlorodibenzo-para-dioxin	Mouse	Skin	Skin and adnexae	Skin and adnexae	30	Skin	11	1		0	1
F	105	2,3,7,8-Tetrachlorodibenzo-para-dioxin	Human	All cancers combined	All cancers combined	All cancers combined	43	Other groupings	15	1		0	1
F	106	Vinyl chloride	Mouse	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
F	106	Vinyl chloride	Human	Hepatocellular carcinoma	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
F	106	Vinyl chloride	Rat	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
F	106	Vinyl chloride	Mouse	Soft tissue	Soft connective tissue	Soft connective tissue	32	Connective tissues	12	1		0	1
F	106	Vinyl chloride	Rat	Soft tissue	Soft connective tissue	Soft connective tissue	32	Connective tissues	12	1		0	1
F	106	Vinyl chloride	Human	Angiosarcoma of the liver	Blood vasculature (endothelium)	Blood vasculature	33	Connective tissues	12	1		0	1
F	106	Vinyl chloride	Mouse	Mammary gland	Breast	Breast	35	Female breast, female reproductive organs and reproductive tract	13	1		0	1
F	106	Vinyl chloride	Rat	Mammary gland	Breast	Breast	35	Female breast, female reproductive organs and reproductive tract	13	1		0	1
F	106	Vinyl chloride	Rat	Zymbal gland	Exocrine glands NOS	Exocrine glands NOS	47	Other groupings	15	1		0	1
105	107	Engine Exhaust, diesel	Human	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
105	107	Engine Exhaust, diesel	Rat	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
106	108	Trichloroethylene	Mouse	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
106	108	Trichloroethylene	Mouse	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
106	108	Trichloroethylene	Human	Kidney	Kidney	Kidney	26	Kidney	8	1		0	1
106	108	Trichloroethylene	Rat	Kidney	Kidney	Kidney	26	Kidney	8	1		0	1
107	109	Polychlorinated biphenyls	Rat	Oral cavity	Oral cavity	Oral cavity	3	Upper aerodigestive tract	1	1		0	1
107	109	Polychlorinated biphenyls	Rat	Liver	Liver parenchyma and bile ducts	Liver	17	Digestive organs	5	1		0	1
107	109	Polychlorinated biphenyls	Human	Skin (melanoma)	Cutaneous melanocytes	Cutaneous melanocytes	31	Skin	11	1		0	1
109	110	Outdoor air pollution	Human	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
109	111	Particulate matter in outdoor air pollution	Human	Lung	Lung	Lung	10	Respiratory system	2	1		0	1
***Reasons for Lack of Animal Data: 1 - Occupational exposure not replicable in laboratory; 2 - Used in combination with no data on mixture; 3 - Animal models problematic due to species-specificity 4 - Animal tests inadequate; 5 - No animal data available; 6 - Limited evidence in animals ; 7 - Sufficient evidence in animals, but no site specified**													

Supplemental Table 3. Data Dictionary for the Anatomically-based Tumour Site Concordance Database

Data Element	Description	Coding
Volume	IARC Monographs Volume from which the data were abstracted	100A, 100B, 100C, 100D and 100F, 105, 106, 107, 109
Agent Number	Number assigned to agents listed in alphabetical order (see Table 1)	1, 2,…,111
Agent Name	Name of the agent as listed in the IARC Monographs	
Species	Species from which the data were derived	Human, Rat, Mouse, Hamster, Dog, Monkey, Baboon
Site	The tumour site, as abstracted from the IARC Monographs (see Table 1)	
Anatomical Site	Coding of the tumour site into an anatomical site based on The Organ and Tumour Site Nomenclature Table	See Table 3
Anatomical Site Number	Number assigned to anatomical tumour site	1, 2,…, 47(see Table 4)
Organ System	Organ and tissue system to which the anatomical tumour site belongs	See Table 3
Organ System Number	Number assigned to the organ and tissue system	1, 2,…,15 (see Table 4)
Animal Data Available	Indicator variable indicating the availability of	0- No animal data available 1- Animal data available
Reason for Lack of Animal Data	Reason for lack of sufficient evidence of carcinogenicity in animals	1-Occupational exposures are complex and likely could not be reliably replicated in the laboratory 2- Used in combination; no data available on mixture 3- Animal tests were conducted by are considered inadequate

		4-The use of animal models is problematic due to species-specificity and other limitations 5- No animal data available
Mechanistic Upgrade	Indicator variable to identify agents assigned to Group-1 on the basis of a mechanistic upgrade	0- No mechanistic upgrade 1- Mechanistic upgrade
Tumour Site Specified	Indicator variable to confirm the determination of a specific tumour site by the WG	0- No tumour site specified 1- Tumour site(s) specified

Supplemental Table 4. Numerical Coding of Anatomically-based Tumour Sites and Organ and Tissue Systems

Anatomical Site	Anatomical Site Number
Upper Aerodigestive Tract (1)	
Nasal cavity and paranasal sinuses	1
Nasopharynx	2
Oral cavity	3
Pharynx	4
Tongue	5
Tonsil	6
Salivary gland	7
Respiratory System (2)	
Trachea	8
Larynx	9
Lung	10
Lower respiratory tract	11
Mesothelium (3)	
Mesothelium	12
Digestive Tract (4)	
Digestive tract, unspecified	13
Oesophagus	14
Stomach	15
Intestine (including colon and rectum)	16
Digestive Organs (5)	
Liver parenchyma and bile ducts	17
Pancreas NOS	18
Gall bladder	19
Nervous System and Eye (6)	

Brain and spinal cord (CNS)	20
Cranial and peripheral nerves	21
Eye	22
Endocrine System (7)	
Thyroid, follicular epithelium	23
Adrenal gland (medulla, cortex, NOS)	24
Pituitary	25
Kidney (8)	
Kidney (renal cortex, renal medulla, kidney NOS)	26
Urothelium (9)	
Urothelium (renal pelvis or ureter or urinary bladder)	27
Lymphoid and Haematopoietic Tissues (10)	
Haematopoietic tissue	28
Lymphoid tissue	29
Skin (11)	
Skin and adnexae	30
Cutaneous melanocytes	31
Connective Tissues (12)	
Soft connective tissue	32
Blood vasculature (endothelium)	33
Hard connective tissue (bone, cartilage)	34
Female Breast, Female Reproductive Organs and Reproductive Tract (13)	
Breast	35
Ovary	36
Uterine cervix	37
Uterus	38
Vulva/vagina	39
Male Reproductive System (14)	

Testis, germ cells	40
Testis, specialized gonadal stroma	41
Prostate	42
Other Groupings (15)	
All cancers combined	43
All solid cancers	44
Solid cancers, aside from lung	45
Multiple or unspecified sites	46
Exocrine glands NOS	47

Concordance between Animal and Human Tumours: An Analysis of 111 Agents Known to Cause Cancer in Humans

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Abstract

Since its inception in 1972, the International Agency for Research on Cancer (IARC) has evaluated 970 agents with respect to their carcinogenic potential, and has identified 111 distinct agents as falling in Group-1 (carcinogenic to humans) of the IARC carcinogen classification scheme through Volume 109 of the *IARC Monographs.* Based on a review and update of Group-1 carcinogens included in Volume 100 of the IARC Monographs Programme, these agents can be divided into six broad categories: pharmaceuticals; biological agents; arsenic, metals, fibres, and dusts; radiation; personal habits and indoor combustions; and chemical agents and related occupations. Using a database on animal and human tumour sites associated with these agents developed by the IARC, we investigated the types of tumours caused by these agents, and the degree of concordance between the types of tumours seen in humans and animals (mice, rats, hamsters, dogs, and primates). Comparisons between animal and human tumours were made using an anatomically based tumour nomenclature system representing 39 tumour sites and 15 organ and tissue systems in which both humans and animals tumours were seen. Lung tumours represent the most common tumour type seen in both humans and animals. Tumours of the upper aerodigestive tract and respiratory system are caused by 47 of the 111 Group 1 carcinogens, comprised mostly of chemicals agents and related occupations (15 agents), arsenic, metals, fibres, and dusts (10 agents), and personal habits and indoor combustions (12 agents). Tumours of lymphoid and haematopoietic tissues are caused by 26 agents, urothelium by 18 agents, and the skin by 14 agents. Radiation (particularly X- and gamma radiation) and tobacco smoking are associated with tumours at multiple sites in humans. Heat maps linking the strength of the association between Group-1 agents and different tumour types identified particularly strong associations between asbestos and mesothelial tumours, between Pu-239 and hard connective tissue tumours, and between 2-napthylamine and urinary tract/uroendothelial tumours, where in each case the same tumours are induced in humans and at least three animal species. Although the IARC Monographs do not focus on the assembly of evidence

regarding quantitative tumour site concordance between animals and humans, substantial concordance between animal and humans was noted for a number of tumour sites. For example, substantial concordance between mice and humans is observed for tumours of the endocrine system ($\kappa = 0.79$), skin ($\kappa = 0.64$), connective tissues ($\kappa = 0.70$), and female breast, female reproductive organs and reproductive tract ($\kappa = 0.63$), and moderate is observed for lymphoid and haematopoietic tissues ($\kappa = 0.57$). For rats, perfect and near perfect concordance is seen for mesothelial ($\kappa = 1$), and urothelial ($\kappa = 0.85$) tumours, respectively, and substantial concordance is seen for endocrine system tumours ($\kappa = 0.79$) and respiratory system ($\kappa = 0.78$) tumours. The present analysis demonstrated that all 91 Group-1 agents that have been appropriately tested in animals also demonstrate *sufficient evidence* (82 agents) or *limited evidence* (9 agents) of carcinogenicity in animals. While concordance between the types of tumours seen in animals and humans is imperfect, these results confirm that the induction of cancer in animals is relevant to human cancer risk assessment.

Introduction

Since the establishment of the *IARC Monographs Programme* within International Agency for Research on Cancer (IARC) in 1970, the Agency has evaluated a large number of agents for which there exists some evidence of a possible increased cancer risk to humans. The Agency has developed detailed criteria against which to evaluate the available scientific evidence on the cancer-causing potential of such agents, which are described in the Preamble to the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans (Cogliano et al., 2004; IARC, 2006). These criteria are used to weigh the evidence provided by human and animal studies, as well as information on possible biological mechanisms of action, to classify agents into the following groups. *Group 1: The agent is carcinogenic to humans; Group 2a: The agent is probably carcinogenic to humans; Group 2b: The agent is possibly carcinogenic to humans; Group 3: The agent is not classifiable as to its carcinogenicity in humans; and Group 4: The agent is probably not carcinogenic to humans.* These evaluations involve classifying both the human and animal evidence as providing *sufficient evidence of carcinogenicity*, *limited evidence of carcinogenicity*, *inadequate evidence of carcinogenicity*, or *evidence suggesting lack of carcinogenicity*. The information on biological mechanisms of action may be evaluated as *strong*, *moderate* or *weak*, thereby lending different levels of support to the overall evaluation.

To date, the Agency has developed 113 Monographs on 982 agents for which there exists some evidence of human cancer risk; of these, 117 agents met the criteria for Group 1. Volume 100 (V100) of the IARC Monographs provides a review and update of the 107 Group-1 agents identified as of 2009. V100 is conveniently separated into six parts, labelled V100A through V100F, focusing on: pharmaceuticals (IARC, 2012a); biological agents (IARC, 2012b); arsenic, metals, fibres, and dusts (IARC, 2012c); radiation (IARC, 2013d); personal habits and indoor combustions (IARC, 2012e); and chemical agents and related occupations (IARC, 2012f), respectively. Since the publication of V100, five additional agents – diesel exhaust (Volume 105; Benbrahim-Tallaa et al., 2012), trichloroethylene (V106; Guha et al., 2012), polychlorinated biphenyls (PCBs) and dioxin-like PCBs (V107; Lauby-Secretan et al., 2013), outdoor air pollution and particulate matter from outdoor air pollution (V109; Loomis et al., 2013) – have been added to Group 1 (IARC, 2014) as of the time the present analysis was undertaken. Had these five agents been evaluated within V100, they will be included within V100F; for ease of reference, we will include these agents in an expanded group of chemicals and related occupations denoted by V100F*.

The 113 agents identified by the IARC as known causes of human cancer through Volume 109 are listed in Table 1. Note that although PCB-126 was evaluated as a separate Group 1 agent in Volume 100F, it is included within the group of

agents comprised of PCBs and dioxin-like PCBs, which were determined to be Group 1 agents in V107. For 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 V100, there are 23, 11, 10, 18, 12, and 37 Group 1 agents in V100A through V100F*, respectively.

Because both animal and human data are considered in evaluating the weight of evidence for human carcinogenicity, the degree of concordance between the types of tumours seen in animals and humans is of interest. A high degree of concordance between the types of tumours seen in animals and humans would further support the use of animal data in classifying agents with respect to human carcinogenicity. From a risk assessment perspective, tumour-site concordance would also support the use of animal cancer data in making quantitative predictions about human cancer risk based on animal data. On the other hand, lack of concordance may trigger further research to identify the underlying mechanisms in humans and animals in order to explain the discordance.

This chapter evaluates tumour-site concordance between animals and humans based on the available data for the 111 distinct agents classified by the IARC as being carcinogenic to humans (Group 1) as of the completion of Volume 109. The analysis is based on the database on tumour-site concordance assembled by Grosse et al. (2015), which was assembled by abstracting relevant data on the carcinogenicity of these agents in animals and humans from V100, 105, 106, 107 and 109. In the next section, we describe how the database used in the present analysis was assembled and discuss the statistical methods used to evaluate tumour-site concordance between animals and humans. A detailed description of the results of the analysis of this data is then presented. A discussion of the results of these analyses and the conclusions drawn from this work are presented in the final two sections of t this chapter.

Methods

Tumour Nomenclature in Animals and Humans. Although human tumours can be coded in a standardized manner using the international statistical classification of diseases coding system (ICD9, 1977; ICD10, 2011), a compatible nomenclature system does not exist for animal tumours. In order to render the animal and human tumours identified in the IARC Monographs comparable, a taxonomy of tumour sites was constructed (Table 2). As detailed in the Supplemental Material I, this taxonomy is anatomically based, and was developed by identifying all of the tumour sites that were cited as having *sufficient* evidence of carcinogenicity in humans or animals within V100A-F* (Grosse et al., 2015). The 39 individual tumour sites seen in either animals or humans through Volume 109 of the *IARC Monographs* were then grouped into 15 anatomically based organ and tissue systems, as shown in Table 2. The 'other groupings' category includes the three sites (all cancers combined; all solid cancers; and exocrine glands NOS) that do not fit into any of the previous 14 groupings. All analyses reported in this chapter are based on the 39 individual tumour sites within 15 organ systems in Table 2.

Aggregation of tumour sites within an organ system was determined by several factors including anatomic and functional relatedness. The individual specialized epithelia of the upper aerodigestive tract, respiratory system, digestive tract, and digestive organs occur for the most part in a single or a few anatomic sites, which are precisely captured by the available epidemiologic and experimental data. In contrast, both kidney and urothelium are data-rich sites and carcinogenic agents for either site display little or no target organ overlap. Accordingly, kidney and urothelium were analysed separately rather than being aggregated as 'urinary tract'. Cancers of soft connective tissues, lymphoid

and haematopoietic tissues, bone and cartilage can arise wherever in the body their progenitor tissues occur, and are aggregated according to tissue of origin without regard to anatomic location. Skin cancers likewise are aggregated without regard to anatomic location, with the exception that malignant melanoma as it occurs in humans is unknown in rats or mice; cutaneous melanocytes are thus included separately in the table as a human tumour site only for the sake of completeness. Estrogen producing and estrogen-responsive tissues are aggregated into the organ system 'female breast, female reproductive organs and reproductive tract'. In contrast to the female reproductive system, however, no carcinogens are known with *sufficient evidence* for the human male reproductive system, which is included in the table also the sake of completeness, despite the high prevalence in humans of prostate and testicular germ cell cancers.

Abstraction of Data on Tumour Occurrence from the IARC Monographs. Grosse et al. (2015) abstracted data from V100, 105. 106, 107 and 109 on tumour sites reported in humans or animals for the 111 Group-1 agents. The information abstracted is illustrated in Table 3, using one compound from each of V 100A-F, as well as diesel exhaust (V105), TCE (V106), PCBs (V107) and air pollution (V109). Table 3 gives the tumour sites for which *sufficient evidence* of increased cancer risk in humans exists, as well as sites for which there is *limited evidence*. Tumour sites for which *sufficient evidence* of increased risk exists in specific animal species are also noted. Information on the histology of animal lesions, when available, is also recorded in Table 3; however, since this information is not generally available in the *IARC Monographs* for human studies, it was not considered in the comparative analyses reported here.

Although tumour sites for which there is *limited evidence* of carcinogenicity in humans is included in Table 3, this information is not considered in the present analysis. (Our original intent was to consider *sufficient* or *limited evidence* in humans when evaluating concordance with *sufficient evidence* in animals, however, there are only two Group-1 agents with *limited*, but not *sufficient*, evidence in humans.)

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 the gender and strain of the test animals, and the route of administration of the test agent. Although this information has been recorded where available, it is difficult to examine concordance with respect to these important factors for a variety of reasons.

Since many epidemiological studies are based on predominantly male occupational cohorts, men tend to be over-represented in the human studies on Group-1 agents. Other agents, such as hormonal oral contraceptives, are evaluated only in females. Certain lesions, notably breast cancer and prostate cancer, are largely gender-specific. Some animal experiments also use only one gender; others do not specify whether males or females – 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. In many cases, information on strain is unavailable, precluding the possibility of strain-specific analyses.

Human exposure to carcinogens can occur by oral ingestion, inhalation, dermal absorption, as well as other routes such as injection of pharmaceutical agents for therapeutic purposes. Animal experiments may involve other routes of exposure, such as intraperitoneal injection or intratracheal instillation. In many cases, the route of exposure used in animal experiments may not correspond to the predominant route by which humans are exposed – in such cases, the dose of the reactive metabolite reaching critical target tissues may be quite different, depending on the route of

administration. Differences in route of exposure between animals and humans could thus contribute to discordance in tumour sites observed in animals and humans. However, since data on cancer outcomes for the same route of exposure are not available across the set of Group-1 agents, a systematic evaluation of concordance for specific exposure routes is not possible.

Species-specific Tumour-site Profiles. Prior to conducting both qualitative and quantitative concordance analyses, we examined the distribution of the types of tumours caused by the 111 distinct Group-1 carcinogens identified by the IARC to date in both humans and animal species. These distributions are of value in demonstrating the spectrum of tumours caused by these agents in different species, including the identification of the most common tumours caused in humans. Human tumours caused by the 11 biological agents reported in Volume 100B were included in these distributions, in order that these results reflect the tumour types caused by all 111 distinct Group-1 carcinogens identified to date.

Heat Maps of Tumour Concordance. Heat maps showing the degree of qualitative concordance between the types of tumours seen in humans and animals were prepared for both the 39 tumour sites and 15 organ and tissue systems included in our anatomically based tumour nomenclature system. The heat maps use a colour coding system in which increasing colour intensity reflects a greater number of species demonstrating the same tumour. The maximum intensity is shown when a Group-1 agents causes tumours at the same tumour site or in the same organ and tissue system in humans and four animal species. In addition to identifying agents that cause the same type of tumour in multiple species, the heat maps can also be used to graphically flag multi-site carcinogens. The 11 biological agents in V100B are included in the heat maps to graphically demonstrate the lack of availability of relevant animal data for these agents.

Organization of Concordance Analyses. Analytical results will be presented first for the 39 tumour sites, and then for the 15 organ systems: as the present database involves only a moderate number of agents with comparable data in animals and humans, results aggregated by organ system may be expected to be more stable.

Measure of Concordance. Statistical analysis of concordance is based on a comparison of animal and human tumours summarized in the form of the following 2x2 table.

2x2 Table for Evaluating Species Concordance

	Humans		
Animals	**Pos**	**Neg**	**Total**
Pos	n_{11}	n_{12}	$n_{1.}$
Neg	n_{21}	n_{22}	$n_{2.}$
Total	$n_{.1}$	$n_{.2}$	$n_{..}$

A simple, intuitive measure of overall concordance used by Gold et al. (1989) is the proportion positive in both species, (n_{11}/n_{++}), plus the percentage negative in both species, (n_{22}/n_{++}), defined by

$$\rho = ((n_{11}+n_{22})/n_{..}).$$

The value of ρ ranges from 0 to 1, where ρ=0 and ρ=1 reflect perfect discordance and perfect concordance, respectively.

Concordance can also be measured using the kappa (κ) statistic discussed by Viera & Garrett (2005), defined by

$$\kappa = (n_o-n_e)/(n_{++}-n_e),$$

where n_o and n_e denote the observed and expected total counts along the diagonal of the 2 x 2 matrix, with $n_o = n_{11}+n_{22}$ and $n_e = (n_{1+}n_{+1}/n_{++}) + (n_{2+}n_{+2}/n_{++})$. This statistic measures concordance as slight (0.01-0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80), and almost perfect (0.81-0.99). Values of $\kappa < 0$ correspond to less than chance agreement (Viera & Garrett, 2005). Although these authors proposed a Monte Carlo approximation to the exact probability distribution of κ as the basis for obtaining confidence limits on κ, we employed an exact approach to confidence limit determination as described in Supplemental Material II. Note that κ is significantly greater than 0 (reflecting the case of no concordance) when the lower confidence limit on κ is positive.

Since these two concordance measures are related by the formula

$$\kappa = (n_{++}\,\rho - n_e)/(n_{++}-n_e),$$

they provide equivalent information on concordance, albeit on a different scale of measurement (although ρ=κ=1 whenever there is perfect concordance, with both off-diagonal counts being 0). In the remainder of this chapter, we will focus on κ as a measure of species concordance. We note that κ can only be calculated when n_{++} is greater than 1 and all marginal counts (n_{11}, n_{12}, n_{21} and n_{22}) are all at least 1. (Rather than specifying an artificial minimum value of n_{++} as a way of avoiding sparse data, will present values of κ whenever it is calculable, and rely on the width of the exact confidence limits on κ to gauge the effects of sparse data.)

In evaluating concordance between animal and human tumour sites, it is important to note that the data included in the concordance database assembled by Grosse et al. (2015) includes only tumour sites for which an IARC Working Group concluded that there is *sufficient evidence* for carcinogenicity in animals and/or humans for the agent or agents under evaluation. In the absence of *sufficient evidence* of expression of a particular tumour site, the agent would be considered to be negative in the above table, even in the presence of *limited* or *inadequate evidence*. This could lead to underestimation of concordance, in the present of *limited* or *inadequate evidence* that, through further study, might become *sufficient evidence*. The absence of any experimental data for a Group 1 agent (as is the case with treosulfan and leather dust), a negative entry for the animal results would also be recorded in the above table. Again, the inclusion of negative entries for animals in the absence of any experimental data, could also lead to underestimation of concordance, should future studies demonstrate a positive result in animal experiments.

In calculating the quantitative concordance between tumour sites seen in animals and humans across the 111 distinct Group-1 agents, we excluded the 11 biological agents in V100B because of the lack of relevant animal models for these agents. We also excluded eight agents (aristolochic acid; benzo[a]pyrene; dyes metabolized to benzidine; ethylene oxide; etoposide; 4,4'-Methylenebis(2-chloroaniline) (MOCA); neutron radiation; and N'-nitrosonornicotine (NNN) and 4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanon (NNK);) falling in Group 1 because of mechanistic upgrades with no human tumour site specified (Table 4). Of the remaining 90 agents, 58 demonstrated *sufficient evidence* of carcinogenicity in both humans and animals, with the remaining 30 agents demonstrating less than *sufficient evidence* of

carcinogenicity in animals. It is emphasized that a positive finding, denoted 'Pos' in the 2x2 table above denotes *sufficient evidence* for carcinogenicity in the species under consideration (animals or humans); a negative finding, denoted 'Neg', refers to less than *sufficient evidence*, either *limited* or *inadequate*.

For purposes of quantitative concordance analysis, kappa statistics are thus calculated only for agents for which there exists *sufficient evidence* of carcinogenicity in both humans and the animal species in which concordance is being evaluated. This is consistent with our focus on the question: *given that an agent produces tumours in both humans and animals, what is the likelihood that the agent produces tumours at the same site in humans and animals?* Because not all Group-1 agents will have been tested in all animal species, the number of agents involved in quantitative concordance analysis will vary by species.

Results

The concordance database assembled by Grosse et al. (2015) includes 111 distinct Group-1 agents summarized in Table 1, through to the completion of Volume 109 of the IARC Monographs. Ten 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 by the Working Groups who conducted the evaluations on the basis of mechanistic upgrades according to the evaluation criteria outlined in the Preamble to the *IARC Monographs*. Benzo(a)pyrene (BaP), for example, was placed in Group-1 on the basis of epidemiological data on exposure to mixtures of PAHs containing BaP providing *sufficient evidence* for lung or skin cancer in humans, coupled with extensive mechanistic data on BaP suggesting that the mechanisms by which BaP causes tumours in animals would also be expected to operate in humans (IARC, 2010). An important aspect of such mechanistic upgrades for purposes of the present analysis is the general lack of identification of a human tumour site: of the ten agents placed in Group-1 on the basis of a mechanistic upgrade, tumour sites were specified by the WGs for only for phenacetin, which was determined to cause tumours of the renal pelvis and ureter, based on results the evaluation of phenacetin as the active ingredient in analgesic mixtures.

In addition to the nine Group-1 mechanistic upgrades for which no human tumour sites were identified, human tumour sites were also not identified for four radiation agents (ionizing radiation (all types); internalized radionuclides that emit alpha particles; internalized radionuclides that emit beta particles; and UV radiation (bandwidth 100-400 nm, encompassing UVC, UVB and UVA)), and two lifestyle agents (areca nut and ethanol in alcoholic beverages).

No animal tumour sites were identified for 35 of the 111 agents considered here (Table 5). These included 20 agents with *inadequate evidence* in animals, comprised of 7 agents representing occupational exposures that would be difficult to replicate in the laboratory; 2 pharmaceutical agents used in combination for which no animal data was available on the mixture; 7 biological agents (all viruses) for which the selection of an appropriate animal model was problematic; 2 agents (etoposide and wood dust) were the available animal tests were considered inadequate; and 2 agents (treosulfan and leather dust) for which no animal data were available. Although the agents lacking any animal test data – treosulfan and leather dust – clearly do not permit an evaluation of concordance between animals and humans, the two agents for which inadequate animal data were available – etoposide and wood dust – warrant further review in order to distinguish between the case in which well-conducted animal studies have failed to demonstrate carcinogenicity or the case in which the animal data is largely uninformative because of inadequate testing.

IARC (2000, 2012) noted that etoposide was tested in only one experiment using wild-type and heterozygous neurofibromatosis type 1 gene (Nf1) knock-out mice treated by gastric intubation for 6 weeks with 100 mg/kg body weight/week etoposide (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 by the IARC (1995) did not show significant carcinogenic or co-carcinogenic potential of beech wood dust, although these studies were subject to a number of limitations as well as inadequacies in data reporting. Re-evaluation of wood dust by the IARC (2012) resulted in the following synthesis of the available animal data:

> *"Several of the studies investigating the carcinogenicity of inhaled wood dust in rats and hamsters used particles with relatively large MMADs, a design that would enhance deposition in the upper respiratory tract, including the nasal cavity. Despite this design, the results of the animal studies do not confirm the nasal carcinogenicity of wood dust observed in humans. No measurement of the actual deposition of wood dust in the respiratory tract was made, and therefore the amount of the exposure is unknown. In one study in mice, a methanol extract of beech wood dust was tested by skin application. Although a dose-dependent increase in the incidence of skin tumours was observed, this result cannot be used in the evaluation of the carcinogenicity in experimental animals of wood dust per se." [reproduced from IARC, 2012c, p. 451].*

The IARC (2012c) concluded of the several studies conducted with wood dust (nearly all with beech wood dust), most had small numbers of animals or were of short duration, thus providing *inadequate evidence* of carcinogenicity in animals. These evaluations suggest that neither etoposide nor wood dust have been subject to adequate animal testing, therefore precluding a determination of their carcinogenic potential in animals.

Nine agents, including five pharmaceutical products (busulfan; chlornaphazine; cyclosporine; combined estrogen-progestogen menopausal therapy (combined); and analgesic mixtures containing phenacetin), three biological agents (infection with Clonorchis sinensis, Opisthorchis viverrini, and Schistosoma haematobium), and one chemical agent (sulfur mustard) provided *limited*, but not *sufficient*, evidence of carcinogenicity in animals. Animal tumour sites are not specified for agents demonstrating only limited evidence of carcinogenicity in animals.

The reasons that these agents were judged as providing only *limited evidence* of carcinogenicity in animals varied. Bulsulfan, for example, resulted in a significant increase in the incidence of thymic lymphomas in BALB/c mice, which WG found difficult to interpret, and a significant increase in the incidence of uterine adenocarcinomas in the offspring of rats treated with *N*-ethyl-*N'*-nitro-*N*-nitrosoguanidine (IARC, 2012a). As a second example, sulfur mustard significantly increased the incidence of lung tumours (not otherwise specified) in mice following inhalation exposure for 15 minutes; pulmonary tumours (not otherwise specified) were also increased in mice following intravenous injection; a significant increase in the incidence of mammary tumours was seen following subcutaneous injection in rats, relative to an external control group; and fore-stomach tumours in rats were numerically, but not significantly, elevated in rats treated by oral gavage. (IARC, 2012f). The WG considered exposure by subcutaneous and intravascular injection to be of limited relevance to the most common human routes of exposure. Although not meeting the stringent criterion for *sufficient evidence* of carcinogenicity in animals, the *limited evidence* provided by bulsulfan, as well as the other six agents with only *limited evidence* of carcinogenicity in animals, does suggests that these agents have the potential to cause cancer in animals.

No tumour sites were specified for 6 agents demonstrating *sufficient evidence* of carcinogenicity in animals, as replicable results were unavailable in two or more studies of adequate design in the same species for any of these agents. Although melphalan showed statistically significant evidence of an increased incidence of tumours of the forestomach, skin and lung in mice, as well as lymphosarcoma, these results were not replicated in two or more independent studies (IARC, 2012f). In the rat, melphalan also produced rat mammary gland tumours and peritoneal sarcoma, but these findings were again not replicated in independent studies. Phosphorous-32 caused leukaemia in mice and osteogenic sarcomas in rats in single studies. Similarly, acetaldehyde in drinking water induced pancreatic adenomas, combined lymphomas and leukaemias, uterine and mammary gland adenocarcinomas, and head osteosarcomas in the rat, but without replication. Betel quid with tobacco produced malignant forestomach and cheek pouch tumours in a single study in hamsters. Sufficient evidence of the carcinogenicity of aluminum refining in animals was based a single limited mouse skin tumour study on particulate PAHs from aluminium-production plants, in conjunction with sufficient evidence of carcinogenicity in experimental animals for many of these PAHs that are detected in air samples from Al production plants and that were previously evaluated in Volume 92 of the *IARC Monographs* (IARC, 2010). Had this animal evidence been eligible for inclusion in the tumour site concordance database, additional concordant results would have been noted, including concordance between lymphoid and haematopoietic tissues in mice and humans for both melphalan and phosphorous-32, and concordance between tumours of the upper aerodigestive tract in hamsters and humans for betel quid with tobacco.

While 2,3,4,7,8-pentachlorodibenzofuran (PeDCF) provided sufficient evidence of carcinogenicity in animals, no animal site was identified by the WG that conducted the evaluation. PeCDF was tested by the U.S. National Toxicology Program in a two-year animal bioassay with exposure by oral gavage (NTP, 2006). There was some evidence of carcinogenic activity of PeCDF in female Harlan Sprague-Dawley rats, based on increased incidences of hepatocellular adenoma and cholangiocarcinoma of the liver and gingival squamous cell carcinoma of the oral mucosa. Occurrences of cystic keratinizing epithelioma of the lung, neoplasms of the pancreatic acinus, and carcinoma of the uterus may have been related to administration of PeCDF. There were also three rat studies of PeCDF in combination with MNNG and NDEA, where increased tumour multiplicity was observed in each case (IARC, 2012f). These observations led the WG to conclude that there is *sufficient evidence* for the carcinogenicity of PeCDF in animals, although there is no specific organ site that can be designated as responsible for this *sufficient evidence*. Because of the absence of a specific tumour site in animals, PeCDF is not included in the quantitative concordance analyses.

A component of four Group-1 agents, but not the agent itself, demonstrated *sufficient evidence* of carcinogenicity in animals (Table 6). These included: fission products including Sr-90, where strontium-90 demonstrated *sufficient evidence* of carcinogenicity in animals; haematite mining with exposure to radon (underground), where radon demonstrated *sufficient evidence* of carcinogenicity in animals; acetaldehyde associated with consumption of alcoholic beverages, where acetaldehyde demonstrated *sufficient evidence* of carcinogenicity in animals; and occupational exposures during aluminium production, where airborne particulate polynuclear organic matter from aluminium-production plants demonstrated *sufficient evidence* of carcinogenicity in animals. While this animal evidence is consistent with the *sufficient evidence* for the carcinogenicity of these four agents in humans, the animal evidence represents only a component of these agents, and may not necessarily reflect the full spectrum of potential carcinogenic risks posed by these agents to humans.

Excluding the 20 agents in Table 5 lacking appropriate animal data, including occupational exposures not replicable in the laboratory (7 agents), agents used in combination with no animal data available on the mixture (2 agents), agents where the use of animal models is problematic due to species-specificity or other limitations (7 agents), and agents for which animal tests were inadequate (2 agents) or unavailable (2 agents), all 91 distinct Group-1 agents identified by the IARC through 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.

In order to further explore the association between tumours seen in animals and humans among the 111 distinct Group-1 agents considered here, we present descriptive statistics on tumour-site profiles by species, followed by qualitative and quantitative concordance between tumour sites seen in animals and humans. Results are presented first for the 39 tumour sites included in the anatomically based tumour nomenclature system seen in either animals or humans, followed by the 15 organ and tissue systems.

Tumour-site Profiles by Species. The number of agents inducing tumours in humans at each of the 39 tumour sites is shown in Figure 1 by type of agent (pharmaceuticals; biologicals; arsenic, metals, fibres, and dusts; radiation; personal habits and indoor combustions; and chemical agents and related occupations). Lung tumours represent the most common tumour type seen in humans, with 28 of the 109 known human carcinogens inducing lesions at this site; the majority of these are associated with exposure to chemical agents and related occupations (13/28 agents) and arsenic, metals, fibres, and dusts (7/28 agents). Tumours of the haematopoietic tissues are associated with exposure to 18 agents, urothelium (18), skin (12), and liver and bile ducts (11); chemicals and related occupations account for the largest number of agents causing these lesions. Chemicals and related occupations account for the largest proportion (9/18) of urinary tract/urothelial tumours, with pharmaceuticals accounting for the largest fraction (9/18) of tumours in haematopoietic tissues.

The number of agents inducing tumours in one or more animal species at each of the 39 tumour sites is shown in Figure 2 by type of agent. As in humans, lung tumours are the most frequent in animals following exposure to any of the 109 known human carcinogens. Animal lung tumours are caused by 29 of the 109 known human carcinogens, with chemicals (10) and arsenic, metals, fibres, and dusts (7), and radiation (7) accounting for the majority of animal lung carcinogens. Tumours of the skin and adnexae (18), liver parenchyma and bile ducts (19), lymphoid tissue (14), soft connective tissue (11) and breast (11) are the animal sites associated with the largest number of agents.

Separate tumour profiles are shown for agents causing tumours in mice (62) and rats (64) in Figures 3 and 4, respectively. In rodents (mice and rats), the lung is the site associated with the largest number of agents.

Organ- and Tissue-Site Profiles by Species. The number of agents inducing tumours in humans in each of the 15 aggregate organ and tissue systems is shown in Figure 5 by type of agent. Tumours of the upper aerodigestive tract and respiratory system are caused by 47 of the 109 known human carcinogens, comprised mostly of chemicals agents and related occupations (16), arsenic, metals, fibres, and dusts (10), and personal habits and indoor combustions (12). Tumours of the lymphoid and haematopoietic systems (26), urothelium (18), and skin and connective tissues (22) are the organ systems associated with the largest number of agents. Chemical agents and related occupations represents the largest group of agents associated with tumours of the urothelium (9 of 17), while pharmaceuticals represents the

largest group of agents associated with tumours of the lymphoid and haematopoietic systems (11 of 26). Radiation represents the largest group of agents associated with tumours of the skin and connective tissues (8 of 22).

The number of agents inducing tumours in one or more animal species at each of the 15 organ systems is given in Figure 6 by type of agent. Tumours of the upper aerodigestive tract and respiratory system are caused by 41 of the 109 agents under study, with chemical agents and related occupations (15), personal habits and indoor combustions (10), and arsenic, metals, fibres, and dusts (8), and radiation (7) accounting for almost all of these 41 agents. Skin and connective tissue tumours are caused by 35 agents, comprised mostly of chemicals (17) and radiation (11). Tumours of the lymphoid and haematopoietic systems are caused by 14 agents, with pharmaceuticals (5) and chemicals (5) accounting for the majority of these.

In mice (Figure 7), tumours of the skin and connective tissues are caused by 30 agents, comprised mostly of tumours caused by chemicals (15) and radiation (10). In rats (Figure 8), tumours of the upper aerodigestive tract and respiratory system are caused by 29 agents, including chemicals (10), arsenic, metals, fibres, and dusts (7), radiation (6), and personal habits and indoor combustions (6).

Qualitative assessment of concordance. Figure 9 provides a 'heat map' of the concordance between tumours observed in animals and humans, based on the 39 individual tumour types considered. As indicated in the legend to this diagram green represents the case in which the tumour is seen only in humans; the four increasingly darker shades of orange/red represent the case in which the tumour is seen in humans and in one, two, three, or four animal species simultaneously; the three decreasingly lighter shades of blue represent the case in which the tumour is seen in three, two or one animal species simultaneously, but not in humans.

Notable aspects of Figure 9 include the apparent induction of lung tumours and liver tumours by a large number of agents, as seen earlier in the tumour-site profiles. The ability of radiation, particularly X- and gamma radiation, and, to a lesser extent, neutron radiation, to cause multiple types of tumour is also apparent. Tobacco smoking is also associated with a large number of different tumour types. Particularly strong associations are apparent between asbestos and mesothelial tumours, between Pu-239 and hard connective tissue tumours, and between 2-napthylamine and urinary tract/urothelial tumours, where in each case the same tumours are induced in humans and in at least three animal species.

Figure 10 provides a 'heat map' of the concordance between tumours observed in animals and humans, based on the fifteen organ systems considered. Tumours of the upper aerodigestive tract and respiratory system are associated with 58 of the 109 agents considered; tumours of the skin and connective tissues are associated with 47 agents known to cause cancer in humans. X- and gamma radiation induce tumours in both humans and animals in 13 of the 15 organ systems; neutron radiation is associated with animal tumours in seven of the 15 organ systems. Particularly strong concordance between animals and humans is observed for asbestos and tumours of the mesothelium; for Pu-239 and connective tissue tumours; and for 2-napthylamine and tumours of the urothelium.

Quantitative assessment of concordance. The quantitative concordance between animal and human tumours based on the κ statistic for the 39 tumour types is shown in Table 7. Although the evaluations of animal data in the IARC Monographs were not conducted to assess the degree of concordance between animals and humans, the present *post hoc* analysis of the database of tumour sites seen an animals and humans developed by Grosse et al. (2015), substantial agreement between animals and humans is seen in a number of cases. In mice, near perfect concordance with humans

is seen for stomach (κ = 1) and thyroid (κ = 1) tumours, while substantial concordance is observed for hard connective tissue (κ = 0.73) and uterine cervix (κ = 0.79) tumours. In rats, almost perfect concordance is seen for tumours of the mesothelium (κ =1), thyroid (κ =1), urothelium (κ = 1), and lung (κ = 0.88). No significant concordance was observed between any one of the other animal species (hamsters, dogs, and primates) and humans, although the data are too sparse to permit meaningful conclusions for these species.

Concordance between tumours seen in *either mice or rats* and in humans is not materially increased relative to the maximum of the concordance between mice and humans or between rats and humans. Because of the preponderance of rats and mice among the animal species tested, concordance between *any animal species* and humans is comparable to that between either rats or mice and humans.

Organ- and Tissue-Site Concordance. The quantitative concordance between animal and human tumours for the 15 organ systems is shown in Table 8. Substantial concordance between mice and humans is observed for tumours in the endocrine system (κ =0.79), connective tissues (κ = 0.70), female breast, female reproductive organs and reproductive tract (κ = 0.63), and skin (κ = 0.64), while moderate concordance is seen for tumours of the lymphoid and haematopoietic tissues (κ = 0.57). For rats, almost perfect concordance is seen for tumours in the mesothelium (κ =1) , and urothelium (κ = 0.88), while substantial concordance is seen for endocrine (κ =0.79) and respiratory system (κ =0.78) tumours. No significant concordance was observed between any one of the other animal species and humans, although data are again sparse.

Concordance between either mice or rats and humans does not increase appreciably, relative to the maximum of the concordance coefficients for mice and for rats. Concordance between any animal species and humans is similar to the concordance between either mice or rats and humans.

Discussion

Since 1972, the International Agency for Research on Cancer has been evaluating potential cancer risks to humans by developing the IARC Monographs. Separate evaluations of the available animal and human evidence are made, and used to make an overall evaluation of the strength of evidence for human carcinogenicity. As of this point, 117 distinct agents have met the IARC criteria for determining causality, and designation of these agents as being in *Group 1: Carcinogenic to humans*. In 2012, V100 of the IARC Monographs provided a review and update of the 107 Group-1 agents identified at that time (IARC, 2012abcdef). Including additional agents identified through Volume 109, the most monograph available at the point at which the present concordance analysis was completed, there were 111 distinct Group-1 agents in the database of tumours in animals and humans developed by Grosse et al. (2015).

An important aspect of the approach by the IARC to identify agents that cause cancer in humans is the well-established weight of evidence evaluation of the available human, animal, mechanistic, and exposure data. These criteria are detailed in the *Preamble to the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* (IARC, 2006). These criteria provide clear guidance to the working groups convened to review agents selected by the IARC for evaluation. The criteria for *sufficient evidence* of carcinogenicity in both animals and humans are sufficiently rigorous to reasonably infer causality when they are met.

An immediate challenge faced at the beginning of this work was how to compare animal and human tumours. A detailed historical discussion of approaches to the coding of human tumours is provided by Muir & Percy (1991), considering the

topographical, morphological, and histological characteristics of the lesion to be classified. In the absence of a common coding system for animal and human tumours, an anatomically based tumour taxonomy system was developed during the course of this work. While 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 and zymbal glands; these unique sites occurred rarely, and were included within the category of 'other groupings' in the anatomically based tumour nomenclature system employed here. Other sites that are unique to animals, but closely related to a similar human site were, however, were aligned with the corresponding human tumour site: the forestomach, for example, was considered as part of the stomach in our anatomically based tumour site concordance system.

The tumour site concordance system included 39 individual tumour sites, which were further aggregated into 15 organ and tissue systems. Concordance analyses were conducted at both the individual site level as well as at the organ system level.

The central issue addressed in this chapter is the extent tumour sites seen in animals and humans for Group-1 agents are similar. Although the present analysis demonstrates generally good agreement between animal and human tumour sites, concordance is not perfect. Imperfect concordance can occur if relevant and reliable data to support a complete analysis of concordance is unavailable for either animals or humans. Some agents, notably the human papilloma viruses, may not have been tested in relevant animal models, thereby precluding the possibility of obtaining concordant results. 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 combination estrogen-progesterone menopausal therapy may also not have been evaluated in animals, particularly if the components of the mixture have been previously evaluated. Even if relevant animal tests have been conducted, they may have provided only *limited* or *inadequate* evidence of carcinogenicity. This could occur because of limitations in study design or conduct, or if the mechanism of action of the agent of interest was specific to humans.

Discordance can also occur when the available human evidence is *limited* or *inadequate*. According to the criteria used by the IARC for evaluating cancer risks, an agent can be placed in Group 1 in the absence of *sufficient evidence* for carcinogenicity in humans based on *sufficient evidence* of carcinogenicity in animals, when it is clear that the mechanisms by which the agent causes cancer in animals also operate in humans. Such 'mechanistic upgrades' have occurred for 11 agents with varying levels of human evidence, including aristocholic acid (*limited* evidence of carcinogenicity in humans; IARC 2012a); benzo(a)pyrene [B(a)P] (*inadequate* evidence in humans; IARC, 2012f); ethylene oxide (*limited* evidence in humans, IARC, 2012f); 4,4'-methylenebis(2-chlorobenzenamine)[MOCA] (*inadequate* in humans); and neutrons (*inadequate* evidence in humans; IARC, 2012d). The mechanisms by which the 111 Group-1 agents are thought to increase human cancer risk are summarized in other chapters in this volume (Birkett et al., 2015; Krewski et al., 2015), based on a detailed analysis of the mechanistic information on these agents compiled by Al-Zoughool et al. (2015).

An absence of *sufficient* human evidence for Group-1 agents may be due to a lack of human evidence in appropriate epidemiological or clinical studies, or the inability of existing studies to detect an association between the agent of interest and the expected carcinogenic response due to study limitations, including inadequate power caused by small sample size. If human exposures to the agent of interest are extremely low, a particularly large, well-conducted study would be required to achieve reasonable sensitivity.

Agents for which sufficient evidence of carcinogenicity exists in both animals and humans may increase cancer risk in one or more animal species. Of the 111 Group-1 agents examined here, three agents caused tumours in humans and four animal species (mice, rats, hamsters and primates): asbestos, which causes lung tumours in all five species; Pu-239, which causes skin tumours in these species; and 2-napthylamine, which causes urinary tract/uroendothelial tumours in these same species. These agents represent examples of carcinogens that cause the same type of tumour in multiple species, thereby demonstrating a high degree of tumour-site concordance across species.

Concordance was evaluated using the database on the 111 distinct Group-1 agents assembled by Grosse et al. (2015), abstracted from the IARC Monographs. These agents do not represent a 'random sample' from the universe of human carcinogens, which is incompletely characterized at this time. All quantitative concordance analyses apply only to the series of 111 Group-1 agents identified by the IARC to date, and are conditional on the available animal and human evidence for these agents. Concordance may change as additional Group-1 agents are identified, or as additional animal or human evidence on current Group 1 agents becomes available. New mechanistic data could affect current IARC evaluations of agents in Groups 2a (*probable* human carcinogens) and Group 2b (*possible* human carcinogens), and hence impact the concordance estimates reported here. Krewski et al. (2015, this volume) noted that while the IARC monograph programme has done an excellent job of summarizing the main mechanistic properties of agents evaluated to date, additional information on the ten mechanistic characteristics of human cancer described by Smith et al. (2015) beyond that summarized in the IARC monographs is available in the general scientific literature.

Both the qualitative and quantitative concordance analysis presented in this article exclude the 11 biological agents in V100B, since, with the possible exception of the HTLV1 virus (human T-cell lymphotropic virus type 1), the use of animals to assess the potential cancer risks of human viruses is problematic (IARC, 2012b, pp. 41-42). The best animal models for human viruses are non-human primates, which are difficult to use experimentally both because of the time and expense involved in conducting experimental studies with long-lived species, but also because the incidence of cancer is low in these species. Although transgenic mouse models have been developed for evaluating human cancer viruses, transgenic animal models are considered more informative in understanding cancer mechanisms than for human cancer risk assessment.

Concordance analyses are based on 2x2 tables showing, along the diagonal, the number of agents which are positive in both the two species being compared, and the number of agents which are negative in both species; off-diagonal cells showing the number of agents which are positive (negative) in one species and negative (positive) in the other species represent discordant results. Because of limitations of the concordance database, the κ statistic used to measure overall concordance may be biased downwards for two reasons. First, the concordance database includes all human studies of the Group-1 agents identified as having *sufficient* evidence of carcinogenicity in the *IARC Monographs*, along with all animal studies with *sufficient* evidence of carcinogenicity for these same agents. If an animal bioassay did not identify a tumour site as having sufficient evidence of carcinogenicity, it was assumed that that site was negative. However, since not animal cancer bioassays will have examined all tissues for evidence of carcinogenicity, it is possible that an assumed negative outcome in a given tissue may have been the result of that tissue not being evaluated. In this event, the κ statistic for that tissue will be biased downward, resulting in a conservative estimate of concordance. Second, the exclusion of bioassays which demonstrate only *limited* evidence of carcinogenicity in animals from the concordance database could also contribute to underestimation of κ, should such evidence later be demonstrated to be *sufficient*. Because information on route of exposure in animal studies was not systematically available in the concordance

database, concordance was necessarily evaluated irrespective of exposure route, possibly weakening concordance between animal and human studies that may have involved different routes of exposure.

The failure to identify a human tumour site for Group-1 agents because of mechanistic upgrades, will affect concordance. Of the ten agents placed in Group-1 as a consequence of mechanistic upgrades, specific human tumour sites were identified only for phenacetin, which was determined to cause tumours of the renal pelvis and ureter, based on the evaluation of phenacetin as the active ingredient in analgesic mixtures. No specific human tumour sites were identified for ionizing radiation (all types); internalized radionuclides that emit alpha particles; Internalized radionuclides that emit beta particles; UV radiation (bandwidth 100-400 nm, encompassing UVC, UVB and UVA); areca nut; ethanol in alcoholic beverages; 2,3,4,7,8-pentachlorodibenzofuran; and dioxin-like PCBs. Identification of specific human tumour sites could be problematic for an aggregate agent such as ionizing radiation. Although the skin was not explicitly mentioned as a human tumour site for UV radiation in Volume 100D, the skin is implicitly suggested by the WG as being a human tumour site for this agent; however, as the WG did not explicitly designate the skin as a human tumour site for UV radiation, this site was not included in the concordance analysis conducted here. A similar situation occurred for areca nut, for which the oral cavity might have been considered as a human tumour site, although this was site was not explicitly designated by the WG.

Concordance could also be affected by the failure of human studies to identify tumour sites affected by the Group-1 agents considered here. This can occur when human studies do not consider all possible tumour sites, as occurs in most case-control studies which focus on only one or a limited number of tumour sites. This could also occur when studies in humans fail to identify a relevant tumour site because of low sensitivity or other limitations of the study. Evidence on specific tumour sites may not yet have accrued at the time an evaluation is done: following the evaluation of tobacco smoke by the IARC (1986), cigarette smoking was subsequently associated with cancers of the nasal cavities and nasal sinuses, oesophagus, stomach, liver, kidney, uterine cervix, and myeloid leukemia in a later evaluation conducted by the IARC (2004). Missing tumour sites for agents for which *sufficient evidence* of carcinogenicity in humans exists may also lead to underestimation of concordance between animals and humans.

The lack of sufficient evidence of carcinogenicity in animals can also impact upon concordance between animal and humans. The criteria for sufficient evidence of carcinogenicity in animals outlined in the Preamble to the IARC Monographs (IARC, 2015) generally require independent replication in two different animal species, or particularly strong results in a single species. In the presence of only *limited evidence* of carcinogenicity in animals, no animal tumour sites were identified by the WGs. Even with *sufficient evidence* in experimental animals, no tumour sites were identified in the absence of two (or more) animal studies of adequate design and quality pointing at the same tumour site with a similar histological origin in the same species. For example, although melphalan, produced tumours of the forestomach, skin, and lung as well as lymphosarcomas in mice and mammary gland tumours and peritoneal sarcomas in rats (IARC 2012f), none of these tumour sites were replicated in a second animal species, and hence were not eligible for inclusion in the concordance database assembled by Grosse et al. (2015).

The effects of cancer-causing substances are strongly dependent on the level of exposure, which in turn is related to dose of the agent or its metabolites reaching target tissues, with cancer risk increasing with increasing dose. Because human exposure to carcinogens is generally much lower than in animal experiments, epidemiologists are often faced with the challenge of designing large-scale population-based studies to detect comparatively low cancer risks. While this challenge can be overcome in laboratory experiments by use of high doses, such high doses can induce mechanistic

pathways that may not operate at lower doses. Indeed, Group-1 agents with complex cancer mechanisms involving multiple mechanistic pathways may demonstrate a series of dose-dependent transitions, in which specific mechanistic pathways may become apparent, or even predominant, as a the dose increases. Andersen et al. (2010), for example, demonstrate a series of dose-dependent transitions in genomic changes, cytotoxicity, and tissue kinetics following inhalation exposure to formaldehyde, a rat nasal carcinogen, which can induce nonlinear dose-response characteristics.

Exposure assessment is one of the most difficult aspects of epidemiological investigations (Nieuwenhuijsen, 2003)). In some cases, such as ecologic studies comparing two population groups subject to notably different exposure circumstances, exposure may not be measured at all. In other cases, however, exposures may be very well determined, as with the use of personal dosimeters to measure exposures to agents such as ambient air pollution or ionizing radiation. In the future, enhanced exposure assessment methodologies may serve to strengthen the ability of epidemiological studies to identify Group-1 agents (Cohen-Hubal et al., 2010; NRC, 2012). Biomarkers of exposure are expected to play an important role in the future of exposure science (Gurusankar et al., 2015).

Multi-site/multi-organ carcinogenicity. The present analysis demonstrated that the ability of a number of agents, notably radiation and tobacco smoke, to induce malignant lesions at multiple sites or in multiple organ and tissue systems. Huff et al. (1995) showed that 1,3-butadiene induces hemangiosarcomas of the heart, malignant lymphomas, alveolar-bronchiolar neoplasms, 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 females. Assessing species concordance with multi-site carcinogens is inherently more difficult than with carcinogens that affect a single organ or tissue. Understanding the mechanistic and other attributes of such multi-site carcinogens will be useful in translating results in experimental animals to humans.

Concordance between rats and mice. Previous studies have examined concordance between carcinogenicity (not site-specific, as considered here) in rats and mice in the National Cancer Institute/National Toxicology Program (NCI/NTP) carcinogenicity bioassays, which follows a standardized testing protocol in these two rodent species (Bucher, 2002). Based on an analysis of 266 bioassays, Haseman et al. (1986) reported that the overall concordance between rats and mice (either carcinogenic in both species or not carcinogenic in either species) exposed to the same agent was 74%; results for males and females of the same species were also highly concordant (87% for rats and 89% for mice). Gold et al. (1989) examined concordance between rats and mice based on experimental data in their Carcinogenic Potency Database; for the 392 chemicals tested in both species, overall concordance was 76%, similar to that reported by Haseman et al. (1986) and Freedman et al. (1996).

Freedman et al. (1996) note that the observed overall concordance 75% between rats and mice may be viewed as low because these two closely related species are tested under the same experimental conditions. However, because of measurement error, Piegorsch et al. (1992) determined that the maximum observable concordance is limited to about 80% under the NCI/NTP bioassay protocol. Freedman et al. (1996) further demonstrated that the true concordance is highly uncertain, with an observed concordance consistent with a true value between 20 and 100%.

The IARC concordance database compiled by Grosse et al (2015), which underpins the present analysis of concordance between animal and human tumour sites, is not particularly well-suited to examine the concordance between rats and mice. Unlike the US National Toxicology Program rodent cancer bioassay program (Bucher, 2002), which systematically conducts parallel tests in both rats and mice on the same test agents, the IARC considers animal cancer bioassay data

only for those agents evaluated within the IARC monograph programme. As such, a comprehensive analysis of concordance between different animal species is not attempted here. Lack of concordance among animal species may be explained by a number of factors, including differences in experimental design related to dose levels, route of exposure, and other factors (Haseman 1989). Since body weight is correlated with tumour occurrence in rodent carcinogenicity bioassays (Haseman, 1997), body weight differences related to diet or comorbidity could contribute to lack of concordance. In some cases, target organ toxicity can also influence carcinogenicity in rodents (Hoel et al., 1987).

Rodent carcinogenicity bioassays have been criticized for the use of high doses, which may produce positive findings which might not appear at the lower doses to which humans might be exposed (Ames & Gold, 1990). This concern is accentuated by meta-analyses conducted by Crump et al. (1998, 1999) suggesting that, due to limitations in statistical sensitivity, not all carcinogenic effects are necessarily identified through NCI/NTP bioassays.

Consideration of mode of action can help in determining the relevance of carcinogenic effects observed at high doses in rodents for humans (Holsapple et al., 2006; Meek et al., 2013). Proctor et al. (2007), for example, use mode of action criteria to question the relevance of forestomach tumours in rodents, particularly epithelial tumours, to humans. These considerations will be relevant in planned future analyses of coherence between animal and human tumours, taking into account the mechanistic characteristics of Group-1 agents described by Krewski et al. (2015).

Carcinogenic potency. The present analysis focuses on qualitative concordance data, reflecting presence or absence of evidence of increased risk of cancer at a given tumour-site in animals and humans. Other investigators have examined species concordance in a more quantitative manner, correlating measures of carcinogenic potency in different species for agents demonstrating carcinogenic potential in both animals and humans. Crump & Allen (1988) reported statistically significant correlations in the carcinogenic potency of 23 agents demonstrating epidemiological evidence of carcinogenicity in humans and toxicological evidence of carcinogenicity in animal bioassays, with correlation coefficients ranging as high as 0.9. Dedrick & Morrison (1992) demonstrated a good correlation between the potency of chemotherapeutic agents causing leukemia in patients treated for cancer or polycythemia vera and lymphosarcoma in rats and mice. The maximum dose tested in rodent bioassays has been shown to be highly correlated with measures of carcinogenic potency (Bernstein et al., 1985; Haseman & Seilkop, 1992; Krewski et al., 1993), which varies over eight orders of magnitude (Gold et al, 2005). Establishing correlations in carcinogenic potency between animals and humans may help in predicting human cancer risks based on animal data, which is a practice employed by some regulatory agencies (Hoover et al., 1995), but outside the scope of the present analysis.

The present analysis is subject to a number of additional limitations, including incomplete information on tumour histology; limited information on the effects of gender, strain, and route of exposure; and limited information on dose-dependent effect. Because the concordance database is comprised entirely of Group-1 agents, estimation of the predictive value (positive, negative, or overall) is not possible. These limitations are discussed briefly below.

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

analyses reported here are based either on 39 tumour sites or on the broader classification of15 organ and tissue systems.

Effects of gender, strain, and route of exposure. Cancer risks can differ between males and females, among different strains of the same animal species, and by route of exposure. Because of incomplete information on these three factors in the database used in the present analysis, it was not possible to evaluate how concordance might vary by gender, strain, or exposure route.

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

Predictive Value of Animal Tests for Carcinogenicity. Using a database comprised of 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. While a statement of the PPV and NPV of animal cancer tests for human carcinogenicity is desirable, this cannot be done on the basis of the IARC concordance database considered in this chapter. This is because both the PPV and NPV depend on the prevalence of true positives in the database (Altman & Bland, 1994). Since the IARC concordance database is comprised of Group 1 agents that are known causes of cancer in humans, the PPV of animal cancer tests will artificially be calculated as 100%, whereas a lower PPV would be obtained using a more representative database that includes other agents that do not cause cancer in humans. Identifying agents that do not cause cancer in humans is not the focus of the IARC Monographs Programme: at present, there is only one agent – caprolactam – in Group 4, *probably not carcinogenic to humans*.

What is possible with the present IARC concordance database is a statement about the likelihood of positive results in animals among the Group 1 agents that have been shown to cause cancer in humans Excluding agents for which animal data is unavailable or uninformative, *all agents known to cause cancer in humans also cause cancer in one or more animal species*, representing a PPV of 100% for animal cancer tests.

Additional evidence of the relevance of animal cancer tests for human cancer risk assessment can be derived from the analysis of mechanistic characteristics of Group -1 agents conducted by Krewski et al. (2015). This analysis profiled ten major mechanistic characteristics described by Smith et al. (2015) – electrophilicty, genotoxicity, DNA repair, chronic inflammation, oxidative stress, receptor-mediated effects, cell proliferation, immunosuppression, epigenetic alteration, and immortalization – demonstrated by these agents. In constructing the mechanistic database on which this analysis was based, Al-Zoughool et al. (2015) considered evidence derived from four sources: human in vivo data, human in vitro data, animal in vivo data, and animal in vitro data. Considering all Group 1 agents combined, information on each of these ten mechanistic characteristics was generally similar across these four sources. Whereas results for genotoxic were particularly similar across these four sources, results for immortalization were derived primarily from in vitro

studies (both animal and human) rather than in vivo studies. Further investigation of what can be learned about the causes of human cancer through joint evaluations of the concordance database assembled by Grosse et al. (2015) and the mechanistic database of Al-Zoughool et al. (2015) will form the basis for future research.

Conclusion

The Monographs Programme of the International Agency for Research on Cancer is widely recognized as one of the most authoritative sources of information on the identification of agents that may present cancer risks to humans. The Monographs are prepared with the involvement of leading scientific experts worldwide, who apply the guidance provided in the Preamble to the IARC Monographs to evaluate the weight of evidence that an agent may present a cancer risk to humans. Through V109, over 2,000 scientists have contributed to the development of the IARC Monographs, with nearly 200 scientists involved in Volume 100 alone. Since its beginnings in 1970, the Programme has evaluated 982 agents for their potential to cause cancer in humans, with 117 of these agents assigned to Group 1, indicating the weight of evidence supports the conclusion that *the agent is carcinogenic to humans*.

Collectively, the IARC Monographs provide a rich source of information on the causes of human cancer. In particular, V100 provides a review and update of 107 Group 1 agents identified in the previous 99 volumes, providing a veritable 'encyclopedia of carcinogens.' This information, supplemented with that on 6 Group 1 agents identified in Volumes 101 through 109, formed the basis for the analyses included in the present chapter.

Descriptive analyses indicated that the lung was the site most often affected by the 111 distinct Group 1 agents: of the 39 tumour sites considered, 28 of these agents were determined to cause lung tumours in humans and 29 caused lung tumours in one or more animal species. Among the 15 organ and tissue systems considered, the upper aerodigestive tract and respiratory system was most frequently affected, with 47 agents causing tumours in this system in humans and 41 agents causing these tumours in animals.

Heat maps served to identify agents that affected multiple species or caused tumours at multiple sites. Particularly strong associations were seen between asbestos and mesothelial tumours, between Pu-239 and connective tissue tumours, and between 2-napthylamine and urinary tract/urothelial tumours, where in the two former cases the same tumours are induced in humans and three animal species, and in the latter case the same tumours are induced in humans and in four animal species. Tobacco smoking affected multiple tumour sites as well as multiple organ and tissue systems in humans. X-rays and gamma radiation affected 13 of the 15 organ systems considered in both animals and humans.

Although a number of quantitative measures of concordance between animals and humans were calculated, these concordance measures are expected to underestimate true concordance for two main reasons. First, the concordance database on which these analyses were based includes only animal experiments that meet the IARC criteria for sufficient evidence of carcinogenicity in animals: if these criteria were not satisfied, it was necessary to assume that animal tumours were not induced by the agent of interest in order to calculate the kappa statistic used to measure concordance. Second, limitations in sensitivity of epidemiological and clinical studies in humans, as well as sources of uncertainty inherent in human studies, may have precluded the identification of a tumour induced in highly controlled animal experiments conducted at high doses. Nonetheless, substantial concordance ($0.61 \leq \kappa\ 0.80$) between mice and

humans was observed for tumours in hard connective tissue and in the lower reproductive tract; substantive concordance between rats and humans was observed for tumours of the mesothelium and of the thyroid. Substantive concordance between mice and humans was also observed for tumours in the nervous and endocrine system and in the lymphoid and hematopoietic system; substantive concordance between rats and humans was also observed for tumours in the urinary system.

Of the 111 agents considered in the present analysis, ten agents were placed in Group 1 in the absence of *sufficient evidence* of carcinogenicity in humans on the basis of mechanistic upgrades; all of these agents demonstrated *sufficient evidence* of carcinogenicity in animals.

An important overarching finding from the present analysis is that, excluding agents for which animal data is lacking or otherwise uninformative, all agents that cause cancer in humans also cause cancer in one more animal species. It is important to note, however, that the present database cannot be used to estimate the predictive value of animal cancer tests for humans, as it comprised by design include only Group-1 agents: the positive and negative predictive values of the animal data for humans would be 100% and 0%, respectively (an artifact of database being comprised entirely of human carcinogens).

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

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Supplemental Material

Supplemental Material I. Database of Anatomically-based Tumour Sites in Animals and Humans

Supplemental Material II. Statistical Evaluation of Concordance between Animal and Human Tumours

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Table 1: Group 1 Agents included in Volumes 100A-F, 105, 106, 107 and 109[1]

Volume	Type of Agent	Number of Agents	Agents
100A	Pharmaceuticals	23	Aristolochic acid; Aristolochic acid, plants containing; Azathioprine; Busulfan; Chlorambucil; Chlornaphazine; Cyclophosphamide; Ciclosporine; 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 and other combined chemotherapy including alkylating agents; 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 papillomavirus type 16; Human T-cell lymphotropic virus type 1; Kaposi sarcoma herpesvirus; Oposthorchis 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, 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 Sr-90; Haematite mining with exposure to radon (underground); Ionizing radiation (all types); Neutron radiation; Phosphorus-32, as phosphate; Pu-239; Radioiodines, including I-131; Internalized radionuclides that emit alpha particles; Internalized radionuclides that emit beta particles; Ra-224 and its decay products; Ra-226 and its decay products; Ra-228 and its decay products; Rn-222 and its decay products; Solar radiation; Th-232 (as Thorotrast); UV radiation (bandwidth 100-400 nm, encompassing UVC, UVB and UVA); UV-emitting tanning devices; X- and Gamma 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 combusion of; Ethanol in alcoholic beverages; N'-Nitrosonornicotine (NNN) and 4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanon (NNK); Salted fish, chinese style; Second-hand tobacco smoke; Tobacco smoking; Tobacco, smokeless

Table 1. Group 1 Agents included in Volumes 100A-F, 105, 106, 107 and 109 (continued)

Volume	Type of Agent	Number of Agents	Agents
100F	Chemical agents and related occupations	32	Acid mists, strong inorganic; Aflatoxins; Aluminum 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;3,4,5,3D,4D-Pentachlorobiphenyl (PCB-126); 2,3,4,7,8-Pentachlorodibenzofuran; Rubber manufacturing industry; Shale oils; Soot (as found in occupational exposure of chimney sweeps); Sulfur mustard; 2,3,7,8-Tetrachlorodibenzo-para-dioxin; Vinyl chloride
105[2]	Diesel and gasoline engine exhausts and some nitroarenes	1	Engine exhaust, diesel
106[2]	Trichloroethylene and some chlorinated agents	1	Trichloroethylene
107[2]	Polychlorinated biphenyls and polybrominated biphenyls	1	Polychlorinated biphenyls (PCBs) and dioxin-like PCBs
109[2]	Outdoor air pollution	2	Outdoor air pollution; Particulate matter in outdoor air pollution

[1]Although 113 Group-1 agents have been identified through 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.

[2]Included with 'chemicals and related occupations' in V100F.

Table 2. Coding of Tumours Occurring in Animals and Humans

Organ System	Sites Coded from Volume 100 (A,B,C,D,E, and F*)
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
	Gall bladder
Nervous System and Eye	Brain and spinal cord (CNS)
	Eye
Endocrine System	Thyroid, follicular epithelium
	Adrenal gland (medulla, cortex, NOS)
	Pituitary
Kidney	Kidney (renal cortex, renal medulla, kidney NOS)
Urothelium	Urothelium (renal pelvis or ureter or urinary bladder)
Lymphoid and Haematopoietic Tissues	Haematopoietic tissue
	Lymphoid tissue
Skin	Skin and adnexae
	Cutaneous melanocytes
Connective Tissues	Soft connective tissue
	Blood vasculature (endothelium)
	Hard connective tissue (bone, cartilage)
Female Breast, Female Reproductive Organs and Reproductive Tract	Breast
	Ovary
	Uterine Cervix
	Uterus
	Vulva/vagina
Other Groupings	All cancers combined
	All solid cancers
	Exocrine glands NOS

Table 3: Abstraction of Information on Animal and Human Tumours for Group-1 Agents in the IARC Monographs (adapted from Grosse et al., 2015)

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 myeoloma, 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.

Table 4. Agents Lacking *Sufficient Evidence* of Carcinogenicity in Humans Placed in Group 1 based on Mechanistic Upgrades

Agent	Human Tumour Site	Basis for Mechanistic Upgrade
Aristolochic acid	Not identified	Herbal remedies containing AA provide *sufficient evidence* for upper urinary tract cancer in humans; genotoxic mechanistic data
Benzo(a)pyrene (BaP)	Not identified	PAH mixtures containing BaP provide *sufficient evidence* for lung or skin cancer in humans; extensive mechanistic data on BaP linking animal and human biology
Dyes metabolized to benzidine	Not identified	Benzidine provides *sufficient evidence* of being a human bladder carcinogen
Ethylene oxide	Not identified	*Limited evidence* for NHL, breast cancer in humans; genotoxic mechanistic data
Etoposide	Not identified	*Limited evidence* of acute myeloid leukaemia in humans; distinctive chromosomal translocations
MOCA	Not identified	Bladder cancer expected in humans, based on mechanistic data and case report [*there was only one!*]
Neutron radiation	Not identified	Biophysics of radiation damage induction similar across different types of radiation
NNN and NNK	Not identified	Target sites correspond to those of smokeless tobacco; mechanistic data on tobacco smoke
PCBs, dioxin-like	Not identified	For PCBs there is *sufficient evidence* for skin melanoma (and *limited evidence* for NHL and breast tumours) in humans. Dioxin-like PCBs are upgraded on the

		basis of support for receptor-mediation and analogies with TCDD.
Penta(2,3,4,7,8)chlorodibenzofuran	Not identified	*Sufficient evidence* in experimental animals combined with strong mechanistic support for receptor-mediated mechanism, with biological activity identical to that of TCDD for every mechanistic step
Phenacetin[1]	Renal pelvis, ureter	Phenacetin was determined to cause tumours of the renal pelvis and ureter, based on evaluation of phenacetin as the active ingredient in analgesic mixtures

[1]The Working Group for Volume 100A placed phenacetin in Group-1 in the absence of sufficient epidemiological evidence of carcinogenicity in humans, but concluded that phenacetin caused tumours of the renal pelvis and ureter in humans as part of its evaluation of the overall evidence for analgesic mixtures containing phenacetin, including human, animal, and mechanistic evidence.

Table 5. Group-1 Agents with No Animal Tumour Sites Specified

Nature of Animal Evidence (number of agents)	Volume: Agent(s)
Agents with Inadequate Evidence in Animals	
Occupational exposures are complex and likely could not be reliably replicated in the laboratory (7 agents)	**Volume 100F:** Auramine production; magenta production; mists from strong inorganic acids; occupational exposures during iron and steel founding; isopropyl alcohol manufacture by the strong-acid process; occupational exposure as a painter; occupational exposures in the rubber-manufacturing industry.
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 due to 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 herpes virus.
Animal tests conducted but considered inadequate (2 agents)	**Volume 100 A:** 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 (9 agents)	**Volume 100A:** Busulfan; chlornaphazine; cyclosporine; estrogen-progestogen menopausal therapy (combined); phenacetin, analgesic mixtures containing. **Volume 100B:** Clonorchis sinensis (infection with); Opisthorchis viverrini (infection with); Schistosoma haematobium (infection with). **Volume 100F**: Sulfur mustard.
Agents with Sufficient Evidence in Animals	
Sufficient evidence in animals, but no tumour sites specified[1] (6 agents)	**Volume 100A:** Melphalan. **Volume 100D:** P-32, as phosphate. **Volume 100E:** Acetaldehyde associated with the consumption of alcoholic beverages; betel quid with tobacco. **Volume 100F:** Aluminum production; PeCDF.

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

Table 6. Group-1 Agents with Sufficient Evidence of Carcinogenicity in Animals for a Component of the Agent

Volume: Agent	Nature of Animal and Human Evidence
Volume 100D: Fission products including Sr-90	"There is *sufficient evidence* in experimental animals for the carcinogenicity of the following β-emitting radionuclides: ^{3}H, ^{32}P, ^{90}Sr, ^{90}Y, ^{91}Y, ^{131}I, ^{137}Cs, ^{144}Ce, ^{147}PM, ^{228}Ra." [IARC, 2012d, p. 297] "There is *sufficient evidence* in humans for the carcinogenicity of external exposure to and internal exposure to fission products, including strontium-90." [IARC, 2012d, p. 297]
Volume 100D: Haematite mining with exposure to radon (underground)	"There is *sufficient evidence* in experimental animals for the carcinogenicity of ^{210}Po, ^{222}Rn, ^{224}Ra, ^{226}Ra, ^{228}Th, ^{230}Th, ^{232}Th, ^{233}U, $^{234,235,238}U$ (natural, enriched and depleted uranium), ^{237}Np, ^{238}Pu, ^{239}Pu, ^{241}Am, ^{244}Cm, ^{249}Cf, ^{252}Cf." [IARC, 2012d, p. 275] "There is *sufficient evidence* in humans for the carcinogenicity of radon-222 and its decay products." [IARC, 2012d, p. 274] "There is *sufficient evidence* in humans for the carcinogenicity of haematite mining with exposure to radon." [IARC, 2012d, p., 274]
Volume 100E: Acetaldehyde associated with consumption of alcoholic beverages	"There is *sufficient evidence* in experimental animals for the carcinogenicity of acetaldehyde." [IARC, 2012e, p. 472] "There is sufficient evidence in humans for the carcinogenicity of acetaldehyde associated with the consumption of alcoholic beverages." [IARC, 2012e, p. 472]

Table 7. Quantitative Concordance between Humans and Animals at Specific Tumour Sites: Kappa Statistics with 90% Confidence Intervals[1]

Organ Site	All Species	Mouse	Rat	Mouse or Rat
Oral cavity	0.49 (-0.01, NE[2])			0.66 (-0.001, 0.87)
Lung	0.90 (5) (0.55, NE)	0.08 (-0.1, 0.43)	0.88 (5) (0.47, 0.98)	0.90 (5) (0.55, NE)
Mesothelium	1 (5) (0.16, NE)		1 (5) (0.16, NE)	1 (5) (0.16, NE)
Stomach	0.48 (-0.02, 0.93)	1 (5) (0.02, NE)	-0.02 (NE, 0.89)	0.48 (-0.02, 0.93)
Intestine, including colon and rectum)	-0.02 (NE, 0.79)			-0.02 (NE, 0.79)
Liver parenchyma and bile ducts	0.35 (-0.03, 0.75)	-0.04 (NE, 0.72)	-0.02 (NE, 0.77)	0.16 (-0.08, 0.66)
Thyroid, follicular epithelium	1 (5) (0.16, NE)	1 (5) (0.02, NE)	1 (5) (0.02, NE)	1 (5) (0.16, NE)
Kidney, renal cell carcinoma	0.32 (-0.02, NE)			-0.01 (NE, 0.89)
Urothelium (renal pelvis or ureter or urinary bladder)	0.88 (5) (0.30, NE)		1 (5) (0.39, NE)	0.88 (5) (0.30, NE)
Haematopoietic tissue	0.18 (-0.05, 0.54)	-0.03 (NE, 0.47)		0.18 (-0.06, 0.54)
Lymphoid tissue	0.16 (-0.06, 0.48)	0.21 (-0.06, 0.59)	-0.02 (NE, 0.77)	0.16 (-0.06, 0.48)
Skin and adnexae (general body surface including scrotum, penis and anus	0.47 (3) (0.02, 0.84)	0.48 (-0.015, NE)	0.39 (-0.02, NE)	0.47 (3) (0.01, 0.84)
Hard connective tissue (bone, cartilage)	0.78 (4) (0.23, 0.96)	0.73 (4) (0.14, 0.95)	0.38 (-0.02, NE)	0.64 (4) (0.11, 0.91)
Breast	0.20 (-0.07, 0.71)	-0.04 (NE, 0.64)	-0.03 (NE, 0.72)	0.2 (-0.07, 0.71)
Ovary	-0.03 (NE, 0.73)	-0.02 (NE, 0.77)		-0.03 (NE, 0.73)
Uterine cervix	0.79 (4) (0.10, 0.91)	0.79 (4) (0.10, 0.95)		0.79 (4) (0.10, 0.92)
Uterus		0.37 (-0.04, 0.85)		0.38 (-0.03, 0.86)

[1]Significant positive kappa statistic are identified by lower confidence limits greater than zero. The degree of concordance for significance kappa statistics is rated as:(1) slight [0.01-0.20]; (2) fair [0.21-0.40]; (3) moderate [0.41-0.60]; (4) substantial [0.61-0.80]; or (5) almost perfect [0.81-0.99], based on the ratings proposed by Viera & Garrett (2005).

[2]NE: no estimate, as confidence limit procedure in Supplemental Material II did not converge.

Table 8: Quantitative Concordance between Humans and Animals at Specific Organ and Tissue Systems: Kappa Statistics and 90% Confidence Intervals[1]

Organ System	All Species	Mouse	Rat	Mouse or Rat
Upper aerodigestive tract	0.25 (-0.06, 0.75)		0.30 (-0.04, 0.79)	0.30 (-0.04, 0.79)
Respiratory system	0.85 (5) (0.48, 0.96)	0.19 (-0.07, 0.51)	0.78 (4) (0.38, 0.93)	0.85 (5) (0.48, 0.96)
Mesothelium	1 (5) (0.16, NE[2])		1 (5) (0.16, NE)	1 (5) (0.16, NE)
Digestive tract	0.30 (-0.05, 0.81)	0.48 (-0.02, 0.93)	-0.02 (NE, 0.69)	0.30 (-0.05, 0.81)
Digestive organs	0.35 (-0.03, 0.75)	-0.05 (NE, 0.62)	0.30 (-0.04, 0.79)	0.16 (-0.08, 0.66)
Endocrine system	0.65 (4) (0.07, NE)	0.79 (4) (0.10, 0.93)	0.79 (4) (0.10, 0.92)	0.65 (4) (0.07, NE)
Kidney	0.32 (-0.02, NE)	-0.02 (NE, 0.89)	-0.01 (NE, 0.89)	-0.01 (NE, 0.89)
Urothelium	0.88 (5) (0.30, NE)		0.88 (5) (0.30, NE)	0.88 (5) (0.30, NE)
Lymphoid and haematopoietic tissues	0.53 (3) (0.10, 0.81)	0.57 (3) (0.13, 0.83)	-0.03 (NE, 0.28)	0.53 (3) (0.1, 0.81)
Skin	0.64 (4) (0.13, NE)	0.64 (4) (0.13, NE)	0.27 (-0.03, NE)	0.64 (4) (0.13,NE)
Connective tissues	0.63 (4) (0.20, NE)	0.70 (4) (0.18, 0.93)	0.16 (-0.08, 0.66)	0.52 (3) (0.1, 0.77)
Female breast, female reproductive organs and reproductive tract	0.57 (3) (0.11, 0.85)	0.63 (4) (0.13, 0.89)	0.36 (-0.01, 0.68)	0.58 (3) (0.11, 0.85)
Other groupings	-0.02 (NE, 0.89)	-0.02 (NE, 0.89)		-0.01 (NE, 0.89)

[1]Significant positive kappa statistic are identified by lower confidence limits greater than zero. The degree of concordance for significance kappa statistics is rated as:(1) slight [0.01-0.20]; (2) fair [0.21-0.40]; (3) moderate [0.41-0.60]; (4) substantial [0.61-0.80]; or (5) almost perfect [0.81-0.99], based on the ratings proposed by Viera & Garrett (2005).

[2]NE: no estimate, as confidence limit procedure in Supplemental Material II did not converge.

Figure 1. Number of Agents Inducing Tumours in Humans in Each of 39 Tumour sites by Type of Agent

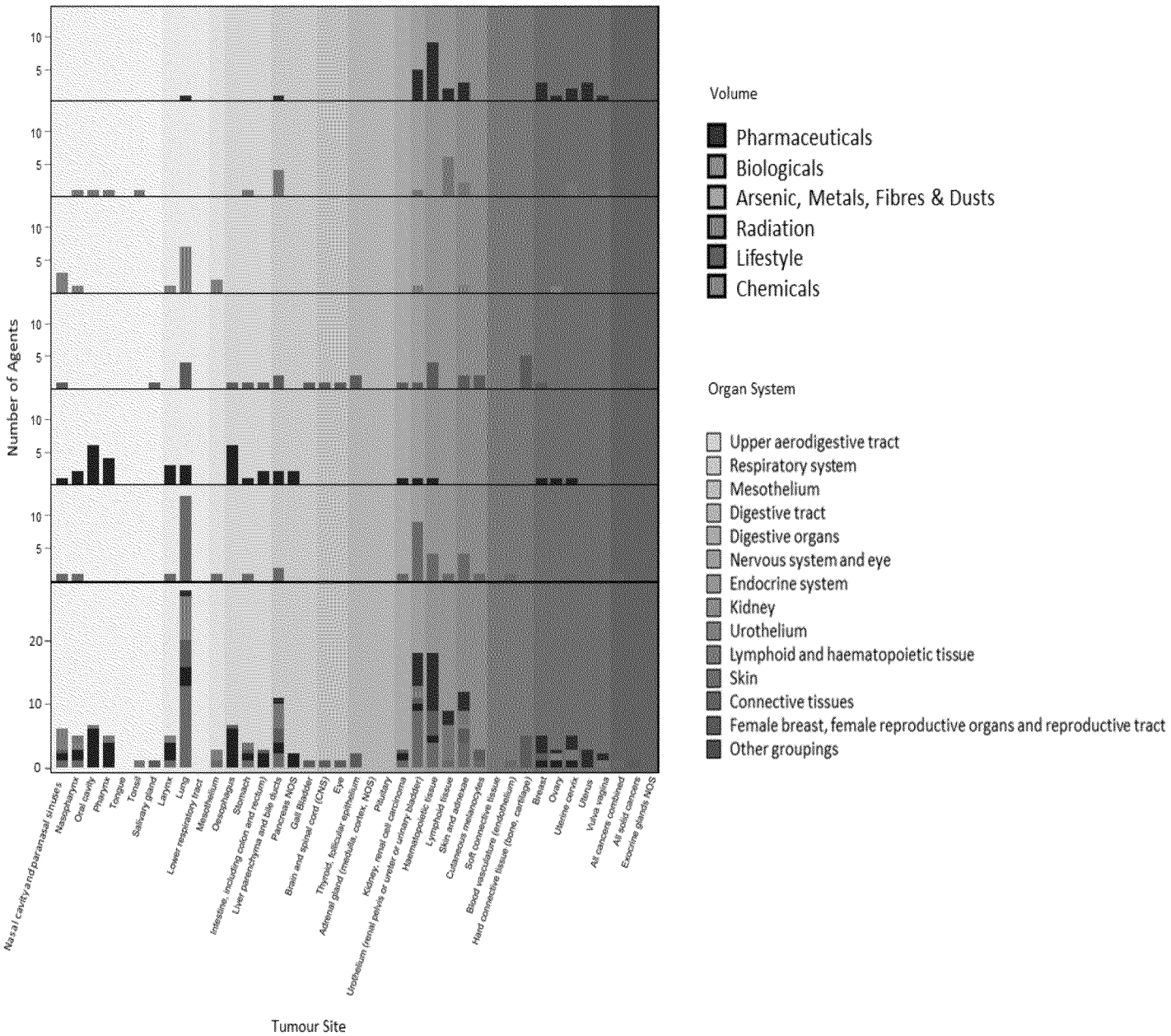


Figure 2. Number of Agents Inducing Tumours in Animals in Each of 39 Tumour sites by Type of Agent

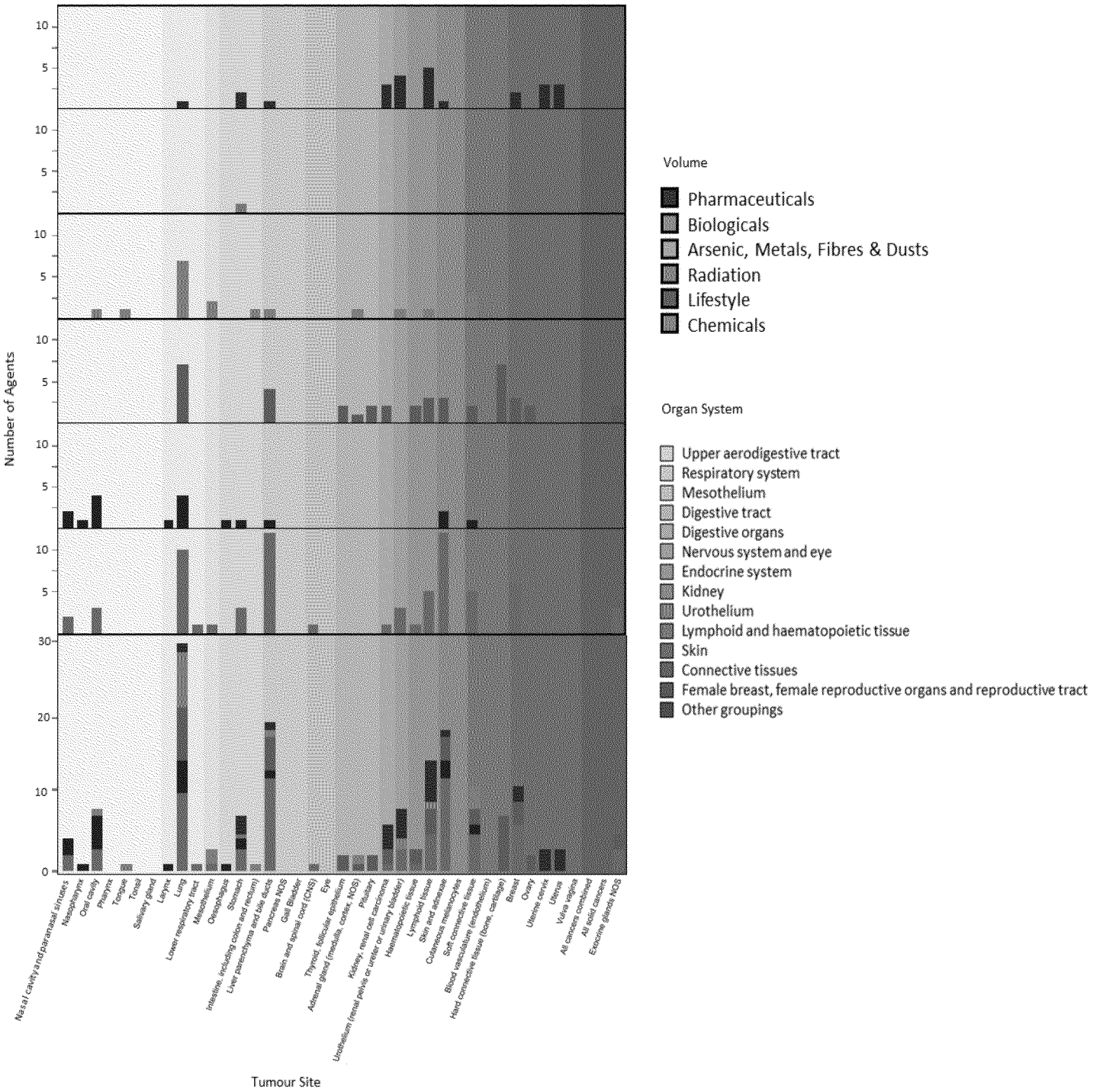


Figure 3. Number of Agents Inducing Tumours in Mice in Each of 39 Tumour sites by Type of Agent

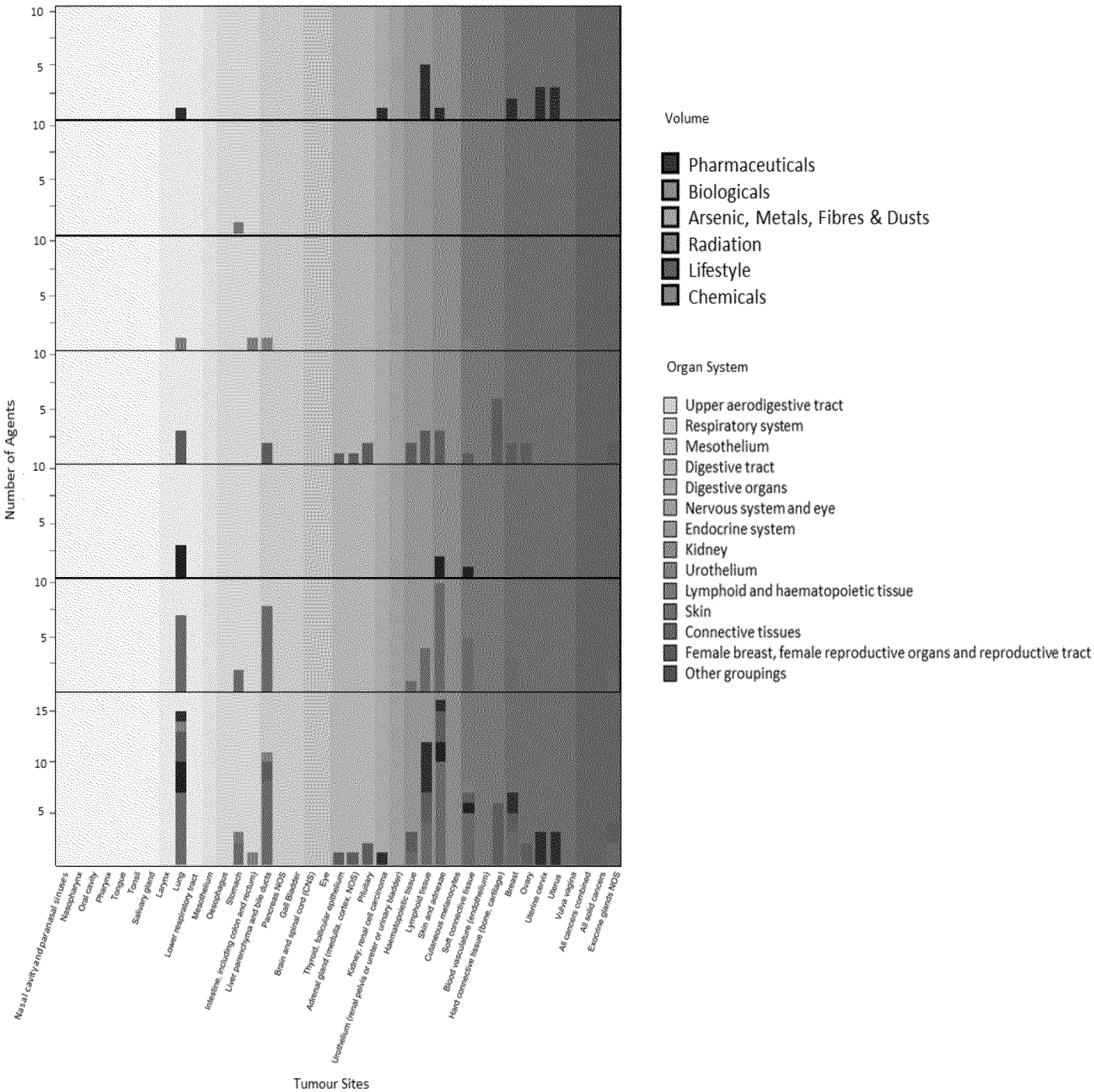


Figure 4. Number of Agents Inducing Tumours in Rats in Each of 39 Tumour sites by Type of Agent

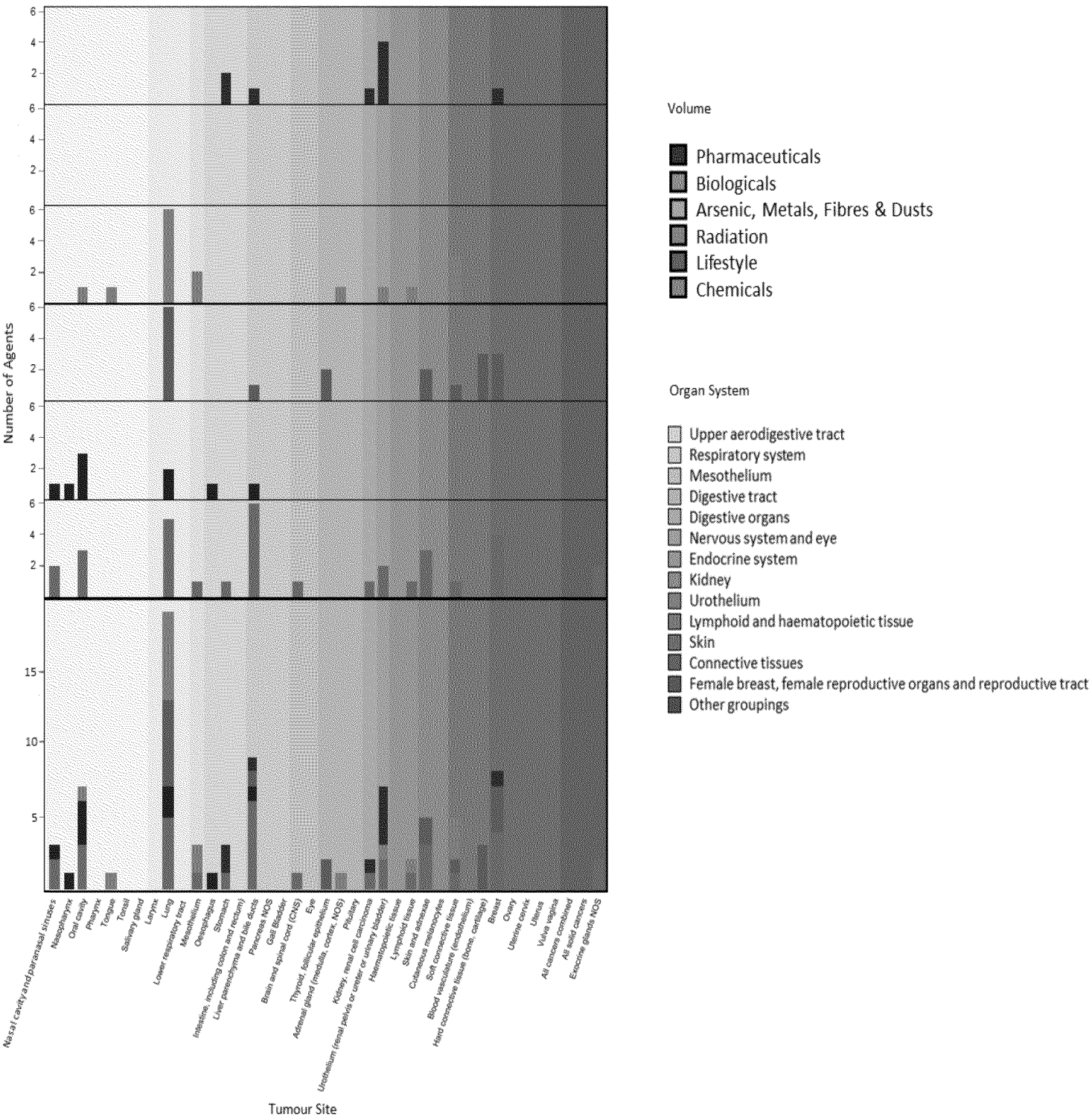


Figure 5. Number of Agents Inducing Tumours in Humans in Each of 15 Organ Systems by Type of Agent

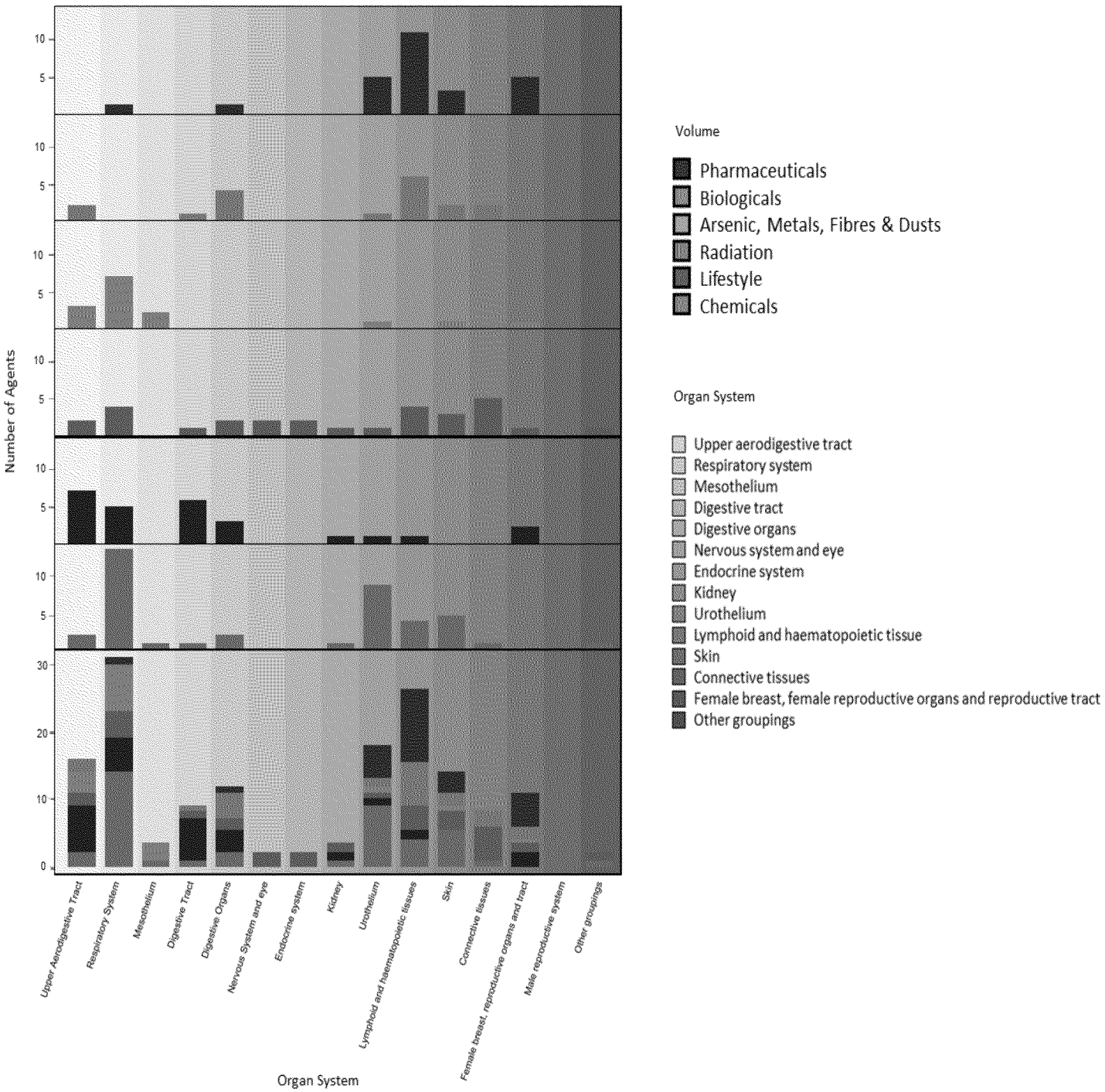


Figure 6. Number of Agents Inducing Tumours in Animals in Each of 15 Organ Systems by Type of Agent

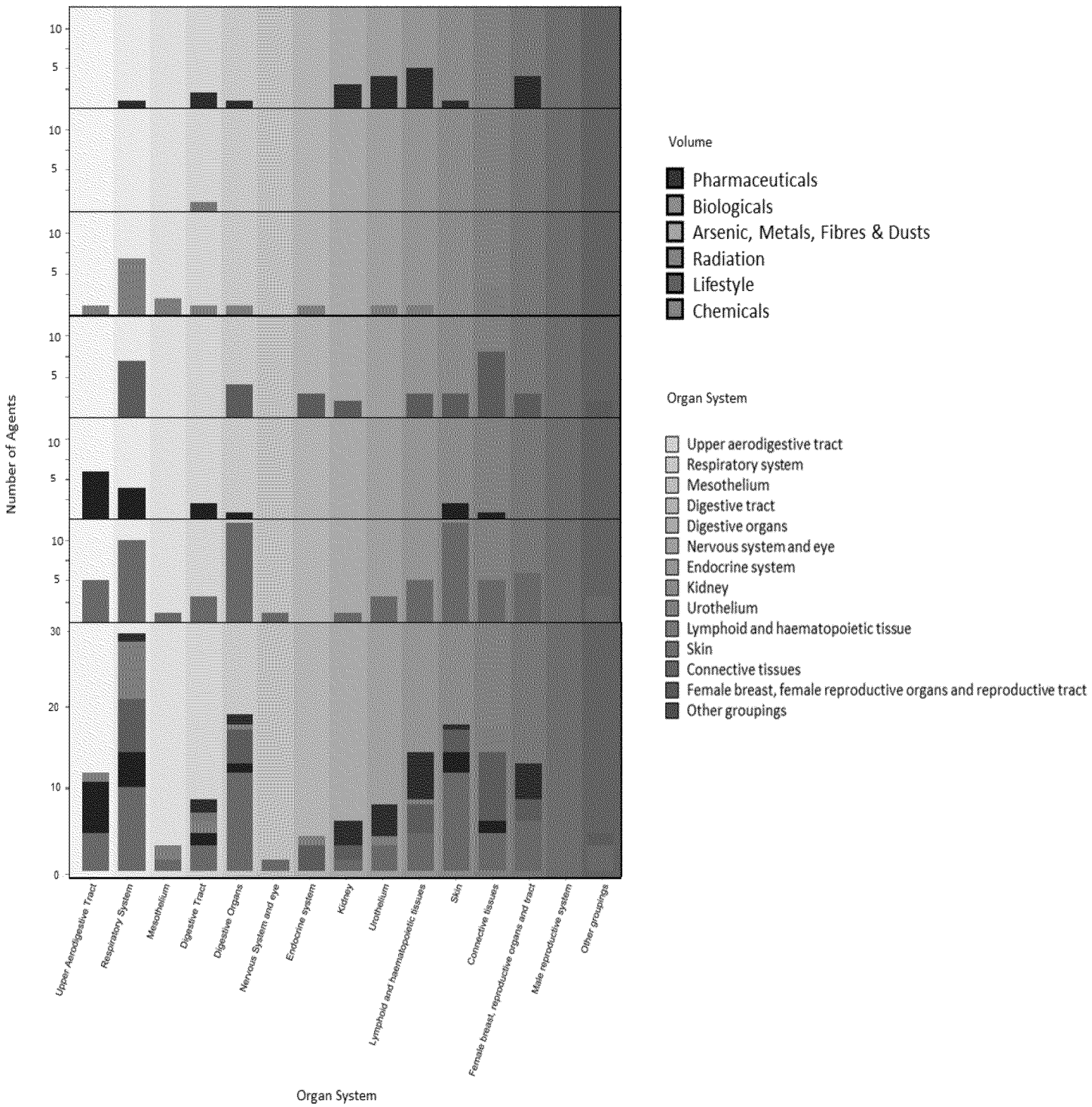


Figure 7. Number of Agents Inducing Tumours in Mice in Each of 15 Organ Systems by Type of Agent

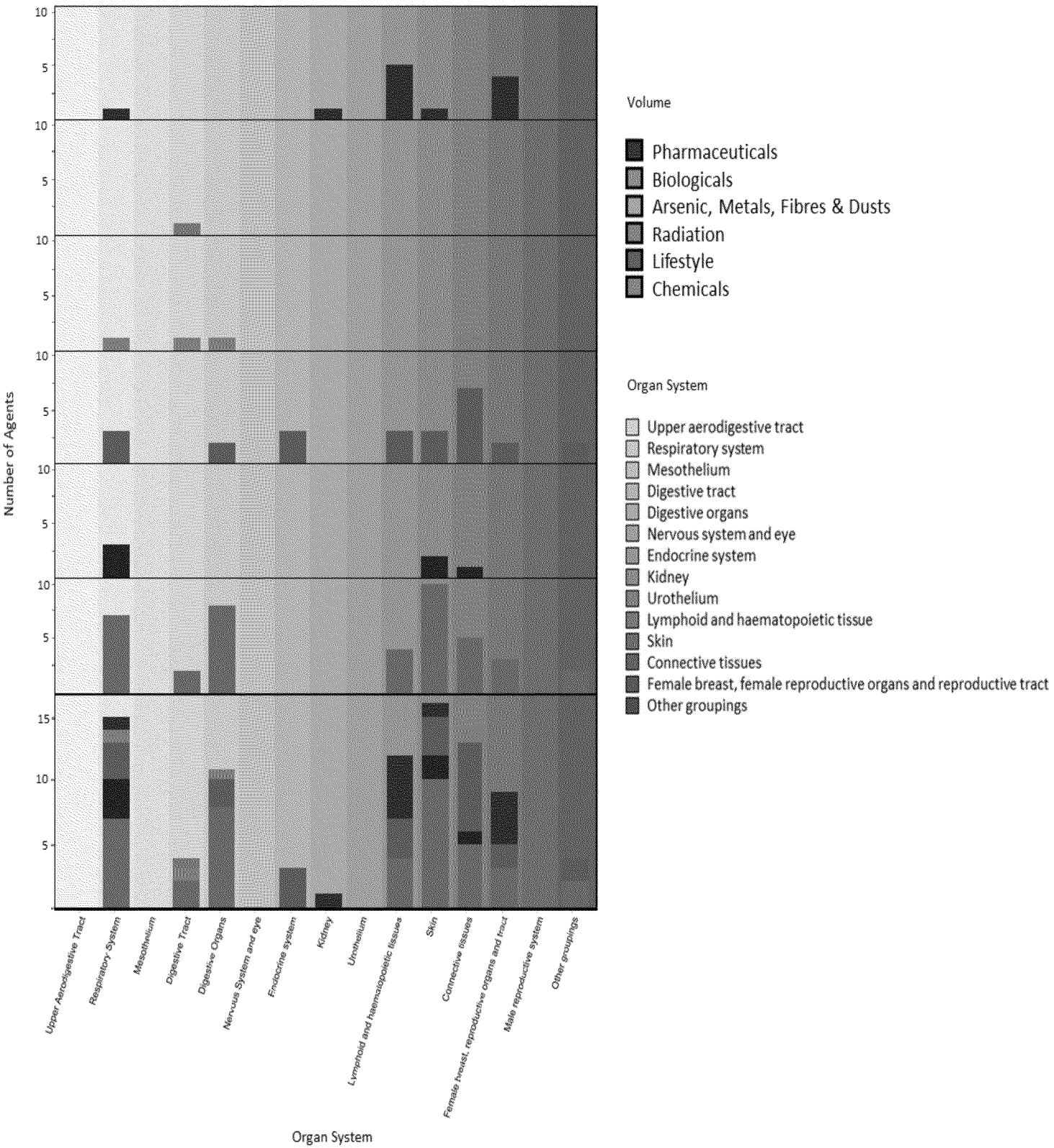


Figure 8. Number of Agents Inducing Tumours in Rats in Each of 15 Organ Systems by Type of Agents

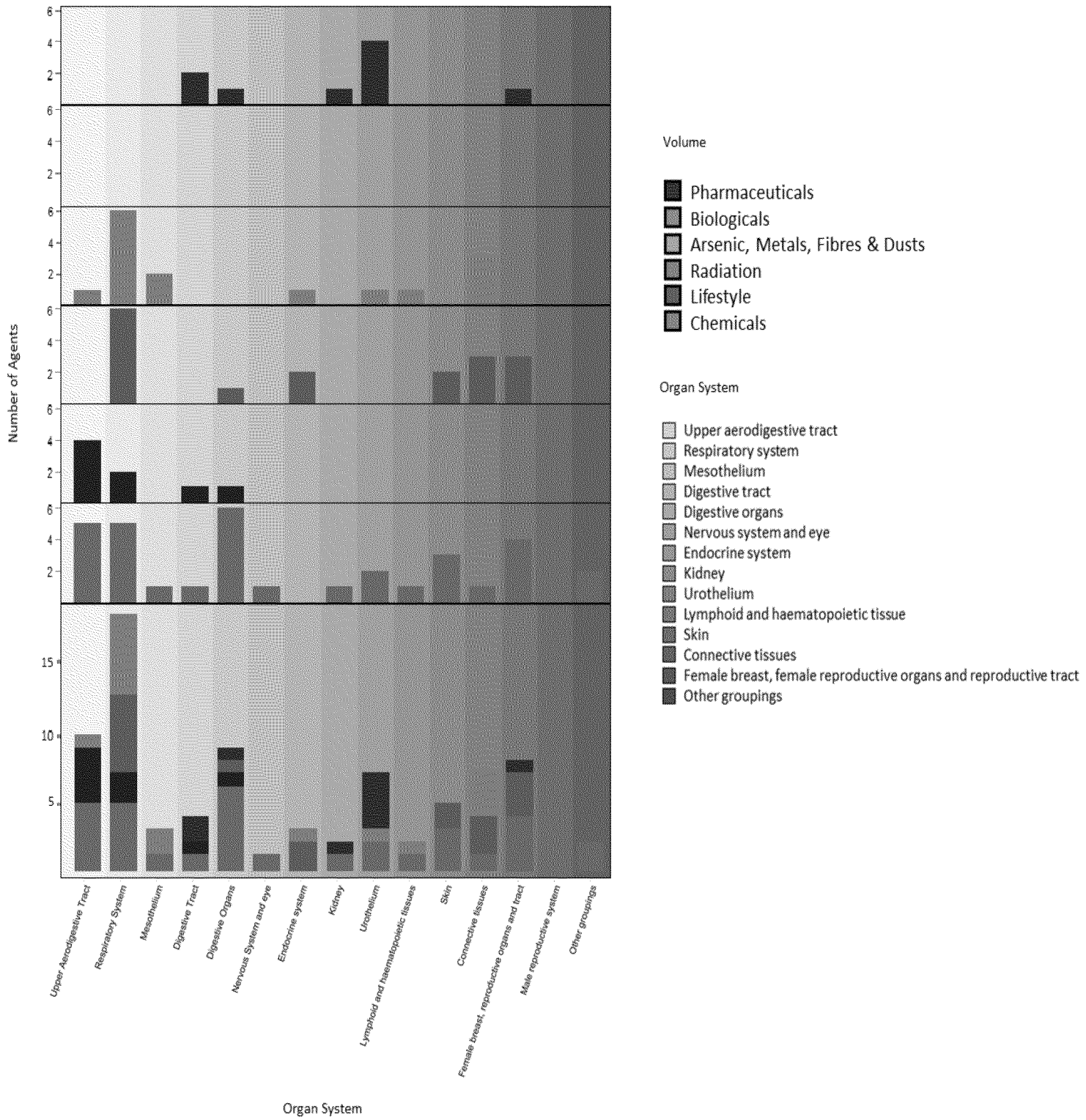


Figure 9. Heat Map of Concordance between Tumours Caused by Group-1 Agents in Humans and Animals in 39 Tumour Sites

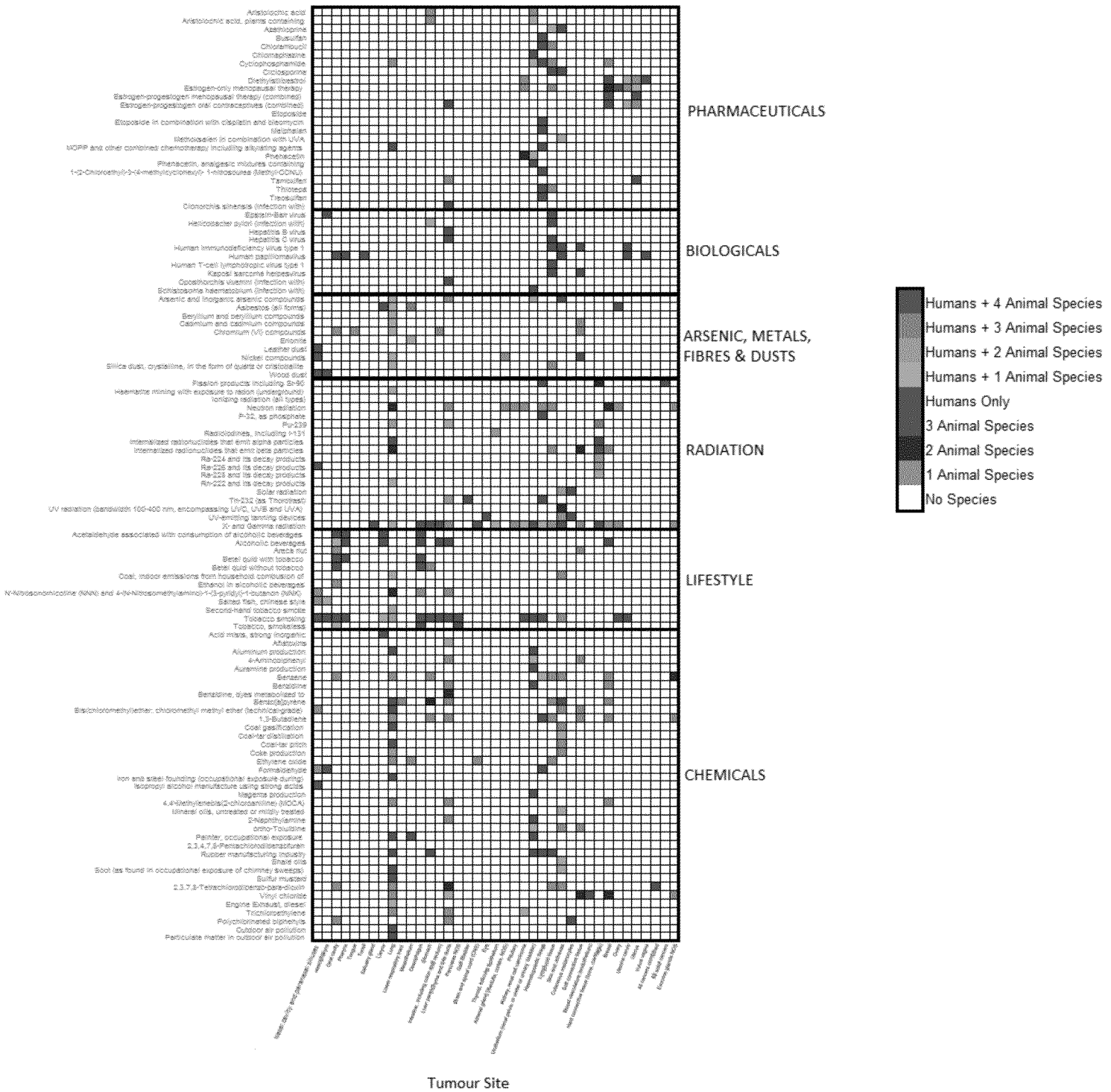
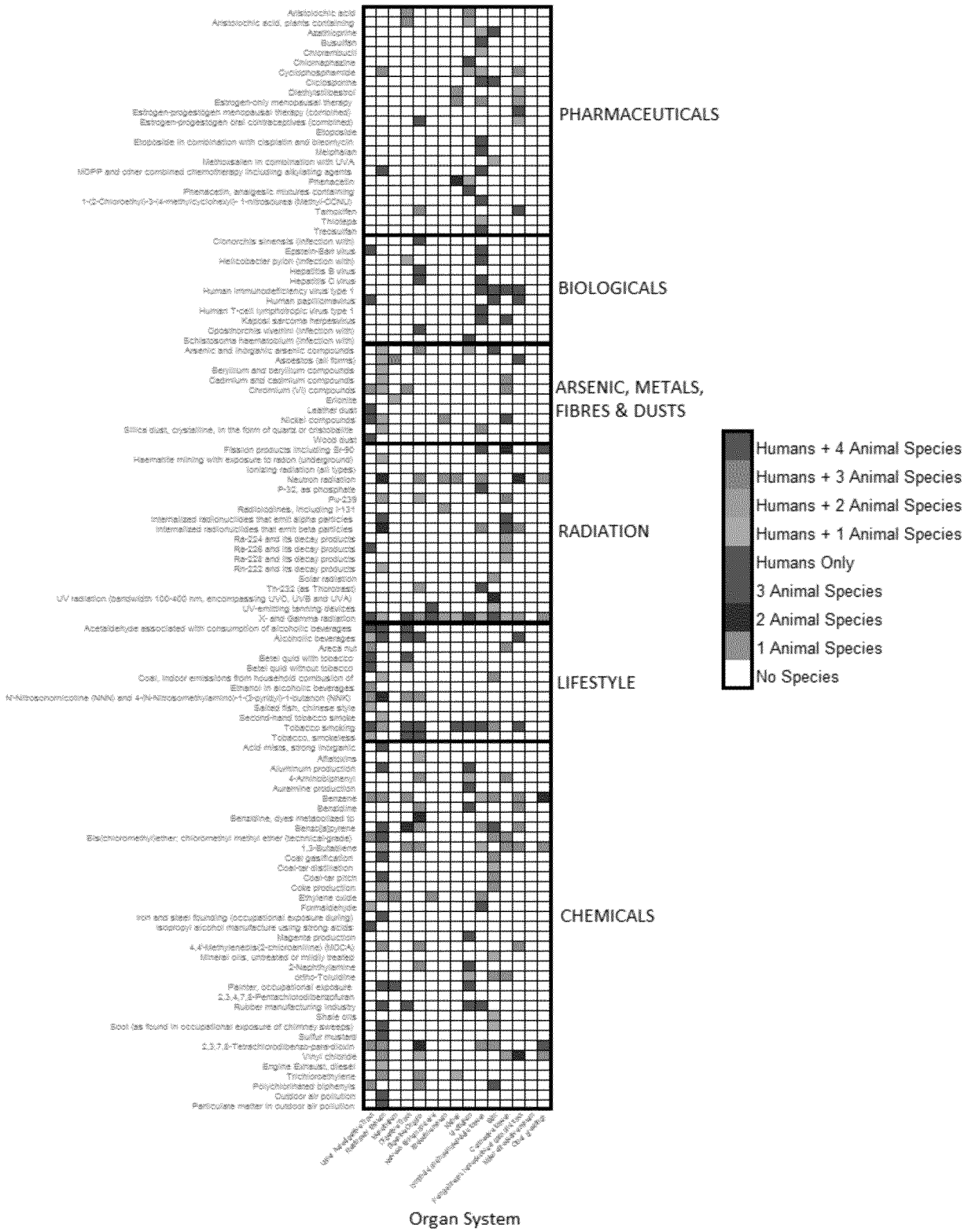


Figure 10. Heat Map of Concordance between Tumours Caused by Group-1 Agents in Humans and Animals in 15 Organ Systems



Concordance between Animal and Human Tumours: An Analysis of 111 Agents Known to Cause Cancer in Humans

Supplemental Material II: Statistical Evaluation of Concordance between Animal and Human Tumours

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on behalf of the IARC Working Group on 'Tumour-site Concordance and Mechanisms of Carcinogenesis' which convened in Lyon April/November 2012

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The Kappa (κ) Statistic

Krewski et al. (2015) used a kappa (κ) statistic described by Viera & Garrett (2005) to measure the concordance between tumours seen in animals and humans for 111 distinct Group-1 agents identified in the IARC Monographs programme through Volume 109. Statistical analysis of concordance is based on a 2x2 table, which gives counts of the number of agents providing *sufficient evidence* of the tumour of interest in both animals and humans (A_{11}), the number of agents for which the tumour of interest was not seen in both animals and humans (A_{22}), the number of agents positive in humans and negative in animals (A_{21}), and the number of agents positive in animals and negative in humans (A_{12}). The total number of agents is given by $N = A_{11} + A_{22} + A_{12} + A_{21}$. [The notation A_{ij} is used here rather than n_{ik} as employed by Krewski et al. (2015) to correspond to the notation used in the derivations below.]

The kappa (κ) statistic used by Viera & Garrett (2005) is defined by

$$\kappa = (A_o - A_e)/(A_{..} - A_e),$$

where A_o and A_e denote the observed and expected total counts along the diagonal of the 2 x 2 matrix, with $A_o = A_{11}+A_{22}$ and $A_e = (A_{1.}A_{.1}/A_{..}) + (A_{2.}A_{.2}/A_{..})$.

Confidence Limits on κ

Calculation of a confidence limit on κ is equivalent to determining the range of kappa values which could have given rise to the observed table. Although Viera & Garrett (2005) propose a bootstrap method for calculating confidence limits, we prefer the approach described below which, by calculating the exact probability of each possible outcome in the 2x2 table, may provide more accurate confidence limits for the true value of κ.

For the 2x2 table, the underlying distribution can be characterised by 3 parameters: π_1 (probability of row 1), π_1 (probability of column 1) and κ (kappa). The individual cell probabilities can be calculated from these 3 values (see Derivation A1 below). The analysis of κ is complicated by the presence of the two nuisance parameters.

The probability of observing an outcome $A = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix}$ given π_1, π_1, κ is

$$P(A \mid \pi_1, \pi_1, \kappa) = \frac{n!}{a_{11}!\, a_{12}!\, a_{21}!\, a_{22}!} \pi_{11}^{a_{11}} \pi_{12}^{a_{12}} \pi_{21}^{a_{21}} \pi_{22}^{a_{22}}$$

where $n = a_{11} + a_{12} + a_{21} + a_{22}$

The probability of observing as extreme an outcome as **A** with an equal or larger value of kappa is

$$P(A \mid \pi_1, \pi_1, \kappa) = \sum_{B} P(B \mid \pi_1, \pi_1, \kappa)$$

where the summation extends over all outcomes where $P(B) \geq P(A)$

The probability of observing as extreme an outcome as **A** with an equal or smaller value of kappa is

$$P(A \mid \pi_1, \pi_1, \kappa) = \sum_{B} P(B \mid \pi_1, \pi_1, \kappa)$$

where the summation extends over all outcomes where $P(B) \leq P(A)$

The confidence interval for kappa of level δ (e.g. 0.8 or 0.9) can be defined as follows:

the upper bound is the largest κ such that $P(A \mid \pi_1, \pi_1, \kappa) \geq$ for some value of π_1 and π_1 and

the lower bound is the smallest κ such that $P(A \mid \pi_1, \pi_1, \kappa) \geq$ for some value of π_1 and π_1

where $= (1 -)/2.$

Given the nuisance parameters π_1 and π_1 it is possible to run a stepwise search for the upper and confidence bounds. However, for each set π_1 and π_1 there is a minimum and maximum value for kappa (Derivation A3). The search for the upper and lower confidence bounds may stop at these extremes. In such cases there is no confidence bound. The complication is how many different values of the nuisance parameters should be examined.

The observed data are discrete counts and hence the probability distribution only takes on discrete values. The probability of a more extreme outcome for different values of kappa can be difficult to anticipate. A small change in kappa change shift relative probabilities and include different outcome matrices in the set of more extreme values. A plot of the probability of more extreme values against the input parameters π_{1+} π_{+1} and κ would not be a smooth graph but would show jumps. This can make a definitive search for the upper and lower confidence bounds difficult.

Illustrative Examples

To understand the complexities in searching for the confidence limits, three examples were examined: one where the observed kappa was at the upper limit, one where it was at the lower limit, and one where it was intermediate between the upper and lower extremes. For all examples N=10, $\pi_{1+}=0.6$ and $\pi_{+1}=0.7$

The maximum possible kappa is 0.7286 which occurs when $\pi = \begin{bmatrix} 6 & 0 \\ 1 & 3 \end{bmatrix}$.

The minimum possible kappa is -0.5217 which occurs when $\pi = \begin{bmatrix} 3 & 3 \\ 4 & 0 \end{bmatrix}$.

The intermediate value of kappa was 0.3478 which occurs when $\pi = \begin{bmatrix} 5 & 1 \\ 2 & 2 \end{bmatrix}$.

In the exploration of these examples, the search for the confidence bounds was done as follows. A pair of nuisance parameters π_{1+} and π_{+1} were selected and a search for kappa was started at the upper or lower extreme value and proceeding inward at steps of 0.001. The values for π_{1+} and π_{+1} were selected at steps of 0.01 along logical search lines. Note that the function has a saw-tooth shape and any stepwise search has the potential to miss identifying the first instance when the function goes above the critical value.

Example 1: Observed Kappa Intermediate between Upper and Lower Extreme

$\pi = \begin{bmatrix} 5 & 1 \\ 2 & 2 \end{bmatrix}$ κ =0.3478

π_{1+}	π_{+1}	Minimum kappa	Maximum kappa	Lower 90% Confidence Bound	Upper 90% confidence bound
0.6	0.7	-0.522	0.783	-0.354	0.724
0.61	0.69	-0.528	0.825	-0.361	0.770
0.62	0.68	-0.532	0.869	-0.354	0.788
0.63	0.67	-0.536	0.912	-0.360	0.824
0.64	0.66	-0.538	0.956	-0.359	0.816
0.65	0.65	-0.538	1.000	-0.351	0.796
0.6	0.7	-0.522	0.783	-0.354	0.724
0.6	0.69	-0.537	0.805	-0.362	0.750
0.6	0.68	-0.552	0.828	-0.362	0.768
0.6	0.67	-0.567	0.850	-0.366	0.778
0.6	0.66	-0.581	0.872	-0.370	0.795

0.6	0.65	-0.596	0.894	-0.379	0.805
0.6	0.64	-0.610	0.915	-0.386	0.830
0.6	0.63	-0.624	0.937	-0.394	0.835
0.6	0.62	-0.639	0.958	-0.404	0.818
0.6	0.61	-0.653	0.979	-0.407	0.827
0.6	0.6	-0.667	1.000	-0.408	0.826
0.61	0.7	-0.513	0.803	-0.351	0.745
0.62	0.7	-0.504	0.823	-0.348	0.754
0.63	0.7	-0.496	0.844	-0.343	0.766
0.64	0.7	-0.486	0.865	-0.333	0.779
0.65	0.7	-0.477	0.886	-0.317	0.799
0.66	0.7	-0.468	0.908	-0.314	0.816
0.67	0.7	-0.458	0.931	-0.299	0.821
0.68	0.7	-0.449	0.953	-0.294	0.813
0.69	0.7	-0.439	0.976	-0.287	0.793
0.7	0.7	-0.429	1.000	-0.274	0.800

The largest upper confidence bound is 0.835 which occurs when $\square_{1\square} = 0.6$ and $\square_{1\square} = 0.63$.

The smallest lower confidence bound is -0.408 which occurs when $\square_{1\square} = 0.6$ and $\square_{1\square} = 0.6$.

The lower and upper values for the confidence bound do not occur at the observed $\square_{1\square}$ and $\square_{1\square}$ and are substantially different than those which would be calculated if the search didn't examine other values for $\square_{1\square}$ and $\square_{1\square}$.

Example 2: Observed Kappa at Upper Extreme

$$\square = \begin{matrix} 6 & 0 \\ 1 & 3 \end{matrix} \qquad \kappa = 0.7826$$

For this example in order to find an upper bound for kappa the search has to find pairs $\square_{1\square}, \square_{1\square}$ which allow values for kappa greater than 0.7826. This requires that $\square_{1\square}, \square_{1\square}$ should be closer to the diagonal of the sample space where $\square_{1\square} = \square_{1\square}$.

$\square_{1\square}$	$\square_{1\square}$	Minimum kappa	Maximum kappa	Lower 90% confidence Bound	Upper 90% confidence bound	
0.6	0.7	-0.522	0.782	-0.052	0.782	x
0.61	0.69	-0.528	0.825	-0.054	0.825	x
0.62	0.68	-0.532	0.869	-0.038	0.868	x
0.63	0.67	-0.536	0.912	-0.029	0.912	x
0.64	0.66	-0.538	0.956	-0.027	0.956	x
0.645	0.655	-0.538	0.978	-0.023	0.978	x
0.65	0.65	-0.538	1.000	-0.019	0.984	
0.6	0.6	-0.667	1.000	-0.049	0.986	
0.61	0.61	-0.639	1.000	-0.045	0.986	
0.62	0.62	-0.613	1.000	-0.044	0.987	

0.63	0.63	-0.587	1.000	-0.038	0.986	
0.64	0.64	-0.563	1.000	-0.022	0.985	
0.65	0.65	-0.538	1.000	-0.019	0.984	
0.66	0.66	-0.515	1.000	-0.020	0.983	
0.67	0.67	-0.493	1.000	-0.026	0.981	
0.68	0.68	-0.471	1.000	-0.023	0.980	
0.69	0.69	-0.449	1.000	-0.001	0.982	
0.7	0.7	-0.429	1.000	0.002	0.981	
0.6	0.69	-0.537	0.805	-0.050	0.805	x
0.6	0.68	-0.552	0.828	-0.050	0.827	x
0.6	0.67	-0.567	0.850	-0.052	0.849	x
0.6	0.66	-0.581	0.872	-0.051	0.871	x
0.61	0.7	-0.513	0.803	-0.053	0.802	x
0.62	0.7	-0.504	0.823	-0.052	0.823	x
0.63	0.7	-0.496	0.844	-0.038	0.843	x
0.64	0.7	-0.486	0.865	-0.037	0.864	x
0.65	0.7	-0.477	0.886	-0.029	0.886	x

X – search stops at boundary

The largest upper confidence bound is 0.987 which occurs when $p_{11} = 0.62$ and $p_{11} = 0.62$

The smallest lower confidence bound is -0.054 which occurs when $p_{11} = 0.61$ and $p_{11} = 0.69$

Example 3: Observed Kappa at Lower Extreme

$$\begin{bmatrix} 3 & 3 \\ 4 & 0 \end{bmatrix} \qquad \kappa = -0.5217$$

For this example in order to find an lower bound for kappa the search has to find pairs p_{11}, p_{11} which allow values for kappa less than -0.05217. This requires that p_{11}, p_{11} should be closer to the diagonal of the sample space where $p_{11} = p_{11} p_{11}$

$p_{11} p_{11}$	$p_{11} p_{11}$	Minimum kappa	Maximum kappa	Lower 90% confidence Bound		Upper 90% confidence bound
0.6	0.7	-0.52174	0.78261	-0.521	x	0.271
0.59	0.68	-0.56116	0.80753	-0.561	x	0.286
0.58	0.66	-0.60202	0.83137	-0.602	x	0.289
0.57	0.64	-0.64446	0.854	-0.644	x	0.295
0.56	0.62	-0.68863	0.876	-0.688	x	0.282
0.55	0.60	-0.73469	0.898	-0.734	x	0.285
0.54	0.58	-0.78282	0.919	-0.781		0.272
0.53	0.56	-0.83320	0.940	-0.818		0.262
0.52	0.54	-0.88604	0.960	-0.675		0.262
0.51	0.52	-0.94155	0.980	-0.680		0.260
0.50	0.50	-1.00000	1.000	-0.462		0.211
0.6	0.6	-0.66667	1.00000	-0.666	x	0.285

0.59	0.59	-0.69492	1.00000	-0.694	x	0.286
0.58	0.58	-0.72414	1.00000	-0.724	x	0.268
0.57	0.57	-0.75439	1.00000	-0.754	x	0.267
0.56	0.56	-0.78571	1.00000	-0.784		0.250
0.55	0.55	-0.81818	1.00000	-0.806		0.260
0.54	0.54	-0.85185	1.00000	-0.833		0.245
0.53	0.53	-0.88679	1.00000	-0.676		0.248
0.52	0.52	-0.92308	1.00000	-0.620		0.245
0.51	0.51	-0.96078	1.00000	-0.492		0.234
0.5	0.5	-1.00000	1.00000	-0.462		0.211

X – search stops at boundary

The largest upper confidence bound is 0.295 which occurs when $\pi_1 = 0.57$ and $\pi_1 = 0.64$

The smallest lower confidence bound is -0.833 which occurs when $\pi_1 = 0.54$ and $\pi_1 = 0.54$

Calculation of Confidence Limits

The examples given above were entered on an Excel spreadsheet. The sample size for the examples was 10 which resulted in a total of 286 possible outcomes. This was a manageable number to be used in the spreadsheet. The search for the upper and lower confidence bounds was done by trial and error.

A set of functions to do the calculations was programmed in R. and the functions were tested to ensure they gave identical results to the spreadsheet.

Practical Considerations

The total number of possible outcomes is (N+1)(N+2)(N+3)/6 (Derivation A2). For the concordance data base the largest value of N is 70 for which the number of possible outcomes is 62,196. With this sample size a search for the confidence bound at a single set of the nuisance parameters π_1 and π_1 can take several minutes. Separate searches have to be run separately for the upper and lower confidence bounds. It was impractical to do a thorough search for the absolute upper and lower confidence bound. The nuisance parameters are examined for a 9 point grid centered at the maximum likelihood estimates. The grid consists of the center of a square, the 4 corners and the 4 centers of the sides. The sides extend 0.02 above and below the centre if both the maximum likelihood estimates are above 0.1 and 0.01 if either of the maximum likelihood estimates is below 0.1.

This is a limited search to find the confidence bounds but results in some working confidence bounds. The kappa statistic is only intended to provide a coarse measure of reproducibility and extremely accurate confidence bounds are not necessary.

For the data at the individual organ level the observed proportion of time tumors occur is usually small. If the observed kappa is at the lower (upper) extreme then it is sometimes impossible to find a lower (upper) confidence bound for the observed value. In such situations there is a limited space of nuisance parameters to find a suitable lower (upper) bound. These results are marked NE (no estimate) in the tables.

Appendix: Derivations

Derivation A.1: CALCULATE 2X2 TABLE FROM $p_{1.}$, $p_{.1}$ and κ

$$p_{11} = p_{1.}p_{.1} + \kappa(1 - p_{1.})(1 - p_{.1})$$

$$p_{12} = p_{1.} - p_{11}$$

$$p_{11} = (p_{1.} - p_{1.} + p_{.1} - 1)/2$$

$$p_{12} = p_{1.} - p_{11}$$

$$p_{21} = p_{.1} - p_{11}$$

$$p_{22} = 1 - p_{11} - p_{12} - p_{21}$$

Derivation A2: 2x2 TABLE NUMBER OF OUTCOMES

For a 2x2 table with a total sample size of n

A11 cell n+1 possible outcomes

A12 cell (n+1-i) outcomes where i is number in cell A11

A13 cell (n+1-i-j) possible outcomes where j is the number in cell A12

A22 cell known from remaining cells

Total possible number of cells is

$$\sum_{i=0}^{n}\sum_{j=0}^{n-i}(n+1-i-j)$$

$$\sum_{i=1}^{n+1}\sum_{j=1}^{n+2-i}(n+3-i-j) = \sum_{i=1}^{n+1}(n+2-i)(n+3-i) - \sum_{i=1}^{n+1}\sum_{j=1}^{i-1}(n+3-i-j)$$

$$= \sum_{i=1}^{n+1}\frac{(n+2-i)(n+3-i)}{2}$$

$$= \sum_{i=1}^{n+1}\frac{(n+2)(n+3) - (2n+5)i + i^2}{2}$$

$$= \frac{(n+1)(n+2)(n+3)}{2} - \frac{(n+1)(n+2)(2n+5)}{4} + \frac{(n+1)(n+2)(2n+3)}{12}$$

$$= \frac{(n+1)(n+2)(n+3)}{6}$$

Derivation A3: 2x2 TABLE: MAXIMUM AND MINIMUM κ GIVEN MARGINAL PROBABILITIES

The maximum κ occurs when

$$p_{11} = \min(p_{1.}, p_{.1})$$

$$p_{12} = p_{1.} - p_{11}$$

$$p_{21} = p_{.1} - p_{11}$$

$$p_{22} = 1 - p_{1.} - p_{21}$$

The observed agreement is $p_o = p_{11} + p_{22} = 1 - p_{1.} - p_{.1} + 2p_{11}$ and the maximum value of kappa is less than 1 unless the $p_{1.} = p_{.1}$.

The minimum κ occurs when

$$p_{21} = \min((1 - p_{1.}), p_{.1})$$

$$p_{11} = p_{.1} - p_{21}$$

$$p_{21} = p_{.1} - p_{11}$$

$$p_{22} = 1 - p_{1.} - p_{21}$$

References

Krewski et al. (2015). Concordance between Animal and Human Tumours: An Analysis of 111 Agents Known to Cause Cancer in Humans. [This volume.]

Viera, A.J. & Garrett, J.M. (2005). Understanding interobserver agreement: the Kappa statistic. *Family Medicine* 37: 360-363.

To: Arzuaga, Xabier[Arzuaga.Xabier@epa.gov]; Jones, Samantha[Jones.Samantha@epa.gov]; Cooper, Glinda[Cooper.Glinda@epa.gov]; D'Amico, Louis[DAmico.Louis@epa.gov]; Cogliano, Vincent[cogliano.vincent@epa.gov]
From: Gibbons, Catherine
Sent: Mon 9/28/2015 9:49:18 PM
Subject: RE: systematic review workshop...

Thank you Xabier!

I also just talked to Kate Guyton, who is implementing similar strategies for searching for and sorting mechanistic data (albeit cancer-specific) at IARC. She said she'd be happy to give a talk and/or participate, although since she's out of leave time and won't be in DC for the holidays until the following week, she may have to give it via webinar, which would probably necessitate an earlier time slot in the day.

Thanks!

Catherine

From: Arzuaga, Xabier
Sent: Monday, September 28, 2015 2:52 PM
To: Jones, Samantha; Cooper, Glinda; D'Amico, Louis; Cogliano, Vincent
Cc: Gibbons, Catherine
Subject: Re: systematic review workshop...

Hello everyone,

Catherine and I discussed the language of the announcement and we drafted a list of potential experts on the topic of mechanisms-MOA for the December. We are OK with Glinda's suggestion or the title: "Systematic review for questions relating to mechanisms/mode of action: what is really needed, and how can it be efficiently applied?" A list of potential speakers and example publications are presented below. Thank you very much!

Xabier

Potential list of speakers and example publications.

Natalia Garcia-Reyero.

Advancing Adverse Outcome Pathways for Integrated Toxicology and Regulatory Applications. Natalia Garcia-Reyero. *Environ. Sci. Technol.*, 2015, 49 (1), pp 3–9.

Grace Patlewicz.

Applying Adverse Outcome Pathways (AOPs) to support Integrated Approaches to Testing and Assessment (IATA). K.E. Tollefsen, S. Scholz, M.T. Cronin, S.W. Edwards, J. de Knecht, K. Crofton, N. Garcia-Reyero, T. Hartung, A. Worth, G. Patlewicz. *Reg. Toxicol. Pharmacol.*, 2014, Volume 70 (December 2014), Pages 629–640.

Lyle Burgoon, and/or Edward Perkins

Using Adverse Outcome Pathways for Regulatory Applications. Edward J Perkins, Philipp Antczak, Lyle Burgoon, Francesco Falciani, Steve Gutsell, Geoff Hodges, Aude Kienzler, Dries Knapen, Mary McBride, Catherine Willett. In preparation.

Quantitative Adverse Outcome Pathways for Regulatory Applications. Edward J Perkins, Philipp Antczak, Lyle Burgoon, Francesco Falciani, Steve Gutsell, Geoff Hodges, Aude Kienzler, Dries Knapen, Mary McBride, Catherine Willett. In preparation.

Andrew Rooney.

Thomas Hartung and Kim Boekelheide

Bouhifd M, Andersen ME, Baghdikian C, Boekelheide K, Crofton KM, Fornace AJ Jr, Kleensang A, Li H, Livi C, Maertens A, McMullen PD, Rosenberg M, Thomas R, Vantangoli M, Yager JD, Zhao L, Hartung T. The human toxome project. ALTEX. 2015;32(2):112-24.

From: Jones, Samantha
Sent: Monday, September 28, 2015 10:45 AM
To: Arzuaga, Xabier; Cooper, Glinda; D'Amico, Louis; Cogliano, Vincent
Cc: Gibbons, Catherine
Subject: RE: systematic review workshop...

Hi all,

I have no comments/edits.

From: Arzuaga, Xabier
Sent: Monday, September 28, 2015 10:33 AM
To: Cooper, Glinda; D'Amico, Louis; Jones, Samantha; Cogliano, Vincent
Cc: Gibbons, Catherine
Subject: Re: systematic review workshop...

Good morning Glinda,

I'm OK with that language. I think it captures the issue. Catherine and I also discussed other possible titles, but I think the one you proposed is good. Thanks!

Xabier

From: Cooper, Glinda
Sent: Monday, September 28, 2015 10:22 AM
To: Arzuaga, Xabier; D'Amico, Louis; Jones, Samantha; Cogliano, Vincent
Cc: Gibbons, Catherine
Subject: RE: systematic review workshop...

Are you OK with this language in the announcement, describing the topic:

- **Systematic review for questions relating to mechanisms/mode of action: what is really needed, and how can it be efficiently applied?**

From: Arzuaga, Xabier
Sent: Sunday, September 27, 2015 8:55 PM
To: Cooper, Glinda; D'Amico, Louis; Jones, Samantha; Cogliano, Vincent
Cc: Gibbons, Catherine
Subject: Re: systematic review workshop...

Hello Glinda,

Thank you for the update. Catherine and I are working on the second topic and a list of potential speakers. We hope the lists captures experts in the evaluation of mechanistic evidence for MOA analysis of cancer and non-cancer effects. We hope to send an update by COB (09/28/2015). Thanks!

Xabier

From: Cooper, Glinda
Sent: Friday, September 25, 2015 4:32 PM
To: D'Amico, Louis; Jones, Samantha; Cogliano, Vincent; Arzuaga, Xabier
Cc: Gibbons, Catherine
Subject: RE: systematic review workshop...

The current plan is for a one-day workshop with two sessions. The reason I want to say Dec 16 or Dec 17 is the final date will depend on availability of various people. Also, we could conceivably do one session on Dec 16 and the other on Dec 17 if that's what is needed.

One session is on developments in study evaluation tools; it will (hopefully) include talks from someone with Cochrane, someone with GRADE, someone with Navigation Guide, and EPA; could include others; could also include a panel discussion.

The second is on mechanistic data. I have used the phrasing from the WHO survey below (I will let Xabier and Catherine focus on this one)

EPA's National Center for Environmental Assessment (NCEA) is hosting a workshop on Systematic Review for Chemical Risk Assessment in Arlington, VA on December 16 or 17, 2015. The purpose of the workshop is to examine developments in methods for evaluation and synthesis of different types of evidence (epidemiology, animal toxicology, and mechanistic), and examples of application of methods. Specific sessions will focus on:

- Systematic review for questions relating to mechanisms/mode of action: what is really needed, and how can it be efficiently applied?

-

- From theory to practice: lessons learned from the assessment of quality for studies of environmental and chemical exposures OR Developments in study quality assessment tools for evaluation of studies of environmental and chemical exposures: new tools, lessons learned, and future directions

Suggestions for speakers pertaining to these topics, and suggestions for additional topics are requested by October XX, 2015.

Glinda

From: D'Amico, Louis
Sent: Thursday, September 24, 2015 2:08 PM

To: Cooper, Glinda; Jones, Samantha; Cogliano, Vincent
Cc: Gibbons, Catherine
Subject: RE: systematic review workshop...

So a couple thoughts/reactions on the draft text:

1) I don't think we can go out with a workshop that describes "possible topics" or is soliciting topics from the public. I think it's on us to identify the topic that would be most helpful to us, and solicit comment/suggestions from the public on speakers and specific things to discuss under a given topic.

2) I appreciate that the EDC papers are informative since they talk about the application of Klimisch scores and study quality, but I think that as soon as we talk about EDC's and non-monotonicity, the discussion on systematic review related topics will be lost in the noise of people wanting to talk about EDC's more broadly. Are there other papers that address the study quality issues, only not in the context of EDC's? If not, and we were to move forward with that topic, we would need to explicitly lay out that we aren't talking about the science of EDC's here, but the approach to the analysis. Thinking about it in total, I would prefer to avoid the EDC topic.

3) I've attached a previous questionnaire that we were sending back to WHO on systematic review through NIEHS (at least I think that's the path it was taking). There we identified 3 topics that were of interest to EPA. Would any of these be appropriate as the focus of a one day discussion? They might be of a scope that would work for this meeting.

It might be worth considering the arc of what we've done so far on SR. We have input from a couple NRC reports, and we followed up with a workshop in 2013 that surveyed a few issues in systematic review. It might be nice here to demonstrate some program evolution from looking at multiple topics like we did in 2013 by drilling down in more detail in a single topic for this workshop (particularly if we're talking about a 1 day event, which at this point seems like all we can handle).

As to the other points Glinda brought up, I definitely agree with the whole overloading issue. Picking one and focusing might be the path of least resistance.

-Lou

Louis D'Amico, Ph.D.

Acting Communications Director, ORD/NCEA

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From: Cooper, Glinda
Sent: Tuesday, September 22, 2015 6:03 PM
To: Jones, Samantha; Cogliano, Vincent; D'Amico, Louis
Cc: Gibbons, Catherine
Subject: RE: systematic review workshop...

One day only (maximum) – can I call in a fire alarm in the middle? I've got some ideas for people, but it will depend on the topics.

The EDC topic was not meant to be about a specific chemical. It was prompted by some recent commentaries. (Zoeller is a response to Lagarde)

Glinda

From: Jones, Samantha
Sent: Tuesday, September 22, 2015 5:09 PM
To: Cooper, Glinda; Cogliano, Vincent; D'Amico, Louis
Cc: Gibbons, Catherine
Subject: RE: systematic review workshop...

Thanks for providing!

We already have a general statement on the NCEA website when we did a "save the date" general announcement. That has been up on the web for quite some time. The next step (release of info) would have to be more than one sentence. What you have provided below is more along the lines of what is needed. Also, we'll need to get going with ICF to start getting people…do you already have folks identified that you want to participate?.

We will pick one day in December, unless you think we could use both. We do not have plans to discuss chemicals at the December meeting, so it's all Systematic Review.

Endocrine disrupting chemicals?? Have we been working the agency group on this? Are we focusing on specific IRIS or PPRTV chemicals?

I agree about overburdening the systematic review team, just wanted to offer up potential help for you and also experience for others. It looks like Catherine is planning to be involved…I meant to include her name in my earlier email ☺

Competing priorities combined with the migration of the EPA website to Drupal (which is occurring by Oct 1st) we are working against a tight timeline. I also anticipate that Ken will ask for a briefing in the near future, especially since he received one today for the less than lifetime workshop that is scheduled for January 2016.

From: Cooper, Glinda
Sent: Tuesday, September 22, 2015 4:57 PM
To: Jones, Samantha; Cogliano, Vincent; D'Amico, Louis
Cc: Gibbons, Catherine
Subject: RE: systematic review workshop...

Samantha,

Thanks for your note. I've been talking to Vince about this for months. Tried to get something on the website a few weeks ago but apparently Lou thought that one sentence was not enough.

Here is an expanded paragraph for Lou's consideration (Catherine, please help rephrase bullet #2):

EPA's National Center for Environmental Assessment (NCEA) is hosting a workshop on Systematic Review for Chemical Risk Assessment in Arlington, VA on December 16 or 17, 2015. The purpose of the workshop is to examine developments in methods for evaluation and synthesis of different types of evidence (epidemiology, animal toxicology, and mechanistic), and examples of application of methods. Possible topics include (but are not limited to):

- Application of systematic review methods to endocrine disrupting chemicals

- Frameworks for evaluating mechanistic data relating to cancer and to effects other than cancer

- Examples of protocol development for review of chemical toxicities

- Recent developments by groups working in systematic review

Suggestions for speakers pertaining to these topics, and suggestions for additional topics are requested by October 15, 2015.

I do not think it is a good idea to place any more burden on the systematic review team, given their current responsibilities in getting the handbook releasable, and in the Lean-related tasks that fall on this group. But if we end up doing a topic that one or two people can help with (in terms of identifying speakers), I would be happy to ask them.

Glinda

From: Jones, Samantha
Sent: Tuesday, September 22, 2015 4:07 PM
To: Cooper, Glinda
Subject: systematic review workshop...

Hey,

I know your are the lead on this and probably haven't had much time to think about it considering all the other stuff you are doing but I was wondering if we could chat about this. We are going to need to start doing outreach and if we want public input on topics and people we'll need to have some more details in mind.

I was also thinking you shouldn't have to do this by yourself. What do you think about having folks who've been working on systematic review internally (namely, folks like April, Teneille, etc) to serve as a steering committee or some sort of planning committee to help share the technical organization burden. We will have Joe and ICF to take care of the logistics as we have been doing with other workshops.

Let me know…

Samantha

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To: Cogliano, Vincent[cogliano.vincent@epa.gov]; Robert Baan[BaanR@visitors.iarc.fr]
From: Bernard Stewart
Sent: Wed 9/23/2015 12:20:08 AM
Subject: RE: Introduction Vol100WS

Thanks Vincent.

I won't address any matters you raise in detail now because I'm due to catch a plane for London shortly. A week later I'll be at the Agency with Robert, where we will do our best to, as you say, have this finished.

Warmest regards

Bernard.

From: Cogliano, Vincent [mailto:cogliano.vincent@epa.gov]
Sent: Wednesday, 23 September 2015 7:55 AM
To: Robert Baan <BaanR@visitors.iarc.fr>
Cc: Bernard Stewart <Bernard.Stewart@SESIAHS.HEALTH.NSW.GOV.AU>
Subject: RE: Introduction Vol100WS

Hello, Robert and Bernard—Attached is a revised Introduction in redline/strikeout format so you can see what I changed.

I also took the liberty of suggesting a re-ordering of papers in the attached table of contents. Briefly, I re-ordered the key characteristics chapters so they match the order in Martyn's chapter. [This author notes that it would have been nice to have a chapter on each key characteristic. A chapter on epigenetics would have been especially nice, as this topic is not often covered in the Monographs.] I also noticed that two chapters mention inflammation and that there are also two chapters that mention susceptibility. I hope they are not inconsistent.

Then I viewed the remaining chapters as covering various groups of agents. The topics of radiation or tumourviruses didn't seem to me to be any different, so I grouped them together, too. But that's an Editor's choice, so take or reject these suggestions as you wish.

One question: what is the status of the consensus report? I hope we have one, but I don't recall seeing it

recently.

It will be good to have this finished. Thank you for your efforts to bring this to completion.

With warm regards,

Vincent

From: Robert Baan [mailto:BaanR@visitors.iarc.fr]
Sent: Wednesday, September 09, 2015 9:47 AM
To: Cogliano, Vincent
Cc: Bernard Stewart
Subject: Introduction Vol100WS

Dear Vincent,

I hope you are doing fine, and that you had a pleasant summer break.

The preparations of the Scientific Publication on 'Concordance and Mechanisms' have advanced to the stage where a 'Table of Contents' (see attached) could be drafted, which for me is an encouraging sign that the end is near! As you will see, this document presents the titles, authors and the proposed order of the chapters in the forthcoming publication. It occurred to me that it might be useful to send you this draft, with the suggestion to take another look at your Introduction (latest version attached), in which you refer to several chapters in the book.

Let me know if you can find the time to adapt and modify your text, so that it is concordant with the Table of Contents.

Best wishes!

Robert

From: Robert Baan
Sent: Monday, September 7, 2015 10:14 PM
To: Kurt Straif; Bernard Stewart
Cc: Yann Grosse