To: Burke, Thomas[Burke.Thomas@epa.gov]
From: Morning Agriculture
Sent: Wed 11/16/2016 3:03:06 PM
Subject: POLITICO's Morning Agriculture: Health advocates fret over Trump transition — The cost of climate change (and crop insurance) — Holding China accountable on biotech

By Helena Bottemiller Evich | 11/16/2016 10:00 AM EDT

With help from Jason Huffman, Eric Wolff, Catherine Boudreau, Adam Behsudi and Jenny Hopkinson

HEALTH ADVOCATES FRET OVER TRUMP TRANSITION: The Center for Science in the Public Interest is none too pleased about the industry lobbyist leading President-elect Donald Trump's transition team for USDA matters - and it's using it as an opportunity to raise money as it girds for battle against the incoming Republican administration. In a letter to supporters this week, Michael Jacobson, president of the group, blasted Trump for appointing veteran food and agriculture lobbyist Michael Torrey as the lead for his USDA transition effort, noting that Torrey currently lobbies on behalf of the American Beverage Association and Dean Foods.

"The hypocrisy is astounding," Jacobson wrote. "And what they end up with will probably be horrifying." The letter, which repeatedly urges supporters to donate to the organization, says CSPI is on "high alert" to defend public health and food safety, arguing that Trump's early decisions point to a coming "war on science."

Torrey, who's highly respected in food and ag circles, has been lobbying on issues ranging from cheese pricing (on behalf of Little Caesars pizza chain) to forest road regulations (on behalf of the Southeastern Lumber Manufacturers Association) and the Dietary Guidelines (on behalf of ABA), according to lobbying disclosures. As of last quarter, he also represented the Illinois Soybean Association, the Crop Insurance and Reinsurance Bureau, WhiteWave Foods and SNAC International (formerly the Snack Foods Association), at rates varying from $20,000 to $80,000 per quarter.

Like other transition leads, Torrey has remained mum on his work for the president-elect, and he did not respond to a request for comment on CSPI's letter. While we're here: In case you missed it (we did), Jacobson announced recently that he is transitioning roles at CSPI. More on that here. (For the fastest, scoop-heavy coverage of the next administration, head to Pro's Transition page and sign up for our Transition 2017 newsletter.)

HAPPY WEDNESDAY, NOV. 16! Welcome to Morning Ag, where your host is amazed at just how much people seem to care about the so-called peach butt emoji (it's back, apparently!). You know the deal: thoughts, news, tips, emoji requests? Send them to hbottemiller@politico.com or @hbottemiller. Follow the whole team at @Morning_Ag.

THE COST OF CLIMATE CHANGE: The Obama administration warned that climate change will cost taxpayers hundreds of billions of dollars, in a new OMB analysis issued Tuesday. The report argues that federal spending for disaster relief, wildfire suppression and crop insurance will surge if climate change goes unchecked.

"Taken together, the total fiscal impact quantified to date could be equivalent to as much as 15 percent of total federal discretionary spending by late-century, if discretionary spending grows commensurately with real GDP," Ali Zaidi, the OMB associate director of natural resources, energy and science, wrote on the White House blog.

Crop insurance is a key part of the cost equation. The report says that USDA Economic Research Service modeling shows that unmitigated climate change "could increase annual crop insurance premium subsidy costs for corn, soybeans, and wheat by 40 percent by 2080 compared to a projected reference scenario characterized by historical weather patterns."

SENATORS ASK OBAMA TO HOLD CHINA ACCOUNTABLE ON BIOTECH: Nearly 40 senators from both sides of the aisle, including almost every member of the Senate Agriculture Committee, have signed on to a letter urging President Barack Obama to hold China's feet to the fire on its biotech approval commitments.

"When the Chinese government fails to remain transparent, science-based, and timely in its regulatory process, it impacts not only our farmers' and ranchers' abilities to access critical markets in China, but also their abilities to utilize the best and most innovative agricultural technologies in our fields at home in the U.S.," the senators write, ahead of a dialogue between the U.S. and China at the Joint Commission on Commerce and Trade.

The letter adds: "We encourage you to continue building on the progress that has been made over the last few years and urge China to move forward in deregulating products awaiting final approval, as well as to eliminate trade barriers due to regulatory systems that don't operate based on scientific assessments." Find the letter here.

EPA PULLS SCIENTIST FROM GLYPHOSATE REVIEW: It's addition and subtraction for the Scientific Advisory Panel tasked with reviewing EPA's evaluation of the carcinogenic potential of glyphosate - and the subtraction is intriguing. Officials have expanded the panel's membership, from 13 to 17, but epidemiologist Peter Infante is no longer a member, according to a roster for the group's December meeting.

Infante, a former Occupational Safety and Health Administration official, was a target of an Oct. 12 letter from the pesticide industry association CropLife America, which claimed that his affiliation with research labs that oppose chemical agriculture makes him too biased to serve on the panel. CropLife also took aim at Kenneth Portier, managing director of the statistics and evaluation center at the American Cancer Society, but he remains on the SAP. An EPA spokesman declined to comment on Infante's removal, calling the situation a personnel matter.

The group of independent scientists was originally expected to meet in October, but the event was delayed due to conflicts with panel members' schedules, EPA said.

'Life in a bubble': Infante responded to CropLife America's charges in an Oct. 21 letter to EPA, arguing that his record shows he has no ethical conflicts in reviewing glyphosate. He wrote that federal advisory committee rules call for panels to be balanced in viewpoint, and do "not require

that every committee member has lived his or her life in a bubble and never expressed an opinion that might be objectionable to a particular interest." Infante added that CropLife's letter suggests it "is attempting to impermissibly skew the composition of the committee in its favor, and is certainly not applying its own purported desire for unquestioned neutrality." More for Pros here.

RABOBANK: 2018 FARM BILL TO FOCUS ON FARMERS' BOTTOM LINE: Due to a weakening U.S. agricultural economy, negotiations over the 2018 Farm Bill will focus on programs that support farmers' bottom line and business sustainability, analysts at Rabobank predicted in a report published Tuesday. And given president-elect Donald Trump's campaign promise to curb regulations, there will likely be a shift away from conservation, the analysts said. Increasing funding for the Conservation Reserve Program, a voluntary program that pays producers to take environmentally sensitive land out of production, along with adjustments to crop support programs like Agriculture Risk Coverage, Price Loss Coverage and crop insurance, are likely to be top issues as well.

Also, small business owners in the agriculture industry could face higher operating costs due to labor shortages should Trump keep his promise to come down hard on illegal immigration, the analysts said. The scenario has already been playing out because Mexican workers have more opportunities in their own country and increasingly strict immigration laws.

"The challenge for U.S. producers is to remain labor-competitive," the report notes. "Producers may need to start thinking more about technological investments." Read the full report here.

OIL LEADERS PRESS CONGRESS TO SCRAP RFS: Let's do a two-step on the RFS, shall we? First, our colleague Eric Wolff on Pro Energy reports that executives from BP and Marathon Petroleum met Tuesday with key congressional leaders on behalf of the American Petroleum Institute, to press lawmakers to pass a bill to rein in the Renewable Fuel Program.

The executives - Doug Sparkman, COO for British Petroleum Fuels, North America, and Don Templin, executive vice president for Marathon Petroleum Corp. - met with Reps. Peter Welch (D-Vt.) and Bill Flores (R-Texas), who are the bipartisan sponsors of a bill that would cap, at 9.7 percent, the amount of ethanol in the gasoline supply. The executives also met with Reps. Greg Walden (R-Ore.) and John Shimkus (R-Ill.) - the two leading candidates to run the House Energy and Commerce Committee in the next Congress - and Sen. Jim Inhofe (R-Okla.), who could shepherd the ethanol bill in the Senate, since it now has no sponsor in the upper chamber.

The energy execs said they wanted to make sure the Welch-Flores bill remained top-of-mind for these members, as attention shifts to the incoming Trump administration and pressure builds in the lame-duck session for Congress to broker a solution to extend government funding beyond the Dec. 9 end of the stopgap spending measure.

"What we are doing, and the reason we are here, is we want to build momentum for this bill," Templin said. "We'd like to see this get done as quickly as possible."

IOWANS EXPECT RFS BACK TO FULL POWER: Alright, let's keep it going: Annette Sweeney, a member of Donald Trump's Agriculture Advisory Committee and a farmer and

former Iowa state legislator from Iowa Falls, told Wolff that Iowa farmers expect the Trump administration to restore ethanol volumes under the Renewable Fuel Standard to their statutory levels.

Sweeney, a former chair of the Iowa House's Agriculture Committee, said she met with The Donald over the summer "for a good long conversation." She said she told him how the four ethanol factories near Iowa Falls had revived the town. "He said, 'That makes a good strong economy, doesn't it?' I said, 'Yes sir, it does,'" Sweeney said.

EPA has used its waiver authority to set ethanol volumes below those set by Congress for 2014, 2015 and 2016, and it proposed lower volumes for 2017. A final rule is expected this month. The oil industry, as represented by its largest industry groups, has made clear it wants the RFS repealed. But that might not go over well with Sweeney and other Iowa farmers. She said getting the ethanol requirements back up to statutory requirements is a high priority. "That's all we want, out here in the heartland - put it to where it's supposed to be," she said.

No need to change the point of obligation, either. Sweeney also said she expects Trump would not change which companies bear responsibility for complying with the program. "I really think shifting the point of obligation would interrupt America's progress toward making clean renewable biofuels," she said. That puts Iowa corn farmers on a collision course with oil refiners - most notably Trump supporter Carl Icahn - who are pushing hard for a change.

HOPING FOR A TPP MIRACLE: Despite President-elect Donald Trump's strong criticism of the TPP on the campaign trail and all of the statements by GOP leaders that Congress won't take up the trade deal during the lame duck, Paul Wenger, president of the California Farm Bureau Federation, told Capital Public Radio that he remains optimistic. California is the nation's largest agricultural state and exports 20 percent of what it produces.

"This administration, as they come in, are going to have to take a look at it. And if he's such a good businessman, he will see this was a good deal," Wenger said.

Dan Sumner, an agricultural economist at the University of California, Davis, also believes there's a chance Trump won't kill TPP. "I can imagine President Trump asking for a delay on that until he renegotiates parts of it," Sumner said. "And if he can renegotiate what he considers a better deal, great. And he may well be very instrumental in getting such a thing through Congress." More here.

THE OLD AND THE NEW FOR STATE AG OFFICIALS ON TRADE: The hopefulness in some quarters aside, TPP is hibernating, at best. Meantime, state agriculture officials, represented by the National Association of State Departments of Agriculture, met at the White House on Tuesday with Agriculture Secretary Tom Vilsack, U.S. Trade Representative Michael Froman, and USTR Chief Agricultural Negotiator Darci Vetter. In a statement, NASDA President and Louisiana Commissioner of Agriculture and Forestry Mike Strain thanked them for their efforts "to advance U.S. agriculture in the international marketplace."

But the future beckons - and for NASDA, multilateral trade agreements are "critical" to open

new markets and tear down trade barriers. "We also look forward to working with the incoming Trump administration," Strain added, "to determine a path forward on trade policies in order to enact agreements that ensure U.S. producers' leadership and competitiveness in the global economy."

MA'S INSTANT OATS:

- We need a big advance in our scientific understanding of antimicrobial resistance and food systems, the FAO said in a new report urging more research.

- Anthony Bourdain unloaded on Donald Trump's culinary tastes during a recent roundtable event, accusing him of not being able to use chopsticks. Food & Wine has it here.

- The discovery that a kind of roundworm carries a particular bacterium opens up a new environmentally friendly way to control the pest, writes Steve Lundeberg for Oregon State University.

- In a new report, Yale researchers dive into the landscape of sustainable farmland investment strategies. Find it here.

THAT'S ALL FOR MA! See you again soon! In the meantime, drop your host and the rest of the team a line: cboudreau@politico.com and @ceboudreau; jhopkinson@politico.com and @jennyhops; hbottemiller@politico.com and @hbottemiller; ikullgren@politico.com and @IanKullgren; mkorade@politico.com and @mjkorade; and jhuffman@politico.com and @jsonhuffman. You can also follow @POLITICOPro and @Morning_Ag on Twitter.

To view online:
http://www.politico.com/tipsheets/morning-agriculture/2016/11/health-advocates-fret-over-trump-transition-217441

To: Burke, Thomas[Burke.Thomas@epa.gov]
From: Morning Agriculture
Sent: Wed 10/26/2016 2:02:10 PM
Subject: POLITICO's Morning Agriculture: U.N. expert suggests junk food a human rights issue — Clinton keeping Obama's lobbying rules — EPA probing dicamba spraying

By Helena Bottemiller Evich | 10/26/2016 10:00 AM EDT

With help from Jenny Hopkinson, Ian Kullgren, Catherine Boudreau, Andrew Hanna and Annie Snider

U.N. EXPERT SUGGESTS JUNK FOOD A HUMAN RIGHTS ISSUE: The fact that cheap, nutrient-devoid dietary patterns are proliferating presents a human rights concern, a top United Nations expert suggested Tuesday. "Within the human rights framework, states are obliged to ensure effective measures to regulate the food industry, ensure that nutrition policymaking spaces are free from private sector influence and implement comprehensive policies that combat malnutrition in all its forms," said Hilal Elver, the U.N.'s special representative on the right to food, the AP reported.

Elver expressed particular concern about food companies' marketing unhealthy foods to children in developing countries, and called on governments to move from more industrial systems to more ecologically based ones, per the AP report: "The first step is to recognize nutrition as an essential component of the human right to adequate food, reinforced by monitoring accountability and transparency," Elver added.

The diet-public health alarm: If you zoom out for a moment, outside the U.S. and our crazy election, you'll find an international public health community that's increasingly focused on noncommunicable diseases like obesity and diabetes and the dietary patterns that fuel them. The call-out on diet as a human rights concern comes two weeks after the World Health Organization urged countries to consider soda taxes as a way to rein in sugar consumption - a move that followed closely on former New York City Mayor and sugar foe Michael Bloomberg being named WHO's Ambassador for Noncommunicable Diseases.

HAPPY WEDNESDAY, OCT. 26! Welcome to Morning Ag, where your host bought candy for trick-or-treaters too early and is now worried there won't be much left for the neighborhood kids this weekend. Fingers crossed! You know the deal: Thoughts, news, tips, extra Halloween candy? Send to hbottemiller@politico.com or @hbottemiller. Follow the whole team at @Morning_Ag.

CLINTON KEEPING OBAMA'S LOBBYING RULES, FOR NOW: "Hillary Clinton's presidential transition team has put in place strict rules that limit the influence of lobbyists in crafting the nominee's policy agenda, POLITICO has learned, an early indication that Clinton is unlikely to abandon all of the lobbying restrictions imposed by Barack Obama," report POLITICO's Anna Palmer and Andrew Restuccia this morning. "The secretive transition operation, which has tried to keep a low profile in order to not appear overly confident in a Clinton victory, is limiting how federal lobbyists can work with the transition teams that are tasked with planning for the transfer of power at dozens of key agencies, according to several

sources familiar with the operation. The Clinton campaign's policy operation, which is a separate entity from the transition team, continues to be the point of contact for companies, consultants and lobbyists to send policy memos." Full take here.

EPA PROBING DICAMBA SPRAYING: Federal search warrants have been executed in at least four Missouri counties in a criminal investigation of alleged misuse of herbicides containing dicamba; the probe follows widespread complaints of drift-related damage to 41,000 acres of crops, the Daily Dunklin Democrat reports. The warrants were served earlier this month to gather evidence of possible violations of the Federal Insecticide, Fungicide and Rodenticide Act and other federal crimes, according to the news outlet. Since June 22 the Missouri Department of Agriculture has received more than 100 complaints related to damage to alfalfa, cantaloupe, cotton, soybeans, peaches, purple-hull peas, rice, soybeans, tomatoes, and watermelons. Read the story here.

DOW, DUPONT MERGER TO CLOSE IN Q1 2017: Andrew Liveris and Ed Breen, the CEOs of Dow Chemical Co. and DuPont Co., respectively, said Tuesday they expect the $59 billion merger of the companies to close in the first quarter of 2017 - Breen said by the end of March - which is beyond the end-of-year target set in June when shareholders approved the link-up. In interviews with Bloomberg on Tuesday, the leaders of the two agrichemical giants said regulators' "greatest concern is agriculture" amid rapid consolidation in the seed and pesticide industry, but that the value created by the Dow-DuPont deal will be worth waiting for. Earlier this month the European Commission pushed its decision deadline to Feb. 6, because it wanted more information on the transaction. Liveris declined to say whether assets will need to be sold to gain approval.

ChemChina's proposed $43 billion takeover of Syngenta also has been delayed until the first quarter of 2017, due to an in-depth probe by the European Commission, said Erik Fyrwald, CEO of the Swiss seed and pesticide maker, in a statement to investors on Tuesday. The two companies missed a deadline last week to submit plans to resolve antitrust regulators' concerns, paving the way for a wider investigation. In August, the deal was cleared by the Committee on Foreign Investment in the United States, which reviews foreign transactions for any national security threats.

FCC COMMISH TO USDA RURAL BROADBAND GIG? Mignon Clyburn, a Democratic FCC commissioner, is being buzzed about in a number of future capacities if she leaves her post at the end of her term (early next year), and one of those possibilities is future head of USDA's Rural Utilities Service, Pro Tech's Alex Byers reports. Clyburn, a top advocate at the FCC for disadvantaged Americans, is the daughter of 12-term Rep. Jim Clyburn (D-S.C.), the No. 3 Democrat in the House (yes, she's getting House speculation, but her father hasn't made any indications he's going anywhere). Sources in Clyburn's orbit said one of the roles she might consider if she stays in government service is USDA's broadband-oriented Rural Utilities Service, which drives to upgrade or expand utility services in rural areas. Pros can find the full story here.

COLICCHIO, PACELLE CANVASS ON BEHALF OF NEW JERSEY DEM: Food Policy Action and the Humane Society Legislative Fund teamed up Tuesday to canvass in support of

Josh Gottheimer, a Democrat challenging Rep. Scott Garrett (D-N.J.), with celebrity chef Tom Colicchio, co-founder of Food Policy Action, and Wayne Pacelle, HSLF vice president, going door to door to talk to voters , the groups reported Tuesday. "Animal welfare and food policy are bread and butter issues for Americans of all political persuasions," said Pacelle, adding that Garrett's "dismal" record prompted their involvement in the race.

Food Policy Action continues to try to make food policy a political issue that resonates beyond the so-called food movement. "Food policy matters in elections, and it's important for voters to know where candidates stand on these important issues," said Colicchio. "We need better leaders in Congress who will prioritize our food system."

ISAKSON LEADS IN GEORGIA, BUT RUNOFF MIGHT BE NEEDED: Georgia Sen. Johnny Isakson, a Republican on the Senate Agriculture Committee and a champion of poultry processors, is up 15 percent (47 percent to 32 percent) over Democratic challenger Jim Barksdale in his reelection bid, based on the latest Atlanta Journal Constitution poll . But that's below the 50 percent-plus needed for Isakson to avoid a runoff, the AJC notes. The poll included 1,003 registered voters and was said to have a margin of error of 3.9 percent. Libertarian challenger Allen Buckley had the support of 11 percent of those surveyed. Read the AJC story here.

AXELROD HINTED AT WHITE HOUSE ROLE FOR VILSACK IN 2008: In case you missed it in the many rounds of WikiLeaks emails that have been released in recent days: President Barack Obama's political guru, David Axelrod, back in 2008, just after Election Day, said he thought Vilsack should have a prime role in the administration. The emails include a passing mention of a "WH role" - a tidbit that may be of interest to ag in the past-is-prologue kind of way since Vilsack is widely thought to be interested in serving in a Clinton administration, perhaps as chief of staff or some other high profile role, after he was passed over for vice president.

Axelrod wrote to Michael Froman, who was working on the Obama transition team at the time, that Vilsack had many strengths: "He was for HRC, but came around quickly and forcefully, and BO likes and respects him." He also touted the former Iowa governor's work on wind and biofuels in his state. The email is here.

SMITH INQUIRES ABOUT GLYPHOSATE DELAY: House Science, Space and Technology Chairman Lamar Smith (R-Texas) is demanding the EPA explain why it postponed the review by independent scientists of its glyphosate cancer assessment, as well as the role agency staff played in crafting the controversial 2015 International Agency for Research on Cancer report on the chemical. In a letter Tuesday to EPA Administrator Gina McCarthy, Smith argued that EPA staff were more involved in the IARC assessment, which found the herbicide to be "probably carcinogenic," than she had admitted during a June 22 hearing.

The apparently contradictory statements by McCarthy and her staff in subsequent correspondence, along with the questionable delay of the review for undisclosed reasons, "cast doubt on the agency's ability to complete an objective review based on the science that has already been well documented on the carcinogenicity of glyphosate," Smith wrote.

As a result, the chairman gave the EPA until Nov. 1 to schedule interviews in front of committee staff for two agency scientists - Matthew Martin and Peter Egeghy, both scientists with the EPA's Office of Research and Development - and Jim Jones, the associate administrator for the Office of Chemical Safety and Pollution Prevention. Jones is under fire for what Smith claims is a close relationship with Kenneth Portier, one of the scientists on the IARC committee who has been outspoken in his support for those findings, and the brother of a member of EPA's review panel for glyphosate.

REUTERS: IARC ASKED EXPERTS TO WITHHOLD DOCS: While we're here, Reuters reported Tuesday that the WHO's International Agency for Research on Cancer, known as IARC, has cautioned scientists who worked on its controversial review of the common weedkiller not to release documents related to the review. That report is here.

LET THE CARRAGEENAN FIGHT BEGIN: There appears to be one issue that will dominate discussion when the National Organic Standards Board holds its meeting in St. Louis next month: whether to keep carrageenan for use in organics. Of the 1,705 public comments filed in advance of the meeting, 1,005 of them are on the seaweed extract, which is used as an emulsifier and thickening agent in food and infant formula.

While opponents say carrageenan has been found to cause inflammation, supporters say it is a safe and irreplaceable ingredient. The comment letters include ones from several employees of the FMC Corporation, from section managers and financial advisers to maintenance mechanics, who have weighed in on the safety of the ingredient, its unique properties in food and the economic benefits it generates for the small communities that produce it.

To be sure, there is also pushback from others who have filed comments, including many who cite a March 2013 report from the organic watchdog group Cornucopia Institute that found the ingredient causes gastrointestinal inflammation, stomach ulcers and even tumors. Cornucopia and many other groups have not weighed in, so it's likely that the opposition will build ahead of the Nov. 16-18 meeting. The comment period closes today. Comments are here. If you are filing, send us a copy at jhopkinson@politico.com.

MA'S INSTANT OATS:

- PBS NewsHour takes a look at the legal fight in Iowa over farm runoff in waterways. Find it here.

- Campbell's Soup Co. is investing $32 million in a personalized nutrition meal kit company. See Philadelphia Business Journal for more.

- Should food makers sneak vegetables into foods for kids? A New York Times column takes a look.

THAT'S ALL FOR MA! See you again soon! In the meantime, drop your host and the rest of the team a line: cboudreau@politico.com and @ceboudreau; jhopkinson@politico.com and @jennyhops; hbottemiller@politico.com and @hbottemiller; ikullgren@politico.com and

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To: Burke, Thomas[Burke.Thomas@epa.gov]
From: Morning Agriculture
Sent: Mon 10/17/2016 2:02:06 PM
Subject: POLITICO's Morning Agriculture, presented by Food Policy Action: GIPSA enters the home stretch — This week: Trump, Clinton ag surrogates face off — Cuba regs not just all rum and cigars

By Ian Kullgren | 10/17/2016 10:00 AM EDT

With help from Jenny Hopkinson, Helena Bottemiller Evich and Adam Behsudi

GIPSA ENTERS THE HOME STRETCH: Hoping to end a six-year regulatory tug of war, the USDA has sent drafts of its Grain Inspection, Packers and Stockyards Administration Act rules to the White House for final review, indicating the department will release them to the public before the Obama administration ends.

Details of the new regulations will be kept under wraps for the next few weeks. But Agriculture Secretary Tom Vilsack explained, in a letter to meat industry groups last week, that USDA has been working on three different issuances, including an interim final rule and a proposal, all of which deal with the way poultry processors work with growers. At the same time, Vilsack said USDA is considering leaving out several provisions that were contained in a GIPSA rule proposed in 2010, including those that would have prevented meatpackers from buying livestock from other packers, banned packers from entering into exclusive agreements with certain livestock dealers, and required packers and live poultry dealers to submit sample contracts to USDA for sharing with the public.

HAPPY MONDAY, OCT. 17! Welcome to Morning Ag, where your host is hoping that something - anything - about ag will come up in the last presidential debate, on Wednesday - but he's not holding his breath. You know the deal: Thoughts, news, tips? Send them to ikullgren@politico.com or @IanKullgren. Follow the whole team at @Morning_Ag.

- Calendar check: 22 days until the election.

THE GIPSA FIGHT IS ON: It remains unclear whether those potential changes will be enough to stop a GIPSA rider in the House ag appropriations bill. For the time being, the meat industry is putting up a fight. "It is irresponsible for USDA to advance this stale six-year-old rulemaking," Barry Carpenter, president and CEO of the North American Meat Institute, said in a statement. "The interim final rule, as described, will open a floodgate of litigation, upend the established system for marketing cattle, pork, and poultry in the U.S., and add costs at every step along the process from producers to consumers."

Senate Agriculture Committee Chairman Pat Roberts (R-Kan.) was also quick to condemn the USDA. "While the impact of these rules is not fully known, if they are in any way similar to the 2010 GIPSA proposal, I have serious concerns that the U.S. livestock, poultry, and meat sectors will be tremendously burdened and experience irreparable harm during already difficult economic times," he said in a statement.

Progressive groups, including National Farmers Union and the National Sustainable Agriculture

Coalition, said the rules are long overdue and will protect farmers. "Livestock producers and poultry growers have been waiting too long for much needed protections against the fraudulent, anti-competitive practices they fall victim to in the marketplace," NFU President Roger Johnson said in a statement.

** **A message from Food Policy Action:** Food Policy Matters. The 2016 National Food Policy Scorecard grades Congress on key votes in the 114th Congress. Find out more at foodpolicyaction.org/Scorecard **

THIS WEEK: GLYPHOSATE COMMENTS DUE; TRUMP, CLINTON AG SURROGATES FACE OFF: The highly anticipated meeting on glyphosate's carcinogenic potential, scheduled for later this week, was postponed - but comments are still due by Monday night on issues that will be considered at the meeting, including the questions to be put before the panel and the selection of independent experts asked to serve. Scores of groups have already weighed in, and things are getting pretty heated.

Glyphosate point: One of the fights stems from an August 24 comment letter submitted by Janet Collins, CropLife America's senior vice president for science and regulatory affairs. She calls the Scientific Advisory Panel's review "unnecessary and an inappropriate use of EPA resources" and takes aim at the International Agency for Research on Cancer for raising concerns in March 2015 about the potential carcinogenicity of glyphosate. CropLife argues that regulatory bodies around the world have found that the chemical doesn't cause cancer at the rates at which people are generally exposed to it, and that IARC's report failed to take into account all available science. The group also accuses IARC panel member Kathryn Guyton of having conflicts of interest because she spoke to nonprofit groups before and after completion of the assessment. CropLife's comments are here.

The counterpoint: Those accusations are false, IARC Director Christopher Wild says in an Oct. 4 letter posted to the docket late Thursday. "IARC examines only scientific reports available in the public domain, adhering to the principle that the basis of the IARC evaluations should be open to scrutiny by others," Wild wrote, adding that the industry studies CropLife is likely referencing are not publicly available. As to Guyton, "IARC absolutely rejects the false statements that [she] had either pre-formed conclusions or conflicts of interest in relation to the glyphosate evaluation," Wild said. His comments are here. And of course, if you are filing today, please send a copy to jhopkinson@politico.com.

Also today: Sodium comments are due: The deadline is tonight for those wanting to weigh in on FDA's short term (2-year) voluntary sodium reduction targets, which cover some 150 categories of food, from chicken wings to bread. The short-term targets try to dial down sodium intake to about 3,000 milligrams per day (we're closer to 3,400 milligrams right now, on average). The targets are on a shorter procedural timeline because the agency hopes that they can finalize them before the clock runs out on the Obama administration. Interested parties have until Dec. 2 to comment on the agency's long-term (10-year) targets, which aim to get sodium consumption down to 2,300 milligrams per day - the amount the Dietary Guidelines recommend. More from FDA here.

On Wednesday, Trump, Clinton ag surrogates face off: Representatives from the two presidential campaigns are set to speak on agricultural issues during a Farm Foundation Forum at the National Press Club, hours before the last presidential debate. Donald Trump will be represented by Nebraska rancher and Agricultural Advisory Committee leader Charles Herbster and campaign co-chair Sam Clovis. Doing battle on behalf of Hillary Clinton will be former Sen. Mark Pryor of Arkansas. Expect a lot of talk about immigration, taxes, EPA and food stamps. Details are here.

On Thursday, FTC and USDA get together over false organic claims: The Federal Trade Commission and the USDA will host a round-table to look at organic claims used on products that fall outside of the scope of USDA's organic program, such as dry cleaners, which the industry says is misleading consumers and harming their certifications. The day-long meeting will first look at consumer misconceptions, then how to prevent deception as well as policy approaches that could be used to address the issue. Miles McEvoy, who heads the organic program, and Jessica Rich, director of the FTC's Bureau of Consumer Protection, are both set to address the session. Details here.

CUBA REGS NOT JUST ALL RUM AND CIGARS - THERE ARE TRACTORS, TOO: Most headlines generated by the White House's big Cuba announcement on Friday focused on eased restrictions on Cuban rum and cigars, but here's how the new rules, effective today, will benefit broader trade with the Communist-run nation.

The rules give Cuba more of an opportunity to be a part of supply chains, now that certain authorized goods exported to Cuba can be imported back into the U.S. This will allow items initially sent to Cuba to come back to the U.S. for repair or service. Also, consumer goods for personal use that are sold online, ranging from air conditioners to toothbrushes, can be sent to Cuban citizens. The amendments also make it possible for exporters to directly finance shipments of tractors, pesticides and other goods used in agriculture, avoiding onerous cash in advance requirements that apply to transactions for agricultural commodities.

The rules could also help ag in more subtle ways. Doug Keesling, the Kansas state director of the U.S. Agriculture Coalition for Cuba, said he believes they'll bring more money into Cuba, giving the country greater purchasing power to buy U.S. products. "Indirectly, it's actually huge," he said.

COURT TOSSES OUT DIETARY GUIDELINES SUIT: A federal court on Friday dismissed a lawsuit alleging undue industry influence in the crafting of the Dietary Guidelines. The Physicians Committee for Responsible Medicine, which promotes a vegan diet, sued the Department of Agriculture and the Department of Health and Human Services in January, arguing that they had allowed the egg industry to improperly influence the Dietary Guidelines Advisory Committee recommendations on cholesterol. The group charged that some DGAC members had close ties to the industry and that the committee had relied too heavily on industry-funded studies. The group also cried foul over the fact that the American Egg Board had nominated one of the DGAC members.

The nonprofit said the court tossed out the suit because there are "no guidelines for determining

how much industry influence is too much," and so the complaint was "non-justiciable." The case's dismissal "means there are no clear limits as to the food industry's role in future nutrition policy decisions," the group said. PCRM's announcement on the dismissal is here.

EPA APPROVES LIMITED USES OF SULFOXAFLOR: The EPA has given the green light to limited uses for the pesticide sulfoxaflor, which was pulled from the market last year after a federal court found that uses allowed by the agency weren't appropriately protective of bees. Under the new registration, issued late Friday, the pesticide can only be used on crops that are not pollinated by bees or after plants have bloomed, when bees are unlikely to be present. There are also new rules restricting spraying the chemical in high winds and requiring a buffer from other crops. Read the agency's statement here.

HOW HILLARY GOT TO 'NO' ON TPP: Hacked emails purportedly reveal how Hillary Clinton's campaign worked to put the Democratic candidate's view on the Trans-Pacific Partnership in line with that of her labor base shortly after the deal was concluded last October - and before she was to take the stage in a debate with longtime TPP opponent Sen. Bernie Sanders.

"We can't survive hemming and hawing for 3 weeks," Clinton campaign manager John Podesta - whose gmail was hacked - wrote in an Oct. 6 exchange. Indeed, Clinton didn't waste any time, and effectively opposed the deal on Oct. 8, a few days after the talks concluded, on Oct. 5. Her labor outreach director, Nikki Budzinski, had advocated that Clinton not take a formal position until the final text of the agreement was released - which ended up happening on Nov. 5 - to avoid making her position look too political.

"We don't have the language yet or much documentation to fall back, that she will be able to credibly say she reviewed and then therefore weighed in on," Budzinski wrote. "If she weighs in now, without viewing the document, some in labor might wonder why she didn't just say she opposed earlier?"

But just a day later, on Oct. 7, Clinton speechwriter Dan Schwerin circulated a draft of her opposition statement, with at least one adviser advocating for broader language that would basically foreclose any support for the deal in the future. "The way it is written here, it sounds like she could flip her position next week or month if she hears new details of the deal," campaign media adviser Mandy Grunwald wrote. "I think we have to close that door."

MORE ON HILLARY AND GMOs: The newest WikiLeaks release also contains more banter between Podesta and GMO labeling advocate Gary Hirshberg. In a lengthy email to Podesta after Campbell Soup Company announced its support for mandatory labeling in January, Hirshberg lays out a case for why a pro-labeling stance from Clinton could help her win votes from women. Another email chain includes Clinton's supposed response to a GMO labeling question at a fundraiser in Denver.

IF YOU CAN'T HANDLE THE HEAT: Podesta took to Twitter on Friday to needle Julian Assange, the WikiLeaks founder: "I bet the lobster risotto is better than the food at the Ecuadorian Embassy."

GET OUT THE VOTE: Starting today, Pro Ag will be testing a new feedback system for POLITICO content. We'll have voting buttons on stories and whiteboards, which subscribers can use to rate how helpful the information is. Help us evaluate how to give you the most of what you need!

CAKE + CANDLES: Happy belated birthday to our talented POLITICO Pro Ag colleague Jenny Hopkinson! She tried to let it slip by over the weekend without anyone noticing, but we figured it out anyway. Shower her with good wishes: jhopkinson@politico.com

POP QUIZ: **T/F? THE GSA IS REQUIRED BY LAW TO SUPPLY OFFICE SPACE AND EQUIPMENT TO PRESIDENTIAL TRANSITION TEAMS?** Not sure? No problem. Over the next several weeks, we'll be sharing the resources you'll need to navigate the changing landscape in Washington. From the "Five Things You Need to Know" (where you'd learn the answer to the above question is true) to the big names under consideration for key positions, you'll be 100 percent ready for Transition 2017. Sign up now.

MA'S INSTANT OATS:

- A Bureau of Land Management program to control the booming wild horse population in the West is buckling under increased costs, The New York Times reports.

- The Times also has a story on how vodka saved a farm in the Hamptons. Read it here.

- DTN looks into how the proposed GIPSA rules would change the court standard for suing meatpackers. Read it here.

- A Michigan-based turkey company has recalled 27 tons of its product because it was contaminated with an unknown black substance, Food Safety News reports.

- Iowa lawmakers are trying to figure out how to protect the state from climate change-induced flooding, The Des Moines Register reports.

THAT'S ALL FOR MA! See you again soon! In the meantime, drop your host and the rest of the team a line: cboudreau@politico.com and @ceboudreau; jhopkinson@politico.com and @jennyhops; hbottemiller@politico.com and @hbottemiller; ikullgren@politico.com and @IanKullgren; mkorade@politico.com and @mjkorade; and jhuffman@politico.com and @jsonhuffman. You can also follow @POLITICOPro and @Morning_Ag on Twitter.

** **A message from Food Policy Action:** There are few issues more important than the food we eat and how its grown. The National Food Policy Scorecard grades Congress on key food and farming votes in the 114th Congress covering issues of domestic and international hunger, food safety, food access, farm subsidies, animal welfare, food and farm labor, nutrition, sustainable fisheries, food transparency, local and regional food production, organic farming and the effects of food production on the environment. The National Food Policy Scorecard lets consumers and voters identify which legislators are working for sensible food policies. Learn more about the

FPA Scorecard at foodpolicyaction.org/Scorecard #votefood **

To view online:
http://www.politico.com/tipsheets/morning-agriculture/2016/10/gipsa-enters-the-home-stretch-216892

To change your alert settings, please go to https://secure.politico.com/settings

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To: Burke, Thomas[Burke.Thomas@epa.gov]; Kavlock, Robert[Kavlock.Robert@epa.gov]; Bahadori, Tina[Bahadori.Tina@epa.gov]
From: Dix, David
Sent: Tue 12/8/2015 6:01:30 PM
Subject: FW: New DG of Health and Food Safety Directorate General

The new DG of SANTE is Mr Xavier Prars Monne. Here are some links to his profile:

On the EC website: https://ec.europa.eu/digital-agenda/events/cf/eip-aha-4th-conference/speaker.cfm?id=449

On LinkedIn: https://www.linkedin.com/profile/view?id=ACgAAALA1DkB_S_4qQeo3x7BV-KtWdiFuQzq4cE&authType=name&authToken=Fy8V

About the glyphosate discussions:

1. This is the announcement of the meeting taking place in the European Parliament last week:

EoV with the Commission, WHO and EFSA on glyphosates

02-12-2015 - 12:33
Glyphosate chemical formula On 1 December the ENVI Committee held an EoV with the Commission, WHO International Agency for Research on Cancer and EFSA on Glyphosate, an active substance that is used in pesticides in the EU and for which EFSA and IARC reached different conclusions as to genotoxicity and carcinogenicity.

The discussion will focus on the methods used to reach IARC and EFSA's assessments and on the future Commission's decision on whether or not to keep glyphosate on the EU list of approved active substances.

2. I talked about the lunch debate organised by the Greens in the Euroepan Parliament; very interesting debate with Jose Tarazona and Chris Portier: http://www.greens-efa-service.org/medialib/mcinfo/pub/en/scc/4289

3. Link to the BfR website dedicated to glyphosate:
http://www.bfr.bund.de/en/a-z_index/glyphosate-193962.html

To: Chris Portier[cportier@me.com]
Cc: bucher@niehs.nih.gov[bucher@niehs.nih.gov]; Burke, Thomas[Burke.Thomas@epa.gov]; Sinks, Tom[Sinks.Tom@epa.gov]
From: Birnbaum, Linda (NIH/NIEHS) [E]
Sent: Fri 11/27/2015 3:31:32 PM
Subject: Re: EFSA Glyphosate Recommendations

not a problem

and Happy Thanksgiving

Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S

Director, National Institute of Environmental Health Sciences

and National Toxicology Program

phone: 919-541-3201

fax: 919-541-2260

e-mail: birnbaumls@niehs.nih.gov

On Nov 27, 2015, at 8:29 AM, Chris Portier <cportier@me.com> wrote:

> Sorry Linda, John, Tom and Tom, I sent you the wrong message. That was sent to NGOs and reporters who had heard about the letter and were pestering me. This is the email I meant to send which went to the Commissioner of Health for the EC.
> C.
>
> Begin forwarded message:
>
> **From:** Chris Portier <cportier@me.com>
> **Date:** November 27, 2015 at 9:56:57 AM GMT+1
> **To:** cab-andriukaitis-webpage@ec.europa.eu, Vytenis.ANDRIUKAITIS@ec.europa.eu
> **Cc:** Bernhard.Url@efsa.europa.eu, giovanni.lavia@europarl.europa.eu, leitung@bfr.bund.de, Director@iarc.fr, Jones.jim@Epa.gov, pesticides.ppr@efsa.europa.eu, phil.hogan@ec.europa.eu, Ladislav.MIKO@ec.europa.eu, poststelle@bmel.bund.de, poststelle@bvl.bund.de, helmut.tschiersky@bvl.bund.de
> **Subject: EFSA Glyphosate Recommendations**

Dear Commissioner Andriukaitis,
Attached to this email is a letter from 96 prominent epidemiologists, toxicologists, statisticians and molecular biologists from 25 countries. We have banded together and write to you at this time to express our deep concern over the recent European Food Safety Agency (EFSA) decision that the widely used herbicide, glyphosate "is unlikely to pose a carcinogenic hazard to humans." We ask that you read our letter and share it with those who will be advising you on accepting or rejecting EFSA's decision. We would greatly appreciate your sharing this with the members of the Standing Committee on Plants, Animals, Food and Feed before their next meeting on December 10, 2015. I will be in Brussels from November 30 to December 2. If you believe it would be helpful for me to discuss these concerns with you or your staff in person, please send email to this address or call +41 79 605 79 58.

Thank you for your attention to this important issue.

Sincerely,

Prof. Christopher J. Portier

cc: Mr. Phil Hogan, European Commissioner for Agriculture and Human Development

Dr. Ladislav Miko, Deputy Director-General, DG Health & Food Safety

Dr. Bernhard Url, Executive Director, EFSA

Dr. Giovanni La Via, Chair, ENVI Committee

EFSA Panel on Plant Protection Products and their Residues

Mr. Christian Schmidt, Minister of Food and Agriculture

Dr. Helmut Tschiersky, President of the Federal Office of Consumer Protection and Food Safety (BVL)

Professor Dr. Dr. Andreas Hensel, President, BFR

Dr. Christopher Wild, Director, IARC

Mr. Jim Jones, Assistant Administrator, USEPA

<EFSA-Glyphosate-Letter.pdf>

To: Chris Portier[cportier@me.com]
Cc: bucher@niehs.nih.gov[bucher@niehs.nih.gov]; Burke, Thomas[Burke.Thomas@epa.gov]; Sinks, Tom[Sinks.Tom@epa.gov]
From: Birnbaum, Linda (NIH/NIEHS) [E]
Sent: Fri 11/27/2015 3:28:49 PM
Subject: Re: EFSA Glyphosate Recommendations

did you see that EPA recently put a hold on their approval of the glyphosate/2,4-D formulation because of effects reported from Dow on non-target plants? at least it's some hold on the extensive use of this....

Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S

Director, National Institute of Environmental Health Sciences

and National Toxicology Program

phone: 919-541-3201

fax: 919-541-2260

e-mail: birnbaumls@niehs.nih.gov

On Nov 27, 2015, at 5:23 AM, Chris Portier <cportier@me.com> wrote:

> FYI. This went out this morning and is embargoed for public release until 0:00 CET on Monday.
> C.
>
> Begin forwarded message:
>
> **From:** Chris Portier <cportier@me.com>
> **Date:** November 27, 2015 at 10:25:35 AM GMT+1
> **To:** Andreas rummel <ak.rummel@t-online.de>, "Sass, Jennifer" <jsass@nrdc.org>, Angeliki Lysimachou <angeliki@pan-europe.info>, Meg Sears <meg@preventcancernow.ca>, Ann Doherty <amsterdamfarmer@xs4all.nl>, Martin Pigeon <martin@corporateeurope.org>, Stéphane Foucart <foucart@lemonde.fr>, Danny Hakim <hakim@nytimes.com>
> **Subject: EFSA Glyphosate Recommendations**
>
> Dear Addressees,
> You have expressed an interest in opinions I or my colleagues might wish to express

concerning the recent European Food Safety Agency (EFSA) decision that the widely used herbicide, glyphosate "is unlikely to pose a carcinogenic hazard to humans." Attached to this email is an open letter from 96 prominent epidemiologists, toxicologists, statisticians and molecular biologists from 25 countries. We have banded together and written a joint criticism of aspects of the EFSA review. Public release of this letter is **EMBARGOED**! Please do not release this letter before 0:00 CET, Monday 30 November, 2015. I will be happy to answer any questions you may have about the content of this letter; my contact information is on the letter. For those of you wishing to prepare newspaper articles or web articles on this letter and/or this issue, I have prepared three quotes from me that you are welcome to use. These are below.

Sincerely,

Prof. Christopher J. Portier

QUOTES:

"My reason for doing all of this work is quite simple, it does the science of risk assessment a disservice when carefully developed methods for analyzing and interpreting the evidence are put aside in favor of ad-hoc approaches that are either wrong, or not amenable to scrutiny by the broader scientific community.

For science to be effective in guiding public health decisions, there needs to be clarity, rigor, transparency, and common sense . The EFSA assessment has serious deficits in all of these areas.

Most importantly, to blindly assess the safety of pure glyphosate to which few people are exposed without considering the evidence on the glyphosate formulations that people are really exposed to is both scientifically flawed and makes little sense to the public."

<EFSA-Glyphosate-Letter.pdf>

To: Chris Portier[cportier@me.com]
From: Burke, Thomas
Sent: Fri 11/27/2015 3:14:50 PM
Subject: Re: EFSA Glyphosate Recommendations

Thanks Chris.

Thomas A. Burke, PhD, MPH
Deputy Assistant Administrator
EPA Science Advisor
Office of Research and Development
202-564-6620
burke.thomas@epa.gov

On Nov 27, 2015, at 7:23 AM, Chris Portier <cportier@me.com> wrote:

FYI. This went out this morning and is embargoed for public release until 0:00 CET on Monday.
C.

Begin forwarded message:

From: Chris Portier <cportier@me.com>
Date: November 27, 2015 at 10:25:35 AM GMT+1
To: Andreas rummel <ak.rummel@t-online.de>, "Sass, Jennifer" <jsass@nrdc.org>, Angeliki Lysimachou <angeliki@pan-europe.info>, Meg Sears <meg@preventcancernow.ca>, Ann Doherty <amsterdamfarmer@xs4all.nl>, Martin Pigeon <martin@corporateeurope.org>, Stéphane Foucart <foucart@lemonde.fr>, Danny Hakim <hakim@nytimes.com>
Subject: EFSA Glyphosate Recommendations

Dear Addressees,
You have expressed an interest in opinions I or my colleagues might wish to express concerning the recent European Food Safety Agency (EFSA) decision that the widely used herbicide, glyphosate "is unlikely to pose a carcinogenic hazard to humans." Attached to this email is an open letter from 96 prominent epidemiologists, toxicologists, statisticians and molecular biologists from 25 countries. We have banded together and written a joint criticism of aspects of the EFSA review. Public release of this letter is **EMBARGOED**! Please do not release this letter before 0:00 CET, Monday 30 November, 2015. I will be happy to answer any questions you may have about the content of this letter; my contact information is on the letter. For

those of you wishing to prepare newspaper articles or web articles on this letter and/or this issue, I have prepared three quotes from me that you are welcome to use. These are below.

Sincerely,

Prof. Christopher J. Portier

QUOTES:

"My reason for doing all of this work is quite simple, it does the science of risk assessment a disservice when carefully developed methods for analyzing and interpreting the evidence are put aside in favor of ad-hoc approaches that are either wrong, or not amenable to scrutiny by the broader scientific community.

For science to be effective in guiding public health decisions, there needs to be clarity, rigor, transparency, and common sense . The EFSA assessment has serious deficits in all of these areas.

Most importantly, to blindly assess the safety of pure glyphosate to which few people are exposed without considering the evidence on the glyphosate formulations that people are really exposed to is both scientifically flawed and makes little sense to the public."

<EFSA-Glyphosate-Letter.pdf>

To: Cogliano, Vincent[cogliano.vincent@epa.gov]
From: Kathryn Guyton
Sent: Mon 12/14/2015 2:49:54 PM
Subject: Re: Preliminary Agenda: EPA Systematic Review Workshop

Dear Vince,
I also wanted to let you know that Doug Weed was on Monsanto's glyphosate panel: http://www.monsanto.com/iarc-roundup/pages/2015-glyphosate-expert-panel.aspx ("Weed finds herbicide is safe"?). Monsanto has posted a brief bio covering other consultancies. Will all of this be disclosed to the Workshop participants?

Thanks,
Kate

From: Kate Guyton <guytonk@iarc.fr>
Date: Wednesday 2 December 2015 at 16:50
To: "Cogliano, Vincent" <cogliano.vincent@epa.gov>
Subject: FW: Preliminary Agenda: EPA Systematic Review Workshop

Dear Vince,

I hope you are well! I'm looking forward to the workshop on systematic review. Don't hesitate if there are any aspects or topics to emphasise. I'll be happy to share my slides in advance for comment.

You might find of interest that Doug Weed applied for Observer status for the v114 meeting, although the Beef Checkoff ultimately did not include him.

Best,
Kate

From: EPA_Sys-Review <EPA_Sys-Review@icfi.com>
Date: Monday 30 November 2015 at 21:21
To: EPA_Sys-Review <EPA_Sys-Review@icfi.com>
Subject: Preliminary Agenda: EPA Systematic Review Workshop

Dear Workshop Participant,

Attached please find the preliminary agenda for EPA's *Workshop on Advancing Systematic Review for Chemical Risk Assessment being held December 10–11, 2015 in Arlington, VA.*

***Non-federal** participants: please be sure to complete and return the COI and W9 forms*

as soon as possible. We are in the process of making your hotel reservations, but cannot do so until this is complete.

***Federal** participants: please advise if you would like for ICF to make a hotel reservation for you.*

Thank you,

The Systematic Review Workshop Team

EPA_Sys-Review@icfi.com

To: Cogliano, Vincent[cogliano.vincent@epa.gov]
Cc: Slimak, Michael[Slimak.Michael@epa.gov]; Ross, Mary[Ross.Mary@epa.gov]; Perovich, Gina[Perovich.Gina@epa.gov]; Jones, Samantha[Jones.Samantha@epa.gov]; D'Amico, Louis[DAmico.Louis@epa.gov]; Soto, Vicki[Soto.Vicki@epa.gov]; Shams, Dahnish[Shams.Dahnish@epa.gov]; Salazar, Keith[Salazar.Keith@epa.gov]; Fritz, Jason[Fritz.Jason@epa.gov]; Hotchkiss, Andrew[Hotchkiss.Andrew@epa.gov]
From: Kathryn Guyton
Sent: Fri 11/4/2016 12:42:01 PM
Subject: Re: Thank you from EPA's IRIS program

Dear Vince, Dear all,

Thank you for your message. It was my pleasure to participate in the meeting. I was especially impressed with the presentations from EPA, and look forward to seeing the ETBE draft move forward.

Please do pass along my kind regards to everyone.

Best from Lyon,
Kate

Kate Z. Guyton PhD DABT

Monographs Section

International Agency for Research on Cancer
150, cours Albert Thomas
69372 Lyon Cedex 08

France

From: "Cogliano, Vincent" <cogliano.vincent@epa.gov>
Date: Thursday, 3 November 2016 at 17:23
To: "jbus@exponent.com" <jbus@exponent.com>, "2940-shoji@kxb.biglobe.ne.jp" <2940-shoji@kxb.biglobe.ne.jp>, Kate Guyton <guytonk@iarc.fr>, "irusyn@cvm.tamu.edu" <irusyn@cvm.tamu.edu>, "bgollapudi@exponent.com" <bgollapudi@exponent.com>, "jswenber@email.unc.edu" <jswenber@email.unc.edu>, "vasilis.vasiliou@yale.edu" <vasilis.vasiliou@yale.edu>, "sborghoff@toxstrategies.com" <sborghoff@toxstrategies.com>, "malarkey@niehs.nih.gov" <malarkey@niehs.nih.gov>, "dale.strother@toxsolve.com" <dale.strother@toxsolve.com>, "kimberly_white@americanchemistry.com" <kimberly_white@americanchemistry.com>, "fu-nishimaki@pecj.or.jp" <fu-nishimaki@pecj.or.jp>, "marcy.banton@LYB.com" <marcy.banton@LYB.com>
Cc: "Slimak, Michael" <Slimak.Michael@epa.gov>, "Ross, Mary" <Ross.Mary@epa.gov>, "Perovich, Gina" <Perovich.Gina@epa.gov>, "Jones, Samantha" <Jones.Samantha@epa.gov>, "D'Amico, Louis" <DAmico.Louis@epa.gov>, "Soto, Vicki" <Soto.Vicki@epa.gov>, "Shams, Dahnish" <Shams.Dahnish@epa.gov>, "Salazar, Keith" <Salazar.Keith@epa.gov>, "Fritz, Jason" <Fritz.Jason@epa.gov>, "Hotchkiss, Andrew" <Hotchkiss.Andrew@epa.gov>, "RWassel@nas.edu" <RWassel@nas.edu>
Subject: Thank you from EPA's IRIS program

Dear Colleagues—Thank you for your contributions as a discussant during last week's IRIS Public Science Meeting on ethyl tert-butyl ether. Your experience and preparation contributed to the success of the meeting, which had more than 70 participants. We are pleased that the discussions focused on the science, covered multiple perspectives, and were informative and collegial.

The IRIS program appreciates and benefits from hearing the perspectives of expert scientists like yourself. Your contributions will help us as we move forward with this and other assessments.

On behalf of my colleagues in the IRIS program, thank you.

Vincent Cogliano

Program Director, Integrated Risk Information System (IRIS)

National Center for Environmental Assessment (8601P)

Office of Research and Development

U.S. Environmental Protection Agency

Washington DC 20460

tel 703-347-0220, fax 703-347-8689, http://www.epa.gov/iris/

courier delivery: 2777 S Crystal Dr, 11th floor, Arlington VA 22202

To: Johnson, Ron (NIH/NCI) [E[rjohnso2@mail.nih.gov]; John-F.Ryan@ec.europa.eu[John-F.Ryan@ec.europa.eu]; Karola.GRODZKI@ec.europa.eu[Karola.GRODZKI@ec.europa.eu]; Cogliano, Vincent[cogliano.vincent@epa.gov]; wolfe@niehs.nih.gov[wolfe@niehs.nih.gov]; 'lunn@niehs.nih.gov' (lunn@niehs.nih.gov)[lunn@niehs.nih.gov]; asamoabaaha@who.int[asamoabaaha@who.int]; chestnovo@who.int[chestnovo@who.int]; bustreof@who.int[bustreof@who.int]; fukudak@who.int[fukudak@who.int]; 'neiram@who.int' (neiram@who.int)[neiram@who.int]; vickersc@who.int[vickersc@who.int]; vandeventere@who.int[vandeventere@who.int]; 'ivanovi@who.int'[ivanovi@who.int]; tritschera@who.int[tritschera@who.int]; 'paunovice@ecehbonn.euro.who.int'[paunovice@ecehbonn.euro.who.int]; "gerard.lasfargues@anses.fr' (gerard.lasfargues@anses.fr)'[gerard.lasfargues@anses.fr]; Salma.ELREEDY@anses.fr[Salma.ELREEDY@anses.fr]; 'Saraiya, Mona (CDC/ONDIEH/NCCDPHP'[yzs2@cdc.gov]; 'Min Kyung Lim'[mickey@ncc.re.kr]; lfrpinto@inca.gov.br[lfrpinto@inca.gov.br]; 'silvia.cazenave@anvisa.gov.br'[silvia.cazenave@anvisa.gov.br]; lucas.sversut@itamaraty.gov.br[lucas.sversut@itamaraty.gov.br]
From: IARC Monograph 119
Sent: Tue 10/18/2016 2:43:38 PM
Subject: Official Invitation: IARC Monographs Vol. 119: Some Chemicals in Food and Consumer Products, Lyon, France, 6-13 June 2017
Timetable_119.doc
Hotel description and directions.doc
Hotel and travel form REPS 119.doc
vol119-doi.pdf
119-Confidentiality_Undertaking.pdf
CodeofConduct.pdf

Official invitation

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans
Volume 119: Some Chemicals in Food and Consumer Products

IARC, Lyon, France, 6-13 June 2017

Dear Colleagues,

In June 2017, the International Agency for Research on Cancer will convene a Working Group to develop Volume 119 of the *IARC Monographs* on the above-mentioned subject.

We have the pleasure of inviting you or a colleague of yours to attend the meeting as a Representative of your agency.

Attached please find the preliminary agenda. Further information can be found at http://monographs.iarc.fr/ENG/Meetings/index.php. The list of participants will be posted there a couple of months before the meeting.

Although we are not in a position to cover your travel and living expenses, we would be pleased to make a hotel reservation for you. We have reserved a block of rooms for the participants.

Attached are a description of the hotels and a hotel reservation form which we kindly ask you to return by 6 April 2017.

All participants at meetings convened by the World Health Organization, of which IARC is a part, are asked to complete the attached Declaration of Interests and Confidentiality Undertaking forms. Attached please also find a Code of Conduct document. **If you plan to attend, please return your completed and signed Declaration of Interests and Confidentiality Undertaking forms.**

Please feel free to call us (tel. Yann Grosse +33-4-72.73.86.56; Kurt Straif: +33-4-72.73.85.07) if you have any suggestions or questions. We look forward to receiving your reservation form, Declaration and Confidentiality Undertaking (by email to monograph119@iarc.fr or by fax to +33-4-72.73.83.19) and to welcoming you to Lyon.

Yours sincerely,

Dr Yann Grosse (Responsible Officer)
Dr Kurt Straif (Head of Section)

IARC Monographs Section

International Agency for Research on Cancer
150, Cours Albert Thomas
F-69372 Lyon cedex 08, France
Tel: 33-4-72.73.86.56
Fax: 33-4-72.73.83.19

E-mail : monograph119@iarc.fr

International Agency for Research on Cancer

World Health Organization

CONFIDENTIALITY UNDERTAKING

1. The International Agency for Research on Cancer (IARC), World Health Organization (WHO), acting through its Section of IARC Monographs, has access to certain information and documentation relating to evaluation of carcinogenic risks of some chemicals in food and consumer products to humans, information and documentation (in whatever format) which IARC/WHO considers to be proprietary to itself or to parties collaborating with it (hereinafter referred to as "the Information").

2. The Undersigned, as a member of the following advisory meeting, group or committee: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans - Volume 119, Some Chemicals in Food and Consumer Products (collectively referred to as the "the Advisory Process"), may have access to the Information in the course of his/her participation in the Advisory Process (whether at or in relation to Advisory Process meetings, internet-based collaborative workspaces, telephone conferences or otherwise).

3. IARC/WHO is willing to provide the Undersigned the Information, or arrange for the provision of the Information to the Undersigned, for the exclusive purpose of performing his/her responsibilities in connection with the activities of the Advisory Process ("the Purpose"), provided that the Undersigned undertakes to treat the Information as confidential and proprietary, and to disclose it only to persons who have a need to know for the Purpose and are bound by like obligations of confidentiality and non-use as are contained in this Undertaking.

4. The Undersigned undertakes to regard the Information as confidential and proprietary to IARC/WHO or parties collaborating with IARC/WHO and agrees to take all reasonable measures to ensure that the Information is not used, disclosed or copied, in whole or in part, other than as provided in this Undertaking, except that the Undersigned shall not be bound by any such obligations if and to the extent he/she is clearly able to demonstrate that the Information:

   a) was known to him/her prior to any disclosure by or for IARC/WHO to the Undersigned; or
   b) was in the public domain at the time of disclosure by or for IARC/WHO to the Undersigned; or
   c) becomes part of the public domain through no fault of the Undersigned; or
   d) becomes available to the Undersigned from a third party not in breach of any legal obligations of confidentiality.

5. If requested to do so, the Undersigned agrees to return to IARC/WHO any and all copies of the Information.

6. The Undersigned also undertakes to exercise the utmost discretion in all matters relating to the Advisory Process and not to communicate the deliberations and decisions of the Advisory Process to third parties except as agreed by IARC/WHO.

7. The Undersigned shall respect the impartiality and independence required of IARC/WHO. In this regard, the Undersigned shall not seek or accept instructions in relation to his/her work within the Advisory Process from any Government or from any authority external to IARC/WHO.

8. The Undersigned agrees that any and all rights in the work performed by him/her in connection with, or as a result of, his/her participation in the Advisory Process shall be exclusively vested in IARC/WHO; the Undersigned hereby irrevocably and unconditionally assigns all such rights to IARC/WHO and waives any moral rights attached to such work. IARC/WHO reserves the right (a) to revise such work, (b) to use it in a different manner from that originally envisaged, or (c) not to use or publish it at all.

9. The obligations of the Undersigned shall survive the termination of his/her membership in the Advisory Process.

10. Any dispute relating to the interpretation or application of this Undertaking shall, unless amicably settled, be subject to a conciliation. In the event of failure of the latter, the dispute shall be settled by arbitration. The arbitration shall be conducted in accordance with the modalities to be agreed upon by the parties or, in the absence of agreement, with the UNCITRAL rules of arbitration. The parties shall accept the arbitral award as final.

Name: _____ Signature: _____ Date: _____

Code of Conduct for IARC/WHO Experts

IARC/WHO values and relies upon the normative and technical advice that is provided by leading subject matter experts in the context of its advisory/technical committees, meetings and other similar processes. Such advice contributes to the formulation of public health policies and norms that are promulgated by IARC/WHO for the benefit of Participating/Member States.

In order to ensure the integrity of such processes, thereby contributing to their credibility in the eyes of IARC/WHO's stakeholders, it is critical that experts appointed by IARC/WHO to render technical or normative advice:

a. fully and honestly disclose all relevant interests and biases on the DOI Form that may give rise to real or perceived conflicts of interest; such disclosure must also be made orally to all fellow expert committee, meeting or group members at the outset i.e. unless this is done by the Chairperson or Secretariat;

b. spontaneously report any material changes to their disclosed interest on an on-going basis during the period in which the expert serves IARC/WHO;

c. respect the confidential nature of committee or meeting deliberations or of the advisory function assigned by IARC/WHO and not make any public statements regarding the work of the committee or meeting or regarding the expert's advice without prior consent from IARC/WHO;

d. undertake not to engage in activities that may bring reputational harm to the I A R C / WHO process that they are involved in;

e. undertake to represent their views in a personal and individual capacity with the best interest of IARC/WHO in mind as opposed to representing the views of their employers, other institutions or governments;

f. actively and fully participate in discussions and deliberations within the relevant advisory group, committee or meeting.

Hotel and travel form

IARC Monographs – Volume 119
Lyon, 6-13 June 2017

First and last name, as to appear on badge:

Date of arrival in Lyon:

Date of departure from Lyon:

HOTEL

|__| Please book a single |__| or double |__| room for me at:

- Cercle Villemanzy |__|
- Hotel La Résidence |__|
- Hotel des Artistes |__| shower |__| bath |__|

|__| I prefer to make my own accommodation arrangements

Please complete and return this form by 6 April 2017 to monograph119@iarc.fr or by fax: *+33-4-72.73.83.19.*

DETAILS ON A FEW HOTELS IN LYON AND ON HOW TO REACH THE IARC

The **Hôtel La Résidence** *** (18 rue Victor Hugo, 69002 Lyon, tel.:+ 33.478.42.63.28; fax: +33.478.42.85.76, e-mail: hotel-la-residence@wanadoo.fr; www.hotel-la-residence.com) is on a pedestrian street in the centre of Lyon, very convenient to the Place Bellecour metro station and Perrache railway station. The hotel has free wifi access throughout the hotel. IARC is given both single and double rooms at the current special rate of **88 €** per night; **breakfast 8 €**.

The **Hôtel des Artistes** *** (8 rue Gaspard André, 69002 Lyon, tel. : +33.478.42.04.88; fax: +33.478.42.93.76, e-mail: hartiste@club-internet.fr; www.hoteldesartistes.fr) is a charming hotel, typically French, recently renovated, on a quiet square, also located in the city centre near Place Bellecour, and is of a higher standard than La Résidence. It has free wifi access throughout the hotel. Rooms at the IARC rate are currently priced between **119 € and 129.60 €** per night (15 € off the price on Friday and Saturday, 25 % off on Sunday); **breakfast 13.5 €**. Please note that cancellations less than 48 hours in advance will be charged.

The **Cercle Villemanzy** *** (21 montée Saint-Sébastien, 69001 Lyon, tel. +33.472.00.19.00; fax +33.472.00.19.99; residence.villemanzy@belambra.fr). This recently renovated residence is a former 13th century convent located on a steep hill near the town centre with an exceptional view of the city. The rooms are reasonably priced, and are equipped with a kitchenette. Wifi access in the rooms is payable but there is free access to a fitness room. Rooms are cleaned weekly. Studios cost from **74 €** per night; **breakfast 9 €**. A credit card number is required for reservations and cancellations less than 48 h in advance will be charged.

Directions from Lyon St Exupéry airport

to the IARC:

Take the airport tramway, i.e. the 'Rhônexpress' at the TGV train terminal. The tram leaves every 30 minutes from 5 AM to 6 AM as well as from 9 PM to midnight and every 15 minutes from 6 AM to 9 PM, and costs 15.90 € for a single ticket and 27.50 € for a return ticket. If you buy them on-line, it is a bit cheaper. Tickets can also be bought at the station or in the tram by cash or credit card. Euros can be obtained at machines at the airport: we advise you to take an odd amount (e.g., 40 or 90 €) as many merchants will not accept large notes. For more information on the Rhônexpress, please see http://www.rhonexpress.fr/. Get off at the *'Vaulx-en Velin – La Soie'* station, then take the metro line A in the direction of *'Perrache'* and at the *'Bellecour'* station change to line D in the direction of *'Gare de Vénissieux'*. Get off at the *'Grange Blanche'* stop and walk one block down Cours Albert Thomas to the IARC. Alternatively, get off the tram at *'Part-Dieu'*, walk across the Part Dieu station and take bus No 28 in the direction of *'Laurent Bonneway'*, get off at *'Grange Blanche'*.

***to** La Résidence **and** Les Artistes*

Get off the tram at the *'Vaulx-en Velin – La Soie'* station, take the metro line A in the direction of *'Perrache'* and get off at the *'Bellecour'* station for the Hôtel des Artistes and at *'Ampère'* for the Hôtel La Résidence, then walk to your hotel.

***to** Villemanzy:* Take the tram to *'Part-Dieu'* and then a taxi to the Cercle Villemanzy.

To reach the IARC

From the **Villemanzy** to the IARC, take the metro (line C) from *'Croix-Paquet'* station (or walk) to *'Hôtel de Ville'*, then take line A and in the direction of *'Perrache'*. At *'Bellecour'*, take line D on the lower level, direction *'Gare de Vénissieux'*, to *'Grange Blanche'*.

The **Hôtel La Résidence** and the **Hôtel des Artistes** are within walking distance of Place Bellecour, where you can take the line D metro on the lower level, direction *'Gare de Vénissieux'*, to *'Grange Blanche'*.

At the *Grange Blanche* metro, walk towards the back of the train and take exit (*'sortie'*) 3. At the top of the steps, walk to the right of McDonald's and continue a block and a half to the IARC tower (the tall bluish-gray building).

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans
VOLUME 119
IARC, Lyon, 6-13 June 2017

MEETING TIMETABLE

Monday, 5 June

15h30 – 17h00	Planning meeting – Meeting Chairs and subgroup Chairs only (rm 101, 1st floor)

Tuesday, 6 June

09h00 – 09h30	Registration (Lobby)
09h30 – 10h30	Opening session: Director's welcome, introductions, programme overview
10h30 – 11h00	Group photo (Lobby, followed by coffee break)
11h00 – 13h00	Subgroup sessions
14h00 – 16h00	Subgroup sessions
16h00 – 16h30	Payment of *per diem* & dinner reservation (Lobby, during coffee break)
16h30 – 17h45	Subgroup sessions
17h45 –	Cocktail reception for participants and their guests (12th floor)
18h15 – 19h00	Co-ordination meeting for the Co-chairs and subgroup Chairs (1st floor)

Wednesday, 7 June

09h00 – 09h30	Plenary session: Evaluation criteria
09h30 – 13h00	Subgroup sessions
14h00 – 18h00	Subgroup sessions
18h00 – 19h00	Co-ordination meeting for the Co-chairs and subgroup Chairs (1st floor)

Thursday, 8 June

09h00 – 09h10	Plenary session: Progress report
09h10 – 13h00	Subgroup sessions
14h00 – 15h45	Subgroup sessions
16h15 – 18h00	Subgroup sessions
18h00 – 19h00	Co-ordination meeting for the Co-chairs and subgroup Chairs (1st floor)

Friday, 9 June

09h00 – 09h10	Plenary session: Progress report
09h10 – 13h00	Subgroup sessions
14h00 – 15h45	Subgroup sessions
16h15 – 18h00	Plenary session: Overview discussion
18h00 – 19h00	Co-ordination meeting for the Co-chairs and subgroup Chairs (1st floor)

Saturday, 10 June

09h00 – 10h30	Subgroup sessions
11h00 – 15h30	Plenary session
20h00	Group dinner for participants and their guests

Monday, 12 June

09h00 – 13h00	Plenary session
14h00 – 18h00	Plenary session

Tuesday, 13 June

09h00 – 13h00	Plenary session
14h00 – 18h00	Plenary session
18h00	Adjourn

Lunch will be served on the 12th floor each day at 13h00 (lunchbox at 12h30 on Saturday).
Coffee will be served in the lobby each day at 10h30 and 15h45 (16h00 on the first day)

DECLARATION OF INTERESTS FOR IARC/WHO EXPERTS

IARC/WHO's work on global health issues requires the assistance of external experts who **may have interests related to their expertise.** To ensure the highest integrity and public confidence in its activities, IARC/WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to a potential conflict of interest related to the subject of the activity in which they will be involved.

All experts serving in an advisory role must disclose any circumstances that could represent a **potential conflict of interest** (i.e. any interest that may affect, or may reasonably be perceived to affect, the expert's objectivity and independence). You must disclose on this Declaration of Interest (DOI) form any financial, professional or other interest relevant to the subject of the work or meeting in which you have been asked to participate in or contribute towards and any interest that could be affected by the outcome of the meeting or work. You must also declare relevant interests of your immediate family members (see definition below) and, if you are aware of it, relevant interests of other parties with whom you have substantial common interests and which may be perceived as unduly influencing your judgement (e.g. employer, close professional associates, administrative unit or department).

Please complete this form and submit it to IARC/WHO Secretariat if possible at least 4 weeks but no later than 2 weeks before the meeting or work. You must also promptly inform the Secretariat if there is any change in this information prior to, or during the course of, the meeting or work. All experts must complete this form before participation in a IARC/WHO activity can be confirmed.

Answering "Yes" to a question on this form does not automatically disqualify you or limit your participation in a IARC/WHO activity. Your answers will be reviewed by the Secretariat to determine whether you have a conflict of interest relevant to the subject at hand. One of the outcomes listed in the next paragraph can occur depending on the circumstances (e.g. nature and magnitude of the interest, timeframe and duration of the interest).

The Secretariat may conclude that no potential conflict exists or that the interest is irrelevant or insignificant. If, however, a declared interest is determined to be potentially or clearly significant, one or more of the following three measures for managing the conflict of interest may be applied. The Secretariat (i) allows full participation, with public disclosure of your interest; (ii) mandates partial exclusion (i.e. you will be excluded from that portion of the meeting or work related to the declared interest and from the corresponding decision making process); or (iii) mandates total exclusion (i.e. you will not be able to participate in any part of the meeting or work).

All potentially significant interests will be **disclosed** to the other participants at the start of the activity and you will be asked if there have been any changes. A summary of all declarations and actions taken to manage any declared interests will be **published** in resulting reports and work products. Furthermore, if the objectivity of the work or meeting in which you are involved is subsequently questioned, the contents of your DOI form may be made available by the Secretariat to persons outside IARC/WHO if the Director/Director-General considers such disclosure to be in the best interest of the Organization, after consulting with you. Completing this DOI form means that you agree to these conditions.

If you are unable or unwilling to disclose the details of an interest that may pose a real or perceived conflict, you must disclose that a conflict of interest may exist and the Secretariat may decide that you be totally recused from the meeting or work concerned, after consulting with you.

Name:	
Institution:	
Email:	

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans
Volume 119: Some Chemicals in Food and Consumer Products
Lyon, France: 6–13 June 2017

Please answer each of the questions below. If the answer to any of the questions is "yes", briefly describe the circumstances on the last page of the form.

The term "you" refers to yourself and your immediate family members (i.e. spouse (or partner with whom you have a similar close personal relationship) and your children). "Commercial entity" includes any commercial business, an industry association, research institution or other enterprise whose funding is significantly derived from commercial sources with an interest related to the subject of the meeting or work. "Organization" includes a governmental, international or non-profit organization. "Meeting" includes a series or cycle of meetings.

EMPLOYMENT AND CONSULTING

Within the past 4 years, have you received remuneration from a commercial entity or other organization with an interest related to the subject of the meeting or work?

1a Employment Yes ☐ No ☐

1b Consulting, including service as a technical or other advisor Yes ☐ No ☐

RESEARCH SUPPORT

Within the past 4 years, have you or has your research unit received support from a commercial entity or other organization with an interest related to the subject of the meeting or work?

2a Research support, including grants, collaborations, sponsorships, and other funding Yes ☐ No ☐

2b Non-monetary support valued at more than US $1000 overall (include equipment, facilities, research assistants, paid travel to meetings, etc.) Yes ☐ No ☐

2c Support (including honoraria) for being on a speakers bureau, providing speeches or training for a commercial entity or other organization with an interest related to the subject of the meeting or work? Yes ☐ No ☐

INVESTMENT INTERESTS

Do you have current investments (valued at more than US $1000) in a commercial entity with an interest related to the subject of the meeting or work?

Please also include indirect investments such as a trust or holding company. You may exclude mutual funds, pension funds or similar investments that are broadly diversified and on which you exercise no control.

3a Stocks, bonds, stock options, other securities (e.g. short sales) Yes ☐ No ☐

3b Commercial business interests (e.g. proprietorships, partnerships, joint ventures, board memberships, controlling interest in a company) Yes ☐ No ☐

INTELLECTUAL PROPERTY

Do you have any intellectual property rights that might be enhanced or diminished by the outcome of the meeting or work?

4a Patents, trademarks, or copyrights (including pending applications) Yes ☐ No ☐

4b Proprietary know-how in a substance, technology or process Yes ☐ No ☐

PUBLIC STATEMENTS AND POSITIONS (during the past 3 years)

5a As part of a regulatory, legislative or judicial process, have you provided an expert opinion or testimony, related to the subject of the meeting or work, for a commercial entity or other organization? Yes ☐ No ☐

5b Have you held an office or other position, paid or unpaid, where you represented interests or defended a position related to the subject of the meeting or work? Yes ☐ No ☐

ADDITIONAL INFORMATION

6a If not already disclosed above, have you worked for the competitor of a product that is the subject of the meeting or work, or will your participation in the meeting or work enable you to obtain access to a competitor's confidential proprietary information, or create for you a personal, professional, financial or business competitive advantage? Yes ☐ No ☐

6b To your knowledge, would the outcome of the meeting or work benefit or adversely affect interests of others with whom you have substantial common personal, professional, financial or business interests (such as your adult children or siblings, close professional colleagues, administrative unit or department)? Yes ☐ No ☐

6c Excluding IARC/WHO, has any person or entity paid or contributed towards your travel costs in connection with this IARC/WHO meeting or work? Yes ☐ No ☐

6d Have you received any payments (other than for travel costs) or honoraria for speaking publicly on the subject of this IARC/WHO meeting or work? Yes ☐ No ☐

6e Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence? Yes ☐ No ☐

7 **TOBACCO OR TOBACCO PRODUCTS** *(answer without regard to relevance to the subject of the meeting or work)*
Within the past 4 years, have you had employment or received research support or other funding from, or had any other professional relationship with, an entity directly involved in the production, manufacture, distribution or sale of tobacco or tobacco products or representing the interests of any such entity? Yes ☐ No ☐

EXPLANATION OF "YES" RESPONSES: If the answer to any of the above questions is **"yes", check above and briefly describe the circumstances on this page. If you do not describe the nature of an interest or if you do not provide the amount or value involved where relevant, the conflict will be assumed to be significant.**

Nos. 1-4, 7: Type of interest, question number and category (e.g. Intellectual Property 4.a copyrights) and basic descriptive details	**Name of company, organization, or institution**	**Belongs to you, a family member, employer, research unit or other?**	**Amount of income or value of interest (if not disclosed, is assumed to be significant)**	**Current interest (or year ceased)**
Nos. 5-6: Describe the subject, specific circumstances, parties involved, time frame and other relevant details.				

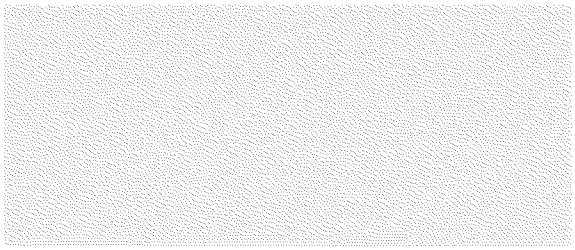
CONSENT TO DISCLOSURE. By completing and signing this form, you consent to the disclosure of any relevant conflicts to other meeting participants and in the resulting report or work product.

DECLARATION. I hereby declare on my honour that the disclosed information is true and complete to the best of my knowledge.

Should there be any change to the above information, I will promptly notify the responsible staff of IARC/WHO and complete a new declaration of interests form that describes the changes. This includes any change that occurs before or during the meeting or work itself and through the period up to the publication of the final results or completion of the activity concerned.

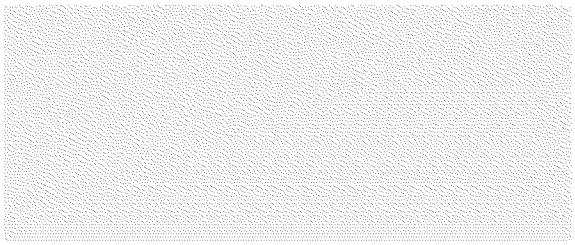
Date:

Signature:



Date:
(to be signed again at the meeting)

Signature:



To: Cogliano, Vincent[cogliano.vincent@epa.gov]; Kurt Straif[StraifK@iarc.fr]
Cc: Sylvia Lesage[LesageS@iarc.fr]; Karen Muller[MullerK@iarc.fr]
From: Robert Baan
Sent: Thur 9/22/2016 10:43:55 AM
Subject: Consensus Statement
Consensus Statement REV 5.docx
Consensus Statement REV 5a.docx

Dear all,

Please find attached two versions of the 'Consensus Statement' for the Scientific Publication, one with, and one without authors' names (see lines 1-4). Kurt suggested that we may present this Statement anonymously (as was done for the Consensus Report in, e.g., SciPub 147). In that case, I guess we can do without the EPA Disclaimer.

Of course, we highly appreciate Vincent's work as lead author of the initial version of this document.

Let me know your thoughts.

Robert

CONSENSUS STATEMENT

Vincent J Cogliano*, Robert A Baan, Kurt Straif

This statement is unanimously endorsed by participants[1] in the IARC Workshop on 'Tumour-site Concordance and Mechanisms of Carcinogenesis', held April/November 2012 in Lyon

Introduction

The *IARC Monographs Programme* is an international consensus approach to the identification of chemicals and other agents that may present carcinogenic hazards to humans. The *Monographs* assess the strength of the published scientific evidence for such identifications, which are based primarily on epidemiological studies of cancer in humans and bioassays for carcinogenicity in laboratory animals. Information that may be relevant to the mechanisms by which the putative carcinogen acts is also considered in making an overall evaluation of the strength of the total evidence for carcinogenicity to humans.

The use of mechanistic data to identify human carcinogens is accelerating. Initially, the *IARC Monographs* required *sufficient evidence* in humans to classify an agent as *carcinogenic to humans*. Scientific understanding of the mechanisms of carcinogenesis, accompanied by the development of assays for studying mechanistic events, has led to new ways of identifying human carcinogens. As examples, ethylene oxide was classified as *carcinogenic to humans* in 1994 based on strong evidence of genotoxicity and limited epidemiological evidence in exposed humans, 2,3,7,8-tetrachlorodibenzo-*para*-dioxin in 1997 based on strong evidence of binding to the aryl hydrocarbon receptor and subsequent events, neutron radiation in 2000 based on the underlying radiation physics, benzidine-based dyes in 2010 because these substances are metabolized to a carcinogen in humans, and several compounds for which single-agent exposure does not exist because they are components of (complex) mixtures, e.g., tobacco-specific nitrosamines in 2007, benzo[*a*]pyrene in 2010, and aristolochic acid and etoposide in 2012. Mechanistic evidence was also important in classifying the carcinogenicity of a number of other agents between 2004 and 2010, and in revising the classification of carcinogenicity for several additional agents in Volume 100.

For the one hundredth volume of the *IARC Monographs*, a review was undertaken during 2008–2009 of all Group-1 human carcinogens previously identified in Volumes 1–99. There was value in a comprehensive review, as about half the human carcinogens had been last reviewed more than 20 years earlier. *Monograph* Volume 100 was organized in six parts covering

[1] L Banks, FA Beland, JA Bond, MC Bosland, JR Bucher, JC Caldwell*, DM DeMarini*, B Fubini, BD Goldstein, SS Hecht, K Hemminki, MA Hill, CW Jameson, AB Kane, RJ Kavlock*, D Krewski, PF Lambert, R Melnick, CJ Portier, JM Rice, I Rusyn, MT Smith, L Stayner, BW Stewart, RL Ullrich, H Vainio, P Vineis, MP Waalkes, L Zeise

Pharmaceuticals (Vol 100A), *Biological Agents* (Vol 100B), *Arsenic, Metals, Fibres, and Dusts* (Vol 100C), *Radiation* (Vol 100D), *Personal Habits and Indoor Combustions* (Vol 100E), and *Chemical Agents and Related Occupations* (Vol 100F). Volume 100 'A Review of Human Carcinogens' was published as a six-part book series in 2012.

IARC explored ways to strengthen the scientific value of Volume 100 by embarking on a review of the Group-1 human carcinogens with respect to cancer sites and mechanistic events, followed by supplementary analyses of cancer-site concordance between humans and experimental animals, and of mechanistic events deemed relevant to the carcinogenicity of these agents. Accordingly, this Scientific Publication on 'Tumour-site Concordance and Mechanisms of Carcinogenesis' was proposed.

To prepare for the supplementary analyses in this Scientific Publication, IARC had asked the six Working Groups for Volume 100 to collect additional information, not routinely developed before, (a) on cancer sites in humans for which there was *sufficient evidence* or *limited evidence* in epidemiological studies, (b) on cancer sites with *sufficient evidence* in experimental animals, and (c) on established and likely mechanisms involved in the cancers observed in humans or experimental animals.

To further develop this Scientific Publication, the *IARC Monographs Programme* convened a group of international scientific experts in a two-part Workshop, held in Lyon in April and November 2012. The Workshop participants used the lists of mechanistic events to develop a set of Key Characteristics to define the mechanistic profile of the Group-1 carcinogens.

The main points of consensus, the conclusions and the recommendations of the Workshop participants are described below.

Tumour-site concordance

1. The results developed in *IARC Monograph* Volume 100 confirm that the induction of cancer in experimental animals is relevant to the identification of a carcinogenic hazard to humans: all human carcinogens identified to date that have been adequately tested in animals have also been shown to cause cancer in animals.

2. For many human carcinogens, there is tumour-site concordance between humans and experimental animals; for many others, there is not. At the present time, the state-of-the-science does not support tumour-site concordance as a general principle. For example, there are four agents that show *sufficient evidence* of breast cancer in humans, seven provide *sufficient evidence* of breast cancer in experimental animals, but only one among these causes breast cancer in both humans and animals.

3. The analyses presented in this Scientific Publication are expected to underestimate concordance. One reason is the limited power and other limitations of many observational epidemiological studies that include populations and cancer sites that have not been adequately investigated. Another reason is that – for the purpose of this concordance analysis – an agent was considered to cause cancer at a site in animals only if positive results were replicated at the same specific site in another animal experiment (at the same time recognizing the concern of a single positive cancer bioassay); however, metabolic or mechanistic considerations might explain tumour induction at different sites in separate animal models.

4. Descriptive statistics of tumour sites identified to date may not be representative of future evaluations or of the incompletely characterized 'universe of human carcinogens.' The carcinogens evaluated in Volume 100 include several classes of agents that have been relatively straightforward to investigate, for example, alkylating agents used in early cancer chemotherapy, viral agents that infect hundreds of millions of people, ionizing radiation that affects multiple anatomical sites, widespread exposures such as tobacco and alcohol, and chemical agents with long histories of occupational exposure at high levels. Agents evaluated in the future may have more subtle effects and different characteristics. Evidence from sources other than human epidemiology will need to be relied upon to determine human cancer hazards.

5. Past evaluations have noted cancer in experimental animals at approximately 40 tumour sites in 15 organ and tissue systems. Use of standard terminology for these sites can facilitate the development of databases and their analysis and linkage to other sources of information. The Workshop participants recommend that future *IARC Monographs* Working Groups consider the anatomically-based taxonomy of tumour sites that appears in this Scientific Publication in the analysis of concordance between sites where animal and human tumours arise.

6. The Workshop participants also recommend that the Evaluation section for 'evidence in experimental animals' in future *IARC Monographs* be expanded to include additional information for agents evaluated as exhibiting *sufficient evidence*. For such agents, an additional sentence following the relevant evaluation should refer to the recognized site(s) of tumorigenesis, by use of the specification system described in the chapter on Concordance (Krewski et al., this Volume).

Mechanisms involved in human carcinogenesis

7. With increasing scientific understanding and availability of information on mechanisms of carcinogenesis, we expect that the *IARC Monographs* will make even greater use of mechanistic data in identifying human carcinogens.

8. Up until now, there has been no generally accepted method for organizing mechanistic data pertinent to the identification of carcinogenic hazards to humans. The Key Characteristics presented here offer a promising foundation for the structured evaluation of mechanistic information, and this should increase the utility of mechanistic evidence in future identifications of carcinogenic hazards and the transparency of systematic reviews of such evidence. The Workshop participants recommend that the *IARC Monographs Programme* use the Key Characteristics in its evaluations of carcinogenicity.

9. It is notable that in-vivo or in-vitro mechanistic data are often available in humans. In most cases, when animal data are available for a Key Characteristic, human data for that characteristic are generally available, too. This supports the notion that carcinogens show their characteristics across species.

10. There should be no expectation that all, or even most, Key Characteristics operate for any human carcinogen. No Key Characteristic is necessary for carcinogenesis, and negative results for one or more Key Characteristics are not an argument against the potential carcinogenicity of an agent. Observation of one or more Key Characteristics in exposed humans can increase the biological plausibility of less-than-*sufficient evidence* in humans. Observation of one or more Key Characteristics in experimental animals can increase confidence in the human relevance of less-than-*sufficient evidence* in experimental animals. In interpreting the biological relevance of information pertaining to the Key Characteristics, it is important to consider aspects of metabolism and kinetics in extrapolating between in-vitro and in-vivo systems.

11. A human carcinogen may act through multiple mechanisms that may interact with each other. Past practice of according greatest concern to those agents demonstrated to be genotoxic, relative to agents whose carcinogenicity is mediated by some other mechanism, possibly involving specific receptors, appears to be overly simplistic.

12. The objective of the *IARC Monographs Programme* is to identify carcinogenic hazards, not to

exhaustively list all mechanistic events and pathways that might contribute to carcinogenesis. Future coverage of mechanistic data should increase as the retrieval of such data becomes more systematic and the Key Characteristics are used as a framework for organization and analysis of mechanistic data.

13. Descriptive statistics of mechanisms identified to date may not be representative of future evaluations. Although genotoxicity is the Key Characteristic most exhibited by the human carcinogens identified to date, this may reflect the relatively greater attention paid in the past to the investigation of genotoxic agents. Future evaluations of carcinogenic agents may involve a larger set of mechanistic events and pathways that are not yet well developed or understood. Accordingly, future shifts in the distribution of the Key Characteristics are to be expected. This does not detract from the value in using these Characteristics now in evaluations of carcinogenic hazards.

**Disclaimer*: The views expressed in this document are those of these authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

CONSENSUS STATEMENT

Endorsed unanimously by the participants in the IARC Workshop on 'Tumour-site Concordance and Mechanisms of Carcinogenesis', held April/November 2012 in Lyon

Introduction

The *IARC Monographs Programme* is an international consensus approach to the identification of chemicals and other agents that may present carcinogenic hazards to humans. The *Monographs* assess the strength of the published scientific evidence for such identifications, which are based primarily on epidemiological studies of cancer in humans and bioassays for carcinogenicity in laboratory animals. Information that may be relevant to the mechanisms by which the putative carcinogen acts is also considered in making an overall evaluation of the strength of the total evidence for carcinogenicity to humans.

The use of mechanistic data to identify human carcinogens is accelerating. Initially, the *IARC Monographs* required *sufficient evidence* in humans to classify an agent as *carcinogenic to humans*. Scientific understanding of the mechanisms of carcinogenesis, accompanied by the development of assays for studying mechanistic events, has led to new ways of identifying human carcinogens. As examples, ethylene oxide was classified as *carcinogenic to humans* in 1994 based on strong evidence of genotoxicity and limited epidemiological evidence in exposed humans, 2,3,7,8-tetrachlorodibenzo-*para*-dioxin in 1997 based on strong evidence of binding to the aryl hydrocarbon receptor and subsequent events, neutron radiation in 2000 based on the underlying radiation physics, benzidine-based dyes in 2010 because these substances are metabolized to a carcinogen in humans, and several compounds for which single-agent exposure does not exist because they are components of (complex) mixtures, e.g., tobacco-specific nitrosamines in 2007, benzo[*a*]pyrene in 2010, and aristolochic acid and etoposide in 2012. Mechanistic evidence was also important in classifying the carcinogenicity of a number of other agents between 2004 and 2010, and in revising the classification of carcinogenicity for several additional agents in Volume 100.

For the one hundredth volume of the *IARC Monographs*, a review was undertaken during 2008–2009 of all Group-1 human carcinogens previously identified in Volumes 1–99. There was value in a comprehensive review, as about half the human carcinogens had been last reviewed more than 20 years earlier. *Monograph* Volume 100 was organized in six parts covering *Pharmaceuticals* (Vol 100A), *Biological Agents* (Vol 100B), *Arsenic, Metals, Fibres, and Dusts* (Vol 100C), *Radiation* (Vol 100D), *Personal Habits and Indoor Combustions* (Vol 100E), and *Chemical Agents and Related Occupations* (Vol 100F). Volume 100 'A Review of Human Carcinogens' was

published as a six-part book series in 2012.

IARC explored ways to strengthen the scientific value of Volume 100 by embarking on a review of the Group-1 human carcinogens with respect to cancer sites and mechanistic events, followed by supplementary analyses of cancer-site concordance between humans and experimental animals, and of mechanistic events deemed relevant to the carcinogenicity of these agents. Accordingly, this Scientific Publication on 'Tumour-site Concordance and Mechanisms of Carcinogenesis' was proposed.

To prepare for the supplementary analyses in this Scientific Publication, IARC had asked the six Working Groups for Volume 100 to collect additional information, not routinely developed before, (a) on cancer sites in humans for which there was *sufficient evidence* or *limited evidence* in epidemiological studies, (b) on cancer sites with *sufficient evidence* in experimental animals, and (c) on established and likely mechanisms involved in the cancers observed in humans or experimental animals.

To further develop this Scientific Publication, the *IARC Monographs Programme* convened a group of international scientific experts in a two-part Workshop, held in Lyon in April and November 2012. The Workshop participants used the lists of mechanistic events to develop a set of Key Characteristics to define the mechanistic profile of the Group-1 carcinogens.

The main points of consensus, the conclusions and the recommendations of the Workshop participants are described below.

Tumour-site concordance

1. The results developed in *IARC Monograph* Volume 100 confirm that the induction of cancer in experimental animals is relevant to the identification of a carcinogenic hazard to humans: all human carcinogens identified to date that have been adequately tested in animals have also been shown to cause cancer in animals.

2. For many human carcinogens, there is tumour-site concordance between humans and experimental animals; for many others, there is not. At the present time, the state-of-the-science does not support tumour-site concordance as a general principle. For example, there are four agents that show *sufficient evidence* of breast cancer in humans, seven provide *sufficient evidence* of breast cancer in experimental animals, but only one among these causes breast cancer in both humans and animals.

3. The analyses presented in this Scientific Publication are expected to underestimate concordance. One reason is the limited power and other limitations of many observational

epidemiological studies that include populations and cancer sites that have not been adequately investigated. Another reason is that – for the purpose of this concordance analysis – an agent was considered to cause cancer at a site in animals only if positive results were replicated at the same specific site in another animal experiment (at the same time recognizing the concern of a single positive cancer bioassay); however, metabolic or mechanistic considerations might explain tumour induction at different sites in separate animal models.

4. Descriptive statistics of tumour sites identified to date may not be representative of future evaluations or of the incompletely characterized 'universe of human carcinogens.' The carcinogens evaluated in Volume 100 include several classes of agents that have been relatively straightforward to investigate, for example, alkylating agents used in early cancer chemotherapy, viral agents that infect hundreds of millions of people, ionizing radiation that affects multiple anatomical sites, widespread exposures such as tobacco and alcohol, and chemical agents with long histories of occupational exposure at high levels. Agents evaluated in the future may have more subtle effects and different characteristics. Evidence from sources other than human epidemiology will need to be relied upon to determine human cancer hazards.

5. Past evaluations have noted cancer in experimental animals at approximately 40 tumour sites in 15 organ and tissue systems. Use of standard terminology for these sites can facilitate the development of databases and their analysis and linkage to other sources of information. The Workshop participants recommend that future *IARC Monographs* Working Groups consider the anatomically-based taxonomy of tumour sites that appears in this Scientific Publication in the analysis of concordance between sites where animal and human tumours arise.

6. The Workshop participants also recommend that the Evaluation section for 'evidence in experimental animals' in future *IARC Monographs* be expanded to include additional information for agents evaluated as exhibiting *sufficient evidence*. For such agents, an additional sentence following the relevant evaluation should refer to the recognized site(s) of tumorigenesis, by use of the specification system described in the chapter on Concordance (Krewski et al., this Volume).

Mechanisms involved in human carcinogenesis

7. With increasing scientific understanding and availability of information on mechanisms of carcinogenesis, we expect that the *IARC Monographs* will make even greater use of mechanistic data in identifying human carcinogens.

8. Up until now, there has been no generally accepted method for organizing mechanistic data pertinent to the identification of carcinogenic hazards to humans. The Key Characteristics presented here offer a promising foundation for the structured evaluation of mechanistic information, and this should increase the utility of mechanistic evidence in future identifications of carcinogenic hazards and the transparency of systematic reviews of such evidence. The Workshop participants recommend that the *IARC Monographs Programme* use the Key Characteristics in its evaluations of carcinogenicity.

9. It is notable that in-vivo or in-vitro mechanistic data are often available in humans. In most cases, when animal data are available for a Key Characteristic, human data for that characteristic are generally available, too. This supports the notion that carcinogens show their characteristics across species.

10. There should be no expectation that all, or even most, Key Characteristics operate for any human carcinogen. No Key Characteristic is necessary for carcinogenesis, and negative results for one or more Key Characteristics are not an argument against the potential carcinogenicity of an agent. Observation of one or more Key Characteristics in exposed humans can increase the biological plausibility of less-than-*sufficient evidence* in humans. Observation of one or more Key Characteristics in experimental animals can increase confidence in the human relevance of less-than-*sufficient evidence* in experimental animals. In interpreting the biological relevance of information pertaining to the Key Characteristics, it is important to consider aspects of metabolism and kinetics in extrapolating between in-vitro and in-vivo systems.

11. A human carcinogen may act through multiple mechanisms that may interact with each other. Past practice of according greatest concern to those agents demonstrated to be genotoxic, relative to agents whose carcinogenicity is mediated by some other mechanism, possibly involving specific receptors, appears to be overly simplistic.

12. The objective of the *IARC Monographs Programme* is to identify carcinogenic hazards, not to exhaustively list all mechanistic events and pathways that might contribute to carcinogenesis. Future coverage of mechanistic data should increase as the retrieval of such data becomes more systematic and the Key Characteristics are used as a framework for organization and analysis of

mechanistic data.

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To: BaanR@visitors.iarc.fr[BaanR@visitors.iarc.fr]; bucher@niehs.nih.gov[bucher@niehs.nih.gov]; Kavlock, Robert[Kavlock.Robert@epa.gov]; jlittle@uottawa.ca[jlittle@uottawa.ca]; jr332@georgetown.edu[jr332@georgetown.edu]; lRusyn@cvm.tamu.edu[lRusyn@cvm.tamu.edu]
Cc: Cogliano, Vincent[cogliano.vincent@epa.gov]; StraifK@iarc.fr[StraifK@iarc.fr]; dkrewski@uottawa.ca[dkrewski@uottawa.ca]
From: jmricewas@aol.com
Sent: Mon 9/19/2016 12:07:40 AM
Subject: Re: Consensus statement
8 Draft Consensus Statement July 15 REV.docx

Dear Rob,

I agree with the revised consensus statement, and have only one small (but I think important) editorial correction to offer.

On lines 26 and 125 of the attached version of the statement, the name of the group 1 carcinogenic PAH benzo[*a*]pyrene is not given in the standard chemical nomenclature, that is, "benzo[square bracket/lower case italic Roman letter *a* /close bracket]pyrene." I urge that this correction be made so that the publication is not marred by any perception that it lacks attention to detail. I have entered the change in the attached version of the statement.

Best regards,

Jerry

-----Original Message-----
From: Robert Baan <BaanR@visitors.iarc.fr>
To: bucher <bucher@niehs.nih.gov>; Kavlock.Robert <Kavlock.Robert@epa.gov>; Julian Little <jlittle@uottawa.ca>; jr332 <jr332@georgetown.edu>; Jmricewas <J[redacted]>; lRusyn <lRusyn@cvm.tamu.edu>
Cc: Cogliano.Vincent <Cogliano.Vincent@epamail.epa.gov>; Kurt Straif <StraifK@iarc.fr>; Daniel Krewski <dkrewski@uottawa.ca>
Sent: Wed, Sep 14, 2016 10:39 am
Subject: Consensus statement

Dear all,

Please find attached a revised version of the 'Consensus Statement' after the IARC Workshop on 'Concordance & Mechanisms'. The revision is based on your comments and suggestions, which are highly appreciated. Many other participants have also responded positively, but they had no further comments.

You will find the modifications as 'tracked changes'. I value your thoughts on two suggestions: (a) a proposal to move statement 7 to the Introduction, and (b) to move statements 3 and 4 (which are recommendations) to below statement 6.

Please let me know if your comments and suggestions have been adequately addressed. In advance, thank you for a rapid reply.

As soon as I have received your response, I will send a 'clean version' to all participants

for their formal approval.

With my best regards,
Robert

PS: Bob & Vincent, I understand that the 'EPA disclaimer' should be added (as a footnote?) to this document; would you provide the text?

CONSENSUS STATEMENT

Vincent J Cogliano, Robert A Baan, Kurt Straif

This statement is endorsed by participants[1] in the IARC Workshop on 'Tumour-site Concordance and Mechanisms of Carcinogenesis', held April/November 2012 in Lyon

Introduction

The *IARC Monographs Programme* is an international consensus approach to the identification of chemicals and other agents that may present carcinogenic hazards to humans. The *Monographs* assess the strength of the published scientific evidence for such identifications, which are based primarily on epidemiological studies of cancer in humans and bioassays for carcinogenicity in laboratory animals. Information that may be relevant to the mechanisms by which the putative carcinogen acts is also considered in making an overall evaluation of the strength of the total evidence for carcinogenicity to humans.

7. The use of mechanistic data to identify human carcinogens is accelerating. Initially, *IARC Monographs* required *sufficient evidence* in humans for classification of an agent as *carcinogenic to humans*. Scientific understanding of the mechanisms of carcinogenesis, accompanied by the development of assays for studying mechanistic events, have led to new ways of identifying human carcinogens. As examples, ethylene oxide was classified as *carcinogenic to humans* in 1994 based on strong evidence of genotoxicity in exposed humans, 2,3,7,8- tetrachlorodibenzo-*para*-dioxin in 1997 based on strong evidence of binding to the aryl hydrocarbon receptor and subsequent events, neutron radiation in 2000 based on the underlying radiation physics, benzidine-based dyes in 2010 because these substances are metabolized to a carcinogen, and several compounds for which single-agent exposure does not exist because they are components of (complex) mixtures, e.g., tobacco-specific nitrosamines in 2007, benzo[*a*]pyrene in 2010, and aristolochic acid and etoposide in 2012. Mechanistic evidence was also important in classifying the carcinogenicity of a number of other agents between 2004 and 2010, and in revising the classification of carcinogenicity for several additional agents in Volume 100.

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IARC explored ways to strengthen the scientific outcome of Volume 100 by embarking on a

[1] L Banks, FA Beland, JA Bond, MC Bosland, JR Bucher, JC Caldwell, DM DeMarini, B Fubini, BD Goldstein, SS Hecht, K Hemminki, MA Hill, CW Jameson, AB Kane, RJ Kavlock, D Krewski, PF Lambert, R Melnick, CJ Portier, JM Rice, I Rusyn, MT Smith, L Stayner, BW Stewart, RL Ullrich, H Vainio, P Vineis, MP Waalkes, L Zeise

review of the Group-1 human carcinogens with respect to cancer sites and mechanistic events, followed by supplementary analyses of cancer-site concordance between humans and experimental animals, and of mechanistic events deemed relevant to the carcinogenicity of these agents. Accordingly, this Scientific Publication on 'Tumour-site Concordance and Mechanisms of Carcinogenesis' was proposed.

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Tumour-Site Concordance

1. The results developed in Volume 100 confirm that the induction of cancer in experimental animals is relevant to the identification of a carcinogenic hazard to humans: all human carcinogens identified to date that have been adequately tested in animals have also been shown to cause cancer in animals.

2. For many human carcinogens, there is tumour-site concordance between humans and experimental animals; for many others, there is not. At the present time, the state-of-the-science does not support tumour-site concordance as a general principle. For example, although several agents are known to cause malignant melanoma in humans, this cancer is unknown in rats or mice. Note that these agents cause cancers at other sites in animals.

~~3. Past evaluations have noted cancer in experimental animals at approximately 40 tumour sites in 15 organ and tissue systems. Use of standard terminology for these sites can facilitate the development of databases and their analysis and linkage to other sources of information. The Workshop participants recommend that future *IARC Monographs* Working Groups consider the anatomically based taxonomy of tumour sites that appears in this Scientific Publication in the analysis of concordance between sites where animal and human tumours arise.~~

~~4. The Workshop participants also recommend that the Evaluation section in a *Monograph* in respect of 'evidence in experimental animals' be expanded to include additional information for agents evaluated as exhibiting *sufficient evidence*. For such agents, an additional sentence following the~~

~~relevant evaluation should refer to the recognized site(s) of tumorigenesis, by use of the specification system described in the chapter on Concordance (Krewski et al., this Volume)~~

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radiation in 2000 based on the underlying radiation physics, benzidine-based dyes in 2010 because these substances are metabolized to a carcinogen, and several compounds for which single-agent exposure does not exist because they are components of (complex) mixtures, e.g., tobacco-specific nitrosamines in 2007, benzo~~(a)~~[*a*]pyrene in 2010, and aristolochic acid and etoposide in 2012. ~~between 2004 and 2010, and several additional agents in Volume 100.~~ Mechanistic evidence was also important in classifying the carcinogenicity of a number of other agents between 2004 and 2010, and in revising the classification of carcinogenicity for several additional agents in Volume 100.

8. Up until now, there has been no generally accepted method for organizing mechanistic data pertinent to the identification of carcinogenic hazards to humans. The Key Characteristics presented here offer a promising foundation for the structured evaluation of mechanistic information, and this should increase the utility of mechanistic evidence in future identifications of carcinogenic hazards and the transparency of ~~the~~ systematic reviews of such evidence. The Workshop participants recommend that the *IARC Monographs Programme* ~~continue to develop the Key Characteristics and to~~ use them in its evaluations of carcinogenicity.

9. It is notable that in-vivo or in-vitro mechanistic data are often available in humans. In most cases ~~For most key characteristics~~, when animal data are available for a key characteristic, human data for that characteristic are generally available, too. This supports the notion that carcinogens show their characteristics across species.

10. There should be no expectation that all, or even most, Key Characteristics operate for any human carcinogen. No Key Characteristic is necessary for carcinogenesis, and negative results for one or more Key Characteristics are not an argument against the potential carcinogenicity of an agent. Observation of one or more Key Characteristics in exposed humans can increase the biological plausibility of less-than-*sufficient evidence* in humans. Observation of one or more Key Characteristics in experimental animals can increase confidence in the human relevance of ~~*limited evidence*~~ less-than-*sufficient evidence* in experimental animals. In interpreting the biological relevance of information pertaining to the Key Characteristics, it is important to consider aspects of metabolism and kinetics in extrapolating between in-vitro and in-vivo systems.

11. A human carcinogen may act through multiple mechanisms. Interrelationships between mechanistic events should facilitate the development of more complex—but also more realistic—adverse-outcome networks. Past practice of according greatest concern in respect of known or putative carcinogens to those agents demonstrated to be genotoxic, relative to agents whose carcinogenicity appeared to be mediated by some other mechanism, possibly involving specific receptors, appears to be overly simplistic.

12. The objective of the *IARC Monographs Programme* is to identify carcinogenic hazards, not to exhaustively list all mechanistic events and pathways that might contribute to carcinogenesis. Future coverage of mechanistic data should increase as the retrieval of such data becomes more systematic

and the Key Characteristics are used as a framework for organization and analysis of mechanistic data.

13. Descriptive statistics of mechanisms identified to date may not be representative of future evaluations. Although genotoxicity is the Key Characteristic most exhibited by the human carcinogens identified to date, this may reflect the relatively greater attention paid in the past to the investigation of genotoxic agents. Future evaluations of carcinogenic agents may involve a larger set of mechanistic events and pathways, many that are not yet well developed or understood. Accordingly, future ~~refinement~~ shifts in the distribution of the Key Characteristics are to be expected. ~~, and this~~ This does not detract from the value in using them now in evaluations of carcinogenic hazards.

To: '?? ??'[htsuda@phar.nagoya-cu.ac.jp]
Cc: Cogliano, Vincent[cogliano.vincent@epa.gov]; 津田研究室 秘書[aiezaki@phar.nagoya-cu.ac.jp]
From: Martel, Susan
Sent: Fri 9/16/2016 11:41:51 AM
Subject: RE: US National Academies and EPA seek discussants for EPA Toxicological Review of ETBE

Dear Professor Tsuda,

I apologize for the confusion about the meeting format and that your participation would be over the internet. We are disappointed that you will not be able to participate via the internet, but understand that the time difference will make it difficult.

Thank you for your consideration.

Regards,
Susan Martel

-----Original Message-----
From: 津田 洋幸 [mailto:htsuda@phar.nagoya-cu.ac.jp]
Sent: Wednesday, September 14, 2016 9:34 PM
To: Martel, Susan
Cc: cogliano.vincent@epa.gov; 津田研究室 秘書
Subject: Re: US National Academies and EPA seek discussants for EPA Toxicological Review of ETBE

Dear Ms Susan Martel,
CC: Dr. Vincent Cogliano

I overlooked your e-mail on August 19th. In your mail on Sept. 12, I found Dr. Vincent Cogliano's name and read through. I learned the meeting is important and I could contribute by presenting the background data of 2-stage carcinogenesis models which were used for the assay of ETBE.

My understanding was to participate in Face-to-Face discussion using a slide presentation. In the followup e-mail that I read, it appeared that I would be able to physically attend the conference, and I accepted the invitation. Unfortunately, in the e-mail I received on Sept. 13, the only option for attending the conference was by internet/telephone. I apologize I will not participate in the internet/internet discussion.

Best wishes,

Hiroyuki Tsuda
Professor, Nanotoxicology Project Lab.
3-1 Tanabedohri, Mizuho-ku
Nagoya 467-8603, Japan
Phone：052-836-3496
FAX: 052-836-3497
http://www.med.nagoya-cu.ac.jp/moltox.dir/nanotoxlab/

> 2016/09/13 23:42、Martel, Susan <SMartel@nas.edu> のメール：
>
> Dear Professor Tsuda,
>
> We are pleased to learn that you are interested in participating in the EPA meeting, and we can arrange for you to participate in the meeting via the internet/telephone. We expect the agenda to be divided into three 90-minute sessions. Because of the time difference (Japan is 13 hours ahead of Virginia), we would schedule the session you would participate in first. That would mean that you would participate

from Japan sometime between 10:00 pm to 12:00 am in the evening of October 26. Could you please confirm that you would be willing to participate in the meeting from Japan in the late evening?
>
> Regards,
> Susan Martel
>
> -----Original Message-----
> From: 津田 洋幸 [mailto:htsuda@phar.nagoya-cu.ac.jp]
> Sent: Tuesday, September 13, 2016 4:41 AM
> To: Martel, Susan
> Cc: 津田研究室 秘書
> Subject: Re: US National Academies and EPA seek discussants for EPA
> Toxicological Review of ETBE
>
> Dear Susan Martel
> Senior Program Officer
> Board on Environmental Studies & Toxicology The National Academies of
> Sciences, Engineering, and Medicine
>
> I am pleased to accept your invitation to participate in the EPA's Integrated Risk Information System (IRIS) toxicological review of Ethyl tert-Butyl Ether (ETBE) to be held on the 26th of October, 2016.
>
> I look forward to receiving details of the meeting schedule.
>
> Best wishes,
>
> Hiroyuki Tsuda
> Professor, Nanotoxicology Project Lab.
> 3-1 Tanabedohri, Mizuho-ku
> Nagoya 467-8603, Japan
> Phone：052-836-3496
> FAX: 052-836-3497
> http://www.med.nagoya-cu.ac.jp/moltox.dir/nanotoxlab/
>
>> 2016/09/12 21:54、Martel, Susan <SMartel@nas.edu> のメール：
>>
>> Dear Dr. Tsuda,
>>
>> I'm following-up on my email below about your possible participation in an EPA workshop to give your perspectives on the use of 2-stage carcinogenesis bioassays.
>> Please let me know if you have any questions.
>>
>> Regards,
>> Susan Martel
>>
>> From: Martel, Susan
>> Sent: Thursday, August 18, 2016 11:29 AM
>> To: 'htsuda@phar.nagoya-cu.ac.jp'
>> Subject: US National Academies and EPA seek discussants for EPA
>> Toxicological Review of ETBE
>>
>> Dear Dr. Tsuda,
>>
>> I'm contacting you on behalf of the National Academies of Sciences, Engineering, and Medicine in Washington, DC, to ask if you are interested in possibly participating in a science meeting to discuss EPA's Integrated Risk Information System (IRIS) toxicological review of Ethyl tert-Butyl Ether (ETBE).

The meeting will be held on October 26 in Arlington, VA under the auspices of the IRIS program. Vince Cogliano remembers working with you while he was at IARC and thought you would make a valuable contribution to the discussions.
>>
>> As part of the IRIS assessment process, EPA holds public science meetings to obtain input from individuals outside of the agency. At the October meeting, EPA will gather scientific input on three science topics (described below). You were suggested to us as a candidate to participate in the session on Topic 3 (use of 2-stage carcinogenesis bioassays). The specific questions that will be posed at the meeting are still in development.
>>
>> As you may know, IRIS assessments focus on the degree of hazard and dose-response relationships resulting from exposures to chemical substances in the environment. The assessments play an important role in supporting EPA's risk management decisions, including regulations. The assessments also serve as a resource for state and local governments and other countries.
>> Key Science Topics – Ethyl tertiary butyl ether (ETBE)
>> 1. Liver tumor modes of action
>> Lifetime inhalation exposure to ETBE increased liver adenomas and carcinomas in male F344 rats. Data are available suggesting that ETBE may activate PPAR, PXR, and/or CAR pathways all of which increase cell proliferation, hypertrophy, and clonal expansion of preneoplastic foci in the liver. Determining the relative contribution of each pathway on tumor development is problematic. In addition, there is uncertainty on the relevance of PPAR-induced tumors to human risk assessment (Guyton et al., 2009; Corton et al., 2014). Acetaldehyde, a metabolite of ETBE, is considered by other agencies to be carcinogenic. Aldh2 deficiency enhanced ETBE-induced genotoxicity in hepatocytes and leukocytes from exposed mice; but while suggestive, the available data overall are inadequate to establish acetaldehyde-mediated mutagenicity as a MOA for ETBE-induced liver tumors. EPA found that the database was inadequate to draw any conclusions regarding a liver MOA.
>>
>> The IRIS program is seeking discussion on PPAR, PXR, CAR, and acetaldehyde as possible modes of action for ETBE-induced liver tumors.
>>
>> 2. The potential for increased susceptibility to toxic effects resulting from a decreased rate of acetaldehyde clearance in the liver
>> Acetaldehyde, a metabolite of ETBE, is considered carcinogenic by other agencies. Acetaldehyde is metabolized by the enzyme ALDH2 and studies in Aldh2 knockout mice have demonstrated increased genotoxicity, centrilobular hypertrophy, and alterations to reproductive tissue compared with wild-type controls following ETBE exposure. Furthermore, one-half of East Asian populations possess a virtually inactive form of ALDH2*2 which is associated with slow metabolism of acetaldehyde and extended exposure to the compound. Analyses have shown that acetaldehyde produced as a result of ethanol metabolism contribute to human carcinogenesis in the upper aerodigestive tract and esophagus following ethanol exposure. Altogether, these data provide plausibility that reduced ALDH2 activity produces more severe health effects than in organisms with functional ALDH2.
>>
>> The IRIS program is seeking discussion on the increased susceptibility of cancer and noncancer effects due to reduced ALDH2 activity in humans and animal models.
>>
>> 3. Use of 2-stage carcinogenicity bioassays
>>
>> Lifetime inhalation, but not oral, ETBE exposure has been associated with increased liver adenomas and carcinomas in male F344 rats. Toxicokinetic analysis comparing oral and inhalation exposures from these studies on the basis of metabolized dose of ETBE or tert-butanol (a metabolite of ETBE) indicated that these studies yielded comparable internal concentrations which suggests that the lack of carcinogenic effects via oral exposure is not likely due to a difference in administered dose. Notably, subchronic oral ETBE exposure increased 2-stage mutagen-initiated carcinogenesis in several tissues, including the liver. The 2-stage initiation-promotion bioassays were decisive in extending the weight of evidence descriptor to the oral route.
>>

>> The IRIS program is seeking public discussion on the use of 2-stage
>> bioassays for assessing carcinogenicity hazard
>>
>>
>> We will be reimbursing participants for travel expenses, as needed. However, we will not be able to provide financial compensation for the participants' professional time. Individuals unable to travel to the meeting could participate remotely over the Internet or by phone.
>>
>> As the meeting is designed to use a discussion format, EPA asks participants to make only brief prepared remarks--spending less than 5 minutes--to introduce his or her perspectives on a particular topic. There is no need to submit any written materials or prepare a set of PowerPoint slides. However, it would be OK to show one or two slides containing summary tables or figures.
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>> After the introductory remarks, each discussant is expected to participate actively throughout the session in a collegial give-and-take roundtable discussion of a designated topic. In doing so, EPA asks that each discussant take a step back from his or her own research and consider the broader body of scientific information that can be brought to bear in addressing the topic.
>>
>> To help us ensure that the group of individuals we identify provides a range of perspectives, please let me know whether you have any strong views with regard to the topic interest. Also, to promote transparency, EPA will ask each discussant to comment on potential conflicts of interests at the start of a meeting session. As part of our initial vetting process, it would be helpful to know how you would respond to these questions:
>>
>> (1) What is the nature of any financial relationships (e.g.,
>> consulting agreements, expert witness support, or research funding)
>> you may have with any organization(s) or entities having an interest
>> in the ETBE assessment or issues under discussion?, and
>>
>> (2) What is the extent to which your planned comments were reviewed by an interested party prior to the meeting?
>>
>> Thanks very much for your consideration, and I look forward to hearing back from you.
>>
>> Regards,
>> Susan Martel
>>
>> **********
>> Susan Martel
>> Senior Program Officer
>> Board on Environmental Studies & Toxicology The National Academies of
>> Sciences, Engineering, and Medicine
>> 500 Fifth Street, N.W.
>> Washington, DC 20001
>> TEL: (202) 334-2021
>> FAX: (202) 334-2752
>> E-mail: smartel@nas.edu
>
>

To: Robert Baan[BaanR@visitors.iarc.fr]; Kavlock, Robert[Kavlock.Robert@epa.gov]; Julian Little[jlittle@uottawa.ca]; jr332@georgetown.edu[jr332@georgetown.edu]; Ex. 6 - Personal Privacy IRusyn@cvm.tamu.edu[IRusyn@cvm.tamu.edu]
Cc: Cogliano, Vincent[cogliano.vincent@epa.gov]; Kurt Straif[StraifK@iarc.fr]; dkrewski@uottawa.ca[dkrewski@uottawa.ca]
From: Bucher, John (NIH/NIEHS) [E]
Sent: Thur 9/15/2016 11:00:21 AM
Subject: Re: Consensus statement

Dear Robert,
I agree with the proposed changes and have no further suggestions.
Best,
John

From: Robert Baan <BaanR@visitors.iarc.fr>
Date: Wednesday, September 14, 2016 at 10:39 AM
To: "John R. Bucher" <bucher@niehs.nih.gov>, "Kavlock.Robert@epa.gov" <Kavlock.Robert@epa.gov>, Julian Little <jlittle@uottawa.ca>, "jr332@georgetown.edu" <jr332@georgetown.edu>, **Ex. 6 - Personal Privacy** **Ex. 6 - Personal Privacy** "IRusyn@cvm.tamu.edu" <IRusyn@cvm.tamu.edu>
Cc: "Cogliano.Vincent@epamail.epa.gov" <Cogliano.Vincent@epamail.epa.gov>, Kurt Straif <StraifK@iarc.fr>, Daniel Krewski <dkrewski@uottawa.ca>
Subject: Consensus statement

Dear all,

Please find attached a revised version of the 'Consensus Statement' after the IARC Workshop on 'Concordance & Mechanisms'. The revision is based on your comments and suggestions, which are highly appreciated. Many other participants have also responded positively, but they had no further comments.

You will find the modifications as 'tracked changes'. I value your thoughts on two suggestions: (a) a proposal to move statement 7 to the Introduction, and (b) to move statements 3 and 4 (which are recommendations) to below statement 6.

Please let me know if your comments and suggestions have been adequately addressed. In advance, thank you for a rapid reply.

As soon as I have received your response, I will send a 'clean version' to all participants for their formal approval.

With my best regards,

Robert

PS: Bob & Vincent, I understand that the 'EPA disclaimer' should be added (as a footnote?) to this document; would you provide the text?

To: Robert Baan[BaanR@visitors.iarc.fr]; bucher@niehs.nih.gov[bucher@niehs.nih.gov]; Kavlock, Robert[Kavlock.Robert@epa.gov]; Julian Little[jlittle@uottawa.ca]; jr332@georgetown.edu[jr332@georgetown.edu]; Ex. 6 - Personal Privacy lRusyn@cvm.tamu.edu[lRusyn@cvm.tamu.edu]
Cc: Cogliano, Vincent[cogliano.vincent@epa.gov]; Kurt Straif[StraifK@iarc.fr]
From: Daniel Krewski
Sent: Thur 9/15/2016 4:00:14 AM
Subject: RE: Consensus statement
8 Draft Consensus Statement July 15 REV (002) DK September 14, 2016.docx

Robert, attached are a few small editorial suggestions for the consensus statement, marked in track changes.

I think statement 7 does fit much better in the introduction, and agree that statements 3 and 4 flow better by their placement after statement 6.

I think the current draft of the consensus statement not only reads well, but includes significant innovation with respect to future evaluations within the IARC Monographs Programme.

Dan K.

From: Robert Baan [mailto:BaanR@visitors.iarc.fr]
Sent: September-14-16 10:40 AM
To: bucher@niehs.nih.gov; Kavlock.Robert@epa.gov; Julian Little <jlittle@uottawa.ca>; jr332@georgetown.edu; Ex. 6 - Personal Privacy lRusyn@cvm.tamu.edu
Cc: Cogliano.Vincent@epamail.epa.gov; Kurt Straif <StraifK@iarc.fr>; Daniel Krewski <dkrewski@uottawa.ca>
Subject: Consensus statement

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CONSENSUS STATEMENT

Vincent J Cogliano, Robert A Baan, Kurt Straif

This statement is endorsed by participants[1] in the IARC Workshop on 'Tumour-site Concordance and Mechanisms of Carcinogenesis', held April/November 2012 in Lyon

Introduction

The *IARC Monographs Programme* is an international consensus approach to the identification of chemicals and other agents that may present carcinogenic hazards to humans. The *Monographs* assess the strength of the published scientific evidence for such identifications, which are based primarily on epidemiological studies of cancer in humans and bioassays for carcinogenicity in laboratory animals. Information that may be relevant to the mechanisms by which the putative carcinogen acts is also considered in making an overall evaluation of the strength of the total evidence for carcinogenicity to humans.

7. The use of mechanistic data to identify human carcinogens is accelerating. Initially, *IARC Monographs* required *sufficient evidence* in humans for classification of an agent as *carcinogenic to humans*. Scientific understanding of the mechanisms of carcinogenesis, accompanied by the development of assays for studying mechanistic events, have led to new ways of identifying human carcinogens. As examples, ethylene oxide was classified as *carcinogenic to humans* in 1994 based on strong evidence of genotoxicity in exposed humans, 2,3,7,8- tetrachlorodibenzo-*para*-dioxin in 1997 based on strong evidence of binding to the aryl hydrocarbon receptor and subsequent events, neutron radiation in 2000 based on the underlying radiation physics, benzidine-based dyes in 2010 because these substances are metabolized to a carcinogen, and several compounds for which single-agent exposure does not exist because they are components of (complex) mixtures, e.g., tobacco-specific nitrosamines in 2007, benzo(a)pyrene in 2010, and aristolochic acid and etoposide in 2012. Mechanistic evidence was also important in classifying the carcinogenicity of a number of other agents between 2004 and 2010, and in revising the classification of carcinogenicity for several additional agents in Volume 100.

For the one hundredth volume of the *IARC Monographs*, a review was undertaken during 2008–2009 of all Group-1 human carcinogens previously identified in Volumes 1–99. There was value in a comprehensive review, as about half the human carcinogens had been last reviewed more than 20 years earlier. *Monograph* Volume 100 was organized in six parts covering *Pharmaceuticals* (Vol 100A), *Biological Agents* (Vol 100B), *Arsenic, Metals, Fibres, and Dusts* (Vol 100C), *Radiation* (Vol 100D), *Personal Habits and Indoor Combustions* (Vol 100E), and *Chemical Agents and Related Occupations* (Vol 100F). Volume 100 'A Review of Human Carcinogens' was published as a six-part book series in 2012.

IARC explored ways to strengthen the scientific outcome of Volume 100 by embarking on a

[1] L Banks, FA Beland, JA Bond, MC Bosland, JR Bucher, JC Caldwell, DM DeMarini, B Fubini, BD Goldstein, SS Hecht, K Hemminki, MA Hill, CW Jameson, AB Kane, RJ Kavlock, D Krewski, PF Lambert, R Melnick, CJ Portier, JM Rice, I Rusyn, MT Smith, L Stayner, BW Stewart, RL Ullrich, H Vainio, P Vineis, MP Waalkes, L Zeise

review of the Group-1 human carcinogens with respect to cancer sites and mechanistic events, followed by supplementary analyses of cancer-site concordance between humans and experimental animals, and of mechanistic events deemed relevant to the carcinogenicity of these agents. Accordingly, this Scientific Publication on 'Tumour-site Concordance and Mechanisms of Carcinogenesis' was proposed.

To prepare for the supplementary analyses in this Scientific Publication, IARC had asked the six Working Groups for Volume 100 to collect additional information, not routinely developed before, (a) on cancer sites in humans for which there was *sufficient evidence* or *limited evidence* in epidemiological studies, (b) on cancer sites with *sufficient evidence* in experimental animals, and (c) on established and likely mechanistic events involved in the cancers observed in humans or experimental animals.

To further develop this Scientific Publication, the *IARC Monographs Programme* convened a group of international scientific experts in a two-part Workshop, held in Lyon in April and November 2012. The Workshop participants developed a list of Key Characteristics to define the mechanistic profile of the Group-1 carcinogens.

The main points of consensus, the conclusions and the recommendations of the Workshop participants are described below.

Tumour-Site Concordance

1. The results developed in Volume 100 confirm that the induction of cancer in experimental animals is relevant to the identification of a carcinogenic hazard to humans: all human carcinogens identified to date that have been adequately tested in animals have also been shown to cause cancer in animals.

2. For many human carcinogens, there is tumour-site concordance between humans and experimental animals; for many others, there is not. At the present time, the state-of-the-science does not support tumour-site concordance as a general principle. For example, although several agents are known to cause malignant melanoma in humans, this cancer is unknown in rats or mice. Note that these agents cause cancers at other sites in animals.

~~3. Past evaluations have noted cancer in experimental animals at approximately 40 tumour sites in 15 organ and tissue systems. Use of standard terminology for these sites can facilitate the development of databases and their analysis and linkage to other sources of information. The Workshop participants recommend that future *IARC Monographs* Working Groups consider the anatomically based taxonomy of tumour sites that appears in this Scientific Publication in the analysis of concordance between sites where animal and human tumours arise.~~

~~4. The Workshop participants also recommend that the Evaluation section in a *Monograph* in respect of 'evidence in experimental animals' be expanded to include additional information for agents evaluated as exhibiting *sufficient evidence*. For such agents, an additional sentence following the~~

~~relevant evaluation should refer to the recognized site(s) of tumorigenesis, by use of the specification system described in the chapter on Concordance (Krewski et al., this Volume)~~

5. The present analyses are expected to underestimate concordance. One reason is the limited power of many observational epidemiological studies that include populations and cancer sites that have not been adequately investigated. Another reason is that – for the purpose of this concordance analysis – an agent was considered to cause cancer at a specific site in animals only if positive results were replicated at ~~that~~ the same site in another animal experiment (at the same time recognizing the concern of a single positive cancer bioassay); however, metabolic or mechanistic considerations might explain tumour induction at different sites in separate animal models. 6. Descriptive statistics of tumour sites identified to date may not be representative of future evaluations or of the incompletely characterized 'universe of human carcinogens.' The carcinogens evaluated in Volume 100 include several classes of agents that have been relatively straightforward to investigate, for example, alkylating agents used in early cancer chemotherapy, viral agents that infect hundreds of millions of people, ionizing radiation that affects multiple anatomical sites, widespread exposures such as tobacco and alcohol, and chemical agents with long histories of occupational exposure at high levels. Agents evaluated in the future may have more subtle effects and different characteristics. Evidence from sources other than human epidemiology will need to be relied upon to determine human cancer hazards.

3. Past evaluations have noted cancer in experimental animals at approximately 40 tumour sites in 15 organ and tissue systems. Use of standard terminology for these sites can facilitate the development of databases and their analysis and linkage to other sources of information. The Workshop participants recommend that future *IARC Monographs* Working Groups consider the anatomically based taxonomy of tumour sites that appears in this Scientific Publication in the analysis of concordance between sites where animal and human tumours arise.

4. The Workshop participants also recommend that the Evaluation section in a *Monograph* in respect of 'evidence in experimental animals' be expanded to include additional information for agents evaluated as exhibiting *sufficient evidence*. For such agents, an additional sentence following the relevant evaluation should refer to the recognized site(s) of tumorigenesis, by use of classification system described in the chapter on concordance (Krewski et al., this Volume)

Mechanisms Involved in Human Carcinogenesis

7. The use of mechanistic data to identify human carcinogens is accelerating. Initially, *IARC Monographs* required *sufficient evidence* in humans for classification of an agent as *carcinogenic to humans*. Scientific understanding of the mechanisms of carcinogenesis, accompanied by the development of assays for studying mechanistic events, have led to new ways of identifying human carcinogens. As examples, ethylene oxide was classified as *carcinogenic to humans* in 1994 based on strong evidence of genotoxicity in exposed humans, 2,3,7,8- tetrachlorodibenzo-*para*-dioxin in 1997

based on strong evidence of binding to the aryl hydrocarbon receptor and subsequent events, neutron radiation in 2000 based on the underlying radiation physics, benzidine-based dyes in 2010 because these substances are metabolized to a carcinogen, and several compounds for which single-agent exposure does not exist because they are components of (complex) mixtures, e.g., tobacco-specific nitrosamines in 2007, benzo(a)pyrene in 2010, and aristolochic acid and etoposide in 2012. ~~between 2004 and 2010, and several additional agents in Volume 100.~~ Mechanistic evidence was also important in classifying the carcinogenicity of a number of other agents between 2004 and 2010, and in revising the classification of carcinogenicity for several additional agents in Volume 100.

8. Up until now, there has been no generally accepted method for organizing mechanistic data pertinent to the identification of carcinogenic hazards to humans. The Key Characteristics presented here provide a framework for the structured evaluation of mechanistic information, and this should increase the utility of mechanistic evidence in future identifications of carcinogenic hazards and the transparency of ~~the~~ systematic reviews of such evidence. The Workshop participants recommend that the *IARC Monographs Programme* ~~continue to develop the Key Characteristics and to~~ use them in its evaluations of carcinogenicity.

9. It is notable that in-vivo or in-vitro mechanistic data are often available in humans. In most cases ~~For most key characteristics~~, when animal data are available for a key characteristic, human data for that characteristic are generally available as well. This supports the notion that carcinogens exhibit similar characteristics across species.

10. There should be no expectation that all, or even most, Key Characteristics operate for any human carcinogen. No Key Characteristic is necessary for carcinogenesis, and negative results for one or more Key Characteristics are not an argument against the potential carcinogenicity of an agent. Observation of one or more Key Characteristics in exposed humans can increase the biological plausibility of less-than-*sufficient evidence* in humans. Observation of one or more Key Characteristics in experimental animals can increase confidence in the human relevance of ~~*limited evidence*~~ less-than-*sufficient evidence* in experimental animals. In interpreting the biological relevance of information pertaining to the Key Characteristics, it is important to consider aspects of metabolism and kinetics in extrapolating between in-vitro and in-vivo systems.

11. A human carcinogen may act through multiple mechanisms. Interrelationships between mechanistic events should facilitate the development of more complex—but also more realistic—adverse-outcome networks. Past practice of according greatest concern in respect of known or putative carcinogens to those agents demonstrated to be genotoxic, relative to agents whose carcinogenicity appeared to be mediated by some other mechanism, possibly involving specific receptors, appears to be overly simplistic.

12. The objective of the *IARC Monographs Programme* has been to identify carcinogenic hazards, not to exhaustively list all mechanistic events and pathways that might contribute to carcinogenesis.

Future coverage of mechanistic data should increase as the retrieval of such data becomes more systematic and the Key Characteristics are used as a framework for organization and analysis of mechanistic data.

13. Descriptive statistics of mechanisms identified to date may not be representative of future evaluations. Although genotoxicity is the Key Characteristic most frequently exhibited by the human carcinogens identified to date, this may reflect the relatively greater attention paid in the past to the investigation of genotoxic agents. Future evaluations of carcinogenic agents may involve a larger set of mechanistic events and pathwaysthat are not yet well developed or understood. Accordingly, future ~~refinement~~ shifts in the distribution of the Key Characteristics are to be expected. ~~, and this~~ This does not detract from the value in using them now in evaluations of carcinogenic hazards.

Cc: Cogliano, Vincent[cogliano.vincent@epa.gov]; 津田研究室 秘書[aiezaki@phar.nagoya-cu.ac.jp]
To: Martel, Susan[SMartel@nas.edu]
From: 津田 洋幸
Sent: Thur 9/15/2016 1:34:23 AM
Subject: Re: US National Academies and EPA seek discussants for EPA Toxicological Review of ETBE

Dear Ms Susan Martel,
CC: Dr. Vincent Cogliano

I overlooked your e-mail on August 19th. In your mail on Sept. 12, I found Dr. Vincent Cogliano's name and read through. I learned the meeting is important and I could contribute by presenting the background data of 2-stage carcinogenesis models which were used for the assay of ETBE.

My understanding was to participate in Face-to-Face discussion using a slide presentation. In the followup e-mail that I read, it appeared that I would be able to physically attend the conference, and I accepted the invitation. Unfortunately, in the e-mail I received on Sept. 13, the only option for attending the conference was by internet/telephone. I apologize I will not participate in the internet/internet discussion.

Best wishes,

Hiroyuki Tsuda
Professor, Nanotoxicology Project Lab.
3-1 Tanabedohri, Mizuho-ku
Nagoya 467-8603, Japan
Phone：052-836-3496
FAX: 052-836-3497
http://www.med.nagoya-cu.ac.jp/moltox.dir/nanotoxlab/

> 2016/09/13 23:42、Martel, Susan <SMartel@nas.edu> のメール：
>
> Dear Professor Tsuda,
>
> We are pleased to learn that you are interested in participating in the EPA meeting, and we can arrange for you to participate in the meeting via the internet/telephone. We expect the agenda to be divided into three 90-minute sessions. Because of the time difference (Japan is 13 hours ahead of Virginia), we would schedule the session you would participate in first. That would mean that you would participate from Japan sometime between 10:00 pm to 12:00 am in the evening of October 26. Could you please confirm that you would be willing to participate in the meeting from Japan in the late evening?
>
> Regards,
> Susan Martel
>
> -----Original Message-----
> From: 津田 洋幸 [mailto:htsuda@phar.nagoya-cu.ac.jp]
> Sent: Tuesday, September 13, 2016 4:41 AM
> To: Martel, Susan
> Cc: 津田研究室 秘書
> Subject: Re: US National Academies and EPA seek discussants for EPA Toxicological Review of ETBE
>
> Dear Susan Martel
> Senior Program Officer
> Board on Environmental Studies & Toxicology The National Academies of Sciences, Engineering, and Medicine
>

> I am pleased to accept your invitation to participate in the EPA's Integrated Risk Information System (IRIS) toxicological review of Ethyl tert-Butyl Ether (ETBE) to be held on the 26th of October, 2016.
>
> I look forward to receiving details of the meeting schedule.
>
> Best wishes,
>
> Hiroyuki Tsuda
> Professor, Nanotoxicology Project Lab.
> 3-1 Tanabedohri, Mizuho-ku
> Nagoya 467-8603, Japan
> Phone：052-836-3496
> FAX: 052-836-3497
> http://www.med.nagoya-cu.ac.jp/moltox.dir/nanotoxlab/
>
>> 2016/09/12 21:54、Martel, Susan <SMartel@nas.edu> のメール：
>>
>> Dear Dr. Tsuda,
>>
>> I'm following-up on my email below about your possible participation in an EPA workshop to give your perspectives on the use of 2-stage carcinogenesis bioassays.
>> Please let me know if you have any questions.
>>
>> Regards,
>> Susan Martel
>>
>> From: Martel, Susan
>> Sent: Thursday, August 18, 2016 11:29 AM
>> To: 'htsuda@phar.nagoya-cu.ac.jp'
>> Subject: US National Academies and EPA seek discussants for EPA
>> Toxicological Review of ETBE
>>
>> Dear Dr. Tsuda,
>>
>> I'm contacting you on behalf of the National Academies of Sciences, Engineering, and Medicine in Washington, DC, to ask if you are interested in possibly participating in a science meeting to discuss EPA's Integrated Risk Information System (IRIS) toxicological review of Ethyl tert-Butyl Ether (ETBE). The meeting will be held on October 26 in Arlington, VA under the auspices of the IRIS program. Vince Cogliano remembers working with you while he was at IARC and thought you would make a valuable contribution to the discussions.
>>
>> As part of the IRIS assessment process, EPA holds public science meetings to obtain input from individuals outside of the agency. At the October meeting, EPA will gather scientific input on three science topics (described below). You were suggested to us as a candidate to participate in the session on Topic 3 (use of 2-stage carcinogenesis bioassays). The specific questions that will be posed at the meeting are still in development.
>>
>> As you may know, IRIS assessments focus on the degree of hazard and dose-response relationships resulting from exposures to chemical substances in the environment. The assessments play an important role in supporting EPA's risk management decisions, including regulations. The assessments also serve as a resource for state and local governments and other countries.
>> Key Science Topics – Ethyl tertiary butyl ether (ETBE)
>> 1. Liver tumor modes of action
>> Lifetime inhalation exposure to ETBE increased liver adenomas and carcinomas in male F344 rats. Data are available suggesting that ETBE may activate PPAR, PXR, and/or CAR pathways all of which increase cell proliferation, hypertrophy, and clonal expansion of preneoplastic foci in the liver. Determining

the relative contribution of each pathway on tumor development is problematic. In addition, there is uncertainty on the relevance of PPAR-induced tumors to human risk assessment (Guyton et al., 2009; Corton et al., 2014). Acetaldehyde, a metabolite of ETBE, is considered by other agencies to be carcinogenic. Aldh2 deficiency enhanced ETBE-induced genotoxicity in hepatocytes and leukocytes from exposed mice; but while suggestive, the available data overall are inadequate to establish acetaldehyde-mediated mutagenicity as a MOA for ETBE-induced liver tumors. EPA found that the database was inadequate to draw any conclusions regarding a liver MOA.
>>
>> The IRIS program is seeking discussion on PPAR, PXR, CAR, and acetaldehyde as possible modes of action for ETBE-induced liver tumors.
>>
>> 2. The potential for increased susceptibility to toxic effects resulting from a decreased rate of acetaldehyde clearance in the liver
>> Acetaldehyde, a metabolite of ETBE, is considered carcinogenic by other agencies. Acetaldehyde is metabolized by the enzyme ALDH2 and studies in Aldh2 knockout mice have demonstrated increased genotoxicity, centrilobular hypertrophy, and alterations to reproductive tissue compared with wild-type controls following ETBE exposure. Furthermore, one-half of East Asian populations possess a virtually inactive form of ALDH2*2 which is associated with slow metabolism of acetaldehyde and extended exposure to the compound. Analyses have shown that acetaldehyde produced as a result of ethanol metabolism contribute to human carcinogenesis in the upper aerodigestive tract and esophagus following ethanol exposure. Altogether, these data provide plausibility that reduced ALDH2 activity produces more severe health effects than in organisms with functional ALDH2.
>>
>> The IRIS program is seeking discussion on the increased susceptibility of cancer and noncancer effects due to reduced ALDH2 activity in humans and animal models.
>>
>> 3. Use of 2-stage carcinogenicity bioassays
>>
>> Lifetime inhalation, but not oral, ETBE exposure has been associated with increased liver adenomas and carcinomas in male F344 rats. Toxicokinetic analysis comparing oral and inhalation exposures from these studies on the basis of metabolized dose of ETBE or tert-butanol (a metabolite of ETBE) indicated that these studies yielded comparable internal concentrations which suggests that the lack of carcinogenic effects via oral exposure is not likely due to a difference in administered dose. Notably, subchronic oral ETBE exposure increased 2-stage mutagen-initiated carcinogenesis in several tissues, including the liver. The 2-stage initiation-promotion bioassays were decisive in extending the weight of evidence descriptor to the oral route.
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>> The IRIS program is seeking public discussion on the use of 2-stage
>> bioassays for assessing carcinogenicity hazard
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>> We will be reimbursing participants for travel expenses, as needed. However, we will not be able to provide financial compensation for the participants' professional time. Individuals unable to travel to the meeting could participate remotely over the Internet or by phone.
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>> As the meeting is designed to use a discussion format, EPA asks participants to make only brief prepared remarks--spending less than 5 minutes--to introduce his or her perspectives on a particular topic. There is no need to submit any written materials or prepare a set of PowerPoint slides. However, it would be OK to show one or two slides containing summary tables or figures.
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>> After the introductory remarks, each discussant is expected to participate actively throughout the session in a collegial give-and-take roundtable discussion of a designated topic. In doing so, EPA asks that each discussant take a step back from his or her own research and consider the broader body of scientific information that can be brought to bear in addressing the topic.
>>
>> To help us ensure that the group of individuals we identify provides a range of perspectives, please let

me know whether you have any strong views with regard to the topic interest. Also, to promote transparency, EPA will ask each discussant to comment on potential conflicts of interests at the start of a meeting session. As part of our initial vetting process, it would be helpful to know how you would respond to these questions:
>>
>> (1) What is the nature of any financial relationships (e.g.,
>> consulting agreements, expert witness support, or research funding)
>> you may have with any organization(s) or entities having an interest
>> in the ETBE assessment or issues under discussion?, and
>>
>> (2) What is the extent to which your planned comments were reviewed by an interested party prior to the meeting?
>>
>> Thanks very much for your consideration, and I look forward to hearing back from you.
>>
>> Regards,
>> Susan Martel
>>
>> **********
>> Susan Martel
>> Senior Program Officer
>> Board on Environmental Studies & Toxicology The National Academies of
>> Sciences, Engineering, and Medicine
>> 500 Fifth Street, N.W.
>> Washington, DC 20001
>> TEL: (202) 334-2021
>> FAX: (202) 334-2752
>> E-mail: smartel@nas.edu
>
>

To: Robert Baan[BaanR@visitors.iarc.fr]
Cc: Brittany Milton[bmilton@risksciences.com]; Michael Bird[r Ex. 6 - Personal Privacy]; Nicholas Birkett[Nicholas.Birkett@uottawa.ca]; Kurt Straif[StraifK@iarc.fr]; Cogliano, Vincent[cogliano.vincent@epa.gov]; Kathryn Guyton[GuytonK@iarc.fr]
From: Daniel Krewski
Sent: Mon 8/8/2016 3:44:59 AM
Subject: Additional Mechanistic Analysis and Possible Addition to Mechanistic Analysis
Figure 2X. Heat Map of Human and Animal Sources Auguest 7, 2016.png
2016 Krewski et al Key Characteristics July 14.pdf
8 Draft Consensus Statement July 15 DK Addition.docx

Robert, I'm attaching an analysis (Figure 2X) provided by Brittany Milton showing that information on the 10 key characteristics of human carcinogens often comes from both animal and human sources, in the form of heat map indicating such agreement for each of the 86 agents included in the mechanisms database.

1. Would it be worth adding Figure 2X to the mechanisms chapter (attached), either in place of or in addition to, the current Figure 2? [This would involve the preparation of only a short amount of text, observing that information on the 10 KCs – particularly for genotoxicity, but also for a number of other KCs – often comes from both human and animal sources.]

2. If we include Figure 2X to demonstrate 'concordance' between human and animal sources of information on the 10 KCs, would this support the addition to item 9 in the consensus statement (attached, and noted below) that I had suggested earlier?

Consensus Statement #9. It is notable that in-vivo or in-vitro mechanistic data are often available in humans. For most key characteristics, when animal data are available for a key characteristic, human data are generally available, too. The observation that similar Key Characteristics are seen in humans and animals further supports the use of animal data in human cancer risk assessment.

3. We still need a decision on whether or not to include the analysis of established/likely mechanisms in Nick Birkett's chapter. In the absence of further comments beyond those provided by Kurt Straif, I wonder if the most expedient approach would be to simply omit the analysis of established/likely mechanisms in Birkett et al, along with the short cross-reference to this analysis in Krewski et al. [As the WPs have not seen this analysis, it could also lead to a further round of discussion among the Workshop Participants about the relevance and/or interpretation of our analysis of established/likely mechanisms.]

I like the inclusion of both Figure 2X and the addition to item 9 if the consensus statement, but would prefer not to make this decision without input from others.

As soon as we have your response to questions 1 – 3 above, we can wrap up both Birkett et al and Krewski et al within a day or two.

Dan K.

CONSENSUS STATEMENT

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This statement is endorsed by participants[1] in the IARC Workshop on 'Tumour-site Concordance and Mechanisms of Carcinogenesis', held April/November 2012 in Lyon

Introduction

The *IARC Monographs Programme* is an international consensus approach to the identification of chemicals and other agents that may present carcinogenic hazards to humans. The *Monographs* assess the strength of the published scientific evidence for such identifications, which are based primarily on epidemiological studies of cancer in humans and bioassays for carcinogenicity in laboratory animals. Information that may be relevant to the mechanisms by which the putative carcinogen acts is also considered in making an overall evaluation of the strength of the total evidence for carcinogenicity to humans.

For the one hundredth volume of the *IARC Monographs*, a review was undertaken during 2008–2009 of all Group-1 human carcinogens previously identified in Volumes 1–99. There was value in a comprehensive review, as about half the human carcinogens had been last reviewed more than 20 years earlier. *Monograph* Volume 100 was organized in six parts covering *Pharmaceuticals* (Vol 100A), *Biological Agents* (Vol 100B), *Arsenic, Metals, Fibres, and Dusts* (Vol 100C), *Radiation* (Vol 100D), *Personal Habits and Indoor Combustions* (Vol 100E), and *Chemical Agents and Related Occupations* (Vol 100F). Volume 100 'A Review of Human Carcinogens' was published as a six-part book series in 2012.

IARC explored ways to strengthen the scientific outcome of Volume 100 by embarking on a review of the Group-1 human carcinogens with respect to cancer sites and mechanistic events, followed by supplementary analyses of cancer-site concordance between humans and experimental animals, and of mechanistic events deemed relevant to the carcinogenicity of these agents. Accordingly, this Scientific Publication on 'Tumour-site Concordance and Mechanisms of Carcinogenesis' was proposed.

To prepare for the supplementary analyses in this Scientific Publication, IARC had asked the six Working Groups for Volume 100 to collect additional information, not routinely developed before, (a) on cancer sites in humans for which there was *sufficient evidence* or *limited evidence* in epidemiological studies, (b) on cancer sites with *sufficient evidence* in experimental animals, and (c) on established and likely mechanistic events involved in the cancers observed in humans or experimental animals.

To further develop this Scientific Publication, the *IARC Monographs Programme* convened a group of international scientific experts in a two-part Workshop, held in Lyon in April and November 2012. The main points of consensus, the conclusions and the recommendations of the Workshop participants are described below.

[1] L Banks, FA Beland, JA Bond, MC Bosland, JR Bucher, JC Caldwell, DM DeMarini, B Fubini, BD Goldstein, SS Hecht, K Hemminki, MA Hill, CW Jameson, AB Kane, RJ Kavlock, D Krewski, PF Lambert, R Melnick, CJ Portier, JM Rice, I Rusyn, MT Smith, L Stayner, BW Stewart, RL Ullrich, H Vainio, P Vineis, MP Waalkes, L Zeise

Tumour-Site Concordance

1. The results developed in Volume 100 confirm that the induction of cancer in experimental animals is relevant to the identification of a carcinogenic hazard to humans: all human carcinogens identified to date that have been adequately tested in animals have also been shown to cause cancer in animals.

2. For many human carcinogens, there is tumour-site concordance between humans and experimental animals; for many others, there is not. At the present time, the state-of-the-science does not support tumour-site concordance as a general principle. For example, although several agents are known to cause malignant melanoma in humans, this cancer is unknown in rats or mice.

3. Past evaluations have noted cancer in experimental animals at approximately 40 tumour sites in 15 organ and tissue systems. Use of standard terminology for these sites can facilitate the development of databases and their analysis and linkage to other sources of information. The Workshop participants recommend that future *IARC Monographs* Working Groups consider the anatomically based taxonomy of tumour sites that appears in this Scientific Publication in the analysis of concordance between sites where animal and human tumours arise.

4. The Workshop participants also recommend that the Evaluation section in a *Monograph* in respect of 'evidence in experimental animals' be expanded to include additional information for agents evaluated as exhibiting *sufficient evidence*. For such agents, an additional sentence following the relevant evaluation should refer to the recognized site(s) of tumorigenesis, by use of the specification system described in the chapter on Concordance (Krewski et al., this Volume)

5. Present analyses are expected to underestimate concordance. One reason is the limited power of many observational epidemiological studies that include populations and cancer sites that have not been adequately investigated. Another reason is that an agent was considered to cause cancer at a site in animals only if positive results were replicated at that site in another animal experiment; however, metabolic or mechanistic considerations might explain tumour induction at different sites in separate animal models.

6. Descriptive statistics of tumour sites identified to date may not be representative of future evaluations or of the incompletely characterized 'universe of human carcinogens.' The carcinogens evaluated in Volume 100 include several classes of agents that have been relative straightforward to investigate, for example, alkylating agents used in early cancer chemotherapy, viral agents that infect hundreds of millions of people, ionizing radiation that affects multiple anatomical sites, widespread exposures such as tobacco and alcohol, and chemical agents with long histories of occupational exposure at high levels. Agents evaluated in the future may have more subtle effects and different characteristics.

Mechanisms Involved in Human Carcinogenesis

7. The use of mechanistic data to identify human carcinogens is accelerating. Initially, *IARC Monographs* required *sufficient evidence* in humans for classification of an agent as *carcinogenic to humans*. Scientific understanding of the mechanisms of carcinogenesis, accompanied by the development of assays for studying mechanistic events, have led to new ways of identifying human carcinogens. Ethylene oxide was classified as *carcinogenic to humans* in 1994 based on strong evidence of genotoxicity in exposed humans, 2,3,7,8- tetrachlorodibenzo-*para*-dioxin in 1997 based on strong evidence of binding to the aryl hydrocarbon receptor and subsequent events, neutron radiation in 2000 based on the underlying radiation physics, some more agents between 2004 and 2010, and several additional agents in Volume 100.

8. Up until now, there has been no generally accepted method for organizing mechanistic data pertinent to the identification of carcinogenic hazards to humans. The Key Characteristics presented here offer a promising foundation for the structured evaluation of mechanistic information, and this should increase the utility of mechanistic evidence in future identifications of carcinogenic hazards and the transparency of the systematic review. The Workshop participants recommend that the *IARC Monographs Programme* continue to develop the Key Characteristics and to use them in its evaluations of carcinogenicity.

9. It is notable that in-vivo or in-vitro mechanistic data are often available in humans. For most key characteristics, when animal data are available for a key characteristic, human data are generally available, too. The observation that similar Key Characteristics are seen in animals and humans further supports the use of animal data in human cancer risk assessment.

10. There should be no expectation that all, or even most, Key Characteristics operate for any human carcinogen. No Key Characteristic is necessary for carcinogenesis, and negative results for one or more Key Characteristics are not an argument against the potential carcinogenicity of an agent. Observation of one or more Key Characteristics in exposed humans can increase the biological plausibility of less-than-*sufficient evidence* in humans. Observation of one or more Key Characteristics in experimental animals can increase confidence in the human relevance of *limited evidence* in experimental animals.

11. Human carcinogens act through multiple mechanisms. Interrelationships between mechanistic events should facilitate the development of more complex—but also more realistic—adverse-outcome networks. Past practice of according greatest concern in respect of known or putative carcinogens to those agents demonstrated to be genotoxic, relative to agents whose carcinogenicity appeared to be mediated by some other mechanism, possibly involving specific receptors, appears to be overly simplistic.

12. The objective of the *IARC Monographs Programme* is to identify carcinogenic hazards, not to

exhaustively list all mechanistic events and pathways that might contribute to carcinogenesis. Future coverage of mechanistic data should increase as the retrieval of such data becomes more systematic and the Key Characteristics are used as a framework for organization and analysis of mechanistic data.

13. Descriptive statistics of mechanisms identified to date may not be representative of future evaluations. Although genotoxicity is the Key Characteristic most exhibited by the human carcinogens identified to date, this may reflect the relatively greater attention paid in the past to the investigation of genotoxic agents. Future evaluations of carcinogenic agents may involve a larger set of mechanistic events and pathways, many that are not yet well developed or understood. Accordingly, future refinement of the Key Characteristics is to be expected, and this does not detract from the value in using them now in evaluations of carcinogenic hazards.

Key Characteristics of Human Carcinogens: An Exploratory Analysis of 86 Agents Known to Cause Cancer in Humans

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In collaboration other participants in the IARC Workshop on 'Tumour-site Concordance and Mechanisms of Carcinogenesis' which convened in Lyon April/November 2012[2]

Abstract

Since its inception in the early 1970s, the *Monographs Programme* of the International Agency for Research on Cancer (IARC) has evaluated 990 agents with respect to their carcinogenic hazard, has so far – through *Monograph* Volume 116 – identified 118 agents as *carcinogenic to humans*, and placed them in Group 1 of the IARC carcinogen classification scheme. Based on the review and update of Group-1 carcinogens included in Volume 100, 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. By extracting data on biological mechanisms of action from the *Monographs*, a database on the basis of 10 key characteristics of human carcinogens was assembled. After some grouping of similar agents, we examined the characteristic profiles of 86 Group-1 agents for which mechanistic information was available in the *IARC Monographs* through Volume 106, based on information derived from human in-vivo, human in-vitro, animal in-vivo, and animal in-vitro studies. The most prevalent key characteristic was genotoxicity, followed by altered cell proliferation and oxidative stress. All agents considered demonstrate multiple characteristics, with an average of four characteristics per agent, a finding consistent with the notion that human cancer development involves multiple pathways. Although a detailed comparison of the characteristics of different types of agent was not attempted here, the overall characteristic profiles for pharmaceutical agents and chemical agents and related occupations appeared similar. Further in-depth analyses of this rich database of characteristics of human carcinogens are expected to provide additional insight into the mechanisms of human cancer.

Introduction

Since the establishment of the *IARC Monographs Programme* within International Agency for Research on Cancer (IARC) in the early 1970s, the Agency has evaluated 990 agents for which there exists some evidence of an increased cancer risk to humans. The Agency has developed detailed criteria against

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which to evaluate the available scientific evidence on the cancer-causing potential of such agents. These criteria are described in the *Preamble to the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* (Cogliano et al., 2004; see http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf) and are used to weigh the evidence provided by human epidemiological studies and animal cancer bioassays, as well as by information on possible biological mechanisms of action, in order to classify agents in one of 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 to humans; and* Group 4: *The agent is probably not carcinogenic to humans.* These evaluations involve assessment of both the human and animal information as providing *sufficient evidence of carcinogenicity*, *limited evidence of carcinogenicity*, *inadequate evidence of carcinogenicity*, or *evidence suggesting lack of carcinogenicity*. The information on biological mechanisms of action may be evaluated as *strong*, *moderate* or *weak*, and is taken into consideration in the overall evaluation of all available evidence.

The role of mechanistic information in evaluating carcinogenicity has increased substantially during the history of the *IARC Monographs Programme*. In 1991, IARC convened a Working Group on the 'Use of Data on Mechanisms of Carcinogenesis in Risk Identification', to explore how mechanistic data could be used to identify agents with the potential to cause cancer in humans. The consensus report of the Working Group documented a number of mechanistic characteristics that were considered to be relevant to human carcinogenesis at that time, including: genotoxicity, cell proliferation, receptor mechanisms in mitogenesis, alterations in DNA repair, intercellular communication, and immune defects and immunosuppression (Vainio et al., 1992). Toxicokinetic and other variables were also identified as factors affecting multistage carcinogenesis. Since 1991, IARC and other organizations – e.g., the US National Toxicology Program (2014) and the US Environmental Protection Agency (2005) – have stressed the increasing importance of mechanistic information in cancer risk assessment. This is consistent with the current trend towards a general risk-assessment practice based on mode of action (Meek et al., 2013) and pathways of toxicity (Krewski et al., 2014; Bourdon-Lacombe et al., 2015; Cote et al., 2016), as well as dosimetric considerations (Gurusankar et al., 2016).

This chapter examines the available data on mechanisms of action of the Group-1 agents identified through Vol 106 of the *IARC Monographs* (Table 1), by use of the classification developed by Smith (this Volume) and Smith et al. (2016) who defined 10 key characteristics of human carcinogens. Information on these characteristics was extracted from the *IARC Monographs* based on guidance provided by the participants in the IARC Workshop on 'Tumour-site Concordance and Mechanisms of Carcinogenesis' (April/November 2012) and used to develop a database of key characteristics for Group-1 agents (see Al-Zoughool et al., this Volume). This chapter presents the results of an exploratory analysis of this database.

Methods

Key Characteristics

The present analysis is based on a systematic approach to the evaluation of human cancer mechanisms, which initially involved retrieval of information from the *IARC Monographs* on 24 toxicological endpoints identified as likely indicators of biological processes at the cellular and molecular level and thought to be relevant to carcinogenesis. Information on these 24 endpoints was derived from human in-vivo, human in-vitro, animal in-vivo, and animal in-vitro studies (see Al-Zoughool et al., this Volume). In their November 2012 meeting, the Workshop identified 10 broader key characteristics that reflect different mechanistic pathways (see Smith, this Volume; and Smith et al., 2016). This chapter focuses on the key characteristics of the Group-1 agents identified through Volume 106.

Smith (this Volume) and Smith et al. (2016) describe ten key characteristics of human carcinogens, as listed in Table 2. The toxicological endpoints initially considered by the Workshop and used as indicators of these characteristics are also noted in Table 2. A brief summary of each of these characteristics and the associated toxicological endpoints is provided below. See Smith (this Volume) and Al-Zoughool et al. (this Volume) for a more detailed discussion.

Characteristic 1: Is Electrophilic or Can Be Metabolically Activated to Electrophiles. The first characteristic refers to agents that act as electrophiles themselves or that can be metabolized to form electrophile(s). Electrophiles are molecules that undergo chemical reactions by accepting electrons. An electrophile can react with cellular macromolecules such as DNA, RNA and proteins to form adducts. Some chemical carcinogens are direct-acting electrophiles (e.g., formaldehyde; sulfur mustards and ethylene oxide), whereas others require biotransformation by enzymes in a process termed metabolic activation (e.g., polycyclic aromatic hydrocarbons and benzene) (Miller, 1970).

Characteristic 2: Is Genotoxic. Genotoxicity is the ability to induce DNA damage that leads to the formation of DNA adducts, single- or double-strand breaks or other chromosomal alterations, as measured by three associated toxicological endpoints: (a) *DNA damage*: an alteration in the chemical structure or integrity of DNA, and includes a break in a DNA strand, and/or chemical modifications such as covalent binding to the nucleotide bases (Hoeijmakers, 2009); (b) *Gene mutations*: changes in the normal nucleotide sequence of cellular DNA that may have a central role in human carcinogenesis (Ding et al. 2008); (c) *Cytogenetic effects* reflect damage to chromosomes, including DNA breakage, or the rearrangement, gain or loss of chromosome fragments (Snyder 2010).

Characteristic 3: Alters DNA Repair or Causes Genomic Instability. Alterations in DNA repair result in defects in processes that monitor and correct DNA replication fidelity that can confer strong mutator phenotypes resulting in genomic instability. The associated toxicological endpoint is an indicator of *DNA-repair alteration*.

Characteristic 4: Induces Epigenetic Alterations. Induced epigenetic alterations are stable changes in gene expression and chromatin organization that are independent of the DNA sequence itself, and can be mitotically inherited through cell division. Epigenetic phenomena include: genomic imprinting, X-chromosome inactivation and global reconfiguration of the DNA methylome, changes in chromatin compaction states and histone modification patterns, and altered microRNA (miRNA) expression. These phenomena occur during organ development and contribute to the lineage-specific epigenome that is

maintained over the lifetime of an organism. Many of these phenomena have been shown to be altered during carcinogenesis.

Characteristic 5: Induces Oxidative Stress. Oxidative stress results from an imbalance in reactive oxygen formation and detoxification within cells and tissues. The resulting reactive oxygen species induce a cascade of events that can include DNA mutation and oxidative DNA damage. Both are key events in carcinogenesis (Klaunig et al., 2011). Toxicological indicators of *oxidative stress* are discussed by Al-Zoughool et al. (this Volume).

Characteristic 6: Induces Chronic Inflammation. Induced chronic inflammation can arise from persistent infection (e.g., with HPV, *H. pylori*) as well as from external irritants (e.g., silica, asbestos fibers). Persistent infection and chronic inflammation disrupt local tissue homeostasis and alter cell signalling, leading to the recruitment and activation of inflammatory cells. Strong links exist between inflammation and the induction of oxidative stress and genomic instability, such that it is difficult to separate out the importance of each of these mechanisms. This linkage to other pathways may be the basis of the relationship between chronic inflammation and cancer (Multhoff & Radons, 2012).

Characteristic 7: Is Immunosuppressive. Immunosuppression refers to an induced reduction in the capacity of the immune system to respond effectively to foreign antigens, including antigens on tumour cells. The immune system also plays a major part in the inflammatory response to injury.

Characteristic 8: Modulates Receptor-mediated Effects. Modulation of receptor-mediated effects can occur when agents mimic the structure of endogenous ligands that bind to cells and activate cell-surface receptors or intracellular receptors, thereby inducing or modifying a plethora of cell transduction pathways that stimulate cell proliferation. *Receptor-mediated* effects can induce *hormonal effects* whereby external agents can interfere with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body. They can also demonstrate reactivity similar to endogenously produced hormones, which can lead to changes in homeostasis, reproduction, development, or behaviour.

Characteristic 9: Causes Immortalization. Immortalization refers to a situation where the cell is induced to evade normal cellular senescence and will proliferate indefinitely. In culture, normal cells have a fixed number of replication cycles before they enter cellular senescence and stop replicating. This is frequently associated with *activation of telomerase* (Willeit et al. 2010), and plays a critical part in carcinogenesis (Reddel, 2014). Carcinogenesis may involve activation of a telomerase that prevents loss of telomere length, leading to immortalization of cells (Willeit et al. 2010).

Characteristic 10: Alters Cell Proliferation, Cell Death or Nutrient Supply. The first of these characteristics – cell proliferation – refers to alteration in the rates of cell growth within a tissue. It may be a direct effect or a secondary regenerative effect after induction of cell death by cytotoxic agents. Two associated toxicological endpoints are (a) C*ell-cycle effects*, i.e. alterations in the functioning of the complex series of factors controlling the cell cycle and cell division, which have been associated with carcinogenesis (Diaz-Moralli et al. 2013); and (b) *Alteration of cell-signaling pathways*, which relates to the ability of the agent to interfere with cell-signalling pathways leading to expression of a carcinogenic

trait/phenotype in the cell. For cell death, necrosis triggers the invasion of cells such as macrophages into the affected area, and enhances the proliferation and spread of cancer cells. Defects in programmed cell death can cause cancer; evasion of apoptosis is a requirement for both neoplastic transformation and sustained growth of cancer cells. Adequate cell nutrition is essential to proliferating cancer cells and agents that promote or inhibit the growth of blood vessels (angiogenesis) will affect tumour growth.

Group-1 Agents included in the Analysis

Since 1971, the IARC has evaluated the potential cancer hazard of 990 agents. As of June 2016, 118 agents met the criteria to be classified as a Group-1 human carcinogen (Table 1). Volume 100 of the *IARC Monographs* provides a review and update of the 107 Group-1 agents identified as of 2009. This Volume was published in six parts, focusing on pharmaceuticals (IARC, 2012a; *Monograph* Volume 100A); biological agents (IARC, 2012b; Vol 100B); arsenic, metals, fibres, and dusts (IARC, 2012c; Vol 100C); radiation (IARC, 2013d; Vol 100D); personal habits and indoor combustions (IARC, 2012e; Vol 100E); and chemical agents and related occupations (IARC, 2012f; Vol 100F), respectively.

Since the publication of Vol 100, mechanistic information on two additional Group-1 agents – diesel-engine exhaust (Vol 105; Benbrahim-Tallaa et al., 2012) and trichloroethylene (Vol 106; Guha et al., 2012) – has become available. Had these two agents been evaluated within Vol 100, they would have been included in Vol 100F; they have therefore been listed with 'other chemicals and related occupations' in Vol 100F*.

Although additional Group-1 agents have since been identified (Table 1), the present analysis is restricted to Group-1 agents identified through Volume 106, this being the most recent volume for which mechanistic information was available at the time of the present analysis. Group-1 agents excluded from the present analysis are polychlorinated biphenyls (PCBs) and dioxin-like PCBs (Vol 107; Lauby-Secretan et al., 2013), outdoor air pollution and particulate matter from outdoor air pollution (Vol 109; Loomis et al., 2013); 1,2-dichloropropane (Vol 110; Brenbrahim-Tallaa et al, 2014); fluro-edenite amphibole asbestos and occupational exposures associated with the Acheson process used in the manufacture of silicon carbide fibres (Vol 111; Grosse et al., 2014); lindane (Vol 113; Loomis et al., 2015); and processed meat (Vol 114; Bouvard et al., 2015).

In some cases, the discussion of mechanisms of action in the Sections 4 of the *IARC Monographs* is based on groups of agents thought to act via the same mechanism. For example, haematite mining with exposure to radon (underground), Pu-239, Th-232 (as Thorotrast), Ra-224 and its decay products, Ra-226 and its decay products, Ra-228 and its decay products, and internalized radionuclides that emit alpha-particles are discussed in the *Monographs* as a group with the same mechanism of action. Birkett et al. (this Volume) reviewed the mechanistic information for 109 Group-1 agents identified in the *IARC Monographs* through Volume 106. The 86 Group-1 agents for which unique mechanistic summaries are provided in the *IARC Monographs* through Volume 106 are listed in Table 3, along with their relationship to the 111 distinct agents identified through Volume 109 used by Krewski et al. (this Volume) in a parallel analysis of concordance between animal and human tumours and tumour sites.

Database of Mechanistic Characteristics

We assembled a database of toxicological endpoints for the 86 Group-1 agents identified by the IARC through Volume 106 of the *IARC Monographs* (see Al-Zhoughool et al., this Volume). The database includes information from in-vivo and in-vitro studies from humans and animals. Information on the 24 toxicological endpoints was retrieved from Sections 4 of the Monographs (Al-Zoughool et al., this Volume). Recognizing that the mechanistic information included in the *Monographs* is not intended to provide a complete summary of scientific literature on cancer mechanisms, we conducted PubMed searches to identify evidence of any of the 24 toxicological endpoints linked to these agents that was not recorded in the *IARC Monographs* (Birkett et al., this Volume). The mechanistic database distinguishes information derived from the *Monographs* from that found in our PubMed search, thereby permitting an assessment of the extent to which Sections 4 of the IARC Monographs captured all relevant information on these endpoints. The analyses in this chapter are restricted to information taken directly from the *IARC Monographs*: Birkett et al. (this Volume) present the results of a sensitivity analysis incorporating the additional information obtained through our PubMed search.

Following collection of information on the toxicological endpoints identified by the Workshop at its first meeting, the database of key characteristics was then created by mapping the 24 toxicological endpoints to the 10 characteristics as indicated in Table 2. As noted by Al-Zoughool et al (this Volume), two of the toxicological endpoints – susceptibility and changes in gene expression – did not link to any of the key characteristics, and thus were not included in the development of the database of key characteristics. As the database includes information derived from human in-vivo, human in-vitro, animal in-vivo and animal in-vitro sources, it is possible to aggregate this information according to human and animal sources (by combining across in-vivo and in-vitro sources) or according to in-vivo and in-vitro sources (by combining across human and animal sources). Of primary interest here is aggregation across all four sources combined in order to obtain an overall indicator of whether or not any of the ten mechanistic characteristics is associated with each of the 86 Group-1 agents of interest.

Statistical Analysis

Descriptive statistical methods were used to explore the key characteristics associated with the 86 Group-1 agents, beginning with a tabulation of the number of agents demonstrating any of the ten characteristics, both overall and stratified by source of information. In order to evaluate the extent to which the Group-1 agents demonstrated more than one key characteristic, the number of agents demonstrating multiple characteristics was also tabulated. A 'heat map' showing the number (0, 1, 2, 3 or 4) of sources of information (human in-vivo, human in-vitro, animal in-vivo, animal in-vitro) supporting a given characteristic for a specified agent was prepared to evaluate the consistency of information provided by different sources. Overall mechanistic profiles were also tabulated by type of agent (pharmaceuticals; biological agents; arsenic, metals, fibres and dusts; radiation; personal habits and indoor combustions; and chemicals and related occupations) in order to identify possible differences in mechanistic profiles by agent type.

Results

The key characteristics of the 86 Group-1 agents considered here are summarized in Figure 1.The most prevalent mechanistic characteristic is genotoxicity, followed by cell proliferation, oxidative stress, electrophilicity, and chronic inflammation. The vast majority of agents demonstrate genotoxicity as one of their mechanistic properties, with 85 of the 86 agents considered having evidence of this characteristic. Evidence of genotoxicity was provided by expression of the following toxicological endpoints: DNA damage, gene mutations, and cytogenetic effects (including chromosomal aberrations, micronucleus formation, and aneuploidy).

Figure 2 shows the key characteristics exhibited by the 86 agents classified according to the source of data (human in-vivo, human in-vitro, animal in-vivo, and animal in-vitro studies) on these characteristics. Information on all the mechanistic characteristics was available to different degrees from all four sources. Information on genotoxicity was available from each of the four sources for at least 65% of the agents. Human in-vitro studies contribute the majority of the evidence on six of the ten key characteristics, including altered DNA repair and genomic instability, oxidative stress, chronic inflammation, receptor-mediated effects, immortalization, and altered cell proliferation/death/nutrition. The prominence of in-vitro sources of information on most key characteristics could be attributed to the fact that many of these characteristics are components of signaling pathways that are often studied in in-vitro test systems. In-vivo animal studies were more prevalent sources of mechanistic information than in-vitro animal studies for seven key characteristics: electrophilicity, genotoxicity, chronic inflammation, oxidative stress, receptor-mediated effects, epigenetic alterations, and immunosuppression.

The prominence of human studies as sources of information on the key characteristics of human carcinogens may be attributed to the increasing use of molecular and genetic markers in human studies. Epidemiological studies conducted in the occupational or general environment often analyze biomarkers of DNA adduct formation, clastogenic effects, and gene mutations, all of which reflect DNA damage. As a consequence, human in-vivo studies are a major source of information on genotoxicity.

Figure 3 shows the number of agents demonstrating multiple characteristics as evidenced from studies in animals and in humans. The 86 Group-1 agents considered here demonstrate an average of 3.8 key characteristics, with the modal value being two characteristics exhibited by 26 agents. All agents demonstrate at least one key characteristic, with one agent demonstrating nine characteristics and 12 agents showing six. No agent demonstrated all 10 key characteristics.

Figure 4 presents a heat map indicating the strength of evidence of the different characteristics for the 86 individual Group 1 agents. The intensity of the color reflects the number of sources of evidence (human in vivo, human in vitro, animal in vivo and animal in vitro studies) on the key characteristics for each agent. As in Figure 1, the single most prominent characteristic is genotoxicity: the majority of agents showed a positive response for genotoxicity in at least one of the four sources of information, with many agents providing evidence of genotoxicity from more than one source. For some agents (e.g., all radiation sources, some pharmaceutical agents, and some chemical agents), genotoxicity was demonstrated in all four test systems, confirming that genotoxicity is central to the carcinogenic pathways of these agents.

Figure 4 also shows that the majority of agents exhibit multiple key characteristics, with evidence drawn from more than one source of mechanistic information. Radiation sources and tobacco smoke are associated with many of the key characteristics, suggesting that these agents act by multiple pathways.

A number of Group-1 agents, including several occupational exposures, are complex mixtures of chemical and other substances. Coal-tar pitch, occupational exposure to soot, and coke production all share similar characteristics, likely due to the strong presence of polycyclic aromatic hydrocarbons, although other factors such as the nature of inorganic substances and sulphur composition could also play a role. Other occupationally relevant agents (e.g. rubber manufacture and aluminium production), demonstrate only a single key characteristic, though this may reflect the difficulty of testing for other characteristics in these occupational exposure situations.

Figure 5 shows the key characteristics of the six categories of Group-1 agents considered in Vol 100: pharmaceutical agents; biological agents; arsenic, metals, fibres and dusts (AMFD); radiation; lifestyle-associated agents; and chemical agents. Genotoxicity is the most frequent characteristic expressed by pharmaceuticals, AMFD, lifestyle-related exposures, and chemical agents, and is exhibited by all agents mentioned under radiation. Genotoxicity and cell proliferation are prominent characteristics of the biological agents. None of the biological agents demonstrated receptor-mediated-effects or electrophilicity, and none of the lifestyle-related agents appeared to act through receptor-mediated effects or immunosuppression. There are five radiation agents, all demonstrating the following key characteristics: genotoxicity; altered DNA repair; immunosuppression; chronic inflammation; oxidative stress; immortalization; and altered cell proliferation/death/nutrition. The profiles of key characteristics for pharmaceutical agents and chemical agents are remarkably similar, possibly reflecting the fact that despite their different exposure circumstances, some of the chemotherapeutic agents and chemical agents interact with the same chemical entities *via* similar cancer mechanisms.

Discussion

The present analysis of key characteristics of 86 agents determined by IARC to be human carcinogens was based on mechanistic information retrieved from the *IARC Monographs* (Birkett et al.; Al-Zoughool et al., this Volume). The profiles of key characteristics of these agents show a number of interesting patterns. First, all agents exhibited multiple characteristics, an observation consistent with previous findings on the complexity and heterogeneity of carcinogenic pathways (Hanahan and Weinberg, 2011; Roessler et al. 2014; Baker et al. 2014; Floor et al. 2012; Pickup et al. 2014). Biological agents, ADMF, lifestyle and radiation agents demonstrated a wide spectrum of biological activity. Radiation has been linked to many hallmarks of cancer (Boss et al. 2014): this mechanistic profile, with multiple pathways being followed by most radiation agents, is consistent with the broad spectrum of tumours associated with exposure to ionizing radiation (Krewski et al., 2016). Viral oncogenesis is also multifaceted, with the multistep nature of viral oncogenesis thought to be influenced by host genetic variability (Mesri et al. 2014).

Genotoxicity was the most prevalent mechanistic characteristic, demonstrated by 85 of the 86 agents considered, possibly reflecting the fact that the process of carcinogenesis necessarily involves genomic changes that must be fixed during cell replication. This finding is consistent with an earlier evaluation of 180 Group-1, -2A and -2B agents conducted by Bartsch & Maleveille (1989), who reported that 80-90% of the agents in these three categories demonstrated genotoxic characteristics. In the present analyses, genotoxicity was considered to include the following endpoints: DNA damage, clastogenic effects (including chromosomal aberrations, micronucleus formation, and aneuploidy), and gene mutations. Information drawn from the *Monographs* showed that the overwhelming majority of the agents examined here induce one or more of these endpoints. Even biological agents such as viruses that act primarily through non-genotoxic mechanisms induce cytogenetic effects and mutations as secondary events through chronic inflammation and oxidative stress.

Some caution must be used in interpreting the distribution of key characteristics across the Group-1 agents considered here. It is possible that the near universality of genotoxicity as a carcinogenic mechanism may be related to the way the *IARC Monograph* Working Groups prepared their reports, with emphasis on the reporting of genotoxicity data. This would have been partially mitigated by the inclusion of mechanistic information from outside the *IARC Monographs* in the preparation of the mechanistic database evaluated separately here by Birkett et al (this Volume). It should also be noted that the *Monographs* were published over a long time span, extending from 1970 to the present (Saracci & Wild, 2015). Studies of agents in earlier Volumes would have focused on changes such as DNA damage that could have been detected by the techniques available at that time. These agents may not have been evaluated exhaustively for more recently identified biological pathways such as those involving the multi-factorial nature of carcinogenesis, and the multiplicity of pathways operating during the process of agent-induced cancer.

Another limitation of the present results is that they are based on the information on mechanisms in Section 4 'Other Relevant Data' of the *Monographs*. As we did not undertake a full series of systematic reviews of the entire body of literature on biological mechanisms of action for all agents, the database may not reflect all characteristics of the different agents. As a sensitivity analysis to examine the extent to which the Monographs captured most of the relevant information in this regard, Birkett et al. (this Volume) conducted a supplementary PubMed search to identify additional information on the key characteristics not cited in the *Monographs*. While this sensitivity analysis was not based on an exhaustive search, it did identify additional information sources (the most notable being the identification of evidence of six additional agents demonstrating receptor-mediated effects, beyond the nine noted in Figure 1). Nonetheless, the findings are largely compatible with those presented (see Birkett et al., this Volume, for further details).

In Supplemental Material, Birkett et al. (this Volume) also examined key characteristics reflected by 'established' and 'likely' mechanistic events associated with Group-1 agents, as documented by the Working Groups that conducted the evaluations of these agents. As the Working Groups focused only on the main 'established' and 'likely' mechanistic events demonstrated by these agents, this sensitivity analysis identified fewer key characteristics that did the analysis presented in this Chapter, which is based on abstraction of all mechanistic information cited in Section 4 of the IARC Monographs.

As the *IARC Monographs Programme* has evolved from its inception in 1970 through to the present time, the guidelines for carcinogen identification as set out in *Preamble* have been updated from time to time, with increasing emphasis on the use of mechanistic information in the most recent updates. Nonetheless, the identification of Group-1 agents continues to rest heavily on the availability of *sufficient evidence* of carcinogenicity in epidemiological or clinical studies. Of 111 distinct agents in Group 1 through *Monograph* Volume 109, no less than 102 demonstrated *sufficient evidence* of carcinogenicity in humans, with the remaining 9 agents being in Group 1 on the basis of mechanistic upgrades (see Table 4 in the Concordance chapter by Krewski et al., this Volume). Despite the heavy reliance on human data in identifying agents that may increase human cancer risk, the Sections 4 of the *IARC Monographs* increasingly provide detailed descriptions of the mechanisms by which agents under review may act, including agents not assigned to Group 1.

The epigenetic characteristics of Group-1 agents considered in Volumes 100A–E were previously assessed by Herceg et al. (2013). As in the present analysis, these authors used DNA methylation, histone marks, and miRNA indicators of epigenetic effects. Considering information from both the *IARC Monographs* and the general scientific literature, they identified 22 of these 74 Group-1 agents (29.7%) as demonstrating epigenetic effects. The present analysis, which examined Group-1 agents in *Monographs* 100A–F and well as Volumes 105 and 106 identified 27 of 86 Group-1 agents (31.4%) as having epigenetic characteristics.

In an earlier evaluation, Hernández et al. (1989) reported that 45 of the 371 agents (12%) in Groups 1, 2A and 2B at the time of their analysis were not genotoxic. In their study, an agent was considered non-genotoxic if it gave negative results in the Ames assay, as well as in the mouse lymphoma assay, the in-vitro chromosomal aberration test, the in-vitro micronucleus test, the in-vivo micronucleus test or the in-vivo chromosomal aberration test in rodent bone-marrow. These results support the role of non-genotoxic pathways in carcinogenesis, an observation that is reinforced by the prevalence of multiple characteristics of human carcinogens not associated with genotoxicity in the present analysis.

The fact that the great majority of carcinogenic agents demonstrate multiple mechanistic characteristics may have implications for the shape of the corresponding exposure-response relationships. Different mechanisms may be prominent at different levels of exposure, leading to dose-dependent transitions in the dose-response curve (Slikker et al., 2004a). In an accompanying paper (Slikker et al., 2004b) these authors note that such dose-dependent transitions can occur when the mechanism includes metabolic activation with agents such as butadiene (Group 1) and methylene chloride (Group 2A); changes in cell kinetics with formaldehyde (Group 1); and adduct formation and DNA repair with vinyl chloride (Group 1). Swenberg et al. (2012) note that formaldehyde causes DNA–protein cross-links (DPC), with disproportionately larger amounts of DPC formed at concentrations above 6 ppm due to saturation of glutathione detoxification pathways. Formaldehyde induces marked cell proliferation in the nasal epithelium in animal models at higher doses. Formaldehyde has also been shown to downregulate miRNAs in human miRNA microarrays, possibly due to apoptosis signalling. Such dose-dependent effects lead to marked non-linearity in the dose-response curve for nasal cancers induced by formaldehyde.

In order to ensure that all relevant evidence on the 10 key characteristics of human carcinogens developed by Smith (this Volume) and Smith et al. (2016) is taken in to account in future evaluations of agents that may cause cancer in humans, a carefully designed systematic review of the scientific literature would be required in conjunction with each evaluation. However, to conduct a series of comprehensive systematic reviews of the key characteristics of all 86 agents considered in the present analysis would represent a considerable effort, and as such was not attempted as part of the present project. The expert opinion of future IARC Working Groups charged with evaluating the mechanistic data on new agents selected for evaluation by the *IARC Monographs* would be of considerable value in this regard, but would ideally be supported by a concomitant systematic review of the relevant scientific literature on the key characteristics in order to ensure that the analysis be as complete as possible.

Another issue that arises when discussing key characteristics of human carcinogens is whether indirect effects should be considered. Many agents have a direct carcinogenic effect, but in other cases the carcinogenic characteristic is the result of a secondary event along the mechanistic pathway. For example, cell proliferation can arise due to a direct action of the agent on the cell, or indirectly, due to cytotoxicity that stimulates cell proliferation to replace cells, through alterations in cell signalling without cytotoxicity, or *via* inhibition of cell proliferation that then results in selection of an altered clone of cells with a high proliferation rate. While the downstream effect is the same (increased cell proliferation), the mechanism leading to that result can be different. A similar issue arises with genotoxicity where many agents are not directly genotoxic but cause DNA damage by stimulating a chain of molecular changes (e.g. chronic inflammation). The current database does not contain the information needed to address these issues and cannot be used to draw conclusions about the detailed mechanism of action of an agent.

It should be noted that the ten key characteristics should be considered as characteristics rather than as mechanisms, in part because the analysis does not address the sequence of events involved in carcinogenesis. For example, if we are interested in the carcinogenic mechanism of action for a genotoxic agent that requires metabolic activation, the mechanism needs to consider the entire metabolic pathway. If the agent is not metabolized to produce an electrophile, DNA damage will not occur. In such a case, characteristics subsequent to DNA damage also would not be observed. This is also apparent for characteristics such as chronic inflammation, which acts through the production of oxidative stress, release of cytokines, and stimulation of cell proliferation, which ultimately produces DNA damage.

The results of the present analysis can provide a basis for future efforts to categorize mechanistic data for carcinogens through a systematic review process. A full systematic review of all agents and all potential carcinogenic mechanisms is an intimidating prospect. However, such a review would provide a more comprehensive examination of mechanisms, since it would include studies that failed to find effects. It might also support a process involving a sequence of mechanistic steps and mechanistic characteristics relevant to the development of cancer in humans.

The importance of systematic review in assembling all relevant evidence on a particular issue has been emphasized in the recent review of the US EPA's Integrated Risk Information System (IRIS) (NRC, 2014), and is currently being implemented within the IRIS program as a way of summarizing all relevant data in a comprehensive and reproducible manner. The US EPA is also currently supporting the

development of software tools specifically designed for systematic review of toxicological and epidemiological data (ICF, 2014).

The strong evidence linking genotoxicity to carcinogenesis is consistent with epidemiological data and experimental research. Genotoxic effects include the formation of DNA adducts or induction of single- and double-strand DNA breaks. Several lines of evidence from epidemiological studies and in experimental animals and model systems have shown that DNA adducts are strongly associated with cancer (Kriek et al. 1998, Phillips et al. 2014). Some genotoxic effects can lead to gene mutation, an important event in the pathway towards carcinogenesis, especially if it involves oncogenes or tumour suppressor genes. Chromosomal changes are another type of genetic alteration that are widely displayed in many tumours, especially solid tumours. Most tumour cells display aneuploidy and, for some tumours, characteristic chromosomal abnormalities have been identified (e.g. the Philadelphia Chromosome in chronic myeloid leukaemia). Consequently, agents that induce genomic instability should be regarded as potential carcinogens.

Recently, a carcinogenic mechanism not linked to any of the key characteristics studied here has achieved prominence in the literature. Tomasetti & Vogelstein (2015) have argued that stem-cell division rates can explain variation in cancer occurrence rates at different sites, with random mutations during DNA replication in normal stem cells increasing cancer risk in proportion to the rate of stem-cell division in different tissues. Strong positive correlations between the rates of stem-cell division and lifetime risk of cancer in different tissue sites are documented in support of this hypothesis. As an example, the authors compare cancer rates in melanocytes and basal epidermal cells of the skin, both of which are subject to similar exposure to ultra-violet radiation, a Group-1 carcinogen. Basal cell carcinomas are much more common than melanomas, and basal cells undergo a higher number of divisions than do melanocytes, providing support for the authors' main hypothesis. Overall, Tomasetti & Vogelstein suggest that only a third of the variation in cancer risk may be due to environmental factors or inherited predispositions, with the majority associated with random mutations, or 'bad luck'. Pointing to methodological limitations, including the focus on less common cancers that make only a small contribution to human cancer burden, the International Agency for Research on Cancer (IARC, 2015) observed that strong geographic and temporal variation in the risk of more common cancers is consistent with environmental causes. Based on current knowledge, IARC suggested that nearly half of all human cancers are associated with preventable causes, and that further research will continue to identify additional modifiable risk factors for human cancer. Nonetheless, stem-cell division would appear to be a mechanistic characteristic of human cancer that is worthy of further investigation.

The complexity of the pathways involved in carcinogenesis and the fact that cellular response to carcinogen exposure is modulated by host-cell physiology, genetics and other variables have prompted development and application of sensitive assays that measure toxicity pathways and perturbations in molecular functioning of the cell. The newly proposed testing paradigm (Krewski et al. 2014) focuses on high-throughput screening to detect changes in the cell's molecular pathways in response to chemical exposure. This new paradigm would be useful in comprehensive cancer risk assessment and would be able to detect distinct and key mechanistic pathways operating after carcinogen exposure. Similar to this initiative, the Kyoto Encyclopedia of Genes and Genomes (KEGG) website has compiled a comprehensive list of pathways associated with specific diseases (see the KEGG pathway database at

http://www.genome.jp/kegg/pathway.html). KEGG also identified major in-vitro assays that can be used to detect targets of these pathways. This attempt to understand the biological mechanisms of carcinogenesis is consistent with current practice of using in-vitro assays to detect changes in critical signaling and other molecular pathways in cancer development, as proposed by Krewski et al. (2014).

Further Analyses

The extensive database on key characteristics of human carcinogens developed here offers considerable potential for further analysis. More in-depth analyses are underway to explore the level of agreement between mechanistic data derived from human and animal sources, as well as from in-vivo and in-vitro sources, issues that have received only limited attention here. An analysis of the key characteristics demonstrated by Group-1 agents on a site-specific basis is also planned: should agents that cause tumours at a specific sites, such as the lung or liver, be shown to demonstrate similar characteristics, this could provide new insights into site-specific carcinogenesis.

Although the present analysis found that the great majority of Group-1 agents demonstrated multiple key characteristics, with an average of four characteristics per agent, no attempt was made to conduct a multivariate analysis of these characteristics to determine if similar agents tended to express similar characteristics. Recalling that pharmaceuticals as a class demonstrated a mechanistic profile similar to that of the chemical agents, it is possible that the chemotherapeutic agents and some of these chemical agents act *via* the same cancer mechanisms. Cyclophosphamide and benzene (once used as a chemotherapeutic agent) may have some commonality in this respect, as might treosulfan and butadiene through the formation of the same diepoxide. Further study of these two groups, both in terms of mechanism of action and tumour concordance, may provide insight into tumours resulting from long-term exposure to chemotherapeutics.

Searching for patterns within homogeneous classes of agents would also be of future research interest. For example, one could examine mechanistic patterns within subgroups of pharmaceuticals, including: antineoplastic agents, hormonal products, immune-suppressants, and analgesic mixtures. In a similar vein, Shin et al. (2015) have recently employed bioactivity profiles for 38 agents derived from high-throughput in-vitro assays to investigate patterns of toxicity associated with different scenarios of use.

Exposure to a single agent may result in more than one type of tumour, perhaps through different pathways involving different mechanistic characteristics. It would be of interest to examine the key characteristics for agents associated with specific tumour types. This would extend the work of Krewski et al (this Volume) that examined concordance between animals and humans for 39 tumour sites and 15 organ and tissue systems, based on the database on tumours and tumour sites in humans and experimental animals developed by Grosse et al. (this Volume). The profiles of key characteristics of agents associated with specific tumour sites could be examined to obtain additional insights into the mechanisms by which specific tumours occur. Of particular interest in this regard would be to analyse whether or not certain tumour sites demonstrate signature profiles.

Baker et al. (2015) have recently applied supervised machine learning techniques to classify PubMed literature according to the hallmarks of cancer. In a case study of basal cell carcinoma and

melanoma, only 46,727 of 121,488 abstracts from their original systematic literature search were classified as relevant, reflecting the potential time savings that may be achieved through automatic classification.

Extending the mechanisms database to include additional information such as structural alerts relevant to carcinogenesis could also be informative. Although the present version of the mechanisms database does include the IUPAC International Chemical Identifier (InChI) for key chemical coding (IUPAC, 2015; Stein et al., 2003), this information has not been taken into account in the analyses completed to date. One possible source of auxiliary information on toxicological endpoints that may be related to the ten mechanistic characteristics is the US Environmental Protection Agency's ToxCast Program (Judson et al., 2014; Knudsen et al., 2015), which now includes in-vitro, in-vitro, and in-silico data on diverse toxicological endpoints for over 10,000 chemical substances, some of which overlap with the set of Group-1 agents considered in this chapter. The ToxCast database also includes information on several hundred toxicological assays, which could enrich the database of key characteristics used in the present analysis.

Future evaluations of new agents undertaken within the *IARC Monographs* could include a comprehensive evaluation of the ten key characteristics articulated by Smith (this Volume) and Smith et al. (2016), based on a systematic review of the relevant scientific literature in support of the Working Group's deliberations. This has been successfully attempted in recent evaluations of red and processed meats (Bouvard et al., 2015) and organochlorine insecticides and chlorphenoxy herbicides (Loomis et al., 2015): the corresponding *Monographs* are currently undergoing editorial review and checking within IARC.

There could be value in re-visiting the present retrospective analysis of the 86 Group-1 agents identified through *Monograph* Volume 106, both with respect to the conduct of a series of comprehensive systematic reviews on the ten key characteristics of these agents, followed by an in-depth evaluation of the findings of the systematic review by experts in relevant disciplines. The development of criteria for evaluating the weight of evidence for the key characteristics, similar to that included in the *Preamble to* the *IARC Monographs* for human and animal data (IARC, 2006) might be contemplated at that time. Group-1 agents identified beyond Volume 106 for which mechanistic information had become available could also be included in such an analysis.

An alternative approach to extracting information on the 10 key characteristics of human carcinogens would be to apply the machine learning techniques and biomedical text mining methods described by Baker et al. (2015) to identify articles associating these key characteristics with specific Group-1 agents in an automated fashion. Because of the enormity of a full systematic review of mechanistic information on all Group-1 agents, the use of automated search algorithms of this type could offer considerable efficiency gains in identifying potentially relevant mechanistic information. Although this approach could expedite identification of relevant articles, expert opinion and application of weight-of-evidence criteria would still have value in terms of reducing the error rates in assigning key characteristics to specific agents.

Conclusion

In this chapter, we examined the key mechanistic characteristics of human carcinogens defined by Smith (this Volume) and Smith et al. (2016) for the 86 Group-1 agents that have been established as causes of human cancer by the IARC. Similar mechanistic information was derived from multiple sources, including human in-vivo, human in-vitro, animal in-vivo and animal in-vitro studies. The prominence of in-vitro sources for the majority of the mechanistic characteristics is consistent with the increasing reliance on in-vitro tests focusing on toxicity pathways and modes of action (Krewski et al., 2014). All 86 agents demonstrated at least one of the key characteristics, with an average of 3.8 characteristics per agent. Genotoxicity was the most prevalent characteristic, demonstrated by 85 of 86 agents, followed by cell proliferation and oxidative stress. A comparison of the mechanistic profiles for the six broad classes of agent considered in Volume 100 of the IARC Monographs – pharmaceutical agents, biological agents; arsenic, metals, fibres and dusts (AMFD); radiation agents; lifestyle agents; and chemical agents – revealed similar profiles for pharmaceutical and chemical agents.

In considering the results presented in this chapter, it is important to emphasize that these mechanistic analyses represent a first step in understanding the biological mechanisms by which cancer may occur in humans. Although considerable effort was expended in developing the database of key characteristics and their analyses in this chapter, these results should be viewed as preliminary, to be refined through more exhaustive systematic reviews of the relevant scientific literature and/or through discussion with a broad panel of experts on the mechanisms of carcinogenesis. The ten key characteristics proposed by Smith (this Volume) and Smith et al. (2016) were endorsed by the participants in the IARC Workshop on 'Tumour-site Concordance and Mechanisms of Carcinogenesis', which provided oversight for this project; nonetheless, additional experience with the exploration of these characteristics in cancer research will serve to define their utility more fully. Equally important is to consider the nature of the evidence needed to establish that specific mechanistic characteristics are demonstrated by human carcinogens. Our current database has relied on the expression of certain toxicological endpoints as evidence of these mechanistic characteristics: further consideration of these and other possible markers of the key characteristics of human carcinogens is warranted.

Finally, it is important to indicate that the inclusion of mechanistic information into the *IARC Monographs* has evolved over time, with greater consideration being given to both mechanistic data and mechanistic upgrades in the absence of *sufficient evidence* of carcinogenicity in humans in more recent *Monographs*. Mechanistic considerations are becoming increasingly prominent in the *IARC Monographs*, thereby enriching the body of evidence on which future analyses of this type may be based. If forthcoming *Monographs* were able to document information on the ten key characteristics considered here, as has been done in several recent *Monographs*, this would support future follow-on analyses that would extend the initial in-depth analyses of these characteristics presented in this chapter.

Acknowledgements

Melissa Billard assembled the tumour-site concordance database analyzed herein while working as a Visiting Scientist under the direction of Dr Yann Grosse and Dr Robert Baan at the International Agency for Research on Cancer during the summers of 2013 and 2014. Julian Little is the Canada Research Chair in Human Genome Epidemiology at the University of Ottawa. Daniel Krewski is the Natural Sciences and Engineering Research Council of Canada Chair in Risk Science at the University of Ottawa. This chapter is dedicated to the memory of Dr Jan Zielinski, who succumbed to cancer in 2016: prior to becoming ill, Dr Zielinski led the analytical team that conducted the analyses reported herein.

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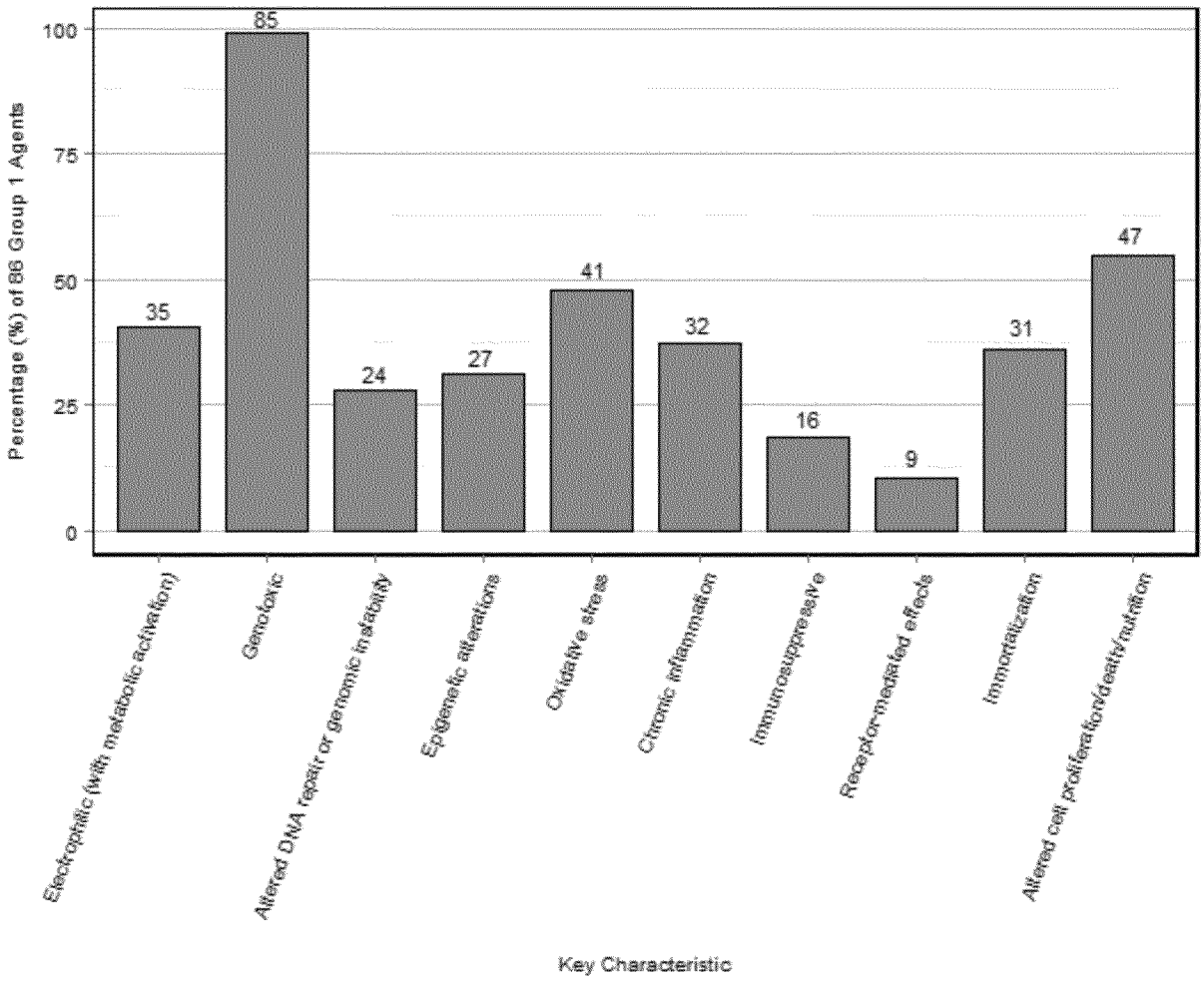


Figure 1. Key Characteristics of 86 Group-1 Agents
(number of agents shown above each characteristic)

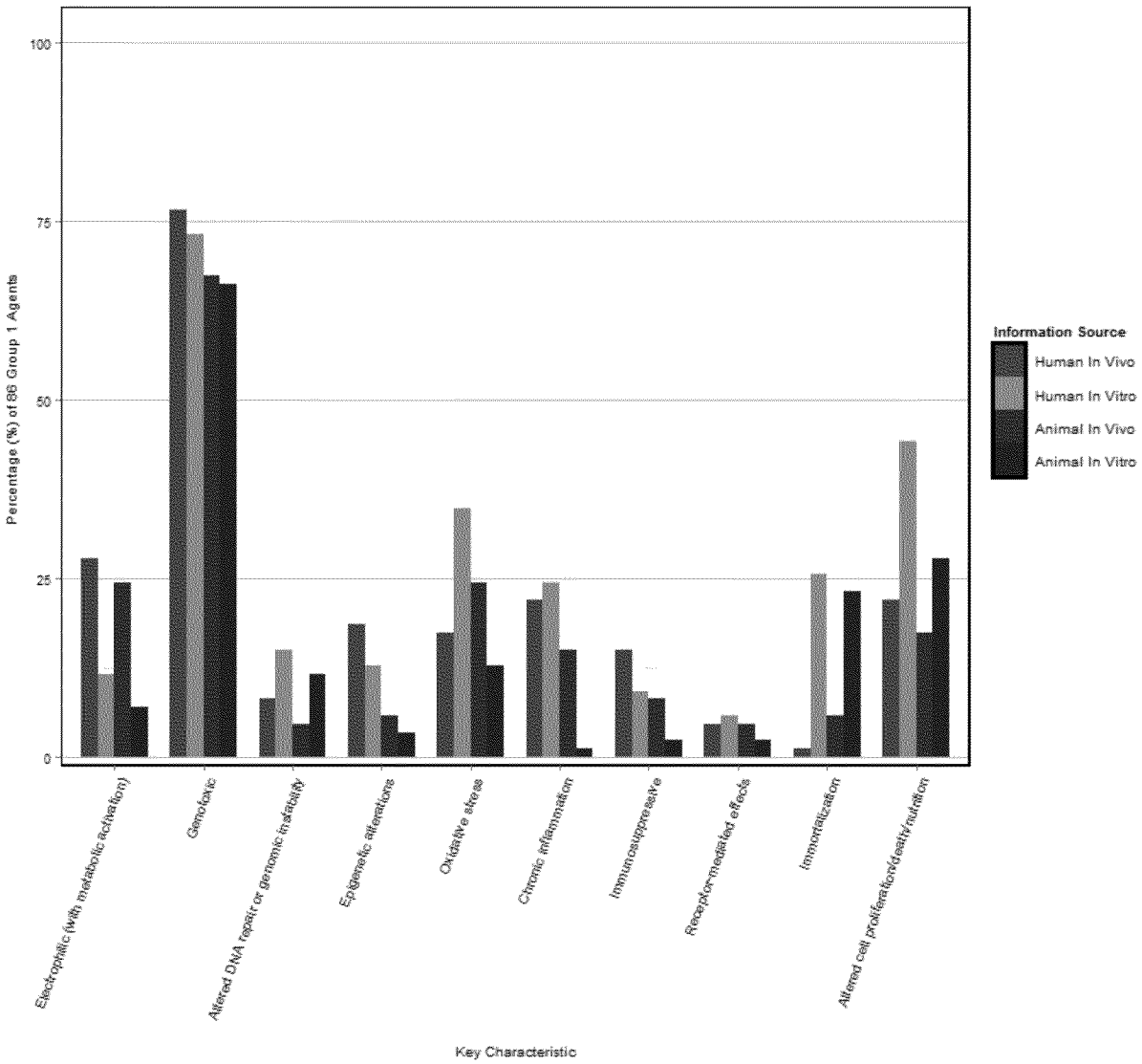


Figure 2. Sources of Information on Key Characteristics of 86 Group-1 Agents
(sources are human in vivo, human in vitro, animal in vivo, animal in vitro studies)

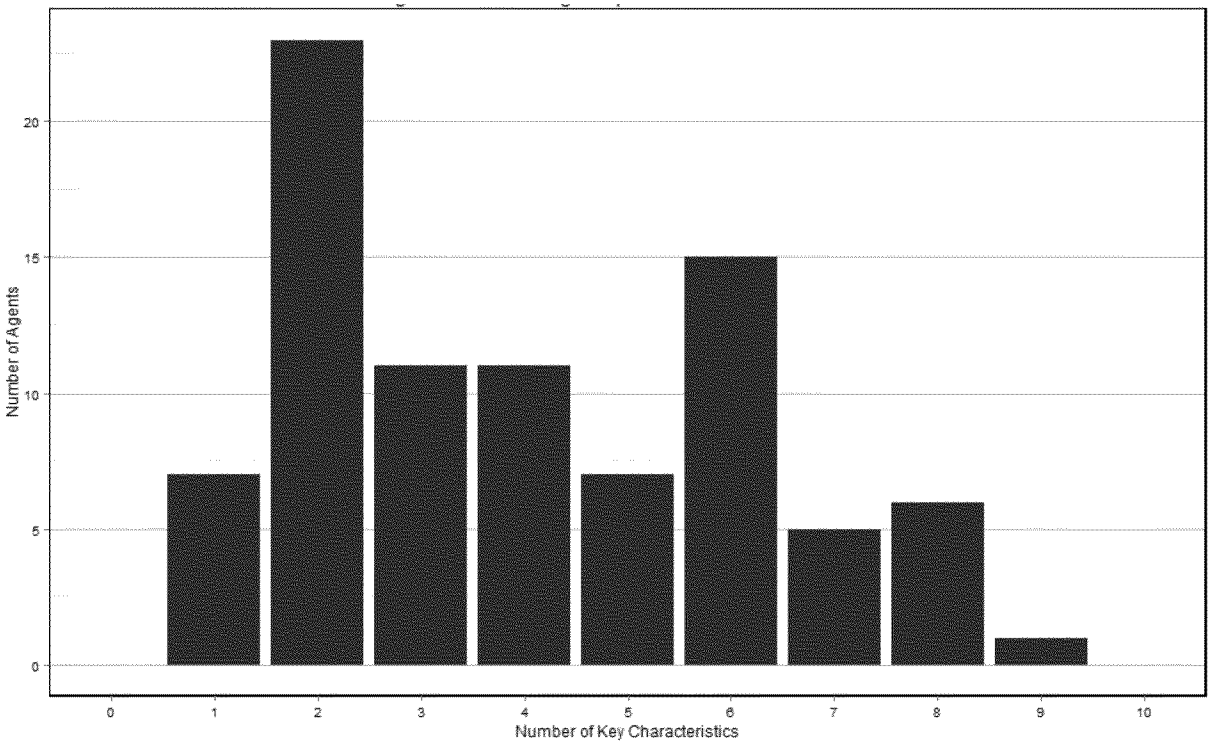


Figure 3. Number of Group-1 Agents Demonstrating One or More Key Characteristics

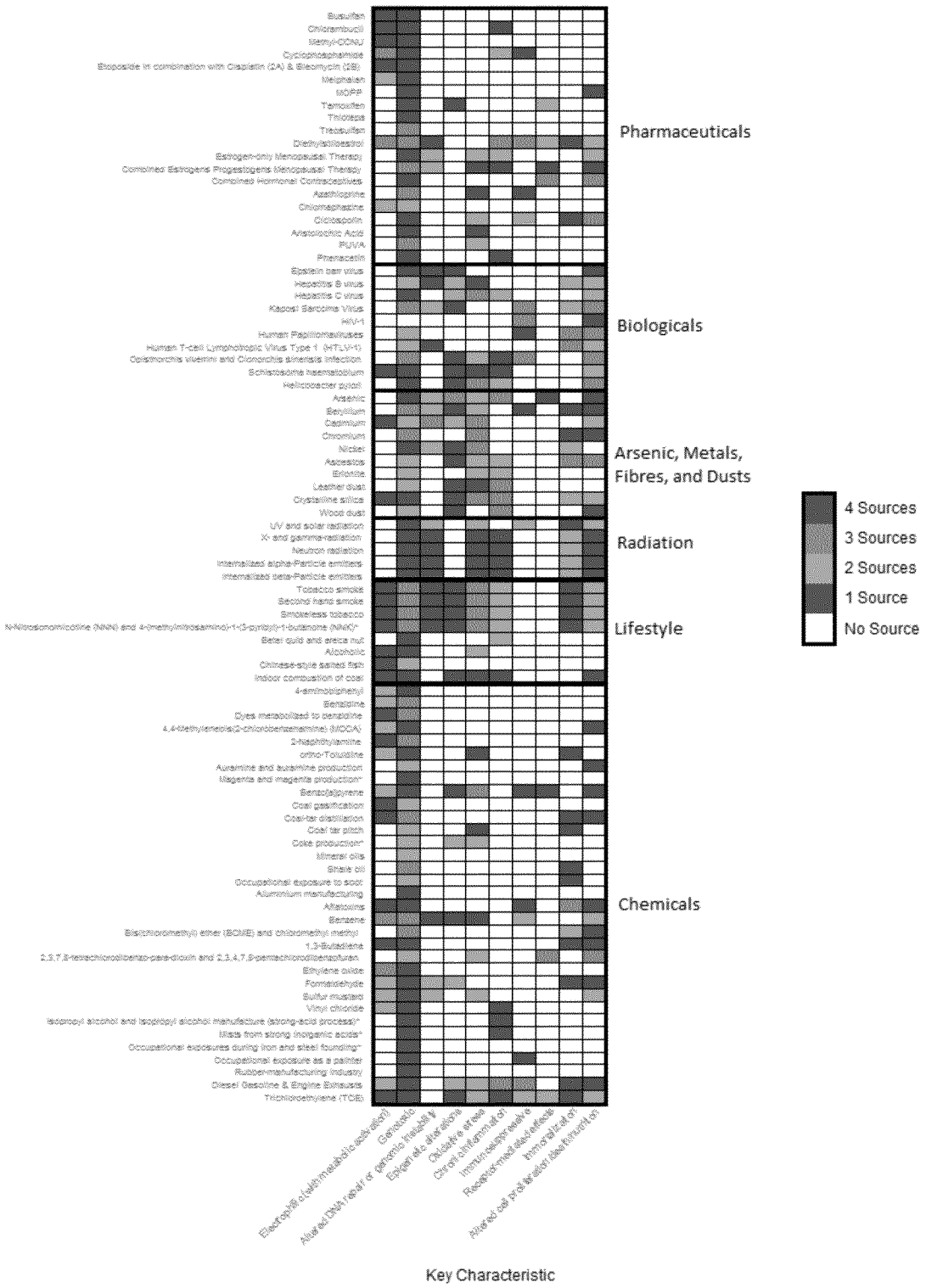


Figure 4. Heat Map Showing the Strength of Evidence for Different Key Characteristics of 86 Group-1 Agents According to the Number of Information Sources (sources are human in vivo, human in vitro, animal in vivo and animal in vitro studies)

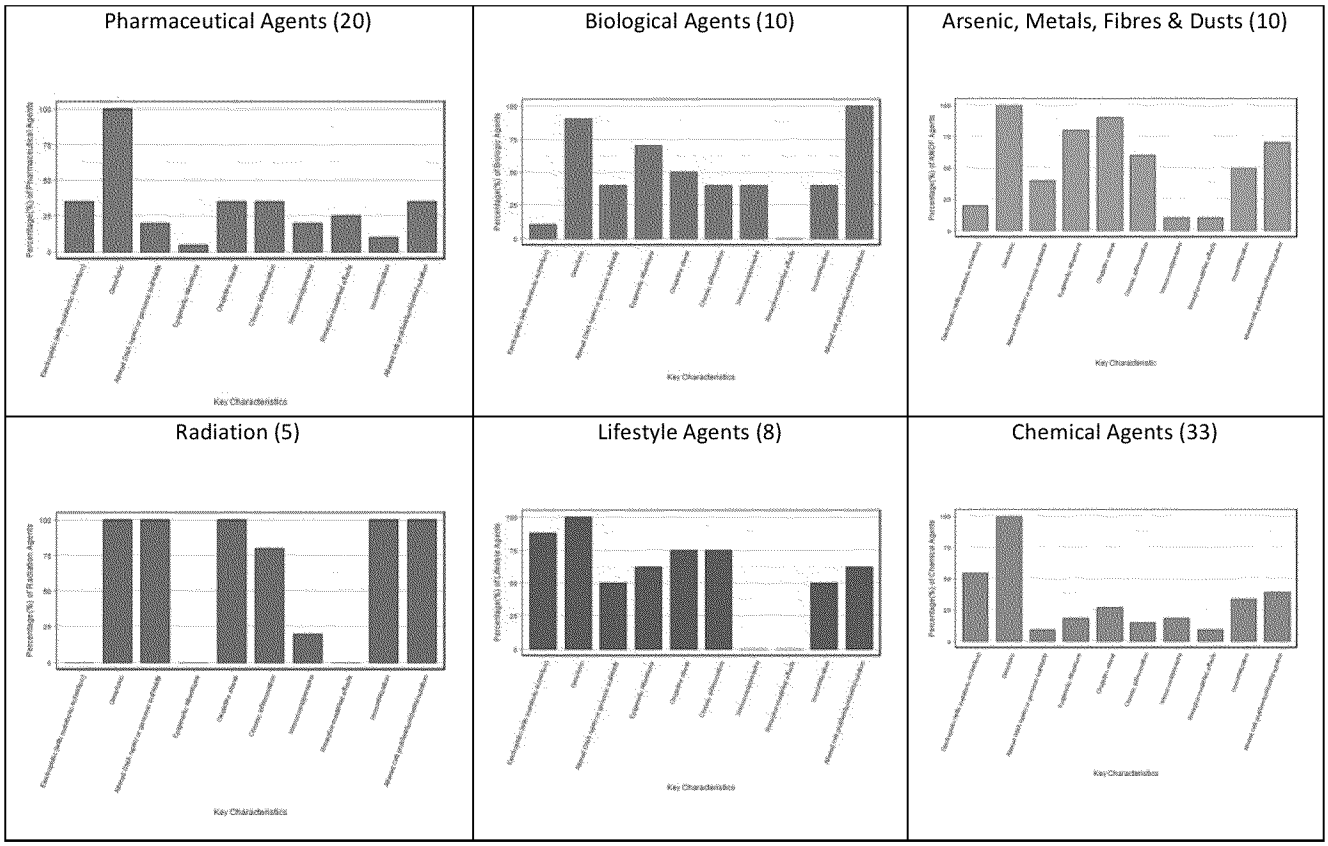


Figure 5. Key Characteristics of 86 Group-1 Agents by Type of Agent
(number of agents of each type shown in parentheses)

Table 1. Number of Group 1 Agents in Volumes 100 through 114 by Type of Agent*

Volume 100			V105	V106	V107	V109	V110	V111	V113	V114	Total
A	Pharmaceuticals	23									23
B	Biological agents	11									11
C	Arsenic, metals, fibres and dusts	10						2[f]			12
D	Radiation	18									18
E	Personal habits and indoor combustions	12								1[h]	13
F	Chemicals and related occupations	33	1[a]	1[b]	2[c]	2[d]	1[e]		1[g]		41
Total		**107**	**1**	**1**	**2**	**2**	**1**	**2**	**1**	**1**	**118**

*At the time the present analysis was conducted, mechanistic information was available only for the 109 Group-1 agents evaluated through Volume 106.

[a]Trichloroethylene; [b]Diesel-engine exhaust; [c]Polychlorinated biphenyls (PCBs); dioxin-like PCBs; [d]Outdoor air pollution; particulate matter from outdoor air pollution; [e]1,2-Dichloropropane (1,2-DCP); [f]Fluoro-edenite amphibole asbestos; occupational exposures associated with the Acheson process in the manufacturing of silicon-carbide fibres; [g]Lindane; [h]Processed meat.

Table 2. Key Characteristics and Toxicological Endpoints Demonstrated by Agents Known to Cause Cancer in Humans (adapted from Al-Zoughool et al., 2015)

Key Characteristic	Corresponding Toxicological Endpoints
Is electrophilic or can be metabolically activated to electrophiles	Reactive metabolites Protein adducts Absorption, distribution, clearance differences
Is genotoxic	DNA damage Clastogenic effects Gene mutation
Alters DNA repair or causes genomic instability	DNA-repair alteration or genomic instability
Induces epigenetic alterations	Epigenetic effects (DNA methylation, histone modification, miRNAs)
Induces oxidative stress	Oxidative stress
Induces chronic inflammation	Chronic inflammation Chronic irritation
Is immunosuppressive	Immune effects
Modulates receptor-mediated effects	Receptor-mediated effects Hormonal effects
Causes immortalization	Immortalization Alterations in telomere length
Alters cell proliferation, cell death or nutrient supply	Cell-cycle effects Bystander effects Alteration of cell-signalling pathways Angiogenic effects Cell death Inhibition of intercellular communication

Table 3. Relationship between 86 Agents used in the Analysis of Key Characteristics of Human Carcinogens and 111 Agents Used in the Analysis of Concordance between Human and Animal Tumours

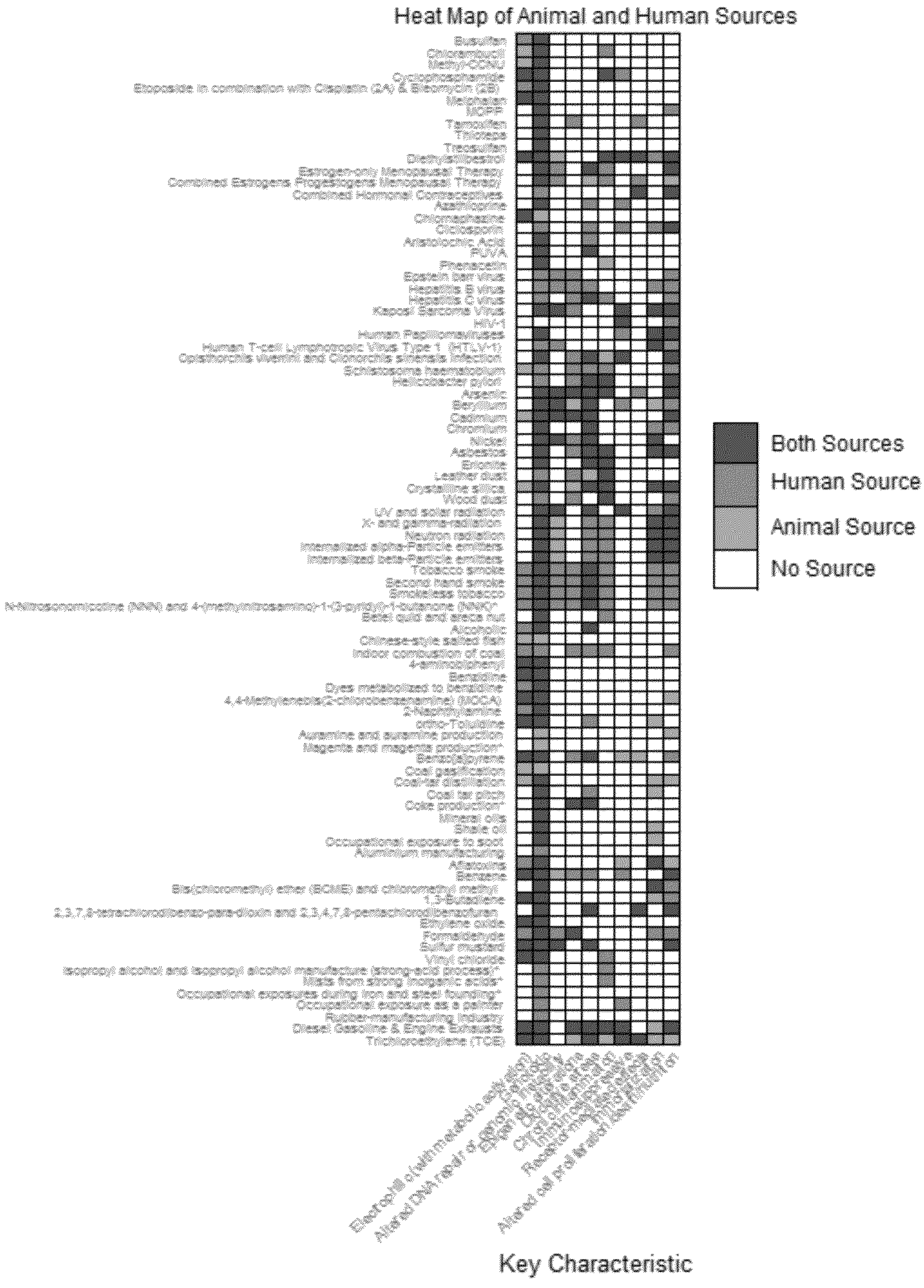
Volume	Number	86 Agents Used in the Analysis of Key Characteristics	111 Agents Used in the Analysis of Concordance between Human and Animal Tumours
A	1	Aristolochic Acid	Aristolochic acid aristolochic acid, plants containing
A	2	Azathioprine	Azathioprine
A	3	Busulfan	Busulfan
A	4	Chlorambucil	Chlorambucil
A	5	Chlornaphazine	Chlornaphazine
A	6	Cyclophosphamide	Cyclophosphamide
A	7	Ciclosporin	Ciclosporin
A	8	Diethylstilbestrol	Diethylstilbestrol
A	9	Estrogen-only menopausal therapy	Estrogen-only menopausal therapy
A	10	Combined estrogen-progestogen menopausal therapy	Estrogen-progestogen menopausal therapy (combined)
A	11	Combined hormonal contraceptives	Estrogen-progestogen oral contraceptives (combined)
A	12	Etoposide in combination with cisplatin (2A) & bleomycin (2B)	Etoposide Etoposide in combination with cisplatin and bleomycin
A	13	Melphalan	Melphalan
A	14	PUVA	Methoxsalen in combination with UVA
A	15	MOPP	MOPP and other combined chemotherapy including alkylating agents
A	16	Phenacetin	Phenacetin Phenacetin, analgesic mixtures containing
A	17	Methyl-CCNU	1-(2-Chloroethyl)-3-(4-methylcyclohexyl)- 1-nitrosourea (Methyl-CCNU)
A	18	Tamoxifen	Tamoxifen
A	19	Thiotepa	Thiotepa
A	20	Treosulfan	Treosulfan
B	21	*Opisthorchis viverrini* and *Clonorchis sinensis*	*Clonorchis sinensis* (infection with) *Opisthorchis viverrini* (infection with)
B	22	Epstein-Barr virus	Epstein-Barr virus
B	23	*Helicobacter pylori*	*Helicobacter pylori* (infection with)
B	24	Hepatitis B virus	Hepatitis B virus

B	25	Hepatitis C virus	Hepatitis C virus
B	26	Human immunodeficiency virus type 1	Human immunodeficiency virus type 1
B	27	Human papillomavirus	Human papillomavirus
B	28	Human T-cell lymphotropic virus type 1	Human T-cell lymphotropic virus type 1
B	29	Kaposi sarcoma herpesvirus	Kaposi sarcoma herpesvirus
B	30	*Schistosoma haematobium*	*Schistosoma haematobium* (infection with)
C	31	Arsenic and arsenic compounds	Arsenic and inorganic arsenic compounds
C	32	Asbestos (actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite)	Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite)
C	33	Beryllium and beryllium compounds	Beryllium and beryllium compounds
C	34	Cadmium and cadmium compounds	Cadmium and cadmium compounds
C	35	Chromium (VI) compounds	Chromium (VI) compounds
C	36	Erionite	Erionite
C	37	Leather dust	Leather dust
C	38	Nickel and nickel compounds	Nickel compounds
C	39	Silica dust, crystalline, in the form of quartz or cristobalite	silica dust, crystalline, in the form of quartz or cristobalite
C	40	Wood Dust	Wood dust
D	41	Solar and Ultraviolet Radiation	UV radiation (bandwidth 100-400 nm, encompassing UVC, UVB and UVA) UV-emitting tanning devices Solar radiation
D	42	X and γ Radiation	X- and Gamma radiation Ionizing radiation (all types)
D	43	Neutron radiation	Neutron radiation
D	44	Internalized α-particle emitting radionuclides	Haematite mining with exposure to radon (underground) Pu-239 Internalized radionuclides that emit alpha-particles Th-232 (as Thorotrast) Ra-224 and its decay products Ra-226 and its decay products Ra-228 and its decay products Rn-222 and its decay products
D	45	Internalized β-particle emitting radionuclides	Fission products including Sr-90 Radioiodines, including I-131 P-32, as phosphate

			Internalized radionuclides that emit beta particles
E	46	Consumption of alcoholic beverages	Acetaldehyde associated with consumption of alcoholic beverages Alcoholic beverages Ethanol in alcoholic beverages
E	47	Betel quid and areca nut	Areca nut Betel quid with tobacco Betel quid without tobacco
E	48	Indoor emissions from household combustion of coal	Coal, indoor emissions from household combusion of
E	49	N'-Nitrosonornicotine (NNN) and 4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanon (NNK)	N'-Nitrosonornicotine (NNN) and 4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanon (NNK)
E	50	Chinese-style salted fish	Salted fish, chinese style
E	51	Second-hand tobacco smoke	Second-hand tobacco smoke
E	52	Tobacco smoking	Tobacco smoking
E	53	Smokeless tobacco	Tobacco, smokeless
F	54	Mists from strong inorganic acids	Acid mists, strong inorganic
F	55	Aflatoxins	Aflatoxins
F	56	Aluminium production	Aluminium production
F	57	4-Aminobiphenyl	4-Aminobiphenyl
F	58	Auramine production	Auramine production
F	59	Benzene	Benzene
F	60	Benzidine	Benzidine
F	61	Benzidine, dyes metabolized to	Benzidine, dyes metabolized to
F	62	Benzo[a]pyrene	Benzo[*a*]pyrene
F	63	Bis(chloromethyl)ether; chloromethyl methyl ether (technical-grade)	Bis(chloromethyl)ether; chloromethyl methyl ether (technical-grade)
F	64	1,3-Butadiene	1,3-Butadiene
F	65	Coal gasification	Coal gasification
F	66	Coal-tar distillation	Coal-tar distillation
F	67	Coal-tar pitch	Coal-tar pitch
F	68	Coke production	Coke production
F	69	Ethylene oxide	Ethylene oxide
F	70	Formaldehyde	Formaldehyde
F	71	Occupational exposure during iron and steel founding	Iron and steel founding (occupational exposure during)
F	72	Isopropyl alcohol manufacture by the strong-acid process	Isopropyl alcohol manufacture using strong acids

F	73	Magenta production	Magenta production
F	74	4,4'-Methylenebis(2-chloroaniline) (MOCA)	4,4'-Methylenebis(2-chloroaniline) (MOCA)
F	75	Mineral oils, untreated or mildly treated	Mineral oils, untreated or mildly treated
F	76	2-Naphthylamine	2-Naphthylamine
F	77	*ortho*-Toluidine	*ortho*-Toluidine
F	78	Occupational exposure as a painter	Painter, occupational exposure as a
F	79	2,3,7,8-Tetrachlorodibenzo-para-dioxin, 2,3,4,7,8-Pentachlorodibenzofuran, 3,3',4,4',5-Pentachlorobiphenyl	2,3,4,7,8-Pentachlorodibenzofuran 2,3,7,8-Tetrachlorodibenzo-para-dioxin 3,3',4,4',5-Pentachlorobiphenyl
F	80	Occupational exposures in the rubber-manufacturing industry	Rubber-manufacturing industry
F	81	Shale oils	Shale oils
F	82	Soot (as found in occupational exposure of chimney sweeps)	Soot (as found in occupational exposure of chimney sweeps)
F	83	Sulfur Mustard	Sulfur mustard
F	84	Vinyl Chloride	Vinyl chloride
105	85	Diesel- and gasoline-engine exhausts	Engine-exhaust, diesel
106	86	Trichloroethylene	Trichloroethylene
107			Polychlorinated biphenyls*
109			Outdoor air pollution*
109			Particulate matter in outdoor air pollution*

*As the mechanistic sections for Monographs 107-109 were not available for review at the time this analysis was done, Group-1 agents in these volumes were necessarily excluded from the present analysis.


Heat Map of Animal and Human Sources
Both Sources
Human Source
Animal Source
No Source
Key Characteristic

Cc: banks@icgeb.org[banks@icgeb.org]; frederick.beland@fda.hhs.gov[frederick.beland@fda.hhs.gov]; toxcon@earthlink.net[toxcon@earthlink.net]; boslandm@uic.edu[boslandm@uic.edu]; bucher@niehs.nih.gov[bucher@niehs.nih.gov]; Caldwell, Jane[Caldwell.Jane@epa.gov]; Cogliano, Vincent[cogliano.vincent@epa.gov]; DeMarini, David[DeMarini.David@epa.gov]; bice.fubini@unito.it[bice.fubini@unito.it]; bdgold@pitt.edu[bdgold@pitt.edu]; hecht002@umn.edu[hecht002@umn.edu]; k.hemminki@dkfz.de[k.hemminki@dkfz.de]; mark.hill@rob.ox.ac.uk[mark.hill@rob.ox.ac.uk]; Ex. 6 - Personal Privacy; Agnes_Kane@Brown.edu[Agnes_Kane@Brown.edu]; Kavlock, Robert[Kavlock.Robert@epa.gov]; dkrewski@uottawa.ca[dkrewski@uottawa.ca]; lambert@oncology.wisc.edu[lambert@oncology.wisc.edu]; Ex. 6 - Personal Privacy; jr332@georgetown.edu[jr332@georgetown.edu]; martynts@uclink4.berkeley.edu[martynts@uclink4.berkeley.edu]; lstayner@uic.edu[lstayner@uic.edu]; ullrich@rerf.or.jp[ullrich@rerf.or.jp]; p.vineis@imperial.ac.uk[p.vineis@imperial.ac.uk]; waalkes@niehs.nih.gov[waalkes@niehs.nih.gov]; lzeise@oehha.ca.gov[lzeise@oehha.ca.gov]; Bernard.Stewart@sesiahs.health.nsw.gov.au[Bernard.Stewart@sesiahs.health.nsw.gov.au]; **Ex. 6 - Personal Privacy** zoughoolm@ksau-hs.edu.sa[zoughoolm@ksau-hs.edu.sa]; melissabillard@me.com[melissabillard@me.com]; jlittle@uottawa.ca[jlittle@uottawa.ca]; bmilton@risksciences.com[bmilton@risksciences.com]; malzough@uottawa.ca[malzough@uottawa.ca]; Nicholas.Birkett@uottawa.ca[Nicholas.Birkett@uottawa.ca]; Harri.Vainio@hsc.edu.kw[Harri.Vainio@hsc.edu.kw]; irusyn@cvm.tamu.edu[irusyn@cvm.tamu.edu]; Mwaalkes@nc.rr.com[Mwaalkes@nc.rr.com]; straif@iarc.fr[straif@iarc.fr]; **Ex. 6 - Personal Privacy** cphra@uottawa.ca[cphra@uottawa.ca]; bullrich@utmb.edu[bullrich@utmb.edu]; cportier@mac.com[cportier@mac.com]; workshops100+@iarc.fr[workshops100+@iarc.fr]
To: Robert Baan[BaanR@visitors.iarc.fr]
From: Chris Portier
Sent: Thur 7/21/2016 1:54:51 PM
Subject: Re: Tumour-site Concordance and Mechanisms of Carcinogenesis

I have nothing new to add beyond what has already been suggested.

C.

Sent from my iPad

On Jul 15, 2016, at 16:51, Robert Baan <BaanR@visitors.iarc.fr> wrote:

> Dear colleagues,
>
> It has been a long time since we had contact; I hope you are doing fine.
>
> I am pleased to announce the near completion of the project 'Tumour-site Concordance and Mechanisms of Carcinogenesis'. Some of you may remember the teleconference in December last year, during which it was decided to delete the numerical results (kappa-statistics) from the concordance analysis proposed by Dan Krewski and his team, leaving

us the task of finding a different way to present the concordance data. During a second teleconference in February of this year, a small group of participants discussed a new proposal to present the data, based on the concept of 'overlap' of tumour sites between humans and experimental animals. This subgroup and the Ottawa team worked out a completely new version of the concordance analysis, with new Figures and Tables. We have greatly appreciated the input and efforts of all involved to arrive at this result.

Today we submit to you the corresponding documents for your approval. Also attached is the analysis of the mechanistic data, based on the 10 Key Characteristics.

Attached you will find the complete analyses on 'Concordance' and 'Mechanisms' in documents 1 and 7. The other documents contain late-incoming corrections, and show details on the data set on which the concordance analysis is based.

Finally, document 8 is a draft Consensus Statement that presents what we suggest to be the main conclusions and recommendations of the Workshop participants.

We hope you can endorse the Consensus Statement and the final results presented in the attached documents.

With your support, we will bring this project to a close.

I hope to hear from you, wishing you pleasant holidays.

With my best regards,

Robert

<1 Krewski et al Concordance Analysis July 13 with Supplemental Material.pdf>

<2 Krewski et al Concordance Analysis July 15.doc>

<3 Krewski et al Concordance Analysis July 5 Figures.pptx>

<4 Grosse et al Concordance Data set (text only).docx>

<5 Grosse et al Concordance Data set Table 1 REV 16 June.xls>

<6 Grosse et al Concordance Data set Supplemental Table 1 REV June 16 2016.xls>

<7 Krewski et al Key Characteristics July 15.docx>

<8 Draft Consensus Statement July 15.docx>

To: Robert Baan[BaanR@visitors.iarc.fr]
Cc: Kurt Straif[StraifK@iarc.fr]; Bernard Stewart[Bernard.Stewart@SESIAHS.HEALTH.NSW.GOV.AU]; Cogliano, Vincent[cogliano.vincent@epa.gov]
From: Daniel Krewski
Sent: Fri 7/15/2016 10:24:59 AM
Subject: IARC Consensus Statement_ks-vjc_ks2-vjc2 rev BWS rev RB DONE DK July 15
IARC Consensus Statement_ks-vjc_ks2-vjc2 rev BWS rev RB DONE DK July 15.docx

Robert, after sending around the concordance and mechanisms chapters, I wondered if the consensus statement might be authored 'in collaboration with the other participants . . .' in the same way that the concordance and mehcnaims chapters are authored.

This would give the impress of greater collaboration in formulating the consensus statement, and possibly promote serve to 'promote' consensus among the WPs.

Happy to hear your thoughts when we speak later today (Friday) . . .

Dan K.

CONSENSUS STATEMENT

Vincent J Cogliano, Robert A Baan, Kurt Straif, in collaboration with other participants[1] in the IARC Workshop on 'Tumour-site Concordance and Mechanisms of Carcinogenesis', held April/November 2012 in Lyon

Introduction

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For the one hundredth volume of the *IARC Monographs*, a review was undertaken during 2008–2009 of all Group-1 human carcinogens previously identified in Volumes 1–99. There was value in a comprehensive review, as about half the human carcinogens had been last reviewed more than 20 years earlier. *Monograph* Volume 100 was organized in six parts covering *Pharmaceuticals* (Vol 100A), *Biological Agents* (Vol 100B), *Arsenic, Metals, Fibres, and Dusts* (Vol 100C), *Radiation* (Vol 100D), *Personal Habits and Indoor Combustions* (Vol 100E), and *Chemical Agents and Related Occupations* (Vol 100F). Volume 100 'A Review of Human Carcinogens' was published as a six-part book series in 2012.

IARC explored ways to strengthen the scientific outcome of Volume 100 by embarking on a review of the Group-1 human carcinogens with respect to cancer sites and mechanistic events, followed by supplementary analyses of cancer-site concordance between humans and experimental animals, and of mechanistic events deemed relevant to the carcinogenicity of these agents. Accordingly, this Scientific Publication on 'Tumour-site Concordance and Mechanisms of Carcinogenesis' was proposed.

To prepare for the supplementary analyses in this Scientific Publication, IARC had asked the six Working Groups for Volume 100 to collect additional information, not routinely developed before, (a) on cancer sites in humans for which there was *sufficient evidence* or *limited evidence* in epidemiological studies, (b) on cancer sites with *sufficient evidence* in experimental animals, and (c) on established and likely mechanistic events involved in the cancers observed in humans or experimental animals.

To further develop this Scientific Publication, the *Monographs Programme* convened a group of international scientific experts in a two-part Workshop, held in Lyon in April and November 2012. The main points of consensus, the conclusions and the recommendations of the Workshop participants are described below.

[1] L Banks, FA Beland, JA Bond, MC Bosland, JR Bucher, JC Caldwell, DM DeMarini, B Fubini, BD Goldstein, SS Hecht, K Hemminki, MA Hill, CW Jameson, AB Kane, RJ Kavlock, D Krewski, PF Lambert, R Melnick, CJ Portier, JM Rice, II Rusyn, MT Smith, L Stayner, BW Stewart, RL Ullrich, H Vainio, P Vineis, MP Waalkes, L Zeise

Tumour-Site Concordance

1. The results developed in Volume 100 confirm that the induction of cancer in experimental animals is relevant to the identification of a carcinogenic hazard to humans: all human carcinogens identified to date that have been adequately tested in animals have also been shown to cause cancer in animals.

2. For many human carcinogens, there is tumour-site concordance between humans and experimental animals; for many others, there is not. At the present time, the state-of-the-science does not support tumour-site concordance as a general principle. For example, although several agents are known to cause malignant melanoma in humans, this cancer is unknown in rats or mice.

3. Past evaluations have noted cancer in experimental animals at approximately 40 tumour sites in 15 organ and tissue systems. Use of standard terminology for these sites can facilitate the development of databases and their analysis and linkage to other sources of information. The Workshop participants recommend that future *IARC Monographs* Working Groups consider the anatomically based taxonomy of tumour sites that appears in this Scientific Publication in the analysis of concordance between sites where animal and human tumours arise.

4. Present analyses are expected to underestimate concordance. One reason is the limited power of many observational epidemiological studies that include populations and cancer sites that have not been adequately investigated. Another reason is that an agent was considered to cause cancer at a site in animals only if positive results were replicated at that site in another animal experiment; however, metabolic or mechanistic considerations might explain tumour induction at different sites in separate animal models.

5. Descriptive statistics of tumour sites identified to date may not be representative of future evaluations or of the incompletely characterized 'universe of human carcinogens.' The carcinogens evaluated in Volume 100 include several classes of agents that have been relative straightforward to investigate, for example, alkylating agents used in early cancer chemotherapy, viral agents that infect hundreds of millions of people, ionizing radiation that affects multiple anatomical sites, widespread exposures such as tobacco and alcohol, and chemical agents with long histories of occupational exposure at high levels. Agents evaluated in the future may have more subtle effects and different characteristics.

6. The Workshop participants recommend that the Evaluation section in the *Monograph* in respect of 'evidence in experimental animals' be expanded to include additional information for agents evaluated as exhibiting *sufficient evidence.* For such agents, an additional sentence following the relevant evaluation should refer to the recognized site(s) of tumorigenesis, by use of the specification system described in this volume by Krewski et al.

Mechanisms Involved in Human Carcinogenesis

7. The use of mechanistic data to identify human carcinogens is accelerating. Initially, IARC required *sufficient evidence* in humans for classification of an agent as *carcinogenic to humans*. Scientific understanding of the mechanisms of carcinogenesis, accompanied by the development of assays for studying mechanistic events, have led to new ways of identifying human carcinogens. Ethylene oxide was classified as *carcinogenic to humans* in 1994 based on strong evidence of genotoxicity in exposed humans, 2,3,7,8- tetrachlorodibenzo-*para*-dioxin in 1997 based on strong evidence of binding to the aryl hydrocarbon receptor and subsequent events, neutron radiation in 2000 based on the underlying radiation physics, some more agents between 2004 and 2010, and several additional agents in Volume 100.

8. Up until now, there has been no generally accepted method for organizing mechanistic data pertinent to the identification of carcinogenic hazards to humans. The Key Characteristics presented here offer a promising foundation for the structured evaluation of mechanistic information, and this should increase the utility of mechanistic evidence in future identifications of carcinogenic hazards and the transparency of the systematic review. The Workshop participants recommend that the *IARC Monographs Programme* continue to develop the Key Characteristics and to use them in its evaluations of carcinogenicity.

9. It is notable that in-vivo or in-vitro mechanistic data are often available in humans. For most key characteristics, when animal data are available for a key characteristic, human data are generally available, too. The observation that similar Key Characteristics are seen in animals and humans further supports the use of animal data in human cancer risk assessment.

10. There should be no expectation that all, or even most, Key Characteristics operate for any human carcinogen. No Key Characteristic is necessary for carcinogenesis, and negative results for one or more Key Characteristics are not an argument against the potential carcinogenicity of an agent. Observation of one or more Key Characteristics in exposed humans can increase the biological plausibility of less-than-*sufficient evidence* in humans. Observation of one or more Key Characteristics in experimental animals can increase confidence in the human relevance of *limited evidence* in experimental animals.

11. Human carcinogens act through multiple mechanisms. Interrelationships between mechanistic events should facilitate the development of more complex—but also more realistic—adverse-outcome networks. Past practice of according greatest concern in respect of known or putative carcinogens to those agents demonstrated to be genotoxic, relative to agents whose carcinogenicity appeared to be mediated by some other mechanism, possibly involving specific receptors, appears to be overly simplistic.

12. The objective of the *IARC Monographs Programme* is to identify carcinogenic hazards, not to

exhaustively list all mechanistic events and pathways that might contribute to carcinogenesis. Future coverage of mechanistic data should increase as the retrieval of such data becomes more systematic and the Key Characteristics are used as a framework for organization and analysis of mechanistic data.

13. Descriptive statistics of mechanisms identified to date may not be representative of future evaluations. Although genotoxicity is the Key Characteristic most exhibited by the human carcinogens identified to date, this may reflect the relatively greater attention paid in the past to the investigation of genotoxic agents. Future evaluations of carcinogenic agents may involve a larger set of mechanistic events and pathways, many that are not yet well developed or understood. Accordingly, future refinement of the Key Characteristics is to be expected, and this does not detract from the value in using them now in evaluations of carcinogenic hazards.

To: dkrewski@uottawa.ca[dkrewski@uottawa.ca]
Cc: Cogliano, Vincent[cogliano.vincent@epa.gov]; Bernard Stewart[Bernard.Stewart@SESIAHS.HEALTH.NSW.GOV.AU]; Kurt Straif[StraifK@iarc.fr]
From: Robert Baan
Sent: Fri 7/15/2016 7:38:24 AM
Subject: IARC Consensus Statement_ks-vjc_ks2-vjc2 rev BWS rev RB DONE DK July 14
IARC Consensus Statement_ks-vjc_ks2-vjc2 rev BWS rev RB DONE DK July 14.docx

Dear Dan,

You raised a final discussion point on two additions in the Consensus Statement.

In my view, the addition in lines 44-45 seems acceptable: the concordance analysis clearly confirms it.

The additional sentence in lines 103-104 deals with 'concordance in the key characteristics', and I am not sure that this is supported equally strongly by the mechanistic analysis: did we address that question specifically? can we indeed show that agents display the same characteristic in humans and in animals?

I would leave the final call to Vincent (the lead author of this text) and the others (Kurt, Bernard?)

Thank you for your continued involvement!

Robert

From: Daniel Krewski <dkrewski@uottawa.ca>
Sent: Thursday, July 14, 2016 9:15 PM
To: Robert Baan
Cc: Kurt Straif; Bernard Stewart; Vincent Cogliano
Subject: IARC Consensus Statement_ks-vjc_ks2-vjc2 rev BWS rev RB DONE DK July 14

Robert, attached is a minor editorial suggestion on the Consensus Statement (line 118), along with the following two more substantive suggestions.

Lines 44-45: In support of the statement that animal data is relevant to human cancer risk assessment, it might be pointed out that all Group-1 agents that have been adequately tested in animals demonstrate carcinogenicity in animals. [This point is made explicitly in the concordance chapter.] (This does not address the predictive value of animal data for human risk assessment, but does demonstrate that human carcinogens are also expressed in animals.)

Lines 103-104: The observation of similar Key Characteristics in animals and humans further supports the use of animal data in human cancer risk assessment. [This point is made in the mechanisms chapter, and is perhaps an even more compelling argument supporting the use of animal data than the previous one.]

I do not feel strongly about the addition of either of the above two points, but wanted to offer them to you as food for thought . . .

I'll be happy to sign off on the final version of the consensus statement when it is circulated to the WPs (along with the final concordance and mechanisms chapters).

With best regards.

Dan K.

CONSENSUS STATEMENT

Vincent J Cogliano, Robert A Baan, Kurt Straif

This statement is endorsed by participants[1] in the IARC Workshop on 'Tumour-site Concordance and Mechanisms of Carcinogenesis', held April/November 2012 in Lyon

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From: Daniel Krewski
Sent: Thur 7/14/2016 9:47:31 PM
Subject: Final Draft of IARC Mechanisms Chapter
2016 Krewski et al Key Characteristics July 14.pdf

Just a note to provide you with the final draft of our chapter on key characteristics of human carcinogens, incorporating all comments received from all authors and some detailed last minute checking by Brittany Milton and Michael Bird.

The chapter has undergone editorial review by the editors of the IARC Scientific Publication in which this chapter will appear. I have spent the last week in Lyon going over the editorial comments provided by the IARC, and have addressed all of the comments provided by the Agency review.

I am very pleased with the final version of the chapter, and would like to take this opportunity to thank all of you for your valuable contributions to this work.

Robert will be sending the chapter to all Workshop Participants shortly, along with the concordance chapter that is also now in final form.

With best regards.

Daniel Krewski, PhD, MHA

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Key Characteristics of Human Carcinogens: An Exploratory Analysis of 86 Agents Known to Cause Cancer in Humans

D. Krewski, M. Al-Zoughool, M. Bird , N. Birkett, M.T. Smith, M. Billard, B. Milton, J.M. Rice, Y. Grosse, R. Baan, V. Cogliano, K.Z. Guyton, K. Straif, M. Hill, J. Little & J.M. Zielinski[1]

In collaboration other participants in the IARC Workshop on 'Tumour-site Concordance and Mechanisms of Carcinogenesis' which convened in Lyon April/November 2012[2]

Abstract

Since its inception in the early 1970s, the *Monographs Programme* of the International Agency for Research on Cancer (IARC) has evaluated 990 agents with respect to their carcinogenic hazard, has so far – through *Monograph* Volume 116 – identified 118 agents as *carcinogenic to humans*, and placed them in Group 1 of the IARC carcinogen classification scheme. Based on the review and update of Group-1 carcinogens included in Volume 100, 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. By extracting data on biological mechanisms of action from the *Monographs*, a database on the basis of 10 key characteristics of human carcinogens was assembled. After some grouping of similar agents, we examined the characteristic profiles of 86 Group-1 agents for which mechanistic information was available in the *IARC Monographs* through Volume 106, based on information derived from human in-vivo, human in-vitro, animal in-vivo, and animal in-vitro studies. The most prevalent key characteristic was genotoxicity, followed by altered cell proliferation and oxidative stress. All agents considered demonstrate multiple characteristics, with an average of four characteristics per agent, a finding consistent with the notion that human cancer development involves multiple pathways. Although a detailed comparison of the characteristics of different types of agent was not attempted here, the overall characteristic profiles for pharmaceutical agents and chemical agents and related occupations appeared similar. Further in-depth analyses of this rich database of characteristics of human carcinogens are expected to provide additional insight into the mechanisms of human cancer.

Introduction

Since the establishment of the *IARC Monographs Programme* within International Agency for Research on Cancer (IARC) in the early 1970s, the Agency has evaluated 990 agents for which there exists some evidence of an increased cancer risk to humans. The Agency has developed detailed criteria against

[1] Deceased.

[2] L. Banks, F.A. Beland, J.A. Bond, M.C. Bosland, J.R. Bucher, J.C. Caldwell, D.M. DeMarini, B. Fubini, B.D. Goldstein, S.S. Hecht, K. Hemminki, C.W. Jameson, A.B. Kane, R.J, Kavlock, P.F. Lambert, R. Melnick, C.J. Portier, I.I. Rusyn, L. Stayner, B.W. Stewart, R.L. Ullrich, H. Vainio, P. Vineis, M.P. Waalkes, L. Zeise.

which to evaluate the available scientific evidence on the cancer-causing potential of such agents. These criteria are described in the *Preamble to the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* (Cogliano et al., 2004; see http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf) and are used to weigh the evidence provided by human epidemiological studies and animal cancer bioassays, as well as by information on possible biological mechanisms of action, in order to classify agents in one of 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 to humans; and* Group 4: *The agent is probably not carcinogenic to humans.* These evaluations involve assessment of both the human and animal information as providing *sufficient evidence of carcinogenicity*, *limited evidence of carcinogenicity*, *inadequate evidence of carcinogenicity*, or *evidence suggesting lack of carcinogenicity*. The information on biological mechanisms of action may be evaluated as *strong*, *moderate* or *weak*, and is taken into consideration in the overall evaluation of all available evidence.

The role of mechanistic information in evaluating carcinogenicity has increased substantially during the history of the *IARC Monographs Programme*. In 1991, IARC convened a Working Group on the 'Use of Data on Mechanisms of Carcinogenesis in Risk Identification', to explore how mechanistic data could be used to identify agents with the potential to cause cancer in humans. The consensus report of the Working Group documented a number of mechanistic characteristics that were considered to be relevant to human carcinogenesis at that time, including: genotoxicity, cell proliferation, receptor mechanisms in mitogenesis, alterations in DNA repair, intercellular communication, and immune defects and immunosuppression (Vainio et al., 1992). Toxicokinetic and other variables were also identified as factors affecting multistage carcinogenesis. Since 1991, IARC and other organizations – e.g., the US National Toxicology Program (2014) and the US Environmental Protection Agency (2005) – have stressed the increasing importance of mechanistic information in cancer risk assessment. This is consistent with the current trend towards a general risk-assessment practice based on mode of action (Meek et al., 2013) and pathways of toxicity (Krewski et al., 2014; Bourdon-Lacombe et al., 2015; Cote et al., 2016), as well as dosimetric considerations (Gurusankar et al., 2016).

This chapter examines the available data on mechanisms of action of the Group-1 agents identified through Vol 106 of the *IARC Monographs* (Table 1), by use of the classification developed by Smith (this Volume) and Smith et al. (2016) who defined 10 key characteristics of human carcinogens. Information on these characteristics was extracted from the *IARC Monographs* based on guidance provided by the participants in the IARC Workshop on 'Tumour-site Concordance and Mechanisms of Carcinogenesis' (April/November 2012) and used to develop a database of key characteristics for Group-1 agents (see Al-Zoughool et al., this Volume). This chapter presents the results of an exploratory analysis of this database.

Methods

Key Characteristics

The present analysis is based on a systematic approach to the evaluation of human cancer mechanisms, which initially involved retrieval of information from the *IARC Monographs* on 24 toxicological endpoints identified as likely indicators of biological processes at the cellular and molecular level and thought to be relevant to carcinogenesis. Information on these 24 endpoints was derived from human in-vivo, human in-vitro, animal in-vivo, and animal in-vitro studies (see Al-Zoughool et al., this Volume). In their November 2012 meeting, the Workshop identified 10 broader key characteristics that reflect different mechanistic pathways (see Smith, this Volume; and Smith et al., 2016). This chapter focuses on the key characteristics of the Group-1 agents identified through Volume 106.

Smith (this Volume) and Smith et al. (2016) describe ten key characteristics of human carcinogens, as listed in Table 2. The toxicological endpoints initially considered by the Workshop and used as indicators of these characteristics are also noted in Table 2. A brief summary of each of these characteristics and the associated toxicological endpoints is provided below. See Smith (this Volume) and Al-Zoughool et al. (this Volume) for a more detailed discussion.

Characteristic 1: Is Electrophilic or Can Be Metabolically Activated to Electrophiles. The first characteristic refers to agents that act as electrophiles themselves or that can be metabolized to form electrophile(s). Electrophiles are molecules that undergo chemical reactions by accepting electrons. An electrophile can react with cellular macromolecules such as DNA, RNA and proteins to form adducts. Some chemical carcinogens are direct-acting electrophiles (e.g., formaldehyde; sulfur mustards and ethylene oxide), whereas others require biotransformation by enzymes in a process termed metabolic activation (e.g., polycyclic aromatic hydrocarbons and benzene) (Miller, 1970).

Characteristic 2: Is Genotoxic. Genotoxicity is the ability to induce DNA damage that leads to the formation of DNA adducts, single- or double-strand breaks or other chromosomal alterations, as measured by three associated toxicological endpoints: (a) *DNA damage*: an alteration in the chemical structure or integrity of DNA, and includes a break in a DNA strand, and/or chemical modifications such as covalent binding to the nucleotide bases (Hoeijmakers, 2009); (b) *Gene mutations*: changes in the normal nucleotide sequence of cellular DNA that may have a central role in human carcinogenesis (Ding et al. 2008); (c) *Cytogenetic effects* reflect damage to chromosomes, including DNA breakage, or the rearrangement, gain or loss of chromosome fragments (Snyder 2010).

Characteristic 3: Alters DNA Repair or Causes Genomic Instability. Alterations in DNA repair result in defects in processes that monitor and correct DNA replication fidelity that can confer strong mutator phenotypes resulting in genomic instability. The associated toxicological endpoint is an indicator of *DNA-repair alteration*.

Characteristic 4: Induces Epigenetic Alterations. Induced epigenetic alterations are stable changes in gene expression and chromatin organization that are independent of the DNA sequence itself, and can be mitotically inherited through cell division. Epigenetic phenomena include: genomic imprinting, X-chromosome inactivation and global reconfiguration of the DNA methylome, changes in chromatin compaction states and histone modification patterns, and altered microRNA (miRNA) expression. These phenomena occur during organ development and contribute to the lineage-specific epigenome that is

maintained over the lifetime of an organism. Many of these phenomena have been shown to be altered during carcinogenesis.

Characteristic 5: Induces Oxidative Stress. Oxidative stress results from an imbalance in reactive oxygen formation and detoxification within cells and tissues. The resulting reactive oxygen species induce a cascade of events that can include DNA mutation and oxidative DNA damage. Both are key events in carcinogenesis (Klaunig et al., 2011). Toxicological indicators of *oxidative stress* are discussed by Al-Zoughool et al. (this Volume).

Characteristic 6: Induces Chronic Inflammation. Induced chronic inflammation can arise from persistent infection (e.g., with HPV, *H. pylori*) as well as from external irritants (e.g., silica, asbestos fibers). Persistent infection and chronic inflammation disrupt local tissue homeostasis and alter cell signalling, leading to the recruitment and activation of inflammatory cells. Strong links exist between inflammation and the induction of oxidative stress and genomic instability, such that it is difficult to separate out the importance of each of these mechanisms. This linkage to other pathways may be the basis of the relationship between chronic inflammation and cancer (Multhoff & Radons, 2012).

Characteristic 7: Is Immunosuppressive. Immunosuppression refers to an induced reduction in the capacity of the immune system to respond effectively to foreign antigens, including antigens on tumour cells. The immune system also plays a major part in the inflammatory response to injury.

Characteristic 8: Modulates Receptor-mediated Effects. Modulation of receptor-mediated effects can occur when agents mimic the structure of endogenous ligands that bind to cells and activate cell-surface receptors or intracellular receptors, thereby inducing or modifying a plethora of cell transduction pathways that stimulate cell proliferation. *Receptor-mediated* effects can induce *hormonal effects* whereby external agents can interfere with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body. They can also demonstrate reactivity similar to endogenously produced hormones, which can lead to changes in homeostasis, reproduction, development, or behaviour.

Characteristic 9: Causes Immortalization. Immortalization refers to a situation where the cell is induced to evade normal cellular senescence and will proliferate indefinitely. In culture, normal cells have a fixed number of replication cycles before they enter cellular senescence and stop replicating. This is frequently associated with *activation of telomerase* (Willeit et al. 2010), and plays a critical part in carcinogenesis (Reddel, 2014). Carcinogenesis may involve activation of a telomerase that prevents loss of telomere length, leading to immortalization of cells (Willeit et al. 2010).

Characteristic 10: Alters Cell Proliferation, Cell Death or Nutrient Supply. The first of these characteristics – cell proliferation – refers to alteration in the rates of cell growth within a tissue. It may be a direct effect or a secondary regenerative effect after induction of cell death by cytotoxic agents. Two associated toxicological endpoints are (a) C*ell-cycle effects*, i.e. alterations in the functioning of the complex series of factors controlling the cell cycle and cell division, which have been associated with carcinogenesis (Diaz-Moralli et al. 2013); and (b) *Alteration of cell-signaling pathways*, which relates to the ability of the agent to interfere with cell-signalling pathways leading to expression of a carcinogenic

trait/phenotype in the cell. For cell death, necrosis triggers the invasion of cells such as macrophages into the affected area, and enhances the proliferation and spread of cancer cells. Defects in programmed cell death can cause cancer; evasion of apoptosis is a requirement for both neoplastic transformation and sustained growth of cancer cells. Adequate cell nutrition is essential to proliferating cancer cells and agents that promote or inhibit the growth of blood vessels (angiogenesis) will affect tumour growth.

Group-1 Agents included in the Analysis

Since 1971, the IARC has evaluated the potential cancer hazard of 990 agents. As of June 2016, 118 agents met the criteria to be classified as a Group-1 human carcinogen (Table 1). Volume 100 of the *IARC Monographs* provides a review and update of the 107 Group-1 agents identified as of 2009. This Volume was published in six parts, focusing on pharmaceuticals (IARC, 2012a; *Monograph* Volume 100A); biological agents (IARC, 2012b; Vol 100B); arsenic, metals, fibres, and dusts (IARC, 2012c; Vol 100C); radiation (IARC, 2013d; Vol 100D); personal habits and indoor combustions (IARC, 2012e; Vol 100E); and chemical agents and related occupations (IARC, 2012f; Vol 100F), respectively.

Since the publication of Vol 100, mechanistic information on two additional Group-1 agents – diesel-engine exhaust (Vol 105; Benbrahim-Tallaa et al., 2012) and trichloroethylene (Vol 106; Guha et al., 2012) – has become available. Had these two agents been evaluated within Vol 100, they would have been included in Vol 100F; they have therefore been listed with 'other chemicals and related occupations' in Vol 100F*.

Although additional Group-1 agents have since been identified (Table 1), the present analysis is restricted to Group-1 agents identified through Volume 106, this being the most recent volume for which mechanistic information was available at the time of the present analysis. Group-1 agents excluded from the present analysis are polychlorinated biphenyls (PCBs) and dioxin-like PCBs (Vol 107; Lauby-Secretan et al., 2013), outdoor air pollution and particulate matter from outdoor air pollution (Vol 109; Loomis et al., 2013); 1,2-dichloropropane (Vol 110; Brenbrahim-Tallaa et al, 2014); fluro-edenite amphibole asbestos and occupational exposures associated with the Acheson process used in the manufacture of silicon carbide fibres (Vol 111; Grosse et al., 2014); lindane (Vol 113; Loomis et al., 2015); and processed meat (Vol 114; Bouvard et al., 2015).

In some cases, the discussion of mechanisms of action in the Sections 4 of the *IARC Monographs* is based on groups of agents thought to act via the same mechanism. For example, haematite mining with exposure to radon (underground), Pu-239, Th-232 (as Thorotrast), Ra-224 and its decay products, Ra-226 and its decay products, Ra-228 and its decay products, and internalized radionuclides that emit alpha-particles are discussed in the *Monographs* as a group with the same mechanism of action. Birkett et al. (this Volume) reviewed the mechanistic information for 109 Group-1 agents identified in the *IARC Monographs* through Volume 106. The 86 Group-1 agents for which unique mechanistic summaries are provided in the *IARC Monographs* through Volume 106 are listed in Table 3, along with their relationship to the 111 distinct agents identified through Volume 109 used by Krewski et al. (this Volume) in a parallel analysis of concordance between animal and human tumours and tumour sites.

Database of Mechanistic Characteristics

We assembled a database of toxicological endpoints for the 86 Group-1 agents identified by the IARC through Volume 106 of the *IARC Monographs* (see Al-Zhoughool et al., this Volume). The database includes information from in-vivo and in-vitro studies from humans and animals. Information on the 24 toxicological endpoints was retrieved from Sections 4 of the Monographs (Al-Zoughool et al., this Volume). Recognizing that the mechanistic information included in the *Monographs* is not intended to provide a complete summary of scientific literature on cancer mechanisms, we conducted PubMed searches to identify evidence of any of the 24 toxicological endpoints linked to these agents that was not recorded in the *IARC Monographs* (Birkett et al., this Volume). The mechanistic database distinguishes information derived from the *Monographs* from that found in our PubMed search, thereby permitting an assessment of the extent to which Sections 4 of the IARC Monographs captured all relevant information on these endpoints. The analyses in this chapter are restricted to information taken directly from the *IARC Monographs*: Birkett et al. (this Volume) present the results of a sensitivity analysis incorporating the additional information obtained through our PubMed search.

Following collection of information on the toxicological endpoints identified by the Workshop at its first meeting, the database of key characteristics was then created by mapping the 24 toxicological endpoints to the 10 characteristics as indicated in Table 2. As noted by Al-Zoughool et al (this Volume), two of the toxicological endpoints – susceptibility and changes in gene expression – did not link to any of the key characteristics, and thus were not included in the development of the database of key characteristics. As the database includes information derived from human in-vivo, human in-vitro, animal in-vivo and animal in-vitro sources, it is possible to aggregate this information according to human and animal sources (by combining across in-vivo and in-vitro sources) or according to in-vivo and in-vitro sources (by combining across human and animal sources). Of primary interest here is aggregation across all four sources combined in order to obtain an overall indicator of whether or not any of the ten mechanistic characteristics is associated with each of the 86 Group-1 agents of interest.

Statistical Analysis

Descriptive statistical methods were used to explore the key characteristics associated with the 86 Group-1 agents, beginning with a tabulation of the number of agents demonstrating any of the ten characteristics, both overall and stratified by source of information. In order to evaluate the extent to which the Group-1 agents demonstrated more than one key characteristic, the number of agents demonstrating multiple characteristics was also tabulated. A 'heat map' showing the number (0, 1, 2, 3 or 4) of sources of information (human in-vivo, human in-vitro, animal in-vivo, animal in-vitro) supporting a given characteristic for a specified agent was prepared to evaluate the consistency of information provided by different sources. Overall mechanistic profiles were also tabulated by type of agent (pharmaceuticals; biological agents; arsenic, metals, fibres and dusts; radiation; personal habits and indoor combustions; and chemicals and related occupations) in order to identify possible differences in mechanistic profiles by agent type.

Results

The key characteristics of the 86 Group-1 agents considered here are summarized in Figure 1.The most prevalent mechanistic characteristic is genotoxicity, followed by cell proliferation, oxidative stress, electrophilicity, and chronic inflammation. The vast majority of agents demonstrate genotoxicity as one of their mechanistic properties, with 85 of the 86 agents considered having evidence of this characteristic. Evidence of genotoxicity was provided by expression of the following toxicological endpoints: DNA damage, gene mutations, and cytogenetic effects (including chromosomal aberrations, micronucleus formation, and aneuploidy).

Figure 2 shows the key characteristics exhibited by the 86 agents classified according to the source of data (human in-vivo, human in-vitro, animal in-vivo, and animal in-vitro studies) on these characteristics. Information on all the mechanistic characteristics was available to different degrees from all four sources. Information on genotoxicity was available from each of the four sources for at least 65% of the agents. Human in-vitro studies contribute the majority of the evidence on six of the ten key characteristics, including altered DNA repair and genomic instability, oxidative stress, chronic inflammation, receptor-mediated effects, immortalization, and altered cell proliferation/death/nutrition. The prominence of in-vitro sources of information on most key characteristics could be attributed to the fact that many of these characteristics are components of signaling pathways that are often studied in in-vitro test systems. In-vivo animal studies were more prevalent sources of mechanistic information than in-vitro animal studies for seven key characteristics: electrophilicity, genotoxicity, chronic inflammation, oxidative stress, receptor-mediated effects, epigenetic alterations, and immunosuppression.

The prominence of human studies as sources of information on the key characteristics of human carcinogens may be attributed to the increasing use of molecular and genetic markers in human studies. Epidemiological studies conducted in the occupational or general environment often analyze biomarkers of DNA adduct formation, clastogenic effects, and gene mutations, all of which reflect DNA damage. As a consequence, human in-vivo studies are a major source of information on genotoxicity.

Figure 3 shows the number of agents demonstrating multiple characteristics as evidenced from studies in animals and in humans. The 86 Group-1 agents considered here demonstrate an average of 3.8 key characteristics, with the modal value being two characteristics exhibited by 26 agents. All agents demonstrate at least one key characteristic, with one agent demonstrating nine characteristics and 12 agents showing six. No agent demonstrated all 10 key characteristics.

Figure 4 presents a heat map indicating the strength of evidence of the different characteristics for the 86 individual Group 1 agents. The intensity of the color reflects the number of sources of evidence (human in vivo, human in vitro, animal in vivo and animal in vitro studies) on the key characteristics for each agent. As in Figure 1, the single most prominent characteristic is genotoxicity: the majority of agents showed a positive response for genotoxicity in at least one of the four sources of information, with many agents providing evidence of genotoxicity from more than one source. For some agents (e.g., all radiation sources, some pharmaceutical agents, and some chemical agents), genotoxicity was demonstrated in all four test systems, confirming that genotoxicity is central to the carcinogenic pathways of these agents.

Figure 4 also shows that the majority of agents exhibit multiple key characteristics, with evidence drawn from more than one source of mechanistic information. Radiation sources and tobacco smoke are associated with many of the key characteristics, suggesting that these agents act by multiple pathways.

A number of Group-1 agents, including several occupational exposures, are complex mixtures of chemical and other substances. Coal-tar pitch, occupational exposure to soot, and coke production all share similar characteristics, likely due to the strong presence of polycyclic aromatic hydrocarbons, although other factors such as the nature of inorganic substances and sulphur composition could also play a role. Other occupationally relevant agents (e.g. rubber manufacture and aluminium production), demonstrate only a single key characteristic, though this may reflect the difficulty of testing for other characteristics in these occupational exposure situations.

Figure 5 shows the key characteristics of the six categories of Group-1 agents considered in Vol 100: pharmaceutical agents; biological agents; arsenic, metals, fibres and dusts (AMFD); radiation; lifestyle-associated agents; and chemical agents. Genotoxicity is the most frequent characteristic expressed by pharmaceuticals, AMFD, lifestyle-related exposures, and chemical agents, and is exhibited by all agents mentioned under radiation. Genotoxicity and cell proliferation are prominent characteristics of the biological agents. None of the biological agents demonstrated receptor-mediated-effects or electrophilicity, and none of the lifestyle-related agents appeared to act through receptor-mediated effects or immunosuppression. There are five radiation agents, all demonstrating the following key characteristics: genotoxicity; altered DNA repair; immunosuppression; chronic inflammation; oxidative stress; immortalization; and altered cell proliferation/death/nutrition. The profiles of key characteristics for pharmaceutical agents and chemical agents are remarkably similar, possibly reflecting the fact that despite their different exposure circumstances, some of the chemotherapeutic agents and chemical agents interact with the same chemical entities *via* similar cancer mechanisms.

Discussion

The present analysis of key characteristics of 86 agents determined by IARC to be human carcinogens was based on mechanistic information retrieved from the *IARC Monographs* (Birkett et al.; Al-Zoughool et al., this Volume). The profiles of key characteristics of these agents show a number of interesting patterns. First, all agents exhibited multiple characteristics, an observation consistent with previous findings on the complexity and heterogeneity of carcinogenic pathways (Hanahan and Weinberg, 2011; Roessler et al. 2014; Baker et al. 2014; Floor et al. 2012; Pickup et al. 2014). Biological agents, ADMF, lifestyle and radiation agents demonstrated a wide spectrum of biological activity. Radiation has been linked to many hallmarks of cancer (Boss et al. 2014): this mechanistic profile, with multiple pathways being followed by most radiation agents, is consistent with the broad spectrum of tumours associated with exposure to ionizing radiation (Krewski et al., 2016). Viral oncogenesis is also multifaceted, with the multistep nature of viral oncogenesis thought to be influenced by host genetic variability (Mesri et al. 2014).

Genotoxicity was the most prevalent mechanistic characteristic, demonstrated by 85 of the 86 agents considered, possibly reflecting the fact that the process of carcinogenesis necessarily involves genomic changes that must be fixed during cell replication. This finding is consistent with an earlier evaluation of 180 Group-1, -2A and -2B agents conducted by Bartsch & Maleveille (1989), who reported that 80-90% of the agents in these three categories demonstrated genotoxic characteristics. In the present analyses, genotoxicity was considered to include the following endpoints: DNA damage, clastogenic effects (including chromosomal aberrations, micronucleus formation, and aneuploidy), and gene mutations. Information drawn from the *Monographs* showed that the overwhelming majority of the agents examined here induce one or more of these endpoints. Even biological agents such as viruses that act primarily through non-genotoxic mechanisms induce cytogenetic effects and mutations as secondary events through chronic inflammation and oxidative stress.

Some caution must be used in interpreting the distribution of key characteristics across the Group-1 agents considered here. It is possible that the near universality of genotoxicity as a carcinogenic mechanism may be related to the way the *IARC Monograph* Working Groups prepared their reports, with emphasis on the reporting of genotoxicity data. This would have been partially mitigated by the inclusion of mechanistic information from outside the *IARC Monographs* in the preparation of the mechanistic database evaluated separately here by Birkett et al (this Volume). It should also be noted that the *Monographs* were published over a long time span, extending from 1970 to the present (Saracci & Wild, 2015). Studies of agents in earlier Volumes would have focused on changes such as DNA damage that could have been detected by the techniques available at that time. These agents may not have been evaluated exhaustively for more recently identified biological pathways such as those involving the multi-factorial nature of carcinogenesis, and the multiplicity of pathways operating during the process of agent-induced cancer.

Another limitation of the present results is that they are based on the information on mechanisms in Section 4 'Other Relevant Data' of the *Monographs*. As we did not undertake a full series of systematic reviews of the entire body of literature on biological mechanisms of action for all agents, the database may not reflect all characteristics of the different agents. As a sensitivity analysis to examine the extent to which the Monographs captured most of the relevant information in this regard, Birkett et al. (this Volume) conducted a supplementary PubMed search to identify additional information on the key characteristics not cited in the *Monographs*. While this sensitivity analysis was not based on an exhaustive search, it did identify additional information sources (the most notable being the identification of evidence of six additional agents demonstrating receptor-mediated effects, beyond the nine noted in Figure 1). Nonetheless, the findings are largely compatible with those presented (see Birkett et al., this Volume, for further details).

In Supplemental Material, Birkett et al. (this Volume) also examined key characteristics reflected by 'established' and 'likely' mechanistic events associated with Group-1 agents, as documented by the Working Groups that conducted the evaluations of these agents. As the Working Groups focused only on the main 'established' and 'likely' mechanistic events demonstrated by these agents, this sensitivity analysis identified fewer key characteristics that did the analysis presented in this Chapter, which is based on abstraction of all mechanistic information cited in Section 4 of the IARC Monographs.

As the *IARC Monographs Programme* has evolved from its inception in 1970 through to the present time, the guidelines for carcinogen identification as set out in *Preamble* have been updated from time to time, with increasing emphasis on the use of mechanistic information in the most recent updates. Nonetheless, the identification of Group-1 agents continues to rest heavily on the availability of *sufficient evidence* of carcinogenicity in epidemiological or clinical studies. Of 111 distinct agents in Group 1 through *Monograph* Volume 109, no less than 102 demonstrated *sufficient evidence* of carcinogenicity in humans, with the remaining 9 agents being in Group 1 on the basis of mechanistic upgrades (see Table 4 in the Concordance chapter by Krewski et al., this Volume). Despite the heavy reliance on human data in identifying agents that may increase human cancer risk, the Sections 4 of the *IARC Monographs* increasingly provide detailed descriptions of the mechanisms by which agents under review may act, including agents not assigned to Group 1.

The epigenetic characteristics of Group-1 agents considered in Volumes 100A–E were previously assessed by Herceg et al. (2013). As in the present analysis, these authors used DNA methylation, histone marks, and miRNA indicators of epigenetic effects. Considering information from both the *IARC Monographs* and the general scientific literature, they identified 22 of these 74 Group-1 agents (29.7%) as demonstrating epigenetic effects. The present analysis, which examined Group-1 agents in *Monographs* 100A–F and well as Volumes 105 and 106 identified 27 of 86 Group-1 agents (31.4%) as having epigenetic characteristics.

In an earlier evaluation, Hernández et al. (1989) reported that 45 of the 371 agents (12%) in Groups 1, 2A and 2B at the time of their analysis were not genotoxic. In their study, an agent was considered non-genotoxic if it gave negative results in the Ames assay, as well as in the mouse lymphoma assay, the in-vitro chromosomal aberration test, the in-vitro micronucleus test, the in-vivo micronucleus test or the in-vivo chromosomal aberration test in rodent bone-marrow. These results support the role of non-genotoxic pathways in carcinogenesis, an observation that is reinforced by the prevalence of multiple characteristics of human carcinogens not associated with genotoxicity in the present analysis.

The fact that the great majority of carcinogenic agents demonstrate multiple mechanistic characteristics may have implications for the shape of the corresponding exposure-response relationships. Different mechanisms may be prominent at different levels of exposure, leading to dose-dependent transitions in the dose-response curve (Slikker et al., 2004a). In an accompanying paper (Slikker et al., 2004b) these authors note that such dose-dependent transitions can occur when the mechanism includes metabolic activation with agents such as butadiene (Group 1) and methylene chloride (Group 2A); changes in cell kinetics with formaldehyde (Group 1); and adduct formation and DNA repair with vinyl chloride (Group 1). Swenberg et al. (2012) note that formaldehyde causes DNA–protein cross-links (DPC), with disproportionately larger amounts of DPC formed at concentrations above 6 ppm due to saturation of glutathione detoxification pathways. Formaldehyde induces marked cell proliferation in the nasal epithelium in animal models at higher doses. Formaldehyde has also been shown to downregulate miRNAs in human miRNA microarrays, possibly due to apoptosis signalling. Such dose-dependent effects lead to marked non-linearity in the dose-response curve for nasal cancers induced by formaldehyde.

In order to ensure that all relevant evidence on the 10 key characteristics of human carcinogens developed by Smith (this Volume) and Smith et al. (2016) is taken in to account in future evaluations of agents that may cause cancer in humans, a carefully designed systematic review of the scientific literature would be required in conjunction with each evaluation. However, to conduct a series of comprehensive systematic reviews of the key characteristics of all 86 agents considered in the present analysis would represent a considerable effort, and as such was not attempted as part of the present project. The expert opinion of future IARC Working Groups charged with evaluating the mechanistic data on new agents selected for evaluation by the *IARC Monographs* would be of considerable value in this regard, but would ideally be supported by a concomitant systematic review of the relevant scientific literature on the key characteristics in order to ensure that the analysis be as complete as possible.

Another issue that arises when discussing key characteristics of human carcinogens is whether indirect effects should be considered. Many agents have a direct carcinogenic effect, but in other cases the carcinogenic characteristic is the result of a secondary event along the mechanistic pathway. For example, cell proliferation can arise due to a direct action of the agent on the cell, or indirectly, due to cytotoxicity that stimulates cell proliferation to replace cells, through alterations in cell signalling without cytotoxicity, or *via* inhibition of cell proliferation that then results in selection of an altered clone of cells with a high proliferation rate. While the downstream effect is the same (increased cell proliferation), the mechanism leading to that result can be different. A similar issue arises with genotoxicity where many agents are not directly genotoxic but cause DNA damage by stimulating a chain of molecular changes (e.g. chronic inflammation). The current database does not contain the information needed to address these issues and cannot be used to draw conclusions about the detailed mechanism of action of an agent.

It should be noted that the ten key characteristics should be considered as characteristics rather than as mechanisms, in part because the analysis does not address the sequence of events involved in carcinogenesis. For example, if we are interested in the carcinogenic mechanism of action for a genotoxic agent that requires metabolic activation, the mechanism needs to consider the entire metabolic pathway. If the agent is not metabolized to produce an electrophile, DNA damage will not occur. In such a case, characteristics subsequent to DNA damage also would not be observed. This is also apparent for characteristics such as chronic inflammation, which acts through the production of oxidative stress, release of cytokines, and stimulation of cell proliferation, which ultimately produces DNA damage.

The results of the present analysis can provide a basis for future efforts to categorize mechanistic data for carcinogens through a systematic review process. A full systematic review of all agents and all potential carcinogenic mechanisms is an intimidating prospect. However, such a review would provide a more comprehensive examination of mechanisms, since it would include studies that failed to find effects. It might also support a process involving a sequence of mechanistic steps and mechanistic characteristics relevant to the development of cancer in humans.

The importance of systematic review in assembling all relevant evidence on a particular issue has been emphasized in the recent review of the US EPA's Integrated Risk Information System (IRIS) (NRC, 2014), and is currently being implemented within the IRIS program as a way of summarizing all relevant data in a comprehensive and reproducible manner. The US EPA is also currently supporting the

development of software tools specifically designed for systematic review of toxicological and epidemiological data (ICF, 2014).

The strong evidence linking genotoxicity to carcinogenesis is consistent with epidemiological data and experimental research. Genotoxic effects include the formation of DNA adducts or induction of single- and double-strand DNA breaks. Several lines of evidence from epidemiological studies and in experimental animals and model systems have shown that DNA adducts are strongly associated with cancer (Kriek et al. 1998, Phillips et al. 2014). Some genotoxic effects can lead to gene mutation, an important event in the pathway towards carcinogenesis, especially if it involves oncogenes or tumour suppressor genes. Chromosomal changes are another type of genetic alteration that are widely displayed in many tumours, especially solid tumours. Most tumour cells display aneuploidy and, for some tumours, characteristic chromosomal abnormalities have been identified (e.g. the Philadelphia Chromosome in chronic myeloid leukaemia). Consequently, agents that induce genomic instability should be regarded as potential carcinogens.

Recently, a carcinogenic mechanism not linked to any of the key characteristics studied here has achieved prominence in the literature. Tomasetti & Vogelstein (2015) have argued that stem-cell division rates can explain variation in cancer occurrence rates at different sites, with random mutations during DNA replication in normal stem cells increasing cancer risk in proportion to the rate of stem-cell division in different tissues. Strong positive correlations between the rates of stem-cell division and lifetime risk of cancer in different tissue sites are documented in support of this hypothesis. As an example, the authors compare cancer rates in melanocytes and basal epidermal cells of the skin, both of which are subject to similar exposure to ultra-violet radiation, a Group-1 carcinogen. Basal cell carcinomas are much more common than melanomas, and basal cells undergo a higher number of divisions than do melanocytes, providing support for the authors' main hypothesis. Overall, Tomasetti & Vogelstein suggest that only a third of the variation in cancer risk may be due to environmental factors or inherited predispositions, with the majority associated with random mutations, or 'bad luck'. Pointing to methodological limitations, including the focus on less common cancers that make only a small contribution to human cancer burden, the International Agency for Research on Cancer (IARC, 2015) observed that strong geographic and temporal variation in the risk of more common cancers is consistent with environmental causes. Based on current knowledge, IARC suggested that nearly half of all human cancers are associated with preventable causes, and that further research will continue to identify additional modifiable risk factors for human cancer. Nonetheless, stem-cell division would appear to be a mechanistic characteristic of human cancer that is worthy of further investigation.

The complexity of the pathways involved in carcinogenesis and the fact that cellular response to carcinogen exposure is modulated by host-cell physiology, genetics and other variables have prompted development and application of sensitive assays that measure toxicity pathways and perturbations in molecular functioning of the cell. The newly proposed testing paradigm (Krewski et al. 2014) focuses on high-throughput screening to detect changes in the cell's molecular pathways in response to chemical exposure. This new paradigm would be useful in comprehensive cancer risk assessment and would be able to detect distinct and key mechanistic pathways operating after carcinogen exposure. Similar to this initiative, the Kyoto Encyclopedia of Genes and Genomes (KEGG) website has compiled a comprehensive list of pathways associated with specific diseases (see the KEGG pathway database at

http://www.genome.jp/kegg/pathway.html). KEGG also identified major in-vitro assays that can be used to detect targets of these pathways. This attempt to understand the biological mechanisms of carcinogenesis is consistent with current practice of using in-vitro assays to detect changes in critical signaling and other molecular pathways in cancer development, as proposed by Krewski et al. (2014).

Further Analyses

The extensive database on key characteristics of human carcinogens developed here offers considerable potential for further analysis. More in-depth analyses are underway to explore the level of agreement between mechanistic data derived from human and animal sources, as well as from in-vivo and in-vitro sources, issues that have received only limited attention here. An analysis of the key characteristics demonstrated by Group-1 agents on a site-specific basis is also planned: should agents that cause tumours at a specific sites, such as the lung or liver, be shown to demonstrate similar characteristics, this could provide new insights into site-specific carcinogenesis.

Although the present analysis found that the great majority of Group-1 agents demonstrated multiple key characteristics, with an average of four characteristics per agent, no attempt was made to conduct a multivariate analysis of these characteristics to determine if similar agents tended to express similar characteristics. Recalling that pharmaceuticals as a class demonstrated a mechanistic profile similar to that of the chemical agents, it is possible that the chemotherapeutic agents and some of these chemical agents act *via* the same cancer mechanisms. Cyclophosphamide and benzene (once used as a chemotherapeutic agent) may have some commonality in this respect, as might treosulfan and butadiene through the formation of the same diepoxide. Further study of these two groups, both in terms of mechanism of action and tumour concordance, may provide insight into tumours resulting from long-term exposure to chemotherapeutics.

Searching for patterns within homogeneous classes of agents would also be of future research interest. For example, one could examine mechanistic patterns within subgroups of pharmaceuticals, including: antineoplastic agents, hormonal products, immune-suppressants, and analgesic mixtures. In a similar vein, Shin et al. (2015) have recently employed bioactivity profiles for 38 agents derived from high-throughput in-vitro assays to investigate patterns of toxicity associated with different scenarios of use.

Exposure to a single agent may result in more than one type of tumour, perhaps through different pathways involving different mechanistic characteristics. It would be of interest to examine the key characteristics for agents associated with specific tumour types. This would extend the work of Krewski et al (this Volume) that examined concordance between animals and humans for 39 tumour sites and 15 organ and tissue systems, based on the database on tumours and tumour sites in humans and experimental animals developed by Grosse et al. (this Volume). The profiles of key characteristics of agents associated with specific tumour sites could be examined to obtain additional insights into the mechanisms by which specific tumours occur. Of particular interest in this regard would be to analyse whether or not certain tumour sites demonstrate signature profiles.

Baker et al. (2015) have recently applied supervised machine learning techniques to classify PubMed literature according to the hallmarks of cancer. In a case study of basal cell carcinoma and

melanoma, only 46,727 of 121,488 abstracts from their original systematic literature search were classified as relevant, reflecting the potential time savings that may be achieved through automatic classification.

Extending the mechanisms database to include additional information such as structural alerts relevant to carcinogenesis could also be informative. Although the present version of the mechanisms database does include the IUPAC International Chemical Identifier (InChI) for key chemical coding (IUPAC, 2015; Stein et al., 2003), this information has not been taken into account in the analyses completed to date. One possible source of auxiliary information on toxicological endpoints that may be related to the ten mechanistic characteristics is the US Environmental Protection Agency's ToxCast Program (Judson et al., 2014; Knudsen et al., 2015), which now includes in-vitro, in-vitro, and in-silico data on diverse toxicological endpoints for over 10,000 chemical substances, some of which overlap with the set of Group-1 agents considered in this chapter. The ToxCast database also includes information on several hundred toxicological assays, which could enrich the database of key characteristics used in the present analysis.

Future evaluations of new agents undertaken within the *IARC Monographs* could include a comprehensive evaluation of the ten key characteristics articulated by Smith (this Volume) and Smith et al. (2016), based on a systematic review of the relevant scientific literature in support of the Working Group's deliberations. This has been successfully attempted in recent evaluations of red and processed meats (Bouvard et al., 2015) and organochlorine insecticides and chlorphenoxy herbicides (Loomis et al., 2015): the corresponding *Monographs* are currently undergoing editorial review and checking within IARC.

There could be value in re-visiting the present retrospective analysis of the 86 Group-1 agents identified through *Monograph* Volume 106, both with respect to the conduct of a series of comprehensive systematic reviews on the ten key characteristics of these agents, followed by an in-depth evaluation of the findings of the systematic review by experts in relevant disciplines. The development of criteria for evaluating the weight of evidence for the key characteristics, similar to that included in the *Preamble to* the *IARC Monographs* for human and animal data (IARC, 2006) might be contemplated at that time. Group-1 agents identified beyond Volume 106 for which mechanistic information had become available could also be included in such an analysis.

An alternative approach to extracting information on the 10 key characteristics of human carcinogens would be to apply the machine learning techniques and biomedical text mining methods described by Baker et al. (2015) to identify articles associating these key characteristics with specific Group-1 agents in an automated fashion. Because of the enormity of a full systematic review of mechanistic information on all Group-1 agents, the use of automated search algorithms of this type could offer considerable efficiency gains in identifying potentially relevant mechanistic information. Although this approach could expedite identification of relevant articles, expert opinion and application of weight-of-evidence criteria would still have value in terms of reducing the error rates in assigning key characteristics to specific agents.

Conclusion

In this chapter, we examined the key mechanistic characteristics of human carcinogens defined by Smith (this Volume) and Smith et al. (2016) for the 86 Group-1 agents that have been established as causes of human cancer by the IARC. Similar mechanistic information was derived from multiple sources, including human in-vivo, human in-vitro, animal in-vivo and animal in-vitro studies. The prominence of in-vitro sources for the majority of the mechanistic characteristics is consistent with the increasing reliance on in-vitro tests focusing on toxicity pathways and modes of action (Krewski et al., 2014). All 86 agents demonstrated at least one of the key characteristics, with an average of 3.8 characteristics per agent. Genotoxicity was the most prevalent characteristic, demonstrated by 85 of 86 agents, followed by cell proliferation and oxidative stress. A comparison of the mechanistic profiles for the six broad classes of agent considered in Volume 100 of the IARC Monographs – pharmaceutical agents, biological agents; arsenic, metals, fibres and dusts (AMFD); radiation agents; lifestyle agents; and chemical agents – revealed similar profiles for pharmaceutical and chemical agents.

In considering the results presented in this chapter, it is important to emphasize that these mechanistic analyses represent a first step in understanding the biological mechanisms by which cancer may occur in humans. Although considerable effort was expended in developing the database of key characteristics and their analyses in this chapter, these results should be viewed as preliminary, to be refined through more exhaustive systematic reviews of the relevant scientific literature and/or through discussion with a broad panel of experts on the mechanisms of carcinogenesis. The ten key characteristics proposed by Smith (this Volume) and Smith et al. (2016) were endorsed by the participants in the IARC Workshop on 'Tumour-site Concordance and Mechanisms of Carcinogenesis', which provided oversight for this project; nonetheless, additional experience with the exploration of these characteristics in cancer research will serve to define their utility more fully. Equally important is to consider the nature of the evidence needed to establish that specific mechanistic characteristics are demonstrated by human carcinogens. Our current database has relied on the expression of certain toxicological endpoints as evidence of these mechanistic characteristics: further consideration of these and other possible markers of the key characteristics of human carcinogens is warranted.

Finally, it is important to indicate that the inclusion of mechanistic information into the *IARC Monographs* has evolved over time, with greater consideration being given to both mechanistic data and mechanistic upgrades in the absence of *sufficient evidence* of carcinogenicity in humans in more recent *Monographs*. Mechanistic considerations are becoming increasingly prominent in the *IARC Monographs*, thereby enriching the body of evidence on which future analyses of this type may be based. If forthcoming *Monographs* were able to document information on the ten key characteristics considered here, as has been done in several recent *Monographs*, this would support future follow-on analyses that would extend the initial in-depth analyses of these characteristics presented in this chapter.

Acknowledgements

Melissa Billard assembled the tumour-site concordance database analyzed herein while working as a Visiting Scientist under the direction of Dr Yann Grosse and Dr Robert Baan at the International Agency for Research on Cancer during the summers of 2013 and 2014. Julian Little is the Canada Research Chair in Human Genome Epidemiology at the University of Ottawa. Daniel Krewski is the Natural Sciences and Engineering Research Council of Canada Chair in Risk Science at the University of Ottawa. This chapter is dedicated to the memory of Dr Jan Zielinski, who succumbed to cancer in 2016: prior to becoming ill, Dr Zielinski led the analytical team that conducted the analyses reported herein.

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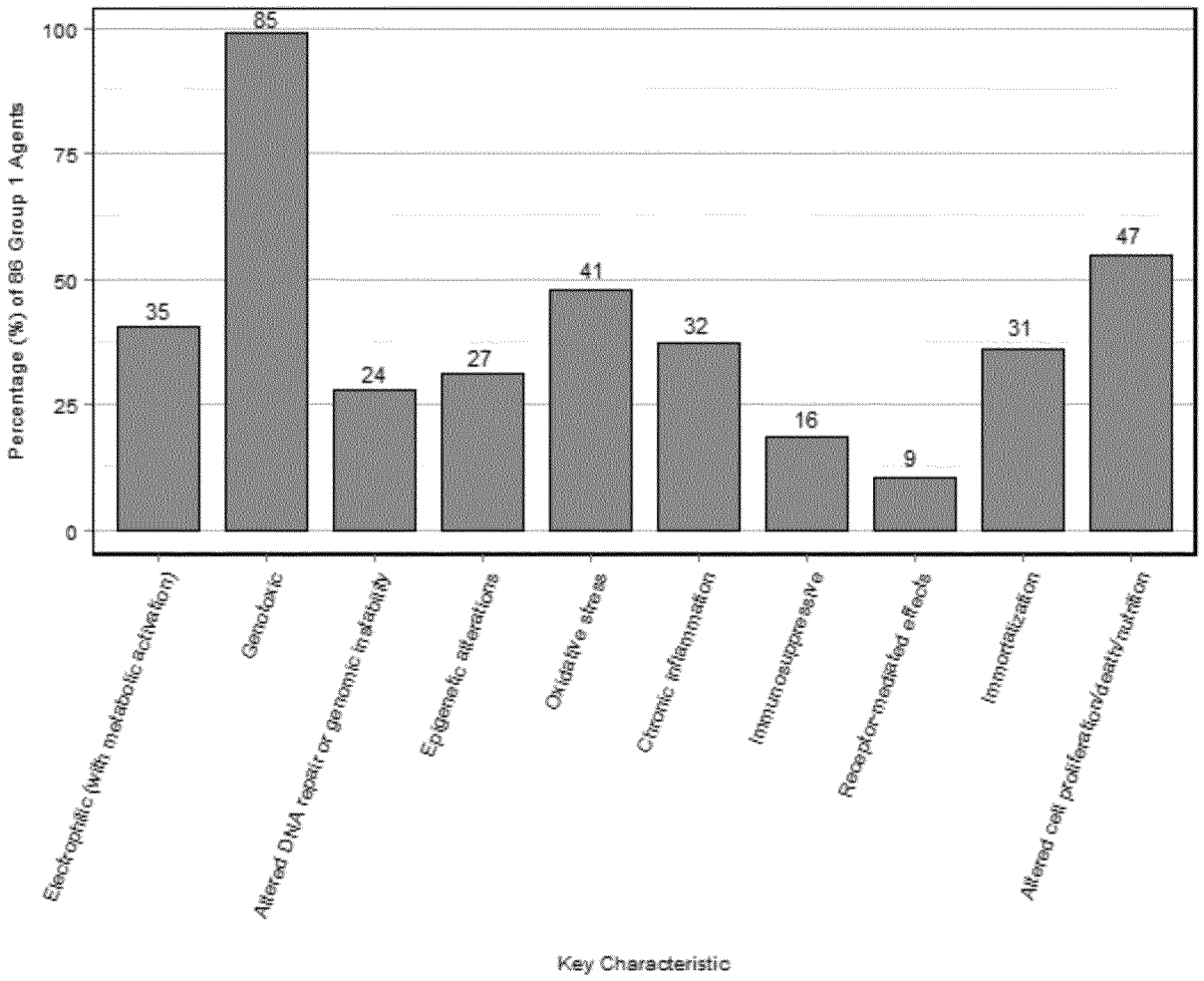

Figure 1. Key Characteristics of 86 Group-1 Agents
(number of agents shown above each characteristic)

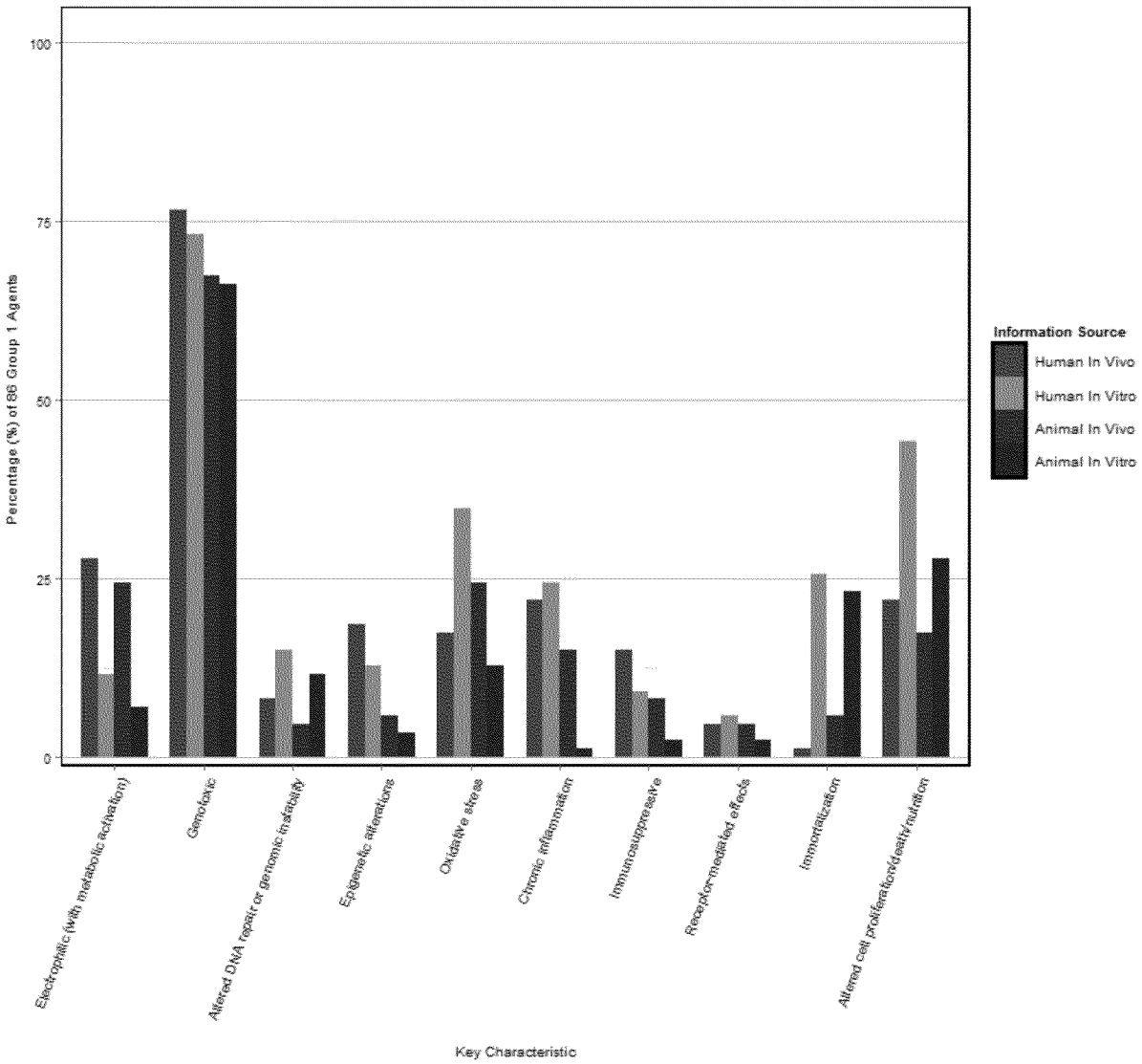

Figure 2. Sources of Information on Key Characteristics of 86 Group-1 Agents
(sources are human in vivo, human in vitro, animal in vivo, animal in vitro studies)

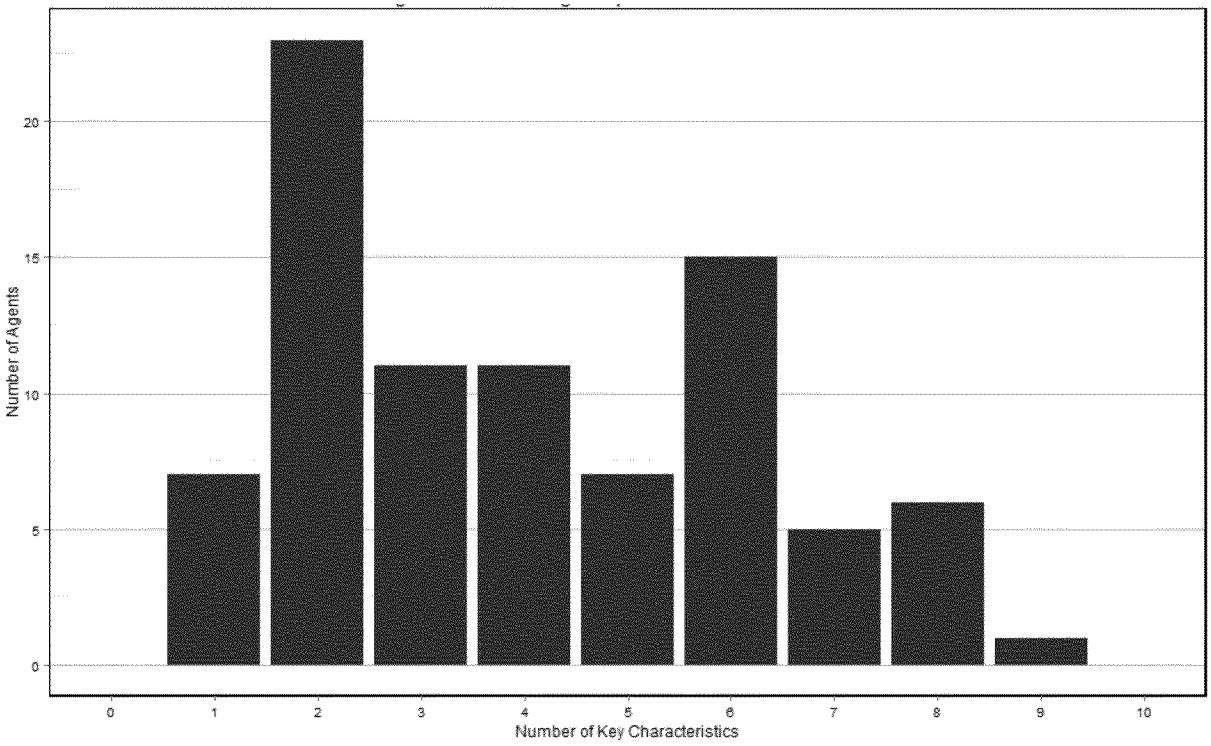

Figure 3. Number of Group-1 Agents Demonstrating One or More Key Characteristics

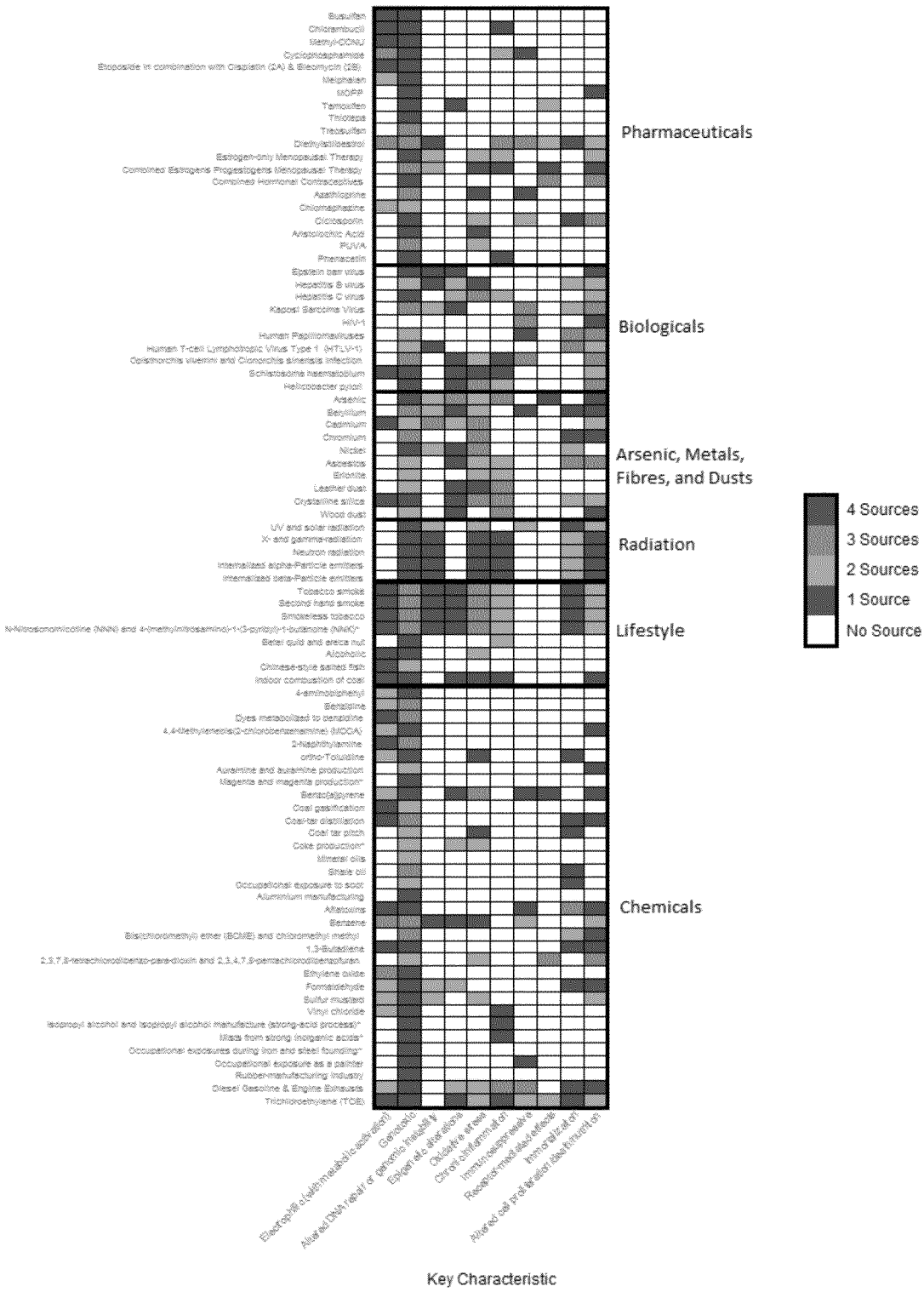

Figure 4. Heat Map Showing the Strength of Evidence for Different Key Characteristics of 86 Group-1 Agents According to the Number of Information Sources (sources are human in vivo, human in vitro, animal in vivo and animal in vitro studies)

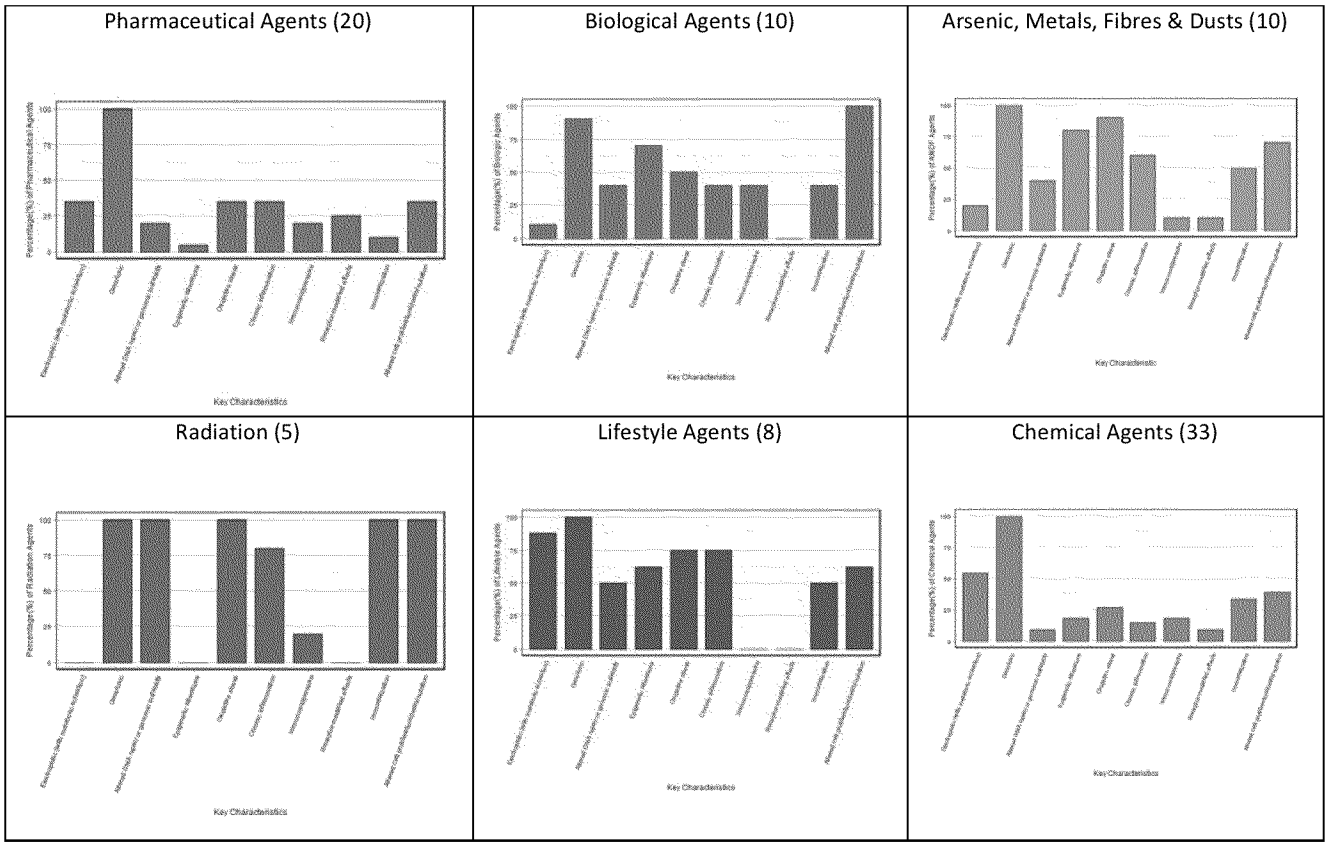

Figure 5. Key Characteristics of 86 Group-1 Agents by Type of Agent
(number of agents of each type shown in parentheses)

Table 1. Number of Group 1 Agents in Volumes 100 through 114 by Type of Agent*

Volume 100			V105	V106	V107	V109	V110	V111	V113	V114	Total
A	Pharmaceuticals	23									23
B	Biological agents	11									11
C	Arsenic, metals, fibres and dusts	10						2[f]			12
D	Radiation	18									18
E	Personal habits and indoor combustions	12								1[h]	13
F	Chemicals and related occupations	33	1[a]	1[b]	2[c]	2[d]	1[e]		1[g]		41
Total		**107**	**1**	**1**	**2**	**2**	**1**	**2**	**1**	**1**	**118**

*At the time the present analysis was conducted, mechanistic information was available only for the 109 Group-1 agents evaluated through Volume 106.

[a]Trichloroethylene; [b]Diesel-engine exhaust; [c]Polychlorinated biphenyls (PCBs); dioxin-like PCBs; [d]Outdoor air pollution; particulate matter from outdoor air pollution; [e]1,2-Dichloropropane (1,2-DCP); [f]Fluoro-edenite amphibole asbestos; occupational exposures associated with the Acheson process in the manufacturing of silicon-carbide fibres; [g]Lindane; [h]Processed meat.

Table 2. Key Characteristics and Toxicological Endpoints Demonstrated by Agents Known to Cause Cancer in Humans (adapted from Al-Zoughool et al., 2015)

Key Characteristic	Corresponding Toxicological Endpoints
Is electrophilic or can be metabolically activated to electrophiles	Reactive metabolites Protein adducts Absorption, distribution, clearance differences
Is genotoxic	DNA damage Clastogenic effects Gene mutation
Alters DNA repair or causes genomic instability	DNA-repair alteration or genomic instability
Induces epigenetic alterations	Epigenetic effects (DNA methylation, histone modification, miRNAs)
Induces oxidative stress	Oxidative stress
Induces chronic inflammation	Chronic inflammation Chronic irritation
Is immunosuppressive	Immune effects
Modulates receptor-mediated effects	Receptor-mediated effects Hormonal effects
Causes immortalization	Immortalization Alterations in telomere length
Alters cell proliferation, cell death or nutrient supply	Cell-cycle effects Bystander effects Alteration of cell-signalling pathways Angiogenic effects Cell death Inhibition of intercellular communication

Table 3. Relationship between 86 Agents used in the Analysis of Key Characteristics of Human Carcinogens and 111 Agents Used in the Analysis of Concordance between Human and Animal Tumours

Volume	Number	86 Agents Used in the Analysis of Key Characteristics	111 Agents Used in the Analysis of Concordance between Human and Animal Tumours
A	1	Aristolochic Acid	Aristolochic acid aristolochic acid, plants containing
A	2	Azathioprine	Azathioprine
A	3	Busulfan	Busulfan
A	4	Chlorambucil	Chlorambucil
A	5	Chlornaphazine	Chlornaphazine
A	6	Cyclophosphamide	Cyclophosphamide
A	7	Ciclosporin	Ciclosporin
A	8	Diethylstilbestrol	Diethylstilbestrol
A	9	Estrogen-only menopausal therapy	Estrogen-only menopausal therapy
A	10	Combined estrogen-progestogen menopausal therapy	Estrogen-progestogen menopausal therapy (combined)
A	11	Combined hormonal contraceptives	Estrogen-progestogen oral contraceptives (combined)
A	12	Etoposide in combination with cisplatin (2A) & bleomycin (2B)	Etoposide Etoposide in combination with cisplatin and bleomycin
A	13	Melphalan	Melphalan
A	14	PUVA	Methoxsalen in combination with UVA
A	15	MOPP	MOPP and other combined chemotherapy including alkylating agents
A	16	Phenacetin	Phenacetin Phenacetin, analgesic mixtures containing
A	17	Methyl-CCNU	1-(2-Chloroethyl)-3-(4-methylcyclohexyl)- 1-nitrosourea (Methyl-CCNU)
A	18	Tamoxifen	Tamoxifen
A	19	Thiotepa	Thiotepa
A	20	Treosulfan	Treosulfan
B	21	*Opisthorchis viverrini* and *Clonorchis sinensis*	*Clonorchis sinensis* (infection with) *Opisthorchis viverrini* (infection with)
B	22	Epstein-Barr virus	Epstein-Barr virus
B	23	*Helicobacter pylori*	*Helicobacter pylori* (infection with)
B	24	Hepatitis B virus	Hepatitis B virus

B	25	Hepatitis C virus	Hepatitis C virus
B	26	Human immunodeficiency virus type 1	Human immunodeficiency virus type 1
B	27	Human papillomavirus	Human papillomavirus
B	28	Human T-cell lymphotropic virus type 1	Human T-cell lymphotropic virus type 1
B	29	Kaposi sarcoma herpesvirus	Kaposi sarcoma herpesvirus
B	30	*Schistosoma haematobium*	*Schistosoma haematobium* (infection with)
C	31	Arsenic and arsenic compounds	Arsenic and inorganic arsenic compounds
C	32	Asbestos (actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite)	Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite)
C	33	Beryllium and beryllium compounds	Beryllium and beryllium compounds
C	34	Cadmium and cadmium compounds	Cadmium and cadmium compounds
C	35	Chromium (VI) compounds	Chromium (VI) compounds
C	36	Erionite	Erionite
C	37	Leather dust	Leather dust
C	38	Nickel and nickel compounds	Nickel compounds
C	39	Silica dust, crystalline, in the form of quartz or cristobalite	silica dust, crystalline, in the form of quartz or cristobalite
C	40	Wood Dust	Wood dust
D	41	Solar and Ultraviolet Radiation	UV radiation (bandwidth 100-400 nm, encompassing UVC, UVB and UVA) UV-emitting tanning devices Solar radiation
D	42	X and γ Radiation	X- and Gamma radiation Ionizing radiation (all types)
D	43	Neutron radiation	Neutron radiation
D	44	Internalized α-particle emitting radionuclides	Haematite mining with exposure to radon (underground) Pu-239 Internalized radionuclides that emit alpha-particles Th-232 (as Thorotrast) Ra-224 and its decay products Ra-226 and its decay products Ra-228 and its decay products Rn-222 and its decay products
D	45	Internalized β-particle emitting radionuclides	Fission products including Sr-90 Radioiodines, including I-131 P-32, as phosphate

			Internalized radionuclides that emit beta particles
E	46	Consumption of alcoholic beverages	Acetaldehyde associated with consumption of alcoholic beverages Alcoholic beverages Ethanol in alcoholic beverages
E	47	Betel quid and areca nut	Areca nut Betel quid with tobacco Betel quid without tobacco
E	48	Indoor emissions from household combustion of coal	Coal, indoor emissions from household combusion of
E	49	N'-Nitrosonornicotine (NNN) and 4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanon (NNK)	N'-Nitrosonornicotine (NNN) and 4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanon (NNK)
E	50	Chinese-style salted fish	Salted fish, chinese style
E	51	Second-hand tobacco smoke	Second-hand tobacco smoke
E	52	Tobacco smoking	Tobacco smoking
E	53	Smokeless tobacco	Tobacco, smokeless
F	54	Mists from strong inorganic acids	Acid mists, strong inorganic
F	55	Aflatoxins	Aflatoxins
F	56	Aluminium production	Aluminium production
F	57	4-Aminobiphenyl	4-Aminobiphenyl
F	58	Auramine production	Auramine production
F	59	Benzene	Benzene
F	60	Benzidine	Benzidine
F	61	Benzidine, dyes metabolized to	Benzidine, dyes metabolized to
F	62	Benzo[a]pyrene	Benzo[*a*]pyrene
F	63	Bis(chloromethyl)ether; chloromethyl methyl ether (technical-grade)	Bis(chloromethyl)ether; chloromethyl methyl ether (technical-grade)
F	64	1,3-Butadiene	1,3-Butadiene
F	65	Coal gasification	Coal gasification
F	66	Coal-tar distillation	Coal-tar distillation
F	67	Coal-tar pitch	Coal-tar pitch
F	68	Coke production	Coke production
F	69	Ethylene oxide	Ethylene oxide
F	70	Formaldehyde	Formaldehyde
F	71	Occupational exposure during iron and steel founding	Iron and steel founding (occupational exposure during)
F	72	Isopropyl alcohol manufacture by the strong-acid process	Isopropyl alcohol manufacture using strong acids

F	73	Magenta production	Magenta production
F	74	4,4'-Methylenebis(2-chloroaniline) (MOCA)	4,4'-Methylenebis(2-chloroaniline) (MOCA)
F	75	Mineral oils, untreated or mildly treated	Mineral oils, untreated or mildly treated
F	76	2-Naphthylamine	2-Naphthylamine
F	77	*ortho*-Toluidine	*ortho*-Toluidine
F	78	Occupational exposure as a painter	Painter, occupational exposure as a
F	79	2,3,7,8-Tetrachlorodibenzo-para-dioxin, 2,3,4,7,8-Pentachlorodibenzofuran, 3,3',4,4',5-Pentachlorobiphenyl	2,3,4,7,8-Pentachlorodibenzofuran 2,3,7,8-Tetrachlorodibenzo-para-dioxin 3,3',4,4',5-Pentachlorobiphenyl
F	80	Occupational exposures in the rubber-manufacturing industry	Rubber-manufacturing industry
F	81	Shale oils	Shale oils
F	82	Soot (as found in occupational exposure of chimney sweeps)	Soot (as found in occupational exposure of chimney sweeps)
F	83	Sulfur Mustard	Sulfur mustard
F	84	Vinyl Chloride	Vinyl chloride
105	85	Diesel- and gasoline-engine exhausts	Engine-exhaust, diesel
106	86	Trichloroethylene	Trichloroethylene
107			Polychlorinated biphenyls*
109			Outdoor air pollution*
109			Particulate matter in outdoor air pollution*

*As the mechanistic sections for Monographs 107-109 were not available for review at the time this analysis was done, Group-1 agents in these volumes were necessarily excluded from the present analysis.

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Ex. 6 - Personal Privacy

From: Daniel Krewski
Sent: Thur 7/14/2016 7:43:07 PM
Subject: Final Draft of IARC Concordance Chapter
2016 Krewski et al Concordance Analysis July 13 with Supplemental Material.pdf

Just a note to provide you with the final draft of our chapter on concordance between animal and human tumours, which has been benefitted greatly from input from the subgroup that has been working with me to finalize this chapter over the last few months.

The chapter has been substantially reworked to accommodate all of the comments and suggestions from the subgroup, and has undergone editorial review by the editors of the IARC Scientific Publication in which this chapter will appear. I have spent the last week in Lyon going over the editorial comments provided by the IARC, and have addressed all of the comments provided by the Agency review.

I am very pleased with the final version of the chapter, and would like to take this opportunity to thank all of you for your valuable contributions to this work.

Robert will be sending the chapter to all Workshop Participants shortly, along with the mechanisms chapter that is also now in final form.

With best regards.

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

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in collaboration with other participants in the IARC Workshop on
'Tumour-site Concordanceand Mechanisms of Carcinogenesis'
which convened in Lyon, April/November 2012[2]

Abstract

Since its inception in the early 1970s, the *Monographs Programme* of the International Agency for Research on Cancer (IARC) has developed 116 *Monographs* on 990 agents for which there exists some evidence of human cancer risk; of these, 118 agents met the criteria for Group 1, *carcinogenic to humans*. Volume 100 (Vol 100) of the *IARC Monographs*, compiled in 2008-2009 and published in 2012, provided a review and update of the 107 Group-1 agents identified as of 2009. These agents have been 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 the data set developed by Grosse et al. (this Volume) for human and animal tumours and tumour sites associated with exposure to these agents – and five additional Group-1 agents defined in subsequent *Monographs* –, we analyzed the degree of concordance between the sites where tumours arise in humans and animals (mice, rats, hamsters, dogs, and primates). An anatomically-based tumour nomenclature system, representing 39 tumour sites and 15 organ and tissue systems for which there was *sufficient evidence* of carcinogenicity in human and/or animals, was developed and used as the basis for species comparison. The present analysis identifies 91 Group-1 agents with *sufficient evidence* (82 agents) or *limited evidence* (9 agents) of carcinogenicity in animals. The most common tumours observed in both humans and animals were those of the respiratory system, followed by the lymphoid and hematopoietic tissues, urothelium, skin, and digestive organs. Tumours of the upper aero-digestive tract and respiratory system were observed for 47 of the 111 distinct Group-1 carcinogens identified through Volume 109 of the *IARC Monographs*, comprising mostly chemical 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 were observed for 26 agents, tumours of the urothelium for 18 agents, and skin tumours for 14 agents. Exposure to radiation (particularly X- and gamma radiation) and tobacco smoking were associated with tumours at multiple sites in humans. Although the *IARC Monographs* do not focus on tumour-site concordance between animals and humans, substantial concordance was observed for a number of organ and tissue systems, even under the stringent criteria for *sufficient evidence* of carcinogenicity employed by the IARC. It should be noted that some caution is needed in interpreting concordance at

[1] Deceased.

[2] L. Banks, F.A. Beland, J.A. Bond, M.C. Bosland, J.R. Bucher, D.M. DeMarini, B. Fubini, B.D. Goldstein, S.S. Hecht, K. Hemminki, C.W. Jameson, A.B. Kane, R.J, Kavlock, P.F. Lambert, L. Stayner, B.W. Stewart, R.L. Ullrich, H. Vainio, P. Vineis, M.P. Waalkes, L. Zeise.

sites where the sample size is particularly small: although perfect (100%) concordance was noted for agents causing tumours of the mesothelium, only two Group-1 agents meeting the criteria for inclusion in the concordance analysis caused tumours at this site. Concordance between the sites of tumour development seen in animals and humans is not perfect. However, the extent of concordance presented here supports the view that tumour sites in experimental animals should be considered with reference to possible or known tumorigenesis in humans, in order to possibly expand mechanistic understanding in relation to particular carcinogens.

Introduction

Since the establishment of the *IARC Monographs Programme* within the International Agency for Research on Cancer (IARC) in the early 1970s, a large number of agents have been evaluated for which there exists some evidence of a possible increased cancer risk to humans. The *Monographs Programme* has developed detailed criteria against which to evaluate the available scientific evidence on the carcinogenic potential of such agents. These criteria are described in the *Preamble* to the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* (Cogliano et al., 2004; IARC, 2006; see http://monographs.iarc.fr/ENG/Preamble/index.php), and used to weigh the evidence provided by human epidemiological studies, animal cancer bioassays, and information on possible biological mechanisms of action, to classify agents into one of the following 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 the data from both the human and the animal studies as providing *sufficient evidence of carcinogenicity*, *limited evidence of carcinogenicity*, *inadequate evidence of carcinogenicity*, or *evidence suggesting lack of carcinogenicity*, whereas 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 IARC has developed 116 *Monographs* on 990 agents for which there exists some evidence of human cancer risk; of these agents, 118 met the criteria for Group 1. Volume 100 of the *IARC Monographs* provided a review and update of the 107 Group-1 agents identified as of 2009. This Volume is conveniently separated into six parts, focusing on pharmaceuticals (Vol 100A; IARC, 2012a); biological agents (Vol 100B; IARC, 2012b); arsenic, metals, fibres, and dusts (Vol 100C; IARC, 2012c); radiation (Vol 100D; IARC, 2013d); personal habits and indoor combustions (Vol 100E; IARC, 2012e); and chemical agents and related occupations (Vol 100F; IARC, 2012f), respectively. Since the publication of Volume 100, five additional agents – diesel exhaust (Vol 105; Benbrahim-Tallaa et al., 2012), trichloroethylene (Vol 106; Guha et al., 2012), polychlorinated biphenyls (PCBs) and dioxin-like PCBs (Vol 107; Lauby-Secretan et al., 2013), outdoor air pollution and particulate matter from outdoor air pollution (Vol 109; 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 Volume 100, they would have been included in Vol 100F; for ease of reference, we will include these agents in an expanded group of chemicals and related occupations denoted by Vol 100F*.

The 113 agents classified 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 Vol 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 Vol 107. 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 Vol 100, there are 23, 11, 10, 18, 12, and 37 Group-1 agents in Vol 100A through Vol 100F*, respectively.

Because both animal and human data are considered in evaluating the weight of evidence for human carcinogenicity, the degree of concordance between species for tumour induction by carcinogenic agents is of importance. A high degree of site concordance between species supports the ability of experimental animal studies to predict not only a potential cancer risk for humans, but also the specific sites of cancer induction expected from human exposure to carcinogenic agents. On the other hand, lack of concordance may indicate the need for further research to make sure all cancer sites have been identified in sensitive human subpopulations or in appropriate experimental animal models, and to identify the underlying mechanisms that species may or may not have in common. This chapter uses the data set assembled by Grosse et al. (this Volume) derived from the available information on the agents classified by the IARC as being *carcinogenic to humans* (Group 1) in Volume 100 through Volume 109, the last *Monograph* for which final data were available at the time this analysis was conducted. This database includes all tumour sites identified in the *Monographs* for which there is *sufficient evidence* of carcinogenicity in humans and/or animals, and includes internationally peer-reviewed and published human and experimental animal data to support analyses of tumour sites seen in humans and animals. Although the database also includes human tumour sites for which there is *limited evidence* of carcinogenicity of the agent, human tumour sites were not systematically identified in the *Monographs* in the case of *limited evidence*. Animal tumour sites were generally not identified in the case of *limited evidence* in animals.

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

Methods

Tumour Nomenclature in Animals and Humans. Although human tumours can be coded in a standardized manner by use of the 'International Classification of Diseases' coding system (ICD9, 1977; ICD10, 2011), a comparable 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 Supplemental Material I, this taxonomy is anatomically based, and includes 47 tumour sites grouped within 15 organ and tissue systems. This includes 39 distinct animal and human tumour sites specified for Group-1 agents in Vol 100A-F*, as well as eight additional tumour sites that were considered to be of importance, even though they did not appear in the tumour-site concordance data set developed by Grosse et al. (this Volume). The 39 individual tumour sites seen in either animals or humans through Volume 109 of the *IARC Monographs* are listed in Table 2. The category 'other groupings' includes the three sites (all cancers combined; all solid cancers; and exocrine glands 'not otherwise specified', NOS) that do not fit in any of the other 14 groupings. All analyses reported in this chapter are based on the 39 individual tumour sites within the 15 organ systems in Table 2.

Aggregation of tumour sites within an organ system was guided by several factors including anatomical and functional relatedness. The individual specialized epithelia of the upper aero-digestive tract, respiratory system, digestive tract, and digestive organs occur for the most part in a single or a few anatomical sites, which are precisely captured by the available epidemiological and experimental data. In contrast, both kidney and urothelium are data-rich sites and carcinogenic agents for either site display little or no overlap in target organ. 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 anatomical location. Likewise, skin cancers are aggregated irrespective of anatomical location, with the exception that malignant melanoma as it occurs in humans is unknown in rats or mice; cutaneous melanocytes are thus included separately in the Table as a human tumour site only for the sake of completeness. Estrogen-producing and estrogen-responsive tissues are aggregated in the organ system 'female breast, female reproductive organs and 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 for the sake of completeness, despite the high prevalence in humans of prostate and testicular germ-cell cancers.

Retrieval of Data on Tumour Occurrence from the IARC Monographs. Grosse et al. (this Volume) extracted data from Volumes 100, 105, 106, 107 and 109 on tumour sites reported in humans or animals for the 111 distinct Group-1 agents considered here. This information is illustrated in Table 3, with one compound from each of Volumes 100A-F, as well as diesel exhaust (Vol 105), trichloroethylene (TCE) (Vol 106), PCBs (Vol 107) and air pollution (Vol 109). Table 3 gives the tumour sites for which the agents provide *sufficient evidence* of carcinogenicity in humans, as well as sites for which there is *limited evidence*. Tumour sites for which *sufficient evidence* of 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 agents show *limited evidence* of carcinogenicity in humans are included in Table 3, this information is not considered in the present analysis. In fact, although our original intent was to consider tumour sites with *sufficient* or *limited evidence* in humans when evaluating concordance with animal tumour sites with *sufficient evidence*, there are only two Group-1 agents with *limited*, but not *sufficient*, evidence of carcinogenicity in humans.

Effects of Sex, Strain, and Route of Administration. The last column in Table 3 provides details on animal studies relevant to the evaluation of the agent of interest, including the sex and strain of the test animals, and the route of administration of the test agent. Although this information has been recorded where available, it is difficult to examine concordance with respect to these important factors for a variety of reasons.

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 sex-specific. Also, some animal experiments use only one sex, while 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. Indeed, in many cases information on strain is unavailable, precluding the possibility of strain-specific analyses.

Human exposure to carcinogens can occur by oral ingestion, inhalation, dermal absorption, as well as *via* other routes such as injection of pharmaceutical agents for therapeutic purposes. Animal experiments may involve other routes of exposure, such as intraperitoneal injection or intra-tracheal 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 lack of concordance between tumour sites observed in animals and humans. However, since data on cancer outcomes for a given 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 the concordance analyses, we examined the organ distribution of the 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 tumours caused by all 111 distinct Group-1 carcinogens considered here.

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.

Results

The concordance data set assembled by Grosse et al. (this Volume) summarized in Table 1 includes 111 distinct Group-1 agents identified in the *IARC Monographs* up to and including Volume 109. 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 on the basis of mechanistic upgrades according to the evaluation criteria outlined in the *Preamble* to the *IARC Monographs*. Benzo(*a*)pyrene (B*a*P), for example, was placed in Group-1 on the basis of epidemiological data on exposure to mixtures of PAHs containing B*a*P that provided *sufficient evidence* for lung or skin cancer in humans, coupled with extensive mechanistic data on B*a*P, suggesting that the mechanisms by which B*a*P causes tumours in animals would also be expected to operate in humans: no data in humans on B*a*P alone were available for evaluation (IARC, 2010). An important aspect of such mechanistic upgrades for purposes of the present analysis is the general lack of identification of a human tumour site: of the ten agents placed in Group-1 on the basis of a mechanistic upgrade, tumour sites in humans were specified only for phenacetin, which was determined to cause tumours of the renal pelvis and ureter, based on results of the evaluation of phenacetin as the active ingredient in analgesic mixtures.

Of the ten agents in Table 4 placed in Group-1 on the basis of mechanistic upgrades, all but one – etoposide – demonstrated *sufficient evidence* of carcinogenicity in animals. In the assignment of etoposide to Group-1 in the absence of *sufficient evidence* in animals, the *Monograph* noted the *limited evidence* of carcinogenicity in humans on the

basis of the induction of acute myeloid leukaemias with distinctive chromosomal translocations by drugs, including etoposide, that target topoisomerase II. One agent (phenacetin as present in an analgesic preparation, mentioned above) demonstrated *sufficient evidence* of carcinogenicity in humans, three showed *limited evidence* in humans, and four had in*adequate evidence* in humans; no epidemiological data were available for two agents (B*a*P and PeCDF).

Apart from the nine Group-1 mechanistic upgrades for which no human tumour sites were identified, there are four other agents for which the same is true (Table 5): 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). These were generic evaluations across a range of agents falling in these categories. In addition, no human tumour site was specified for the lifestyle agents, areca nut and ethanol in alcoholic beverages, as no epidemiological data were available for areca nut alone or for ethanol in alcoholic beverages alone (Grosse et al., this Volume).

No animal tumour sites were identified for 38 of the 111 agents considered here (Table 6). These included 20 agents with *inadequate evidence* in animals: seven agents representing occupational exposures that would be difficult to replicate in the laboratory; two pharmaceutical agents used in combination for which no animal data were available on the mixture; seven biological agents (all viruses) for which the selection of an appropriate animal model was problematic; two agents, etoposide and wood dust, for which the available animal tests were considered inadequate; and two agents, treosulfan and leather dust, for which no animal data were available. Although the latter two agents, lacking any animal test data, 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 discussion 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 are largely uninformative because of inadequate testing.

IARC Monographs 76 (IARC 2000) and 100A (IARC 2012a) noted that etoposide was tested in only one experiment with wild-type and heterozygous *Nf1* (neurofibromatosis type 1 gene) knock-out mice treated by gastric intubation for six weeks with etoposide at 100 mg/kg body weight/week (Mahgoub *et al*., 1999). This single short-duration study was judged as providing *inadequate evidence* of carcinogenicity in animals. The available studies with wood dust originally considered in *IARC Monograph* 62 (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. Upon re-evaluation of wood dust in *Monograph* 100C (IARC 2012c) it was concluded that most of the studies conducted with wood dust (nearly all with beech wood dust) had small numbers of animals or were of short duration, thus providing *inadequate evidence* of carcinogenicity in animals. These considerations suggest that neither etoposide nor wood dust have been subject to adequate animal testing, therefore precluding a determination of their carcinogenic potential in animals.

Ten agents, including six pharmaceutical products (busulfan; chlornaphazine; cyclosporine; combined estrogen-progestogen menopausal therapy; methyl-CCNE; 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. As mentioned above, 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. Treatment with busulfan, for example, resulted in a significant increase in the incidence of thymic and ovarian tumours in BALB/c mice, which was found difficult to interpret, while in another study busulfan, when given to rats during gestation, affected the incidence of uterine adenocarcinomas in the offspring upon intra-uterine treatment 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, and of pulmonary tumours (not otherwise specified) in mice following intravenous injection; a significant increase in the incidence of mammary tumours was seen following subcutaneous injection of sulfur mustard in rats, relative to an external control group, while fore-stomach tumours were numerically, but not significantly, elevated in rats treated by oral gavage (IARC, 2012f). The exposure by subcutaneous and intravascular injection was considered to be of limited relevance to the most common human routes of exposure. Although not meeting the stringent criterion for *sufficient evidence* of carcinogenicity in animals, the *limited evidence* provided by busulfan, as well as by the other six 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 eight agents demonstrating *sufficient evidence* of carcinogenicity in animals, as reproducible results were unavailable in two or more studies of adequate design in the same species for any of these agents. Although melphalan showed evidence of a statistically significant increase in the incidence of tumours of the forestomach, skin and lung in mice, as well as lymphosarcoma, these results were not replicated in two or more independent studies (IARC, 2012f). In the rat, melphalan also produced mammary gland tumours and peritoneal sarcoma, but these findings were again not replicated in independent studies. Phosphorous-32 caused leukaemia in mice and osteogenic sarcomas in rats in single studies. Similarly, acetaldehyde in drinking-water induced pancreatic adenomas, combined lymphomas and leukaemias, uterine and mammary gland adenocarcinomas, and head osteosarcomas in 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 aluminium refining in animals was based on a single limited mouse skin-tumour study with PAH-containing particulates from aluminium-production plants, in conjunction with *sufficient evidence* of carcinogenicity in experimental animals for many of the PAHs detected in air samples from such plants and previously evaluated in *IARC Monograph* Volume 92 (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 aero-digestive tract in hamsters and humans for betel quid with tobacco.

While 2,3,4,7,8-pentachlorodibenzofuran (PeCDF) provided *sufficient evidence* of carcinogenicity in animals, no animal site was identified. PeCDF was tested by the U.S. National Toxicology Program in a two-year animal bioassay (female rats only) with exposure by oral gavage (NTP, 2006). There was some evidence of carcinogenic activity of PeCDF, based on increased incidences of hepatocellular adenoma and cholangiocarcinoma of the liver and gingival squamous cell carcinoma of the oral mucosa. 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 (Vol 100F; IARC, 2012f). These observations led to the conclusion that there is *sufficient evidence* for the carcinogenicity

of PeCDF in animals, although there is no specific organ site that can be designated as responsible for this *sufficient evidence*. Because of the absence of a specific tumour site in animals, PeCDF is not included in the concordance analyses.

A component of four Group-1 agents, but not the agent itself, demonstrated *sufficient evidence* of carcinogenicity in animals. These are: fission products including Sr-90, where strontium-90 demonstrated *sufficient evidence* of carcinogenicity in animals (Vol 100D, pg 297; IARC, 2012d); haematite mining with exposure to radon (underground), where radon demonstrated *sufficient evidence* of carcinogenicity in animals (Vol 100D, pg 274; IARC, 2012d); acetaldehyde associated with consumption of alcoholic beverages, where acetaldehyde demonstrated *sufficient evidence* of carcinogenicity in animals (Vol 100E, pg 472; IARC, 2012e); and occupational exposures during aluminium production, where airborne particulate polynuclear organic matter from aluminium-production plants demonstrated *sufficient evidence* of carcinogenicity in animals (Vol 100F, pg 221; IARC, 2012f). 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.

Excluding the 20 agents in Table 5 lacking appropriate animal data, i.e. seven occupational exposures not reproducible in the laboratory, two agents used in combination with no animal data available on the mixture, seven agents where the use of animal models is problematic due to species-specificity or other limitations, and four 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 correspondence between sites where tumours are 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 an evaluation of concordance between tumour sites seen in animals and humans. Results are presented first for the 39 tumour sites included in the anatomically based tumour nomenclature system seen in either animals or humans, followed by the 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; biological agents; arsenic, metals, fibres, and dusts; radiation; personal habits and indoor combustions; and chemical agents and related occupations). Lung tumours represent the most common tumour seen in humans, with 28 of the 111 known human carcinogens inducing lesions at this site; of these, thirteen are associated with exposure to chemical agents and related occupations, and seven are in the category of arsenic, metals, fibres, and dusts. Tumours of the haematopoietic tissues are associated with exposure to 18 agents, urothelial tumours with 18, skin tumours with 12, and liver and bile duct tumours with 11 agents; chemicals and related occupations account for the largest number of agents causing these lesions. This category also accounts for half (9/18) of the urinary tract/urothelial tumours, with pharmaceuticals accounting for half (9/18) of the 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, i.e. caused by 29 of the 111 known

human carcinogens, with the categories of chemicals (10), arsenic, metals, fibres, and dusts (7), and radiation (7) accounting for the majority. After the lung, the animal sites associated with the largest number of agents are the skin and adnexae (18 agents), liver parenchyma and bile ducts (19), lymphoid tissue (14), soft connective tissue (11) and breast (11). Separate tumour profiles are shown for agents causing tumours in mice (62 agents) and rats (64 agents) in Figures 3 and 4, respectively. In rodents (mice and rats combined), the lung is the site associated with the largest number of carcinogens.

Organ- and Tissue-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 aero-digestive tract and respiratory system are caused by 47 of the 111 human carcinogens, comprised mostly of chemicals agents and related occupations (16), arsenic, metals, fibres, and dusts (10), and personal habits and indoor combustions (12). After the upper aero-digestive tract and respiratory system, the organ systems associated with the largest number of agents are the lymphoid and haematopoietic systems (26 agents), the skin and connective tissues (22), and the urothelium (18). The category chemical agents and related occupations represents the largest group of carcinogens 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 aero-digestive tract and respiratory system are caused by 41 of the 111 agents under study, with chemical agents and related occupations (15 agents), 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, comprising mostly 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 aero-digestive 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

Of the 111 distinct Group-1 agents identified through Volume 109, there are 60 for which both a human tumour site and an animal tumour site have been identified. Of the 111 Group-1 agents in Table 1, 15 had no human tumour site specified (Table 5) and 38 agents had no animal tumour site identified (Table 6). With two agents—aristolochic acid, and plants containing aristolochic acid—having neither a human nor an animal tumour site specified, there are 111 – 15 – 38 + 2 = 60 agents with at least one tumour site identified in both humans and animals. These 60 agents may be used to evaluate concordance between tumour sites seen in animals and humans, as at least one tumour site has been identified in both.

The overlap between human and animal tumour sites targeted by these 60 agents is summarized in Table 7 by organ and tissue system/tumour site. The category 'other groupings' of tumours – which comprises all cancers combined, all solid cancers, and exocrine glands (NOS) – was created to accommodate tumour sites reported in the *IARC Monographs* that did not fall into any of the other categories in Table 2. Because this category lacks biological cohesiveness, 'other groupings' of tumours were not considered in the concordance analysis.

Nine agents cause tumours in the upper aero-digestive tract in humans, and nine agents demonstrate tumours in this organ and tissue system in animals; four agents demonstrate tumours in this system in both humans and animals. There are 9+9-4=14 distinct agents that demonstrate tumours in this system in either humans or animals, for an overlap of 4/14, or 28.6%. Within the upper aero-digestive tract, there are three agents that demonstrate tumours in the nasal cavity and paranasal sinuses in humans and three agents that demonstrate tumours at this site in animals, with no overlap. Of the three agents inducing tumours in the nasopharynx, one agent caused tumours in both humans and animals, for an overlap of 33.3%. In the oral cavity, overlap is 25%. Overlap is not calculated when there are no agents demonstrating tumours in either humans or animals, as in the pharynx, tongue, and salivary gland.

The lung is the most common site at which tumours are observed, with 61.5% overlap among the 26 agents causing lung tumours in humans or animals. Among the 10 agents causing tumours in the urothelium (renal pelvis, ureter or urinary bladder), there is 70% overlap between agents causing tumours in humans or animals.

As results for individual tumour sites are often based on small numbers, emphasis is placed on interpretation of results at the organ and tissue system level where the sample size is generally larger than for individual tumour sites within organ and tissue systems. Overlap varies among the organ and tissue systems, ranging from 20% (based on 10 agents) in the digestive tract to 100% in the mesothelium. Overall, high overlap is seen for some organ and tissue systems, but not for others. Some caution is needed in interpreting concordance at sites where the sample size is particularly small: although 100% concordance was noted for agents causing tumours of mesothelium, only two Group-1 agents – asbestos and erionite - meeting the criteria for inclusion in the concordance analysis caused tumours at this site.

The results in Table 7 are depicted in graphical form in Figure 9. Of the 14 Group-1 agents causing tumours of the upper aero-digestive tract in either humans or animals, nine cause tumours in the upper aero-digestive tract in humans, 22 cause upper aero-digestive tract tumours in animals, and 16 agents cause such tumours in both humans and animals, for an overlap of 28.6%. Of the 27 agents causing tumours of the respiratory system in either humans or animals, 21 cause respiratory tumours in humans, 22 cause respiratory tumours in animals, and 16 agents cause respiratory tumours in both humans and animals, for an overlap of 59.3%. While presenting the same data as shown in Table 7, the graphical representations of these results in Figure 9 for all organ and tissue systems also illustrate the large variation in sample size among the organ/tissue systems, with the area of the circles being proportional to sample size.

The results presented in Table 7 are based on concordance between tumour sites seen in humans and all animal species, reflecting our interest in evaluating the extent to which tumours caused by Group-1 agents occur in similar organs or organ systems in humans and animals. The animal data included in this analysis are dominated by results obtained in studies with rats and mice: of the 60 Group-1 agents included in the analysis, 40, 38, 8, 7, and 3 agents demonstrated tumours in mice, rats, hamsters, dogs, and monkeys, respectively. As a consequence, including only mice and rats in the

analysis yielded results similar to those in Table 7 (see details in Supplemental Material II, where Supplemental Table 6 presents results for all animals and Supplemental Table 7 presents results for mice and rats only).

Figure 10 shows the percentage of Group-1 agents causing tumours in specific organ and tissue systems in humans that are also associated with tumours in animals (Panel A), as well as the percentage of agents causing tumours in specific organ and tissue systems in animals that are also associated with tumours in humans (Panel B).

As detailed in Supplemental Material II, it is important to note that the measures of concordance presented in Figure 10 differ from those in Table 7. The percentage overlap in Table 7 (and Figure 9) reflects the number of agents causing tumours in a specific organ/tissue system in *both* humans *and* animals, relative to the number of agents causing tumours in that system in *either* humans *or* animals, providing an overall measure of overlap between animal and human carcinogens in a specific organ/tissue system. The percentage overlap in Panel A of Figure 10 provides a measure of the overlap between agents causing tumours in a specific organ/tissue system in animals with agents causing tumours in that system in humans. Conversely, the percentage overlap in Panel B of Figure 10 provides a measure of the overlap between agents causing tumours in a specific organ/tissue system in humans with agents causing tumours in that system in animals. Note that unless the numbers of agents causing tumours in humans and animals in a specific organ/tissue system are the same (as is the case for tumours of the upper aero-digestive tract), the results in Panel A, where human Group-1 agents constitute the reference set against which animal Group-1 agents are compared, will differ from those in Panel B, where animal Group-1 agents constitute the reference set for comparison with human Group-1 agents.

As indicated in Panel A of Figure 10, all agents (100%) causing tumours of the mesothelium, endocrine system, and connective tissues also cause tumours in those organ and tissue systems in animals. Overlap of at least 50% is observed for all other organ and tissue systems, with the exception of the upper aero-digestive tract (44%) and the digestive tract (33%). Conversely, there is less overlap between agents causing tumours in specific organ and tissue systems in animals with results in humans (Figure 10, panel B), possibly reflecting either a greater spectrum of tissue sites expressed in animal studies than in human studies, or the greater number of studies conducted in animals as compared to humans. As is the case with the concordance results focusing on overall overlap presented in Table 7, caution is required when interpreting results where there are few agents for comparison in Figure 10 (both Panels A and B).

The 60 agents included in the present concordance analysis are listed in Table 8 in boldface type. This table presents the tumour site data for humans and animals at the organ and tissue system level only, as results for individual tumour sites are too sparse to support meaningful comparisons of this type. The human data are presented in the column on the left, the animal data in the column on the right, and overlap in the middle column. Using this display, potential relationships among agents causing tumours within the same organ/tissue system can be examined. Overlap between human and animal carcinogens acting within the same organ and tissue system can also be examined both for individual agents and for groups of agents.

In order to permit a more complete comparison between animal and human tumour sites, tumour sites with only *limited evidence* in humans are included in Table 8 in light grey font. For agents such as diethylstilbestrol (a synthetic non-steroidal estrogen widely used in the US between the 1940s and 1970s, but now rarely used), there is difficulty in generating newer data regarding human exposure. Because men exposed to diethylstilbestrol *in utero* have passed the

age of highest risk for testicular cancer, further study cannot clarify the association between this exposure and testicular cancer (Vol 100A; IARC, 2012a). Human data for this agent will remain limited for this endpoint, although supported by the induction of testicular tumours in rodents.

With ongoing studies, more evidence can be gathered that provides increasing certainty about potential human cancer risks. Although IARC had previously evaluated trichloroethylene (TCE) in 1979, 1987, and 1995, this substance was not declared to be *carcinogenic to humans* – causing kidney cancer – until 2012 due to the emergence of new data (Vol 106; IARC, 2014). Although it was noted that a positive association had been observed between liver cancer and exposure to TCE, the lack of data was cited as the rationale for its designation as having only *limited evidence* of carcinogenicity in humans in the previous evaluations. In 2013, an updated pooled analysis of three Nordic studies with 10-15 years of additional follow-up demonstrated that human exposure to TCE was associated with a possibly increased risk of liver cancer (Hansen et al. 2013). Inclusion of the limited human data for TCE-induced liver cancer in humans allows for the observation of overlap between animals and human for this endpoint.

This example illustrates that the inclusion of agents with *limited evidence* of carcinogenicity in humans enhances the ability to identify concordance relationships. Comparisons between Table 7, which includes only sites with *sufficient evidence* in humans, and Table 8, which includes sites with *limited evidence* in humans, illustrates increased coherence among agents that have similar chemical and mechanistic characteristics when limited human data are considered.

There are also examples of increased site concordance if less stringent criteria are applied than are used by the IARC for determining *sufficient evidence* of carcinogenicity. Although no human tumour site with *sufficient evidence* of carcinogenicity in humans is identified for ethylene oxide, there is *limited evidence* of breast cancer and non-Hodgkin lymphoma in humans (see Supplemental Table 2). In evaluating the available animal data on estrogen and progestogen oral contraceptives (Vol 100A; IARC 2012a) it was concluded that 'The data evaluated showed a consistent carcinogenic effect of several estrogen-progestogen combinations across different animal models in several organs.' Similarly, the synthesis statement in the evaluation of diethylstilbestrol notes:

> "The oral administration of diethylstibestrol induced tumors of the ovary, endometrium and cervix, and mammary adenocarcinomas in female mice. Osteosarcomas and Leydig cell tumors were induced in rasH2 and Xpa/p53 male mice, respectively. Subcutaneous implantation of diethylstilbestrol induced mammary tumors in female Wistar rats. Perinatal exposure to diethylstilbestrol induces lymphoma, uterine sarcomas, adenocarcinomas and pituitary, vaginal, and ovarian tumours in female mice. Uterine adenocarcinomas and mammary and vaginal tumors were also induced in female rats. In hamsters, diethylstilbestrol perinatal exposure induced kidney tumour." [Vol 100A; IARC, 2012a]

Agents affecting male reproductive organs are also included in Table 8, although they are not part of the concordance analyses in Table 7 due to a lack of *sufficient evidence* in either humans or animals. TCDD (2,3,7,8-tetrachlorodibenzo-para-dioxin) is included in Table 8, but its designation as an agent affecting 'all cancers combined' in humans precludes site-specific tumour concordance analyses. These examples illustrate increased site concordance by applying less stringent criteria than those applied for the concordance analysis presented in Table 7.

Table 8 shows human data indicating biological plausibility for the upper aero-digestive tract and lung to be targets for agents for which the portal of entry is the lung (as with dusts, particles, and particles that serve as a vehicle for a mixture of other carcinogens such as during tobacco smoking and coke production). Lympho-haematopoietic cancers are a consistent endpoint for antineoplastic alkylating agents that induce these cancers after their use in chemotherapy for the eradication of other neoplasms (Vol 100A; IARC, 2012a), radioactive materials (Vol 100D; IARC, 2012d), and a number of chemical agents and related compounds that are metabolized to or are in themselves agents that are reactive with DNA (Vol 100F; IARC, 2012f).

Table 8 also illustrates some of the potential relationships between agents that may act in a similar fashion in humans. Tobacco smoke and its related agents (smokeless tobacco and second-hand tobacco smoke) affect a number of similar organ/tissue systems. For radioactive materials, almost all organs/sites are affected by ionizing radiation: these agents affect multiple target tissues because they are able to reach the nucleus and cause a variety of DNA lesions and other effects reflected by the key characteristics of human carcinogens (Smith, this Volume; Krewski et al., this Volume; see also Smith et al., 2016). Radioactive materials also do not require metabolism in order to induce cancer. Several dyes are associated with urothelial cancer in humans and act through a similar mechanism (Vol 100F; IARC, 2012f). Agents that disrupt the endocrine system and related organs (e.g., polychlorinated biphenyls, diethylstilbestrol, estrogen-only menopausal therapy, estrogen-progestogen oral contraceptives (combined), and tamoxifen) induce cancer at similar sites, including female reproductive organs and breast. Metals appear to have many target sites in common, including the upper aero-digestive tract, respiratory system, kidney, and prostate.

As noted previously, the animal database is predominantly populated by results from studies in rodents. Respiratory tract tumours are induced in rodents by many of the same agents that cause such tumours in humans. For the mesothelium, a rare tumour in humans or animals and one specifically induced by a small number agents, there is good agreement between the human and animal databases. Many agents metabolized in the liver to reactive compounds induce liver cancer in animal models, with less apparent overlap with the human data (see digestive organs, Table 8). Susceptibility of rodent liver to cancer induction is species-, sex-, and strain-specific, and varies widely. Nonetheless, all agents that induce liver cancer in rodents induce cancer at some other site in humans. In some instances the apparent lack of overlap between animal and human databases can still reflect mechanistic concordance for similar agents. Dyes such as magenta, 4-amino biphenyl, benzidine, 2-napthylamine all cause liver cancer in rodents and urothelial cancers in humans. 2,3,7,8-Tetrachlorodibenzo-paradioxin and polychlorinated biphenyls are both associated with liver cancer in rodents and lymphoid and haematopoietic tissue cancers in humans.

Human exposures to diethylstilbestrol, estrogen-only menopausal therapy, and combined estrogen-progestogen oral contraceptives are all associated with cancers of the female breast, female reproductive organs and reproductive tract. Kidney cancer is induced in male hamsters upon exposure to either diethylstilbestrol or estrogen-only menopausal therapy. Estrogen-only data presented in the *Monograph* on combined estrogen-progestogen oral contraceptives indicate a similar result (Vol 100A; IARC, 2012a). Although there appears to be concordance within species for the tumours these agents induce, there does not appear to be overlap in rodent kidney and human female sites. However, there may be mechanistic concordance between these two endpoints, as both diethylstilbestrol and estrogen may damage DNA through oxidative damage, formation of unstable adducts, and induction of apurinic sites. In male Syrian hamsters the major metabolites of diethylstilbestrol are catechols that easily oxidize to catechol *o*-quinones, which are

DNA-reactive. Implantation of estrone or estradiol in male hamsters results in the induction of renal carcinomas exclusively (Li et al., 1983). Metabolic activation of estrogens by cytochrome P450 may also be related to a mechanism similar to that for PAHs (Cavalieri and Rogan, 2014). Thus, diethylstilbestrol and estrogen may have mechanistic similarities that result in an apparent lack of organ/tissue system overlap, with the hamster kidney being indicative of human risk.

Discussion

Since the early 1970s, the *Monographs Programme* at the International Agency for Research on Cancer has been evaluating potential cancer risks to humans (Saracci & Wild, 2015). Separate evaluations of the available animal and human evidence are made, and then combined to make an overall evaluation of the strength of evidence for human carcinogenicity. As of the time of this analysis, 118 distinct agents have met the IARC criteria for determining causality, and designation of these agents as being in Group 1: *Carcinogenic to humans*, with 111 distinct Group-1 agents available for inclusion in the data set of tumours and tumour sites in animals and humans developed by Grosse et al. (this Volume).

The well-established weight-of-evidence criteria for the evaluation of the available human, animal, mechanistic, and exposure data used by IARC are detailed in the *Preamble to the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* (IARC, 2006; see http://monographs.iarc.fr/ENG/Preamble/index.php) and provide clear guidance to the Working Groups convened to review agents. Satisfying the criteria for *sufficient evidence* of carcinogenicity in both animals and humans reasonably infers causality, which can be strengthened by mechanistic considerations. However, an immediate challenge in making comparisons for tumour-site concordance between species 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; tumours at 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, 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. This tool, developed for tumour comparisons across and within species, included 39 individual tumour sites for which agents showed *sufficient evidence* of carcinogenicity in humans and/or animals, which were further aggregated into 15 organ and tissue systems. This aggregation allows comparisons to be made at a higher level of organization and a portal of entry that may reflect anatomical and physiological similarities, with, for example, the lung and lower respiratory tract being considered together as the respiratory system. Aggregation also allows more data to be considered for analyses, which increases the robustness of the ensuing conclusions. For our concordance analyses, data at both the individual site level as well as at the organ system level were examined.

Although the present analysis demonstrates generally good agreement between animal and human tumour sites after exposure to Group-1 carcinogens, concordance was not demonstrated with every agent and tumour site. There are several factors and important limitations that may result in lack of tumour concordance based on these data. Relevant and reliable data to support a complete analysis of concordance are unavailable for either animals or humans for many of the 111 agents. Some agents, notably the human papillomaviruses, 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 in combined estrogen-progesterone menopausal therapy may also not have been evaluated in animals, particularly if the components of the mixture had been previously evaluated separately. Relevant animal tests may still provide only *limited* or *inadequate* evidence of carcinogenicity through limitations in study design or conduct, or if the mechanism of action of the agent of interest was specific to human exposures and not easily replicated in an experimental animal model. Animal studies may also show tumours that are species- and/or sex-specific.

As part of the determination of weight of evidence, agents that induce tumours at multiple sites and across multiple species are considered to present a more robust cancer hazard to humans. However, the experimental animal database used for our analysis consists primarily of rodent data. It is notable that of the 111 Group-1 agents examined here, three agents caused tumours in humans and 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 inter-species tumour-site concordance.

Our analyses exclude the 11 biological agents in Vol 100B, 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 (see Vol 100B, pp 41–42; IARC, 2012b). 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 (see Lambert & Banks, this Volume).

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. *IARC Monographs* generally do not identify animal tumour sites for agents with only *limited evidence* of carcinogenicity in animals. The criteria developed by Grosse et al. (this Volume) further restrict the use of tumour data for agents with *sufficient evidence* in experimental animals (e.g., 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). 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 (Vol 100F; IARC 2012f), none of these tumour sites were replicated in a second animal species, and hence are not included in the Grosse et al. data set.

Human evidence is also subject to limitations. As noted above, the opportunity to conduct further informative studies in humans of a substance like diethylstilbestrol may no longer be available. The absence of *sufficient evidence* in humans may be due to a lack of evidence in appropriate epidemiological or clinical studies, or to the inability of existing studies to detect an association between exposure to the agent of interest (including early or later-in-life exposures) and a tumour outcome. Study limitations may also include 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.

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

How human study data are reported in the *Monographs* may also affect the ability to conduct analyses to establish tumor-site concordance. Ionizing radiation is a specific example of this constraint. No specific human tumour sites were identified for 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). Although the skin was not explicitly mentioned as a human tumour site for UV radiation in Volume 100D, the skin is implicitly suggested as being a human tumour site for this agent. In our analysis, the lack of explicit designation of the skin as a human tumour site for UV radiation precluded its use. A similar situation occurred for areca nut, for which the oral cavity might have been considered as a human tumour site, although this was site was not explicitly designated in the *Monograph*.

An agent can be categorized by IARC as Group-1 carcinogen in the absence of *sufficient evidence* for carcinogenicity in humans when it is clear that the mechanisms by which the agent causes cancer in animals also operate in humans. Such 'mechanistic upgrades' have occurred with various levels of human evidence, including for aristolochic acid (*limited evidence* of carcinogenicity in humans; Vol 100A, IARC 2012a); benzo(*a*)pyrene [B(*a*)P] (*inadequate evidence* in humans; Vol 100F, IARC 2012f); ethylene oxide (*limited evidence* in humans; Vol 100F, IARC 2012f); 4,4'-methylenebis(2-chlorobenzenamine)[MOCA] (*inadequate evidence* in humans; Vol 100F, IARC 2012f); and neutrons (*inadequate evidence* in humans; Vol 100D, IARC 2012d). For further discussion of mechanistic upgrades and key characteristics of Group-1 agents developed for this analysis see Birkett et al., Krewski et al., and Smith (this Volume) and Smith et al (2016). Ten key characteristics of human carcinogens described by Smith et al. (2016) focus on whether the agent is: is electrophilic or can be metabolically activated to electrophiles; is genotoxic; alters DNA repair or causes genomic instability; induces epigenetic alterations; induces oxidative stress; induces chronic inflammation; is immunosuppressive; modulates receptor-mediated effects; causes immortalization; or alters cell proliferation, cell death or nutrient supply. These considerations will be relevant in planned future analyses of coherence between animal and human tumours,

taking into account key characteristics of carcinogens. However, mechanistic upgrades limit the ability to identify tumour-site concordance when human tumour sites are not identified. Of the ten agents placed in Group-1 as a consequence of mechanistic upgrades, specific human tumour sites were identified only for phenacetin.

Exposure assessment is one of the most difficult aspects of epidemiological investigations (Nieuwenhuijsen, 2003). In some cases, such as ecological 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, or in the dose regimens of pharmaceutical drugs or medical radiation. In the future, enhanced exposure assessment methodologies may serve to strengthen the ability of epidemiological studies to identify Group-1 agents (Cohen-Hubal et al., 2010; NRC, 2012). Biomarkers of exposure are expected to play an important part in the future of exposure science (Gurusankar et al., 2016).

The data set assembled and evaluated by Grosse et al. (this Volume) was retrieved from the *IARC Monographs*. As such, these agents do not represent a 'random sample' of all potential human carcinogens and is populated by the available animal and human evidence that were the focus of the *Monographs* from which they were drawn. The ability to determine concordance may change as additional Group-1 agents are identified, or as additional animal or human evidence on current Group-1 agents becomes available. New mechanistic data could affect current IARC evaluations of agents in Groups 2a (*probably carcinogenic to humans*) and Group 2b (*possibly carcinogenic to humans*), hence impact the concordance estimates reported here. Birkett et al. (this Volume) noted that while the *IARC Monographs Programme* has done an excellent job of summarizing the key characteristics of agents evaluated to date, additional information on the ten key characteristics of human carcinogens described by Smith et al. (2016) beyond what is summarized in the *IARC Monographs* is available in the general scientific literature.

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

a. *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 aero-digestive tract and respiratory system). Concordance analyses reported here are based either on 39 tumour sites or on the broader classification of 15 organ and tissue systems.

b. *Effects of sex, 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 sex, strain, or exposure route.

c. *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.

d. *Multi-site/multi-organ Carcinogenicity.* A number of agents, notably radiation and tobacco smoke, induce malignant lesions at multiple sites or in multiple organ and tissue systems. *Monograph* Volume 100F (IARC 2012f) summarizes the evidence that 1,3-butadiene induces haemangiosarcomas 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.

e. *Measures of Concordance.* For simplicity of presentation, concordance was evaluated here in terms of the overlap between tumour sites seen in animals and humans. Although more formal statistical analyses of concordance as described in Supplemental Material II were considered during the course of this work, the consensus of the Working Group was to represent concordance in terms of the simpler, more directly interpretable, indicators of 'overlap' in Table 7 and Figure 10.

f. *Small Sample Size.* After filtering the 111 Group-1 agents tabulated by Grosse et al. (this Volume) through Volume 109 of the IARC Monographs to include only agents that provided *sufficient evidence* of carcinogenicity in at least one tumour site in humans and at least one tumour site in animals, 60 agents remained for concordance analysis. As the sample size for some tumour sites is small (only two agents – asbestos and erionite – caused tumours in the mesothelium), caution is warranted in interpreting the concordance results presented in this chapter when the sample size is small.

g. *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 may be desirable, this cannot be done on the basis of the IARC concordance database considered in this chapter. This is because both the PPV and 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 with a more representative database that includes other agents that do

not cause cancer in humans. However, identifying agents that do not cause cancer in humans is not the focus of the *IARC Monographs Programme*: at present, there is only one agent – caprolactam – in Group 4, *probably not carcinogenic to humans*.

In considering the relevance of animal data in the context of the *IARC Monographs*, it is important to keep in mind how animal data are used in the identification of Group-1 agents, according to the criteria outlined in the *Preamble* to the *IARC Monographs* (IARC, 2006). Most Group-1 agents are identified on the basis of *sufficient evidence* in humans, and for the purpose of the overall evaluation, there is no immediate recourse to animal data. Of the 111 Group-1 agents considered in this chapter, 102 demonstrated *sufficient evidence* of carcinogenicity in humans; the remaining nine agents were placed in Group-1 because the mechanisms by which tumours occurred in animals were considered to be directly relevant to humans, or on the basis of other relevant mechanistic considerations. Neutron radiation, for example, was placed in Group-1 in the presence of *inadequate evidence* in humans, as the biophysics of radiation damage is similar for different types of ionizing radiation. Bearing in mind the contribution of animal data to the identification of Group-1 agents in the *IARC Monographs*, it is possible with the present IARC concordance database to make a statement about the likelihood of positive results in animals among the Group-1 agents that have been shown to cause cancer in humans. Excluding mechanistic upgrades (ten agents) and Group-1 agents lacking appropriate animal data (20 agents) , *all* Group-1 agents with *sufficient evidence* of carcinogenicity in humans have also provided *sufficient* or *limited evidence* of carcinogenicity in one or more animal species, representing a PPV of 100%. Because the concordance database is comprised entirely of Group-1 agents, estimation of the predictive value (positive, negative, or overall) is not possible.

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 be carcinogenic to humans. The *Monographs* are prepared with the involvement of leading scientific experts worldwide, who apply the guidance provided in the *Preamble* to the *IARC Monographs* to evaluate the weight of evidence that an agent may present a cancer risk to humans. Through *Monograph* Volume 109, over 2,000 scientists have contributed to the development of the *IARC Monographs*, with nearly 200 scientists involved in Volume 100 alone. Since its beginning in 1971-72 (Saracci & Wild, 2015), the *Programme* has evaluated 990 agents for their potential to cause cancer in humans, with 118 of these agents assigned to Group 1, indicating that the weight of evidence supports the conclusion that the agent is *carcinogenic to humans*.

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

Collectively, the *IARC Monographs* provide a rich source of information on the causes of human cancer. In particular, Volume 100 presents a review and update of 107 Group-1 agents identified in the previous 99 volumes, providing a veritable 'encyclopaedia of carcinogens.' This information, supplemented with that on six *Group-1* agents identified in Volumes 101 through 109, formed the basis for the analyses included in the present chapter. Subsuming both PCB-126 and dioxin-like PCBs within the broader category of PCBs, 113 – 2 = 111 district *Group-1* agents were included in the concordance analyses presented in this chapter. All but nine of these 111 *Group-1* agents demonstrated *sufficient evidence* of carcinogenicity in humans.

Analysis of concordance between animal and human tumour sites was restricted to 60 Group-1 agents demonstrating *sufficient evidence* of at least one tumour site in animals and in humans. Substantial overlap between animal and human tumours was seen in some organ and tissue systems, but not in others. This analysis focused on tumours seen in the 15 organ and tissue systems in our anatomically based tumour classification system rather than 39 individual tissue sites, because of the sparseness of data at the individual tumour site level. The importance of human data in the IARC carcinogen evaluation process is highlighted by the observation that 102 of the 111 distinct Group-1 agents identified at the time this analysis was done demonstrated *sufficient evidence* of carcinogenicity in humans.

The principle that agents that are carcinogenic in experimental animals should be regarded as presenting a carcinogenic risk to humans, is further confirmed in the course of this investigation. Excluding agents for which animal data are lacking or otherwise uninformative, all agents that cause cancer in humans also cause cancer in one more animal species. 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 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 a database comprising human carcinogens only).

Despite the challenges in evaluating concordance between animal and human tumour sites, the IARC concordance database represents a useful source of information for comparing animal and human data with respect to the tumours caused in different species by the 111 distinct Group 1 agents identified by 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, sex, and animal strain would also support comparisons of animal and human tumours at a finer level of biological resolution. Data on the exposure or dose levels at which tumours are seen in animals and humans would further support evaluation of the relative carcinogenic potency of agents evaluated in animals and humans. Information on tumour sites affected by agents evaluated within the *IARC Monographs Programme* should be recorded in as much detail as possible to facilitate future evaluations of the concordance between tumours seen in animals and humans on a site-specific basis.

Acknowledgements

Pascal Lajoie assembled the tumour-site concordance database analyzed herein while working as a Visiting Scientist under the direction of Dr Yann Grosse at the International Agency for Research on Cancer during the summers of 2011 and 2012. Mélissa Billard also contributed to the development of the concordance database while working at the

Agency in the summers of 2013 and 2014. Daniel Krewski is the Natural Sciences and Engineering Research Council of Canada Chair in Risk Science at the University of Ottawa. Julian Little is the Canada Research Chair in Human Genome Epidemiology at the University of Ottawa. This chapter is dedicated to the memory of Dr Jan Zielinski, who succumbed to cancer in 2016: prior to becoming ill, Dr Zielinski led the team that conducted the analyses reported herein.

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Supplemental Material

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

Supplemental Material II. Statistical Measures 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; *Opisthorchis viverrini* (infection with); *Schistosoma haematobium* (infection with)
100C	Arsenic, metals, fibres, and dusts	10	Arsenic and inorganic arsenic compounds; Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, 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; Radio-iodines, 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 combustion 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 as a; 3,4,5,3D,4D-Pentachloro-biphenyl (PCB-126)[1]; 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[1]
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] During the concordance analyses, the Group-1 agents in these Volumes were included with 'chemicals and related occupations' in Vol 100F*.

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 aero-digestive 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

* These sites are derived from all site descriptors used in *IARC Monographs* to describe human and experimental animal data (see Supplemental Table 1. Animal and Human Tumour Sites for 111 Group-1 Agents Identified through Volume 109 of the *IARC Monographs*). NOS, not otherwise specified

Table 3: Information on Animal and Human Tumours and Tumour Sites for Group-1 Agents in the *IARC Monographs* (adapted from Grosse et al., this Volume)

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 placed in Group 1 based on Mechanistic Upgrades[1]

Agent	Human/Animal Evidence	**Human Tumour Site**	**Basis for Mechanistic Upgrade**
Aristolochic acid	Limited/Sufficient	Not specified	Herbal remedies containing aristolochic acid provide *sufficient evidence* for upper urinary tract cancer in humans; genotoxic mechanistic data
Benzo(*a*)pyrene (B*a*P)	[No epidemiological data]/Sufficient	Not specified	PAH mixtures containing B*a*P provide *sufficient evidence* for lung or skin cancer in humans; extensive mechanistic data on B*a*P linking animal and human biology
Dyes metabolized to benzidine	Inadequate/Sufficient	Not specified	Benzidine provides *sufficient evidence* of being a human bladder carcinogen
Ethylene oxide	Limited/Sufficient	Not specified	*Limited evidence* for non-Hodgkin lymphoma, breast cancer in humans; genotoxic mechanistic data
Etoposide	Limited/Inadequate	Not specified	*Limited evidence* of acute myeloid leukaemia in humans, with distinctive chromosomal translocations
4,4'-methylenebis(2-chlorobenzenamine) (MOCA)	Inadequate/Sufficient	Not specified	Bladder cancer expected in humans, based on mechanistic data and human case report.
Neutron radiation	Inadequate/Sufficient	Not specified	Biophysics of radiation damage induction similar across different types of radiation
NNN and NNK	Inadequate/Sufficient	Not specified	Target sites correspond to those of smokeless tobacco; mechanistic data on tobacco smoke

Penta(2,3,4,7,8)chlorodibenzofuran (PeCDF)	[No epidemiological data]/Sufficient	Not specified	*Sufficient evidence* in experimental animals combined with strong mechanistic support for receptor-mediated mechanism, with biological activity identical to that of TCDD for every mechanistic step
Phenacetin[2]	Sufficient/Sufficient	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] Although dioxin-like PCBs evaluated in Volume 107, were also upgraded to Group-1 on the basis of support for receptor-mediated mechanisms and analogies with TCDD (IARC, 2015), dioxin-like PCBs have been subsumed within the broader category of PCBs for purposes of the present analysis of 111 distinct Group-1 agents, and are therefore not included in Table 4.

[2] Phenacetin (Vol 100A) was placed in Group 1 in the absence of *sufficient evidence* of carcinogenicity from epidemiological studies in humans. It was concluded that phenacetin caused tumours of the renal pelvis and ureter in humans as part of the evaluation of the overall evidence for analgesic mixtures containing phenacetin, including human, animal, and mechanistic evidence.

Table 5. Group-1 Agents with No Human Tumour Sites Specified (15 agents)

Nature of Human Evidence (number of agents)	Volume: Agent(s)
Mechanistic Upgrades	
Mechanistic upgrade with no human tumour site specified (9 agents)	**Volume 100A:** Aristolochic acid; etoposide. **Volume 100D:** Neutron radiation. **Volume 100E:** Nitrosonornicotine (NNN) and 4-(N-Nitrosomethylamino)-1-(3- pyridyl)-1-butanon (NNK). **Volume 100F:** Benzo(*a*)pyrene (B*a*P); dyes metabolized to benzidine; ethylene oxide; 4,4'-methylenebis(2-chlorobenzenamine) (MOCA); (2,3,4,7,8)penta-chloro-dibenzofuran (PeCDF).
Generic Evaluations	
Generic evaluation, of all types of ionizing radiation; internalized radionuclides that emit alpha-particles; internalized radionuclides that emit beta-particles; and the UV region (100-400 nm) of the electromagnetic spectrum (4 agents)	**Volume 100D:** 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)
Absence of Epidemiologic Data on the Agent Alone	
No epidemiological data available for agent alone (2 agents)	**Volume 100E:** Areca nut; ethanol in alcoholic beverages.

Table 6. Group-1 Agents with No Animal Tumour Sites Specified (38 agents)

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 (10 agents)	**Volume 100A:** Busulfan; chlornaphazine; ciclosporin; estrogen-progestogen menopausal therapy (combined); methyl-CCNU; phenacetin, analgesic mixtures containing. **Volume 100B:** *Clonorchis sinensis* (infection with); *Opisthorchis viverrini* (infection with); *Schistosoma haematobium* (infection with). **Volume 100F**: Sulfur mustard.
Agents with Sufficient Evidence in Animals	
Sufficient evidence in animals, but no tumour sites specified[1] (8 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:**

	Aluminium production; PeCDF; **Volume 109:** Outdoor air pollution; particulate matter in outdoor air pollution.

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

Table 7. Concordance between Tumours seen in Humans and Animals for 60 Group-1 Agents

by Organ and Tissue System/Tumour Site

Organ and Tissue System[1] *Tissue Site*[1]	Number of Agents			Overlap[2] (%)
	Humans	Animals	Both	
Upper Aero-digestive Tract	9	9	4	28.6
Nasal cavity and paranasal sinuses	*3*	*3*	*0*	*0.0*
Nasopharynx	*3*	*1*	*1*	*33.3*
Oral cavity	*4*	*6*	*2*	*25.0*
Pharynx	*2*	*0*	*0*	*N/A*
Tongue	*0*	*1*	*0*	*N/A*
Salivary gland	*1*	*0*	*0*	*N/A*
Respiratory System	21	22	16	59.3
Larynx	*3*	*1*	*1*	*33.3*
Lung	*20*	*22*	*16*	*61.5*
Mesothelium	2	2	2	100.0
Mesothelium	*2*	*2*	*2*	*100.0*
Digestive Tract	6	6	2	20.0
Oesophagus	*5*	*0*	*0*	*N/A*
Stomach	*3*	*5*	*1*	*14.3*
Intestine (including colon and rectum)	*3*	*1*	*0*	*0.0*
Digestive Organs	8	14	4	22.2
Liver parenchyma and bile ducts	*7*	*14*	*4*	*23.5*
Pancreas NOS	*2*	*0*	*0*	*N/A*
Gall bladder	*1*	*0*	*0*	*N/A*
Nervous System and Eye	2	0	0	N/A
Brain and spinal cord (CNS)	*1*	*0*	*0*	*N/A*
Eye	*1*	*0*	*0*	*N/A*
Endocrine System	2	3	2	66.7
Thyroid, follicular epithelium	*2*	*2*	*2*	*100.0*
Adrenal gland (medulla, cortex, NOS)	*0*	*1*	*0*	*N/A*
Pituitary	*0*	*1*	*0*	*N/A*

Kidney	3	5	2	33.3
Kidney (renal cortex, renal medulla, kidney NOS) (26)	*3*	*5*	*2*	*33.3*
Urothelium	10	7	7	70.0
Urothelium (renal pelvis or ureter or urinary bladder)	*10*	*7*	*7*	*70.0*
Lymphoid and Haematopoietic Tissues	12	10	7	46.7
Haematopoietic tissus	*10*	*2*	*2*	*20.0*
Lymphoid tissue	*2*	*10*	*1*	*9.1*
Skin	11	16	7	35.0
Skin and adnexae	*9*	*16*	*6*	*31.6*
Cutaneous melanocytes	*3*	*0*	*0*	*N/A*
Connective Tissues	6	14	6	42.9
Soft connective tissue	*0*	*9*	*0*	*N/A*
Blood vasculature (endothelium)	*1*	*0*	*0*	*N/A*
Hard connective tissue (bone, cartilage)	*5*	*5*	*4*	*66.7*
Female Breast, Female Reproductive Organs and Reproductive Tract	8	9	4	30.8
Breast (35)	*4*	*7*	*1*	*10.0*
Ovary (36)	*3*	*1*	*0*	*0.0*
Uterine cervix (37)	*3*	*3*	*2*	*50.0*
Uterus (38)	*2*	*3*	*1*	*25.0*
Vulva/vagina (39)	*1*	*0*	*0*	*N/A*
Other Groupings	2	4	0	0.0
All cancers combined	*1*	*0*	*0*	*N/A*
All solid cancers	*1*	*0*	*0*	*N/A*
Exocrine glands NOS	*0*	*4*	*0*	*N/A*

[1] Systems/sites in the anatomically based tumour nomenclature system (see Table 2) lacking *sufficient evidence* in both humans and animals not shown. (For example, there was insufficient evidence of tumours of the male reproductive tract in both humans and animals.)

[2] Percentage overlap calculated as $(N_b/(N_h+N_a-N_b))x100\%$, where N_h, N_a, and N_b denote the number of agents with *sufficient evidence* in humans, animals, or both humans and animals, respectively.

N/A: entry assigned to sites/systems when overlap is not possible (positive data available in either humans or animals, but not in both).

Table 8. Comparison of 60 Group-1 Agents with *Sufficient* or *Limited Evidence* of Carcinogenicity in Humans and *Sufficient Evidence* in Animals Expressing Tumours in Specific Organ and Tissue Systems[1]

Humans[2] Agent (*Monograph* Volume)[4]	Humans and Animals[2] Agent (*Monograph* Volume)	Animals[2] Agent (*Monograph* Volume)
Upper Aero-digestive Tract (28.6% overlap[3])		
Chromium (VI) compounds (C)	Alcoholic Beverages (E)	Chromium VI (C)
Nickel Compounds (C)	Salted Fish (E)	Alcoholic Beverages (E)
Ra-226 and decay products(D)	Smokeless Tobacco (E)	Salted Fish (E)
X-and Gamma radiation (D)	Formaldehyde (F)	Smokeless Tobacco (E)
Radioiodines including I-131(D)	*Chromium (VI) compounds (C)*	Formaldehyde (F)
Betel Quid W/O tobacco (E)		Benzene (F)
Alcoholic Beverages (E)		TCDD (F)
Salted Fish (E)		Polychlorinated biphenyls (F)
Second-hand tobacco smoke (E)		Bis(Chloromethyl)ether/Chloromethylmethyl ether (F)
Smokeless Tobacco (E)		
Tobacco Smoking (E)		
Formaldehyde (F)		
Respiratory System (59.3% overlap)		
Arsenic and inorganic arsenic compounds (C)	Arsenic and inorganic arsenic compounds (C)	Cyclophosphamide(A)
Asbestos (all forms), including actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite) (C)	Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite) (C)	Arsenic and inorganic arsenic compounds (C)
Beryllium and beryllium compounds (C)	Beryllium and beryllium compounds (C)	Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite(C)
Cadmium and cadmium compounds (C)	Cadmium and cadmium compounds (C)	Beryllium and beryllium compounds (C)
Chromium (VI) compounds (C)	Chromium (VI) compounds (C)	Cadmium and cadmium compounds (C)
Nickel compounds (C)	Nickel compounds (C)	Chromium (VI) compounds (C)
Silica dust, crystalline, in the form of quartz or cristobalite (C)	Silica dust, crystalline, in the form of quartz or cristobalite (C)	Nickel compounds (C)
Haematite mining with exposure to radon (underground) (D)	Haematite mining with exposure to radon (underground) (D)	Silica dust, crystalline, in the form of quartz or cristobalite (C)
Pu-239 (D)	Pu-239 (D)	Haematite mining with exposure to radon (underground)(D)
Rn-222 and its decay products (D)	Rn-222 and its decay products (D)	Pu-239 (D)
X- and Gamma radiation (D)	X- and Gamma radiation (D)	Rn-222 and its decay products (D)
Alcoholic beverages (E)	Coal, indoor emissions from household combustion of (E)	

Coal, indoor emissions from household combustion of (E) Second-hand tobacco smoke (E) Tobacco smoking (E) Bis(chloromethyl)ether; chloromethyl methyl ether (technical-grade) (F) Coal gasification (F) Coal-tar pitch (F) Coke production (F) Soot (as found in occupational exposure of chimney sweeps) (F) Engine Exhaust, diesel (F)	Second-hand tobacco smoke (E) Tobacco smoking (E) Coke production (F) Engine Exhaust, diesel (F)	X- and Gamma radiation (D) Coal, indoor emissions from household combustion of (E) Second-hand tobacco smoke (E) Tobacco smoking (E) Benzene (F) 1,3-Butadiene (F) Coke production (F) Vinyl Chloride (F) Engine Exhaust, diesel (F*) 2,3,7,8-Tetrachlorodibenzo-para-dioxin (F*) Trichloroethylene (F*)
Mesothelium (100.0% overlap)		
Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite) (C) Erionite (C)	Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite) (C) Erionite (C)	Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite) (C) Erionite (C)
Digestive Tract (20.0% overlap)		
Helicobacter pylori (infection with) (B) X- and Gamma radiation (D) *Radioiodines including I-131(D)* Alcoholic beverages (E) Betel quid without tobacco (E) *Salted fish, chinese style (E)* Tobacco smoking (E) Tobacco, smokeless (E)	*Helicobacter pylori* (infection with) (B) Betel quid without tobacco (E)	Aristolochic acid, plants containing (A) *Helicobacter pylori* (infection with) (B) Chromium (VI) compounds (C) Betel quid without tobacco (E) Benzene (F) 1,3-Butadiene (F)
Digestive Organs (22.2% overlap)		
Estrogen-progestogen oral contraceptives (combined) (A) *Arsenic and inorganic arsenic compounds (C)* Th-232 (as Thorotrast) (D) Pu-239 (D) *X-and Gamma radiation (D)*	Arsenic and inorganic arsenic compounds (C) Pu-239 (D) Th-232 (as Thorotrast) (D) X-and Gamma radiation (D) Aflatoxins (F) Vinyl chloride (F)	Tamoxifen (A) Arsenic and inorganic arsenic compounds (C) Th-232 (as Thorotrast) (D) Pu-239 (D) X- and Gamma radiation (D) Aflatoxins (F)

Alcoholic beverages (E) *Betel quid without tobacco (E)* **Tobacco smoking (E)** **Tobacco, smokeless (E)** **Aflatoxins (F)** **Vinyl chloride (F)** *Trichloroethylene (F*)*	Trichloroethylene (F*)	**4-Aminobiphenyl (F)** **Benzidine (F)** **1,3-Butadiene (F)** **2-Naphthylamine (F)** **2,3,7,8-Tetrachlorodibenzo-para-dioxin (F)** **Vinyl chloride (F)** **Trichloroethylene (F*)** **Polychlorinated biphenyls (F)**
Nervous System and Eye (N/A)		
UV-emitting tanning devices (D) **X- and Gamma radiation (D)** *Solar radiation (D)*		
Endocrine System (66.7% overlap)		
Radioiodines, including I-131 (D) **X- and Gamma radiation (D)**	**Radioiodines, including I-131 (D)** **X- and Gamma radiation (D)**	**Nickel compounds (C)** **Radioiodines, including I-131 (D)** **X- and Gamma radiation (D)**
Kidney (33.3% overlap)		
Arsenic and inorganic arsenic (C) *Cadmium and cadmium compounds (C)* **X- and Gamma radiation (D)** **Tobacco smoking (E)** **Trichloroethylene (F*)**	**X- and Gamma radiation (D)** **Trichloroethylene (F*)**	**Diethylstilbestrol (A)** **Estrogen-only menopausal therapy (A)** **Phenacetin (A)** **X- and Gamma radiation (D)** **Trichloroethylene (F*)**
Urothelium (70.0% overlap)		
Aristolochic acid, plants containing (A) **Cyclophosphamide (A)** **Phenacetin (A)** **Arsenic and inorganic arsenic compounds (C)** **X- and Gamma radiation (D)** **Tobacco smoking (E)** *Coal-tar pitch (F)* *Soot (as found in occupational exposure of chimney sweeps) (F)* **4-Aminobiphenyl (F)**	**Aristolochic acid, plants containing (A)** **Cyclophosphamide (A)** **Phenacetin (A)** **Arsenic and inorganic arsenic compounds (C)** **4-Aminobiphenyl (F)** **2-Naphthylamine (F)** ***ortho*-Toluidine (F)**	**Aristolochic acid, plants containing (A)** **Cyclophosphamide (A)** **Phenacetin (A)** **Arsenic and inorganic arsenic compounds (C)** **2-Naphthylamine (F)** **4-Aminobiphenyl (F)** ***ortho*-Toluidine (F)**

Benzidine (F) **2-Naphthylamine (F)** ***ortho*-Toluidine (F)** Engine Exhaust, diesel (F*)		
Lymphoid and Haematopoietic Tissues (46.7% overlap)		
Azathioprine (A) **Chlorambucil (A)** **Cyclophosphamide (A)** **Thiotepa (A)** ***Helicobacter pylori* (infection with) (B)** **Fission products including Sr-90 (D)** **Th-232 (as Thorotrast) (D)** **X- and Gamma radiation (D)** *Radioiodines including I-131(D)* *Rn-222 and its decay products (D)* **Tobacco smoking (E)** *Ethylene oxide (F)* **Benzene (F)** **1,3-Butadiene (F)** **Formaldehyde (F)** *Trichloroethylene (F*)* *Polychlorinated biphenyls (F*)*	**Azathioprine (A)** **Chlorambucil (A)** **Cyclophosphamide (A)** **Thiotepa (A)** **X- and Gamma radiation (D)** **Benzene (F)** **1,3-Butadiene (F)**	**Azathioprine (A)** **Chlorambucil (A)** **Cyclophosphamide (A)** **Estrogen-only menopausal therapy (A)** **Thiotepa (A)** **Silica dust, crystalline, in the form of quartz or cristobalite (C)** **X- and Gamma radiation (D)** **Ethylene oxide (F)** **Benzene (F)** **1,3-Butadiene (F)**
Skin (35.0% overlap)		
Azathioprine (A) **Methoxsalen in combination with UVA (A)** **Arsenic and inorganic arsenic compounds (C)** **Solar radiation (D)** **UV-emitting tanning devices (D)** **X- and Gamma radiation (D)** **Coal-tar distillation (F)** **Mineral oils, untreated or mildly treated (F)** **Shale oils (F)** **Soot (as found in occupational exposure of chimney sweeps) (F)**	**Methoxsalen in combination with UVA (A)** **Solar radiation (D)** **UV-emitting tanning devices (D)** **Coal-tar distillation (F)** **Mineral oils, untreated or mildly treated (F)** **Shale oils (F)** **Soot (as found in occupational exposure of chimney sweeps) (F)**	**Methoxsalen in combination with UVA (A)** **Solar radiation (D)** **UV-emitting tanning devices (D)** **Coal, indoor emissions from household combustion of (E)** **Tobacco smoking (E)** **Benzene (F)** **Bis(chloromethyl)ether;chloromethyl methyl ether (technical-grade) (F)** **Coal gasification (F)** **Coal-tar distillation (F)**

Polychlorinatedbiphenyls (F*)		**Coal-tar pitch (F)** **Coke production (F)** **Mineral oils, untreated or mildly treated (F)** **Shale oils (F)** **Soot (as found in occupational exposure of chimney sweeps) (F)** **2,3,7,8-Tetrachlorodibenzo-para-dioxin (F)** ***ortho*-Toluidine (F)**
Connective Tissues (42.9% overlap)		
Pu-239 (D) **Ra-224 and its decay products (D)** **Ra-226 and its decay products (D)** **Ra-228 and its decay products (D)** **X- and Gamma radiation (D)** *Radioiodines including I-131(D)* **Vinyl chloride (F)**	**Pu-239 (D)** **Ra-224 and its decay products (D)** **Ra-226 and its decay products (D)** **Ra-228 and its decay products (D)** **X- and Gamma radiation (D)** **Vinyl chloride (F)**	**Cadmium and cadmium compounds (C)** **Chromium (VI) compounds (C)** **Nickel compounds (C)** **Fission products including Sr-90 (D)** **Pu-239 (D)** **Ra-224 and its decay products (D)** **Ra-226 and its decay products (D)** **Ra-228 and its decay products (D)** **X- and Gamma radiation (D)** **4-Aminobiphenyl (F)** **Bis(chloromethyl)ether;chloromethyl methyl ether (technical-grade) (F)** **1,3-Butadiene (F)** ***ortho*-Toluidine (F)** **Vinyl chloride (F)**
Female Breast, Female Reproductive Organs and Reproductive Tract (30.8% overlap)		
Diethylstilbestrol (A) **Estrogen-only menopausal therapy (A)** **Estrogen-progestogen oral contraceptives (combined) (A)** **Tamoxifen (A)** **Asbestos (all forms, including actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite) (C)** **X- and Gamma radiation (D)** **Alcoholic beverages (E)**	**Diethylstilbestrol (A)** **Estrogen-only menopausal therapy (A)** **Estrogen-progestogen oral contraceptives (combined) (A)** **X- and Gamma radiation (D)**	**Cyclophosphamide (A)** **Diethylstilbestrol (A)** **Estrogen-only menopausal therapy (A)** **Estrogen-progestogen oral contraceptives (combined) (A)** **X- and Gamma radiation (D)** **Benzene (F)** **Benzidine (F)** **1,3-Butadiene (F)**

Tobacco smoking (E) *Ethylene oxide (F)* *Polychlorinated biphenyls (F*)*		**Vinyl chloride (F)**
Male Reproductive Organs Including Prostate and Testicular Tumours (NA overlap)		
Diethylstilbestrol (A) *Arsenic and inorganic arsenic compounds (C)* *Cadmium and cadmium compounds (C)* *Th-232 (as Thorotrast) D* *X-and Gamma radiation (D)*		
All Cancers Combined		
2,3,7,8-Tetrachlorodibenzo-para-dioxin (F)		

[1]Organ and tissue systems in the anatomically based tumour nomenclature system (see Supplemental Table 1. 'Animal and Human Tumour site for 111 Group 1 identified through Volume 108 of the *IARC Monographs*'). Data inputs for human and animal data with *sufficient evidence* of carcinogenicity are from Supplemental Table 2 'Database of Animal and Human Tumour Sites for 111 Distinct Group-1 Agents Through Volume 109 of the *IARC Monographs*.' Agents lacking sufficient evidence in both humans and animals are not shown with the exception of limited additional data inputs for limited evidence of human sites are from Monographs 100A-F, Monograph 107, and Monograph109 (in italics) and included data for ethylene oxide estrogens and progestogen oral contraceptives, diethylstilbestrol. Data for male reproductive organs are also included in although not part of the concordance analyses. 2,3,7,8-Tetrachlorodibenzo-para-dioxin is included to but its designation of all cancers combined for human data precludes specific site analyses between species.

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

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

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

N/A denotes organ/tissue systems when overlap is not possible (positive data is available in either humans or animals, but not both).

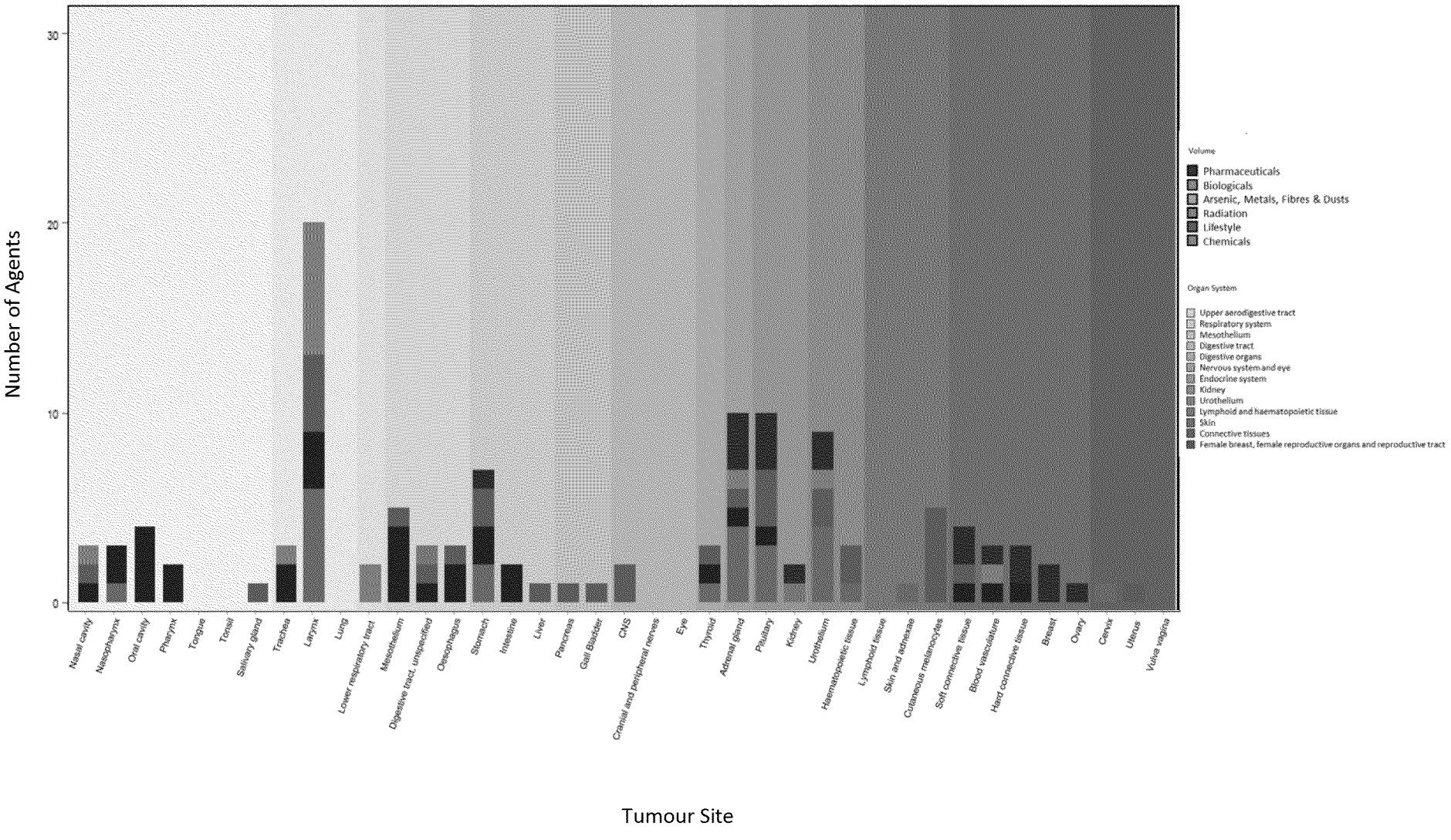

Figure 1. Number of Agents Inducing Tumours in Humans in Each of 39 Tumour sites by Type of Agent

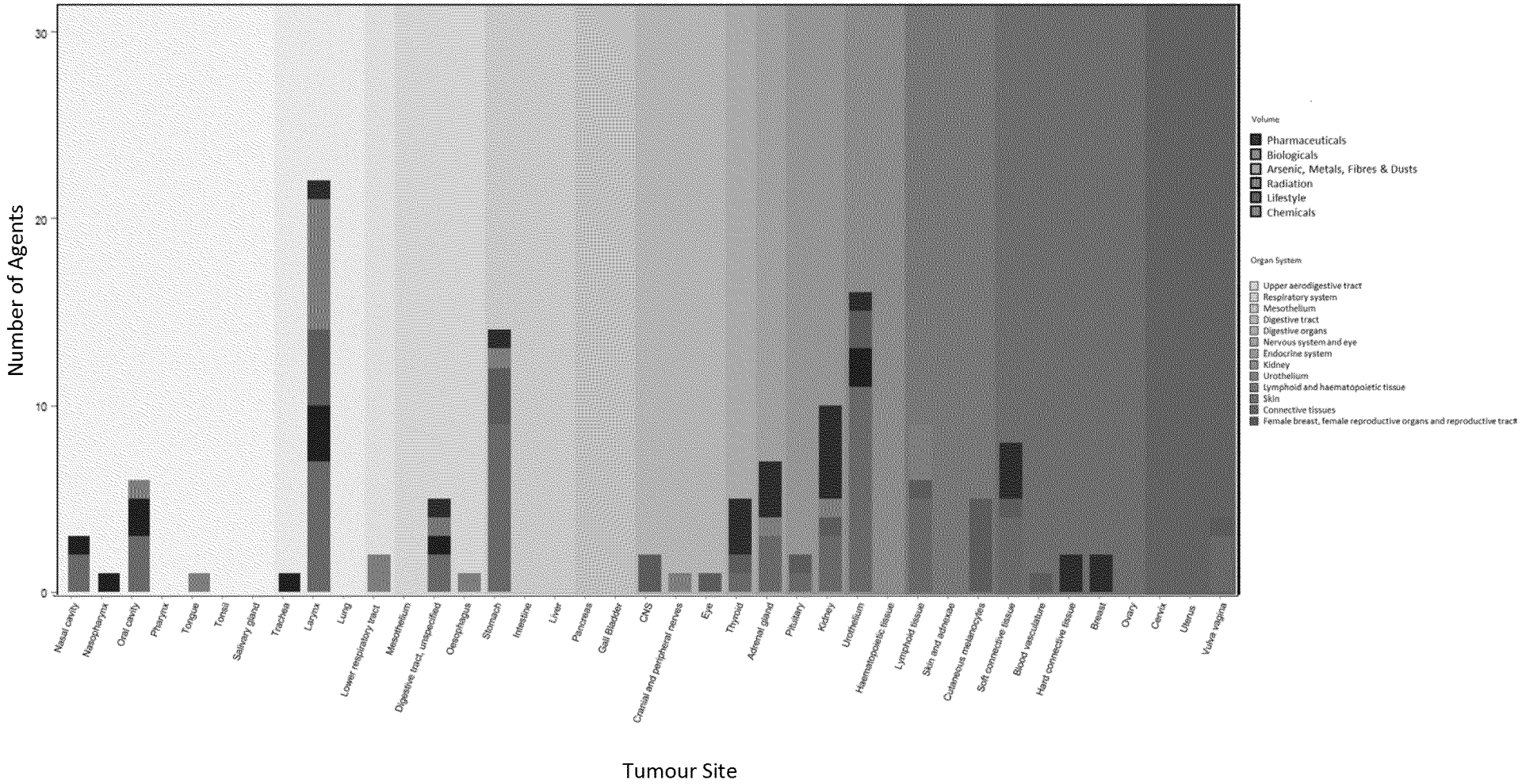

Figure 2. Number of Agents Inducing Tumours in Animals in Each of 39 Tumour sites by Type of Agent

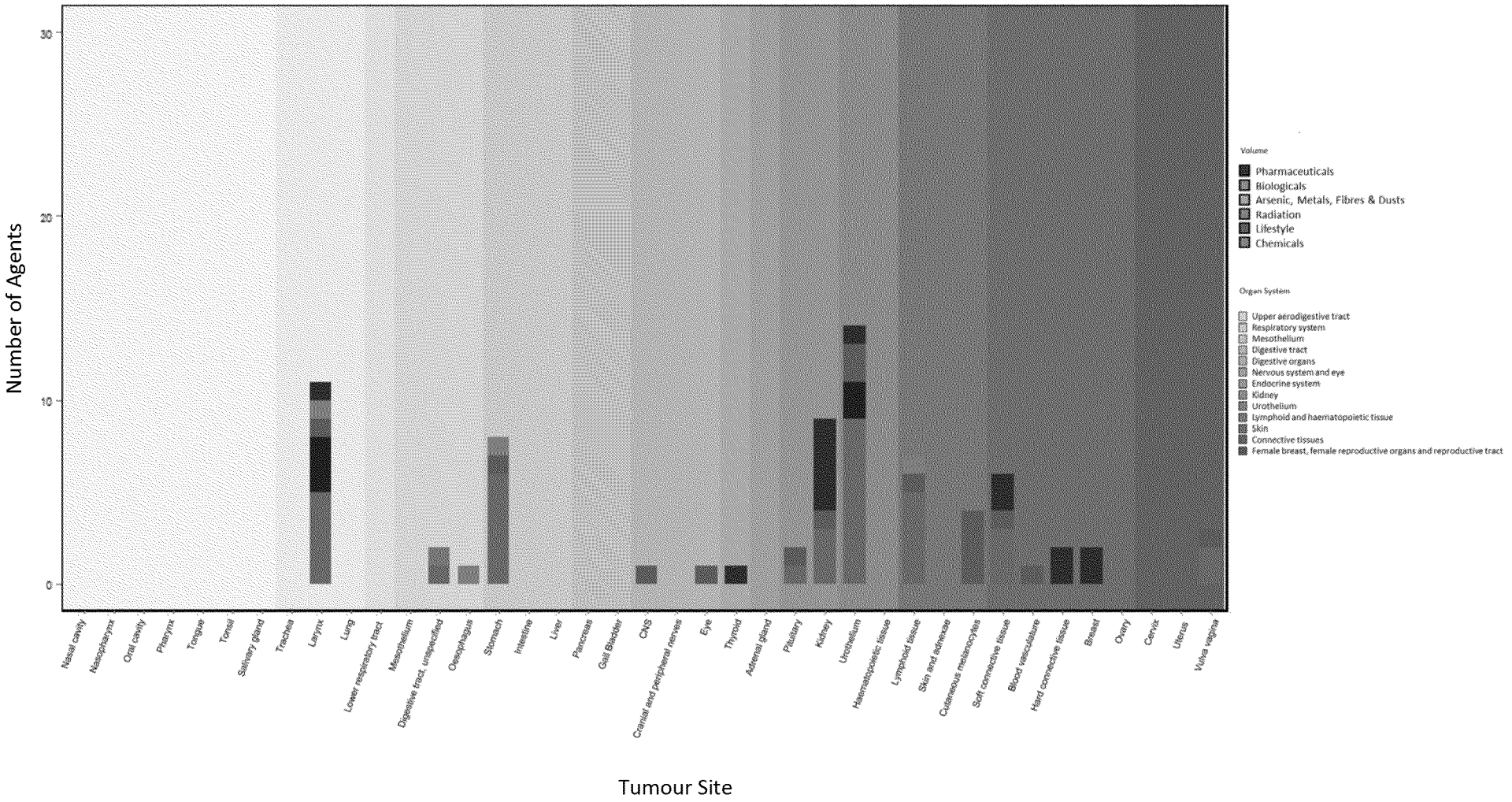

Figure 3. Number of Agents Inducing Tumours in Mice in Each of 39 Tumour sites by Type of Agent

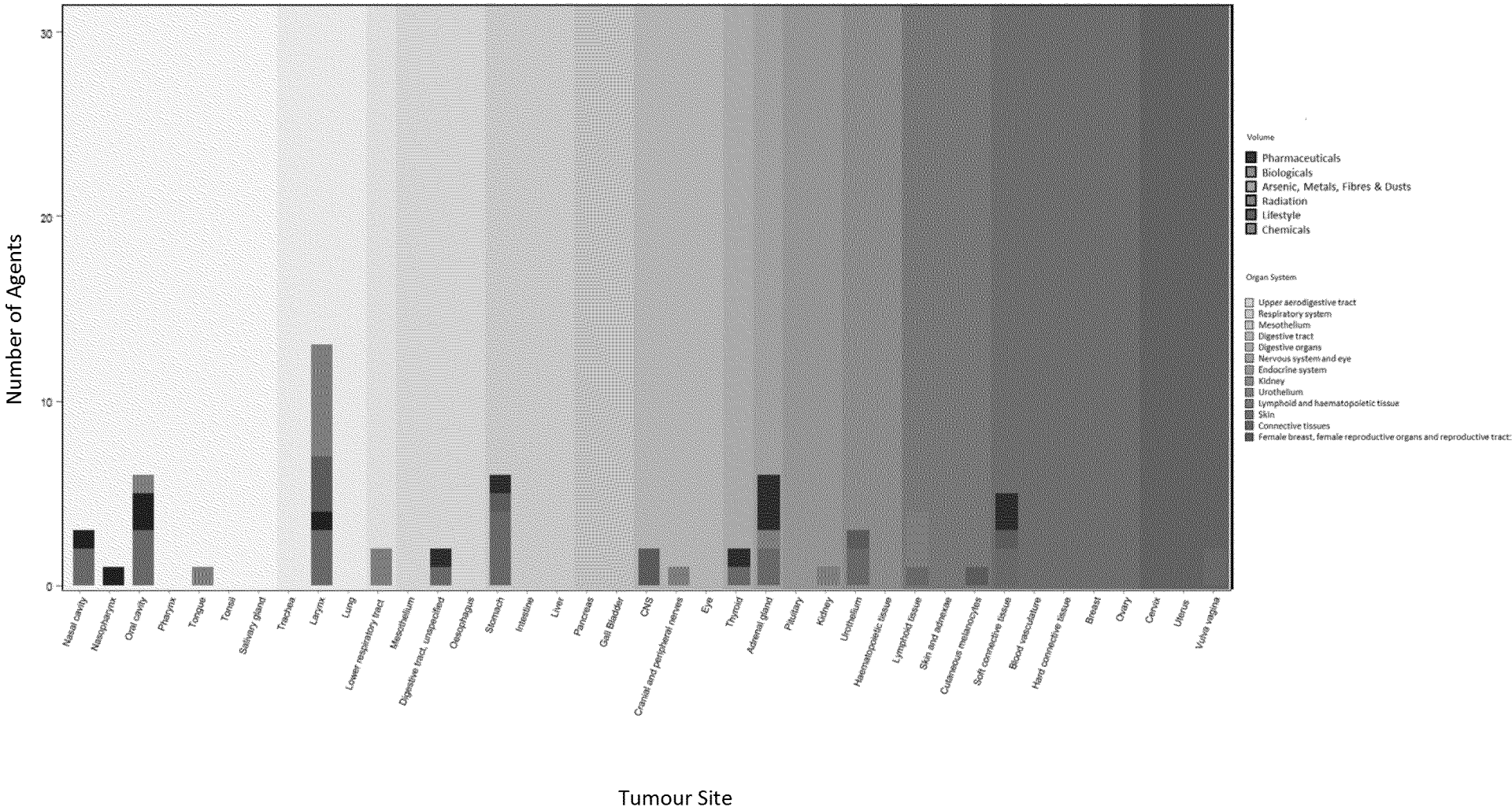

Figure 4. Number of Agents Inducing Tumours in Rats in Each of 39 Tumour sites by Type of Agent

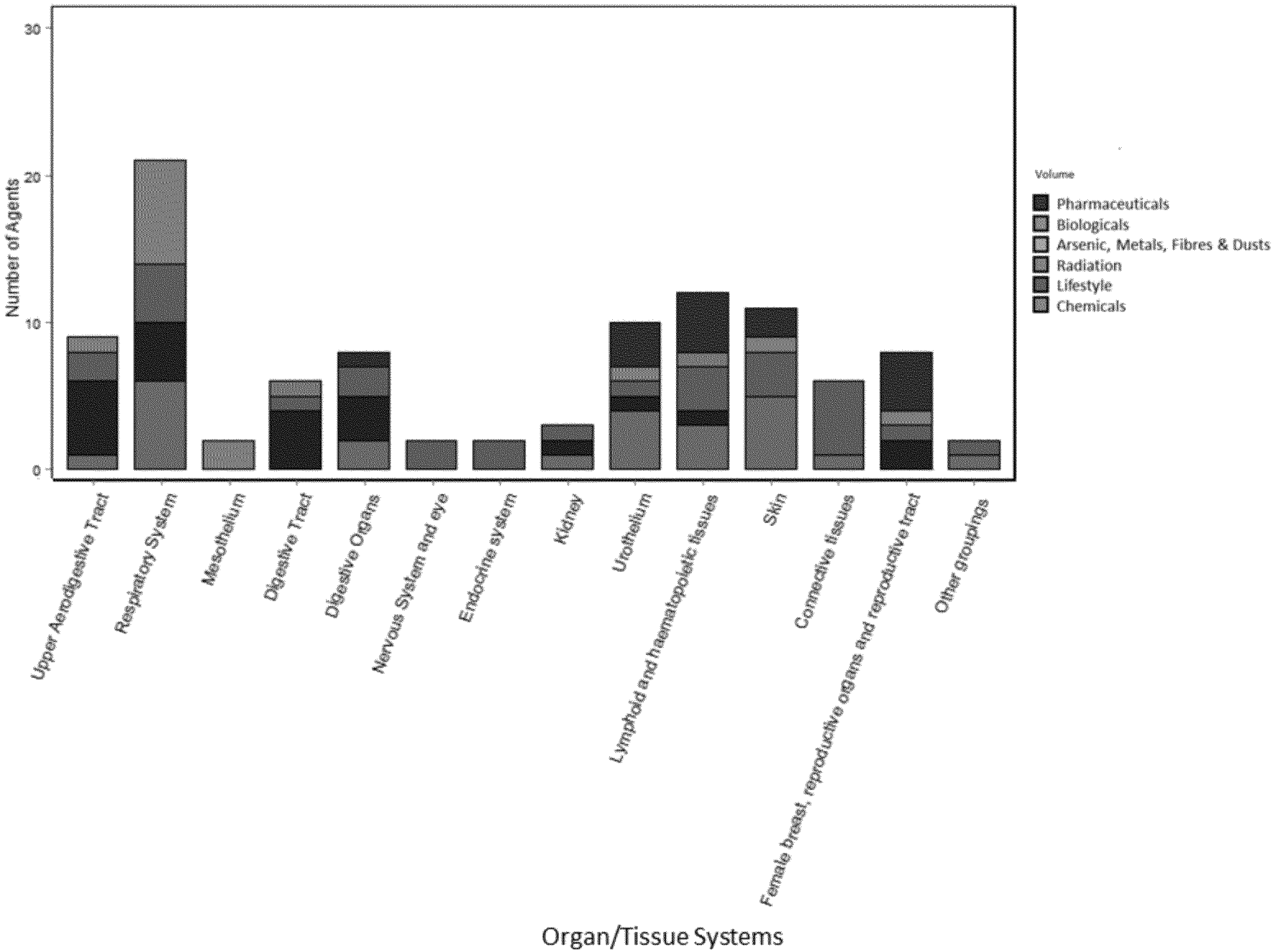

Figure 5. Number of Agents Inducing Tumours in Humans in Each of 15 Organ/Tissue Systems by Type of Agent

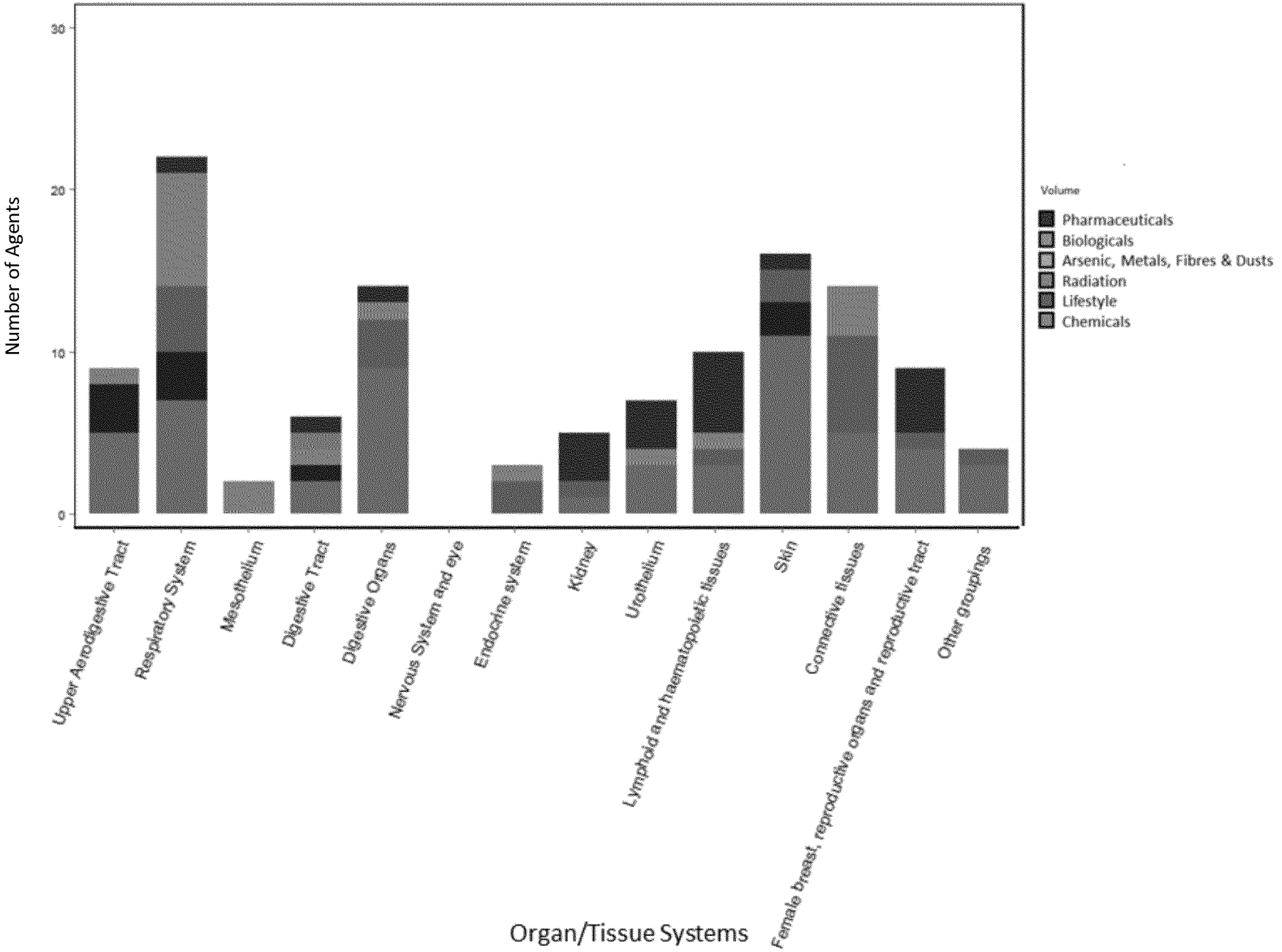

Figure 6. Number of Agents Inducing Tumours in Animals in Each of 15 Organ/Tissue Systems by Type of Agent

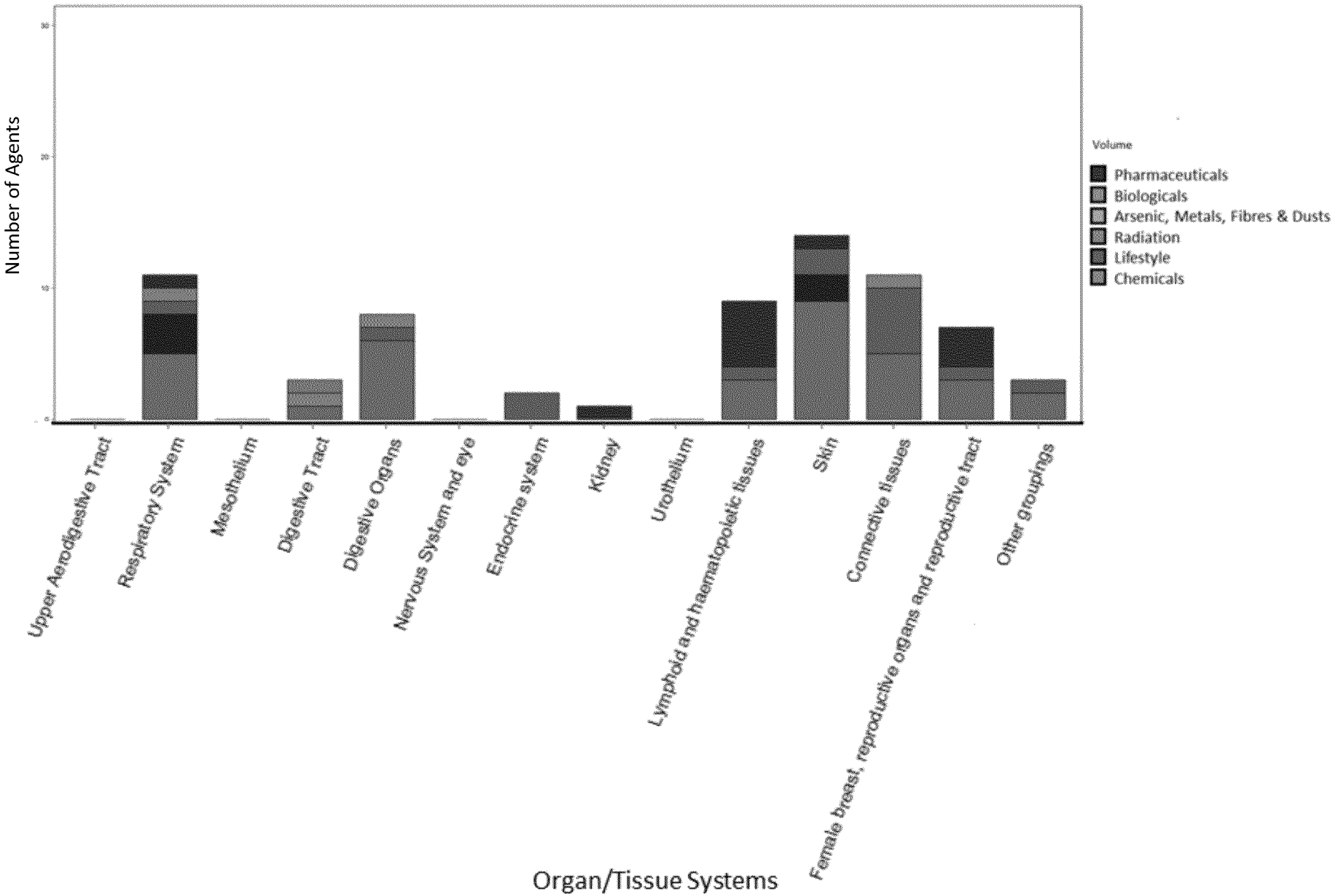

Figure 7. Number of Agents Inducing Tumours in Mice in Each of 15 Organ/Tissue Systems by Type of Agent

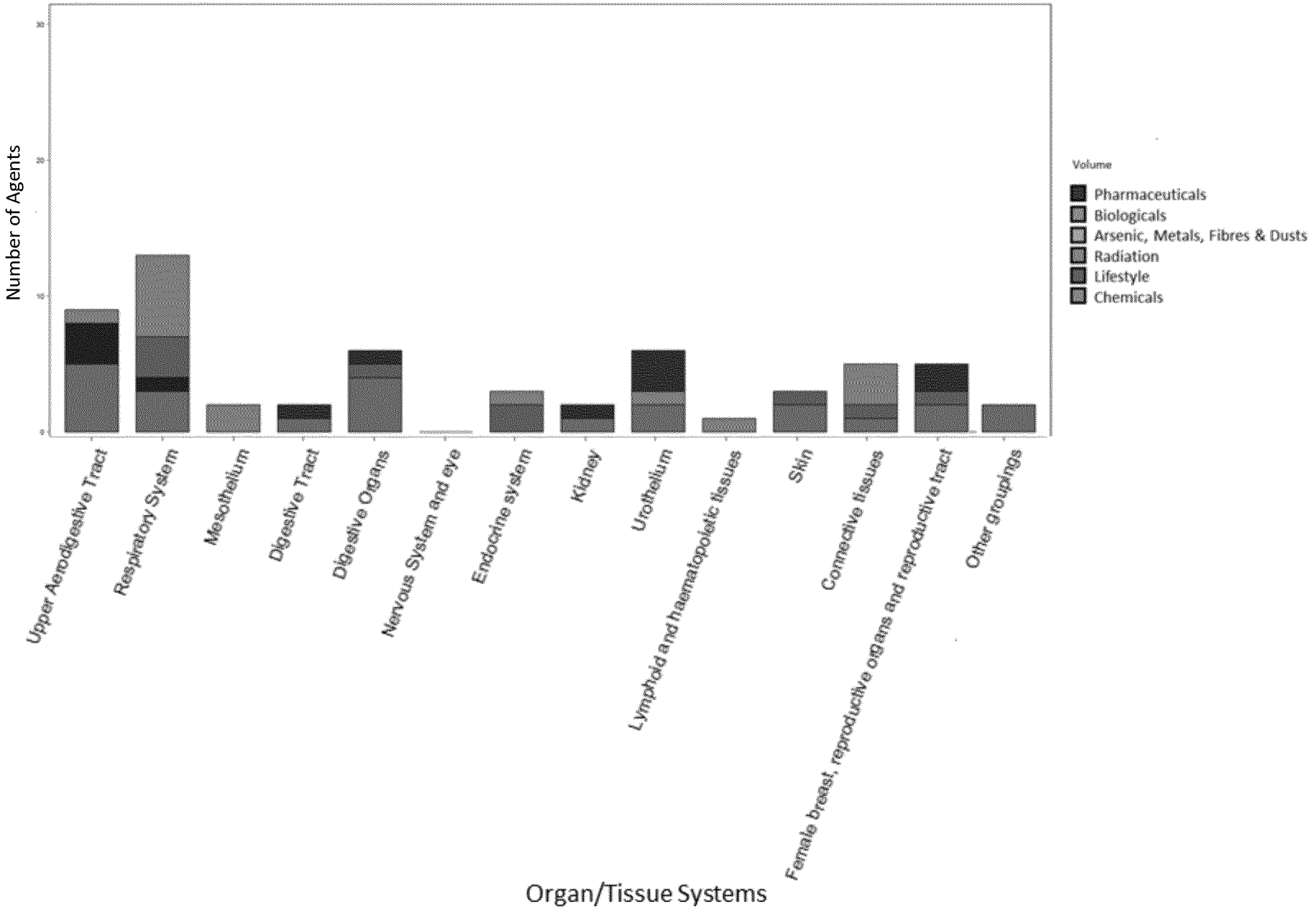

Figure 8. Number of Agents Inducing Tumours in Rats in Each of 15 Organ/Tissue Systems by Type of Agent

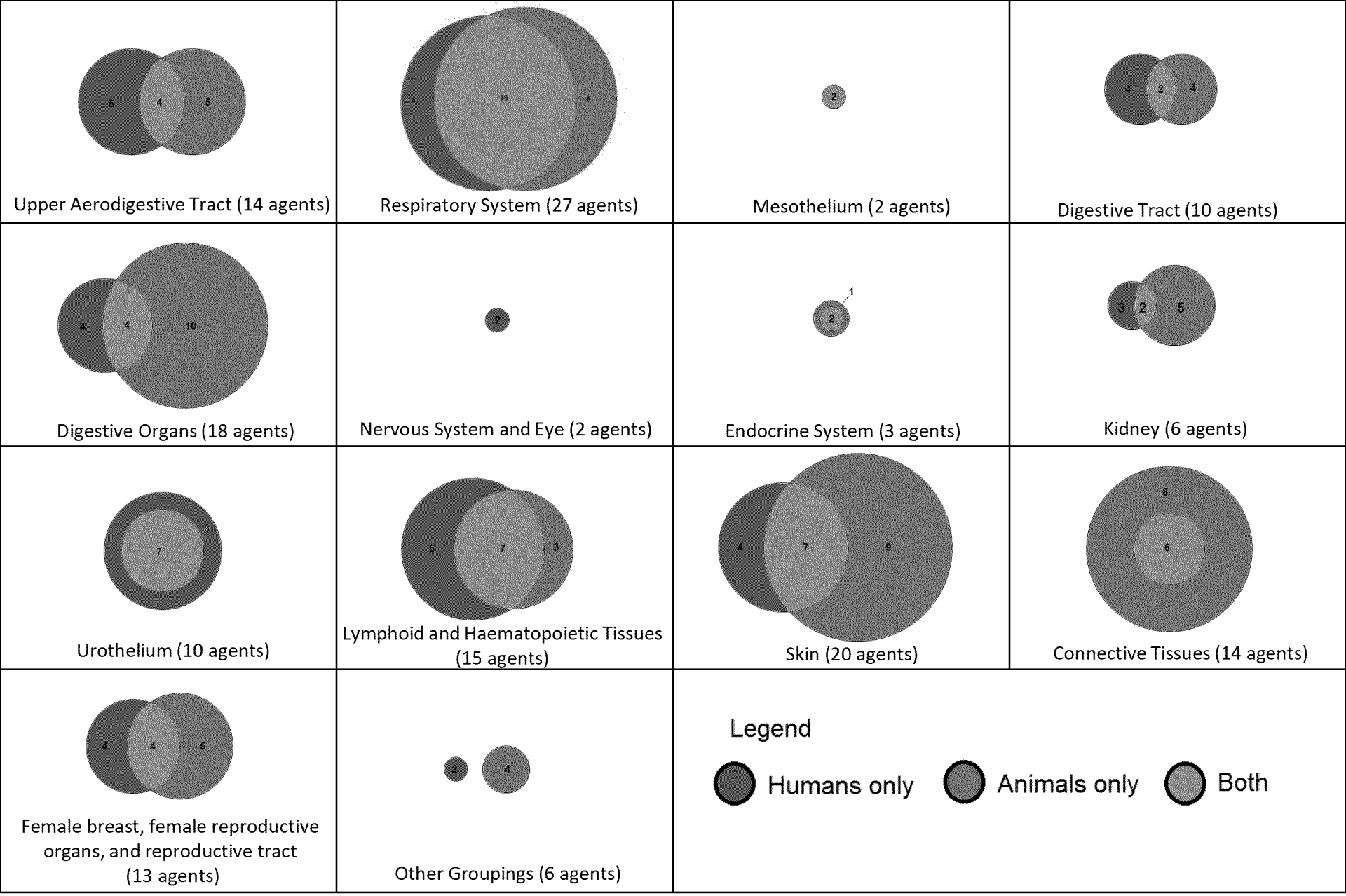

Figure 9. Concordance between Tumour sites seen in Humans and Animals for 60 Group-1 Agents by Organ and Tissue System

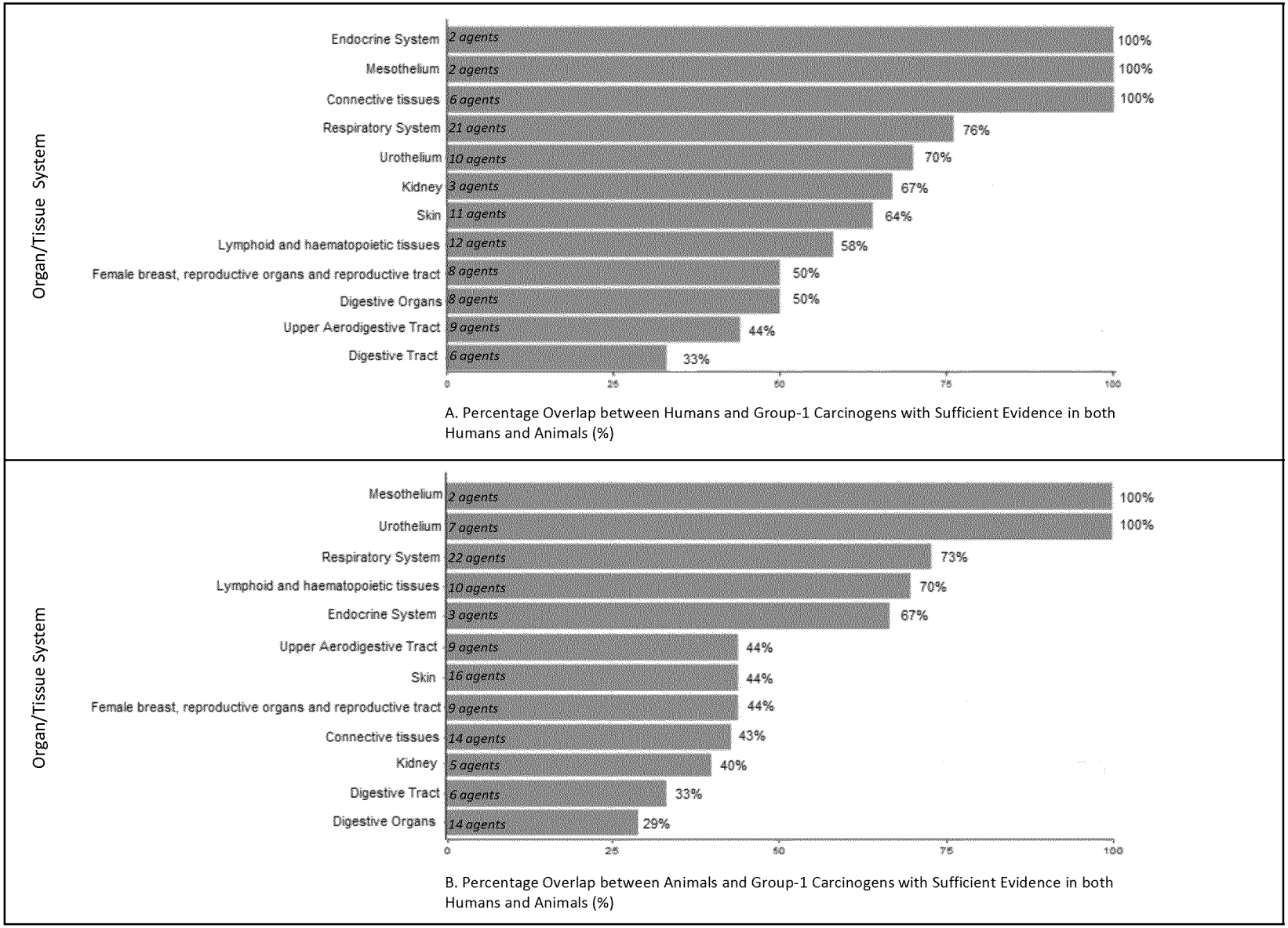

Figure 10. Overlap between Group- 1 Agents with Sufficient Evidence of Carcinogenicity in Humans and Animals Expressing Tumours in Specific Organ and Tissue Systems. (A. Overlap between animals and humans; B. Overlap between humans and animals. Number of Group-1 agents expressing tumours in specific organ/tissue systems shown in Panel A; number of animal Group-1 agents expressing tumours in specific organ/tissue systems shown in Panel B.)

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

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

D. Krewski, J. M. Rice, M. Bird, B. Milton, B. Collins, P. Lajoie, M. Billard, Y. Grosse, R. Baan, V. Cogliano, K. Straif, J. Caldwell, I.I. Rusyn, C.J. Portier, R. Melnick, J. Little & J.M. Zielinski[1]

in collaboration with other participants in the IARC Workshop on
'Tumour-site Concordanceand Mechanisms of Carcinogenesis'
which convened in Lyon, April/November 2012[2]

Krewski et al. (2016) 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. (2016). The format of data abstracted from the Monographs by Grosse et al. (2016) is illustrated in Table 3 of Krewski et al. (2016), 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. (2016, 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. (2016), 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. (2016) 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

[1] Deceased.

[2] L. Banks, F.A. Beland, J.A. Bond, M.C. Bosland, J.R. Bucher, D.M. DeMarini, B. Fubini, B.D. Goldstein, S.S. Hecht, K. Hemminki, C.W. Jameson, A.B. Kane, R.J, Kavlock, P.F. Lambert, L. Stayner, B.W. Stewart, R.L. Ullrich, H. Vainio, P. Vineis, M.P. Waalkes, L. Zeise.

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.

Distributions of tumours expressed by across the tumour sites listed in Supplemental Table 4 for humans, (all) animals, mice, and rats are shown in Supplemental Figures 1-4, respectively, by type of agent. [Although there are 47 tumour sites listed in Supplemental Table 4, the 111 Group-1 agents considered here demonstrated animal and/or human tumours at only 39 of these 47 sites.] Similar results for the 15 organ and tissue systems are shown in Supplemental Figures 5-8.

The 60 Group-1 agents included in the analysis of concordance between animal and human tumours reported by Krewski et al. (2016) are summarized in Supplemental Table 5. Concordance analysis was necessarily restricted to these 60 agents because of the requirement of sufficient evidence of at least one tumour site in animals and sufficient evidence of at least one tumour site in humans.

References

Grosse. Y., Lajoie, P., Billard, M., Krewski, D., Rice, J.R., Cogliano, V., Straif, K., Bird, M. & Zielinski, J.M. (2016). Database of animal and human tumours based on 111 distinct Group-1 agents known to cause cancer in humans. [This volume.]

Krewski, D., Rice, J.M., Bird, M., Milton, B., Collins, B., Lajoie, P, Billard, M., Grosse, Y., Baan, R., Cogliano, V., Straif, K., Caldwell, J., Rusyn, I.I., Portier, C.J., Melnick, R., Little, J. & Zielinski, J.M., in collaboration with other participants in the IARC Workshop on 'Tumour-site Concordance and Mechanisms of Carcinogenesis' which convened in Lyon, April/November 2012 (2016). Concordance between sites of tumour development in humans and in experimental animals for 111 agents that are carcinogenic to humans. [This volume.]

List of Tables

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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	Chlomaphazine	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)	Rat	Mammary gland	Breast	Breast	35	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	0	6	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	Extranodal 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 immunodeficiencyvirus type 1	Human	Hodgkin lymphoma	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	0	3	0	1
B	29	Human immunodeficiencyvirus type 1	Human	Non-Hodgkin lymphoma	Lymphoid tissue	Lymphoid tissue	29	Lymphoid and haematopoietic tissues	10	0	3	0	1
B	29	Human immunodeficiencyvirus type 1	Human	Anus	Skin and adnexae	Skin and adnexae	30	Skin	11	0	3	0	1
B	29	Human immunodeficiencyvirus type 1	Human	Conjuctiva	Skin and adnexae	Skin and adnexae	30	Skin	11	0	3	0	1
B	29	Human immunodeficiencyvirus type 1	Human	Kaposi sarcoma	Soft connective tissue	Soft connective tissue	32	Connective tissues	12	0	3	0	1
B	29	Human immunodeficiencyvirus 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

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	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
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

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	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
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

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	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
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'-Nitrosonomicotine (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'-Nitrosonomicotine (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'-Nitrosonomicotine (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'-Nitrosonomicotine (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'-Nitrosonomicotine (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

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
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
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

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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	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
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

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	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
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	0	7	0	1
109	111	Particulate matter in outdoor air pollution	Human	Lung	Lung	Lung	10	Respiratory system	2	0	7	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, 100E, 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)	

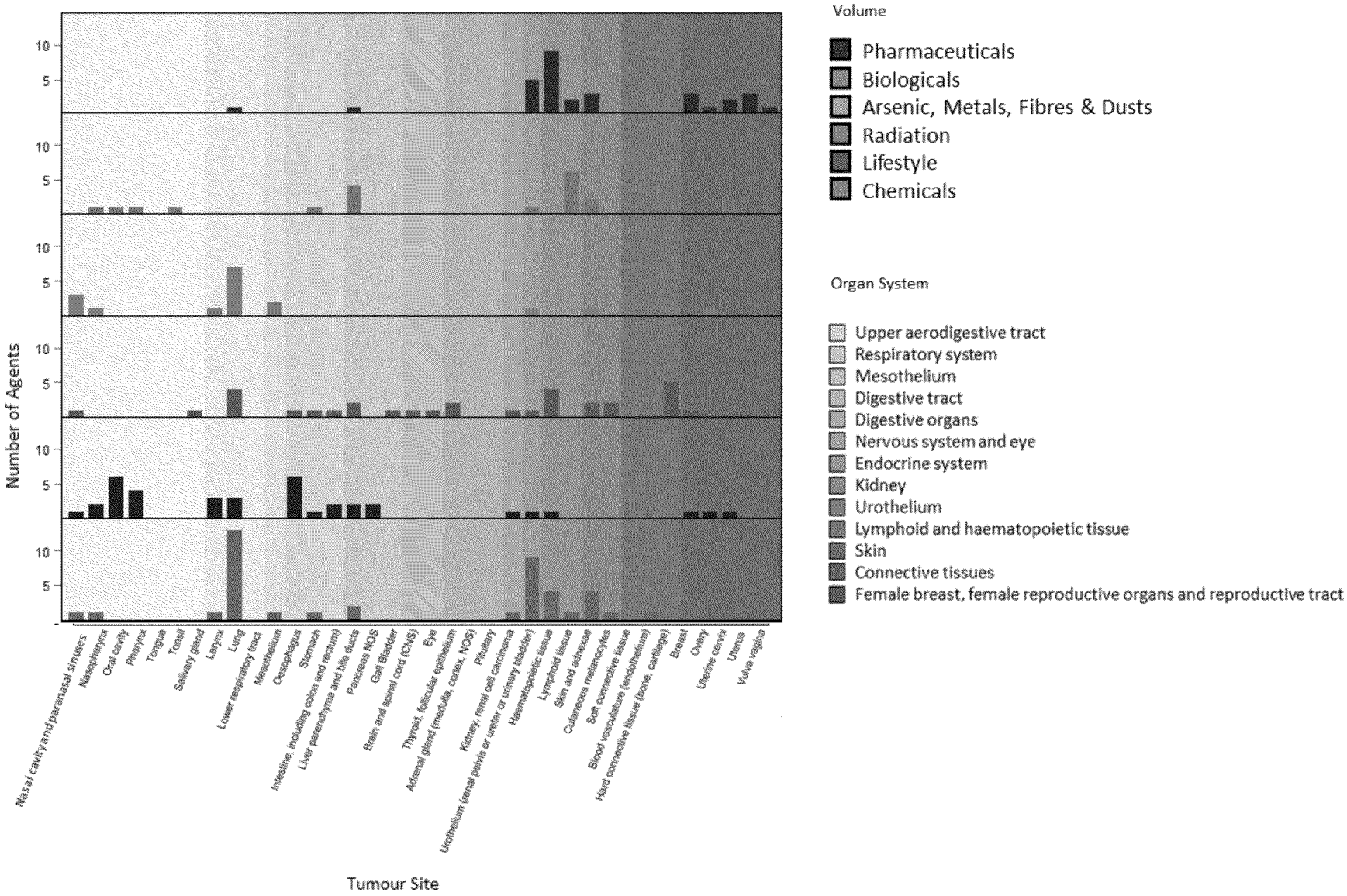
Testis, germ cells	40
Testis, specialized gonadal stroma	41
Prostate	42
Other Groupings (15)	
All cancers combined	43
All solid cancers	44
Solid cancers, aside from lung	45
Multiple or unspecified sites	46
Exocrine glands NOS	47

Supplemental Table 5. Group-1 Agents With at Least One Tumour Site Specified in Humans and in Animals (60 agents)				
Volume	Agent	Species	Tissue Site	Organ and Tissue System
A	Aristolochic acid, plants containing	Rat	Stomach	Digestive tract
A	Aristolochic acid, plants containing	Human	Urothelium	Urothelium
A	Aristolochic acid, plants containing	Rat	Urothelium	Urothelium
A	Aristolochic acid, plants containing	Human	Urothelium	Urothelium
A	Azathioprine	Mouse	Lymphoid tissue	Lymphoid and haematopoietic tissues
A	Azathioprine	Human	Lymphoid tissue	Lymphoid and haematopoietic tissues
A	Azathioprine	Mouse	Lymphoid tissue	Lymphoid and haematopoietic tissues
A	Azathioprine	Human	Skin and adnexae	Skin
A	Chlorambucil	Human	Haematopoietic tissue	Lymphoid and haematopoietic tissues
A	Chlorambucil	Mouse	Lymphoid tissue	Lymphoid and haematopoietic tissues
A	Cyclophosphamide	Mouse	Lung	Respiratory system
A	Cyclophosphamide	Human	Urothelium	Urothelium
A	Cyclophosphamide	Rat	Urothelium	Urothelium
A	Cyclophosphamide	Human	Haematopoietic tissue	Lymphoid and haematopoietic tissues
A	Cyclophosphamide	Mouse	Lymphoid tissue	Lymphoid and haematopoietic tissues
A	Cyclophosphamide	Mouse	Breast	Female breast, female reproductive organs and reproductive tract
A	Diethylstilbestrol	Hamster	Kidney	Kidney
A	Diethylstilbestrol	Human	Breast	Female breast, female reproductive organs and reproductive tract
A	Diethylstilbestrol	Human	Cervix	Female breast, female reproductive organs and reproductive tract
A	Diethylstilbestrol	Mouse	Cervix	Female breast, female reproductive organs and reproductive tract
A	Diethylstilbestrol	Mouse	Uterus	Female breast, female reproductive organs and reproductive tract
A	Diethylstilbestrol	Human	Vulva/vagina	Female breast, female reproductive organs and reproductive tract
A	Estrogen-only menopausal therapy	Hamster	Kidney	Kidney
A	Estrogen-only menopausal therapy	Mouse	Lymphoid tissue	Lymphoid and haematopoietic tissues
A	Estrogen-only menopausal therapy	Mouse	Breast	Female breast, female reproductive organs and reproductive tract
A	Estrogen-only menopausal therapy	Rat	Breast	Female breast, female reproductive organs and reproductive tract
A	Estrogen-only menopausal therapy	Human	Ovary	Female breast, female reproductive organs and reproductive tract
A	Estrogen-only menopausal therapy	Mouse	Cervix	Female breast, female reproductive organs and reproductive tract
A	Estrogen-only menopausal therapy	Human	Uterus	Female breast, female reproductive organs and reproductive tract
A	Estrogen-only menopausal therapy	Mouse	Uterus	Female breast, female reproductive organs and reproductive tract
A	Estrogen-progestogen oral contraceptives (combined)	Human	Liver	Digestive organs
A	Estrogen-progestogen oral contraceptives (combined)	Human	Breast	Female breast, female reproductive organs and reproductive tract
A	Estrogen-progestogen oral contraceptives (combined)	Human	Cervix	Female breast, female reproductive organs and reproductive tract
A	Estrogen-progestogen oral contraceptives (combined)	Rat	Breast	Female breast, female reproductive organs and reproductive tract
A	Methoxsalen in combination with UVA	Mouse	Skin and adnexae	Skin
A	Methoxsalen in combination with UVA	Human	Skin and adnexae	Skin
A	Phenacetin	Mouse	Kidney	Kidney
A	Phenacetin	Rat	Kidney	Kidney
A	Phenacetin	Human	Urothelium	Urothelium
A	Phenacetin	Rat	Urothelium	Urothelium
A	Phenacetin	Human	Urothelium	Urothelium
A	Tamoxifen	Rat	Liver	Digestive organs
A	Tamoxifen	Human	Uterus	Female breast, female reproductive organs and reproductive tract
A	Thiotepa	Human	Haematopoietic tissue	Lymphoid and haematopoietic tissues
A	Thiotepa	Mouse	Lymphoid tissue	Lymphoid and haematopoietic tissues
B	Helicobacter pylori (infection with)	Mouse	Stomach	Digestive tract
B	Helicobacter pylori (infection with)	Human	Stomach	Digestive tract
B	Helicobacter pylori (infection with)	Human	Lymphoid tissue	Lymphoid and haematopoietic tissues
C	Arsenic and inorganic arsenic compounds	Human	Lung	Respiratory system
C	Arsenic and inorganic arsenic compounds	Mouse	Lung	Respiratory system
C	Arsenic and inorganic arsenic compounds	Mouse	Liver	Digestive organs
C	Arsenic and inorganic arsenic compounds	Human	Urothelium	Urothelium
C	Arsenic and inorganic arsenic compounds	Rat	Urothelium	Urothelium
C	Arsenic and inorganic arsenic compounds	Human	Skin and adnexae	Skin
C	Asbestos (all forms)	Human	Larynx	Respiratory system
C	Asbestos (all forms)	Human	Lung	Respiratory system
C	Asbestos (all forms)	Rat	Lung	Respiratory system
C	Asbestos (all forms)	Human	Mesothelium	Mesothelium
C	Asbestos (all forms)	Baboon	Mesothelium	Mesothelium
C	Asbestos (all forms)	Hamster	Mesothelium	Mesothelium
C	Asbestos (all forms)	Rat	Mesothelium	Mesothelium
C	Asbestos (all forms)	Human	Ovary	Female breast, female reproductive organs and reproductive tract
C	Beryllium and beryllium compounds	Human	Lung	Respiratory system
C	Beryllium and beryllium compounds	Rat	Lung	Respiratory system
C	Cadmium and cadmium compounds	Human	Lung	Respiratory system
C	Cadmium and cadmium compounds	Rat	Lung	Respiratory system
C	Cadmium and cadmium compounds	Rat	Soft connective tissue	Connective tissues
C	Chromium (VI) compounds	Rat	Oral cavity	Upper aerodigestive tract
C	Chromium (VI) compounds	Rat	Tongue	Upper aerodigestive tract
C	Chromium (VI) compounds	Human	Lung	Respiratory system
C	Chromium (VI) compounds	Rat	Lung	Respiratory system
C	Chromium (VI) compounds	Mouse	Intestine	Digestive tract
C	Chromium (VI) compounds	Mouse	Intestine	Digestive tract
C	Chromium (VI) compounds	Mouse	Intestine	Digestive tract
C	Chromium (VI) compounds	Mouse	Intestine	Digestive tract
C	Chromium (VI) compounds	Rat	Soft connective tissue	Connective tissues
C	Erionite	Human	Mesothelium	Mesothelium
C	Erionite	Rat	Mesothelium	Mesothelium
C	Nickel compounds	Human	Nasal cavity	Upper aerodigestive tract
C	Nickel compounds	Human	Lung	Respiratory system
C	Nickel compounds	Rat	Lung	Respiratory system

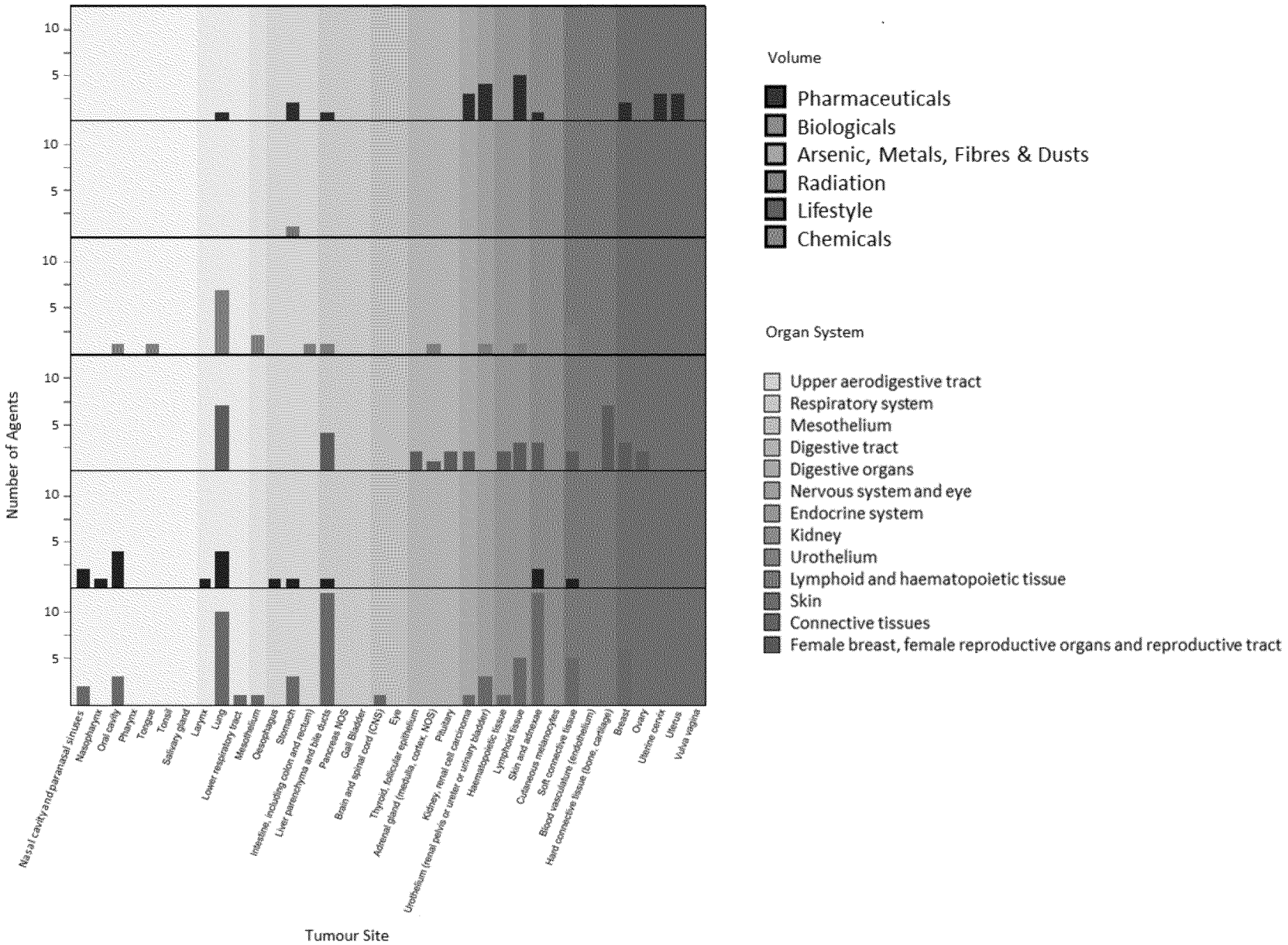
Supplemental Table 5. Group-1 Agents With at Least One Tumour Site Specified in Humans and in Animals (60 agents)				
Volume	Agent	Species	Tissue Site	Organ and Tissue System
C	Nickel compounds	Rat	Adrenal gland	Endocrine system
C	Nickel compounds	Hamster	Soft connective tissue	Connective tissues
C	Nickel compounds	Mouse	Soft connective tissue	Connective tissues
C	Nickel compounds	Rat	Soft connective tissue	Connective tissues
C	Silica dust, crystalline, in the form of quartz or cristobalite	Human	Lung	Respiratory system
C	Silica dust, crystalline, in the form of quartz or cristobalite	Rat	Lung	Respiratory system
C	Silica dust, crystalline, in the form of quartz or cristobalite	Rat	Lymphoid tissue	Lymphoid and haematopoietic tissues
D	Fission products including Sr-90	Human	Haematopoietic tissue	Lymphoid and haematopoietic tissues
D	Fission products including Sr-90	Dog	Hard connective tissue	Connective tissues
D	Fission products including Sr-90	Mouse	Hard connective tissue	Connective tissues
D	Fission products including Sr-90	Human	All solid cancers	Other groupings
D	Haematite mining with exposure to radon (underground)	Human	Lung	Respiratory system
D	Haematite mining with exposure to radon (underground)	Rat	Lung	Respiratory system
D	Pu-239	Dog	Lung	Respiratory system
D	Pu-239	Human	Lung	Respiratory system
D	Pu-239	Rat	Lung	Respiratory system
D	Pu-239	Dog	Liver	Digestive organs
D	Pu-239	Human	Liver	Digestive organs
D	Pu-239	Human	Hard connective tissue	Connective tissues
D	Pu-239	Dog	Hard connective tissue	Connective tissues
D	Pu-239	Mouse	Hard connective tissue	Connective tissues
D	Pu-239	Rat	Hard connective tissue	Connective tissues
D	Radioiodines, including I-131	Human	Thyroid	Endocrine system
D	Radioiodines, including I-131	Mouse	Thyroid	Endocrine system
D	Radioiodines, including I-131	Rat	Thyroid	Endocrine system
D	Ra-224 and its decay products	Human	Hard connective tissue	Connective tissues
D	Ra-224 and its decay products	Dog	Hard connective tissue	Connective tissues
D	Ra-224 and its decay products	Mouse	Hard connective tissue	Connective tissues
D	Ra-226 and its decay products	Human	Nasal cavity	Upper aerodigestive tract
D	Ra-226 and its decay products	Human	Hard connective tissue	Connective tissues
D	Ra-226 and its decay products	Human	Hard connective tissue	Connective tissues
D	Ra-226 and its decay products	Dog	Hard connective tissue	Connective tissues
D	Ra-226 and its decay products	Mouse	Hard connective tissue	Connective tissues
D	Ra-228 and its decay products	Human	Hard connective tissue	Connective tissues
D	Ra-228 and its decay products	Dog	Hard connective tissue	Connective tissues
D	Rn-222 and its decay products	Human	Lung	Respiratory system
D	Rn-222 and its decay products	Rat	Lung	Respiratory system
D	Solar radiation	Mouse	Skin and adnexae	Skin
D	Solar radiation	Rat	Skin and adnexae	Skin
D	Solar radiation	Human	Skin and adnexae	Skin
D	Solar radiation	Human	Cutaneous melanocytes	Skin
D	Th-232 (as Thorotrast)	Human	Liver	Digestive organs
D	Th-232 (as Thorotrast)	Hamster	Liver	Digestive organs
D	Th-232 (as Thorotrast)	Human	Liver	Digestive organs
D	Th-232 (as Thorotrast)	Rat	Liver	Digestive organs
D	Th-232 (as Thorotrast)	Human	Gall bladder	Digestive organs
D	Th-232 (as Thorotrast)	Human	Haematopoietic tissue	Lymphoid and haematopoietic tissues
D	UV-emitting tanning devices	Human	Eye	Nervous system and eye
D	UV-emitting tanning devices	Mouse	Skin and adnexae	Skin
D	UV-emitting tanning devices	Human	Cutaneous melanocytes	Skin
D	X- and Gamma radiation	Human	Salivary gland	Upper aerodigestive tract
D	X- and Gamma radiation	Human	Lung	Respiratory system
D	X- and Gamma radiation	Mouse	Lung	Respiratory system
D	X- and Gamma radiation	Human	Oesophagus	Digestive tract
D	X- and Gamma radiation	Human	Stomach	Digestive tract
D	X- and Gamma radiation	Human	Intestine	Digestive tract
D	X- and Gamma radiation	Mouse	Liver	Digestive organs
D	X- and Gamma radiation	Human	CNS	Nervous system and eye
D	X- and Gamma radiation	Human	Thyroid	Endocrine system
D	X- and Gamma radiation	Rat	Thyroid	Endocrine system
D	X- and Gamma radiation	Mouse	Pituitary	Endocrine system
D	X- and Gamma radiation	Human	Kidney	Kidney
D	X- and Gamma radiation	Monkey	Kidney	Kidney
D	X- and Gamma radiation	Human	Urothelium	Urothelium
D	X- and Gamma radiation	Mouse	Haematopoietic tissue	Lymphoid and haematopoietic tissues
D	X- and Gamma radiation	Human	Haematopoietic tissue	Lymphoid and haematopoietic tissues
D	X- and Gamma radiation	Mouse	Lymphoid tissue	Lymphoid and haematopoietic tissues
D	X- and Gamma radiation	Mouse	Lymphoid tissue	Lymphoid and haematopoietic tissues
D	X- and Gamma radiation	Human	Skin and adnexae	Skin
D	X- and Gamma radiation	Mouse	Soft connective tissue	Connective tissues
D	X- and Gamma radiation	Human	Hard connective tissue	Connective tissues
D	X- and Gamma radiation	Human	Breast	Female breast, female reproductive organs and reproductive tract
D	X- and Gamma radiation	Mouse	Breast	Female breast, female reproductive organs and reproductive tract
D	X- and Gamma radiation	Rat	Breast	Female breast, female reproductive organs and reproductive tract
D	X- and Gamma radiation	Mouse	Ovary	Female breast, female reproductive organs and reproductive tract
D	X- and Gamma radiation	Mouse	Exocrine glands NOS	Other groupings
E	Alcoholic beverages	Human	Oral cavity	Upper aerodigestive tract
E	Alcoholic beverages	Rat	Oral cavity	Upper aerodigestive tract
E	Alcoholic beverages	Human	Pharynx	Upper aerodigestive tract
E	Alcoholic beverages	Human	Larynx	Respiratory system
E	Alcoholic beverages	Human	Oesophagus	Digestive tract

Supplemental Table S. Group-1 Agents With at Least One Tumour Site Specified in Humans and in Animals (60 agents)				
Volume	Agent	Species	Tissue Site	Organ and Tissue System
E	Alcoholic beverages	Human	Intestine	Digestive tract
E	Alcoholic beverages	Human	Liver	Digestive organs
E	Alcoholic beverages	Human	Breast	Female breast, female reproductive organs and reproductive tract
E	Betel quid without tobacco	Human	Oral cavity	Upper aerodigestive tract
E	Betel quid without tobacco	Human	Oesophagus	Digestive tract
E	Betel quid without tobacco	Hamster	Stomach	Digestive tract
E	Coal, indoor emissions from household combusion of	Human	Lung	Respiratory system
E	Coal, indoor emissions from household combusion of	Mouse	Lung	Respiratory system
E	Coal, indoor emissions from household combusion of	Mouse	Skin and adnexae	Skin
E	Salted fish, chinese style	Rat	Nasal cavity	Upper aerodigestive tract
E	Salted fish, chinese style	Rat	Nasal cavity	Upper aerodigestive tract
E	Salted fish, chinese style	Rat	Nasopharynx	Upper aerodigestive tract
E	Salted fish, chinese style	Human	Nasopharynx	Upper aerodigestive tract
E	Second-hand tobacco smoke	Human	Lung	Respiratory system
E	Second-hand tobacco smoke	Mouse	Lung	Respiratory system
E	Tobacco smoking	Human	Nasal cavity	Upper aerodigestive tract
E	Tobacco smoking	Human	Nasal cavity	Upper aerodigestive tract
E	Tobacco smoking	Human	Nasopharynx	Upper aerodigestive tract
E	Tobacco smoking	Human	Oral cavity	Upper aerodigestive tract
E	Tobacco smoking	Human	Pharynx	Upper aerodigestive tract
E	Tobacco smoking	Human	Larynx	Respiratory system
E	Tobacco smoking	Human	Lung	Respiratory system
E	Tobacco smoking	Hamster	Larynx	Respiratory system
E	Tobacco smoking	Mouse	Lung	Respiratory system
E	Tobacco smoking	Rat	Lung	Respiratory system
E	Tobacco smoking	Human	Oesophagus	Digestive tract
E	Tobacco smoking	Human	Stomach	Digestive tract
E	Tobacco smoking	Human	Intestine	Digestive tract
E	Tobacco smoking	Human	Liver	Digestive organs
E	Tobacco smoking	Human	Liver	Digestive organs
E	Tobacco smoking	Human	Pancreas	Digestive organs
E	Tobacco smoking	Human	Kidney	Kidney
E	Tobacco smoking	Human	Urothelium	Urothelium
E	Tobacco smoking	Human	Urothelium	Urothelium
E	Tobacco smoking	Human	Haematopoietic tissue	Lymphoid and haematopoietic tissues
E	Tobacco smoking	Mouse	Skin and adnexae	Skin
E	Tobacco smoking	Human	Ovary	Female breast, female reproductive organs and reproductive tract
E	Tobacco smoking	Human	Cervix	Female breast, female reproductive organs and reproductive tract
E	Tobacco, smokeless	Rat	Oral cavity	Upper aerodigestive tract
E	Tobacco, smokeless	Human	Oral cavity	Upper aerodigestive tract
E	Tobacco, smokeless	Rat	Oral cavity	Upper aerodigestive tract
E	Tobacco, smokeless	Human	Oesophagus	Digestive tract
E	Tobacco, smokeless	Human	Pancreas	Digestive organs
F	Aflatoxins	Human	Liver	Digestive organs
F	Aflatoxins	Rat	Liver	Digestive organs
F	4-Aminobiphenyl	Mouse	Liver	Digestive organs
F	4-Aminobiphenyl	Dog	Urothelium	Urothelium
F	4-Aminobiphenyl	Human	Urothelium	Urothelium
F	4-Aminobiphenyl	Mouse	Soft connective tissue	Connective tissues
F	Benzene	Rat	Oral cavity	Upper aerodigestive tract
F	Benzene	Mouse	Lung	Respiratory system
F	Benzene	Rat	Stomach	Digestive tract
F	Benzene	Human	Haematopoietic tissue	Lymphoid and haematopoietic tissues
F	Benzene	Mouse	Haematopoietic tissue	Lymphoid and haematopoietic tissues
F	Benzene	Mouse	Lymphoid tissue	Lymphoid and haematopoietic tissues
F	Benzene	Mouse	Lymphoid tissue	Lymphoid and haematopoietic tissues
F	Benzene	Rat	Skin and adnexae	Skin
F	Benzene	Mouse	Breast	Female breast, female reproductive organs and reproductive tract
F	Benzene	Mouse	Exocrine glands NOS	Other groupings
F	Benzene	Mouse	Exocrine glands NOS	Other groupings
F	Benzene	Rat	Exocrine glands NOS	Other groupings
F	Benzidine	Mouse	Liver	Digestive organs
F	Benzidine	Human	Urothelium	Urothelium
F	Benzidine	Rat	Breast	Female breast, female reproductive organs and reproductive tract
F	Bis(chloromethyl)ether; chloromethyl methyl ether (technical-grade)	Rat	Nasal cavity	Upper aerodigestive tract
F	Bis(chloromethyl)ether; chloromethyl methyl ether (technical-grade)	Human	Lung	Respiratory system
F	Bis(chloromethyl)ether; chloromethyl methyl ether (technical-grade)	Mouse	Skin and adnexae	Skin
F	Bis(chloromethyl)ether; chloromethyl methyl ether (technical-grade)	Mouse	Soft connective tissue	Connective tissues
F	1,3-Butadiene	Mouse	Lung	Respiratory system
F	1,3-Butadiene	Mouse	Stomach	Digestive tract
F	1,3-Butadiene	Mouse	Liver	Digestive organs
F	1,3-Butadiene	Human	Haematopoietic tissue	Lymphoid and haematopoietic tissues
F	1,3-Butadiene	Mouse	Lymphoid tissue	Lymphoid and haematopoietic tissues
F	1,3-Butadiene	Mouse	Soft connective tissue	Connective tissues
F	1,3-Butadiene	Mouse	Breast	Female breast, female reproductive organs and reproductive tract
F	1,3-Butadiene	Mouse	Exocrine glands NOS	Other groupings
F	1,3-Butadiene	Mouse	Exocrine glands NOS	Other groupings
F	Coal gasification	Human	Lung	Respiratory system
F	Coal gasification	Mouse	Skin and adnexae	Skin
F	Coal-tar distillation	Human	Skin and adnexae	Skin
F	Coal-tar distillation	Mouse	Skin and adnexae	Skin

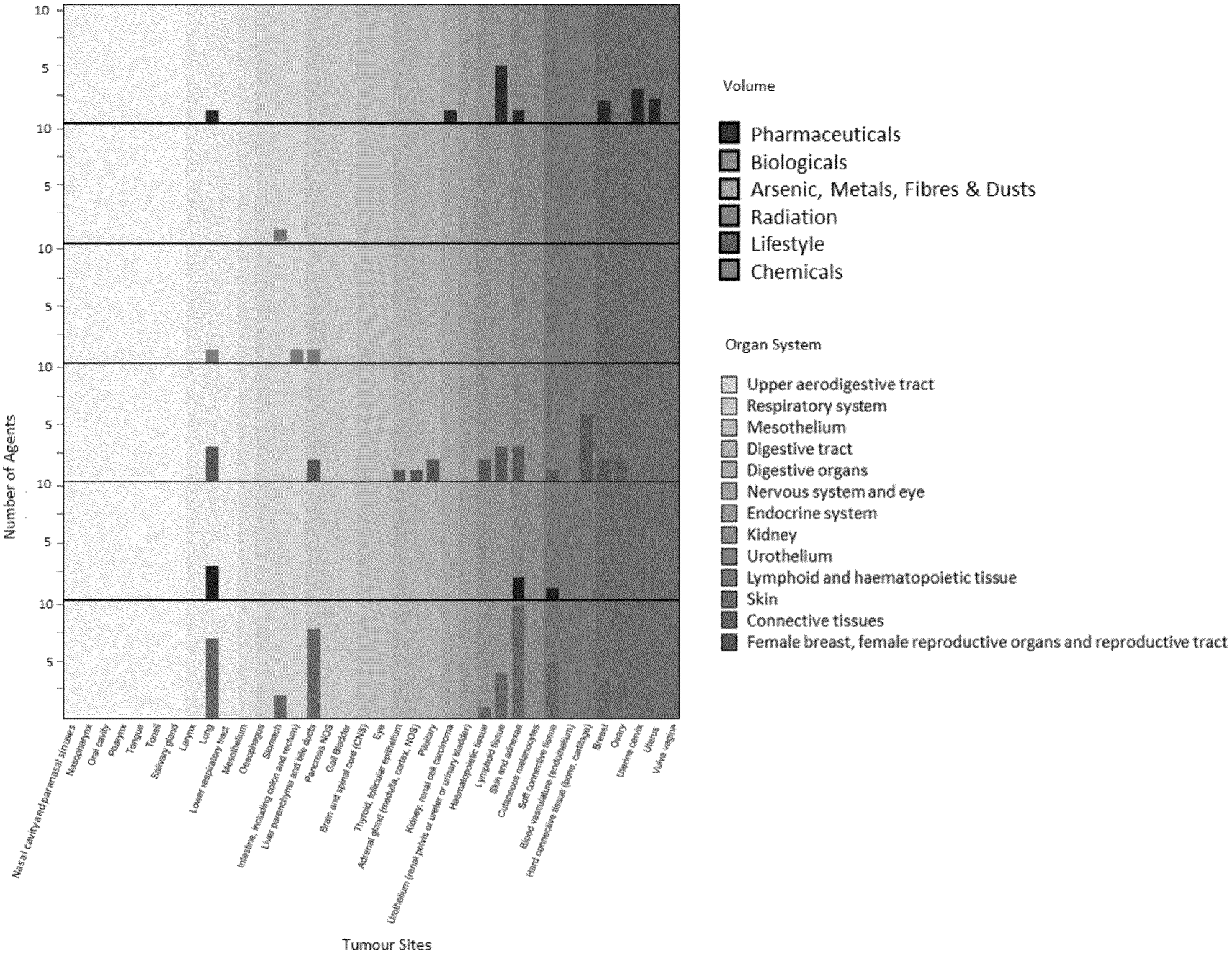
Supplemental Table 5. Group-1 Agents With at Least One Tumour Site Specified in Humans and in Animals (60 agents)				
Volume	Agent	Species	Tissue Site	Organ and Tissue System
F	Coal-tar pitch	Human	Lung	Respiratory system
F	Coal-tar pitch	Mouse	Skin and adnexae	Skin
F	Coke production	Human	Lung	Respiratory system
F	Coke production	Mouse	Lung	Respiratory system
F	Coke production	Rat	Lung	Respiratory system
F	Coke production	Mouse	Skin and adnexae	Skin
F	Formaldehyde	Rat	Nasal cavity	Upper aerodigestive tract
F	Formaldehyde	Human	Nasopharynx	Upper aerodigestive tract
F	Formaldehyde	Human	Haematopoietic tissue	Lymphoid and haematopoietic tissues
F	Mineral oils, untreated or mildly treated	Human	Skin and adnexae	Skin
F	Mineral oils, untreated or mildly treated	Mouse	Skin and adnexae	Skin
F	2-Naphthylamine	Mouse	Liver	Digestive organs
F	2-Naphthylamine	Dog	Urothelium	Urothelium
F	2-Naphthylamine	Hamster	Urothelium	Urothelium
F	2-Naphthylamine	Human	Urothelium	Urothelium
F	2-Naphthylamine	Monkey	Urothelium	Urothelium
F	2-Naphthylamine	Rat	Urothelium	Urothelium
F	ortho-Toluidine	Human	Urothelium	Urothelium
F	ortho-Toluidine	Rat	Urothelium	Urothelium
F	ortho-Toluidine	Rat	Skin and adnexae	Skin
F	ortho-Toluidine	Mouse	Soft connective tissue	Connective tissues
F	Shale oils	Human	Skin and adnexae	Skin
F	Shale oils	Mouse	Skin and adnexae	Skin
F	Soot (as found in occupational exposure of chimney sweeps)	Human	Lung	Respiratory system
F	Soot (as found in occupational exposure of chimney sweeps)	Human	Skin and adnexae	Skin
F	Soot (as found in occupational exposure of chimney sweeps)	Mouse	Skin and adnexae	Skin
F	2,3,7,8-Tetrachlorodibenzo-para-dioxin	Rat	Oral cavity	Upper aerodigestive tract
F	2,3,7,8-Tetrachlorodibenzo-para-dioxin	Rat	Lung	Respiratory system
F	2,3,7,8-Tetrachlorodibenzo-para-dioxin	Mouse	Liver	Digestive organs
F	2,3,7,8-Tetrachlorodibenzo-para-dioxin	Rat	Liver	Digestive organs
F	2,3,7,8-Tetrachlorodibenzo-para-dioxin	Mouse	Lymphoid tissue	Lymphoid and haematopoietic tissues
F	2,3,7,8-Tetrachlorodibenzo-para-dioxin	Mouse	Lymphoid tissue	Lymphoid and haematopoietic tissues
F	2,3,7,8-Tetrachlorodibenzo-para-dioxin	Mouse	Skin and adnexae	Skin
F	2,3,7,8-Tetrachlorodibenzo-para-dioxin	Human	All cancers combined	Other groupings
F	Vinyl chloride	Mouse	Lung	Respiratory system
F	Vinyl chloride	Human	Liver	Digestive organs
F	Vinyl chloride	Rat	Liver	Digestive organs
F	Vinyl chloride	Mouse	Soft connective tissue	Connective tissues
F	Vinyl chloride	Rat	Soft connective tissue	Connective tissues
F	Vinyl chloride	Human	Blood vasculature	Connective tissues
F	Vinyl chloride	Mouse	Breast	Female breast, female reproductive organs and reproductive tract
F	Vinyl chloride	Rat	Breast	Female breast, female reproductive organs and reproductive tract
F	Vinyl chloride	Rat	Exocrine glands NOS	Other groupings
F	Engine Exhaust, diesel	Human	Lung	Respiratory system
F	Engine Exhaust, diesel	Rat	Lung	Respiratory system
F	Trichloroethylene	Mouse	Lung	Respiratory system
F	Trichloroethylene	Mouse	Liver	Digestive organs
F	Trichloroethylene	Human	Kidney	Kidney
F	Trichloroethylene	Rat	Kidney	Kidney
F	Polychlorinated biphenyls	Rat	Oral cavity	Upper aerodigestive tract
F	Polychlorinated biphenyls	Rat	Liver	Digestive organs
F	Polychlorinated biphenyls	Human	Cutaneous melanocytes	Skin



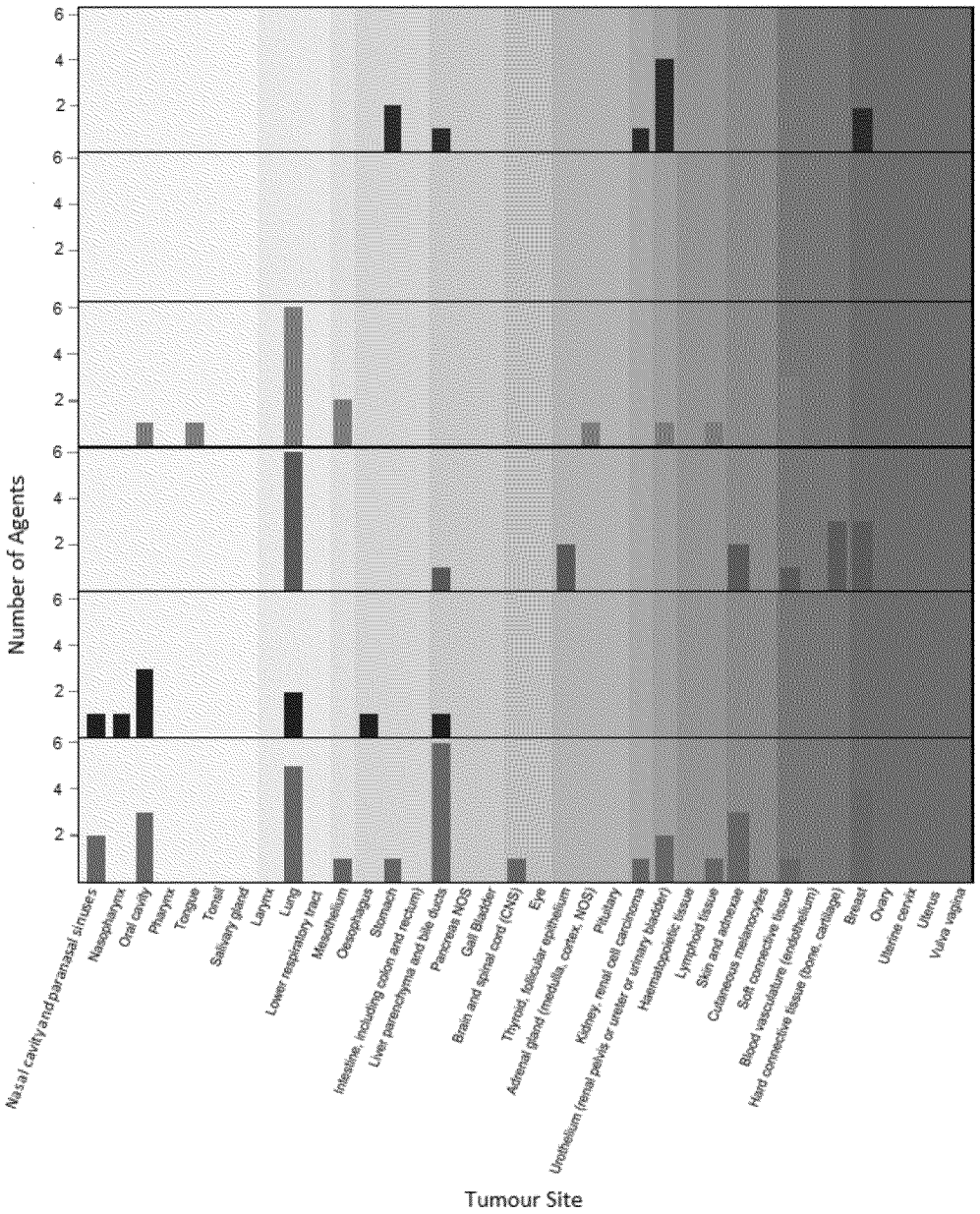
Supplemental Figure 1: Number of Agents Inducing Tumours in Humans in Each of 39 Tumour Sites by Type of Agent



Supplemental Figure 2: Number of Agents Inducing Tumours in Animals in Each of 39 Tumour Sites by Type of Agent



Supplemental Figure 3: Number of Agents Inducing Tumours in Mice in Each of 39 Tumour Sites by Type of Agent



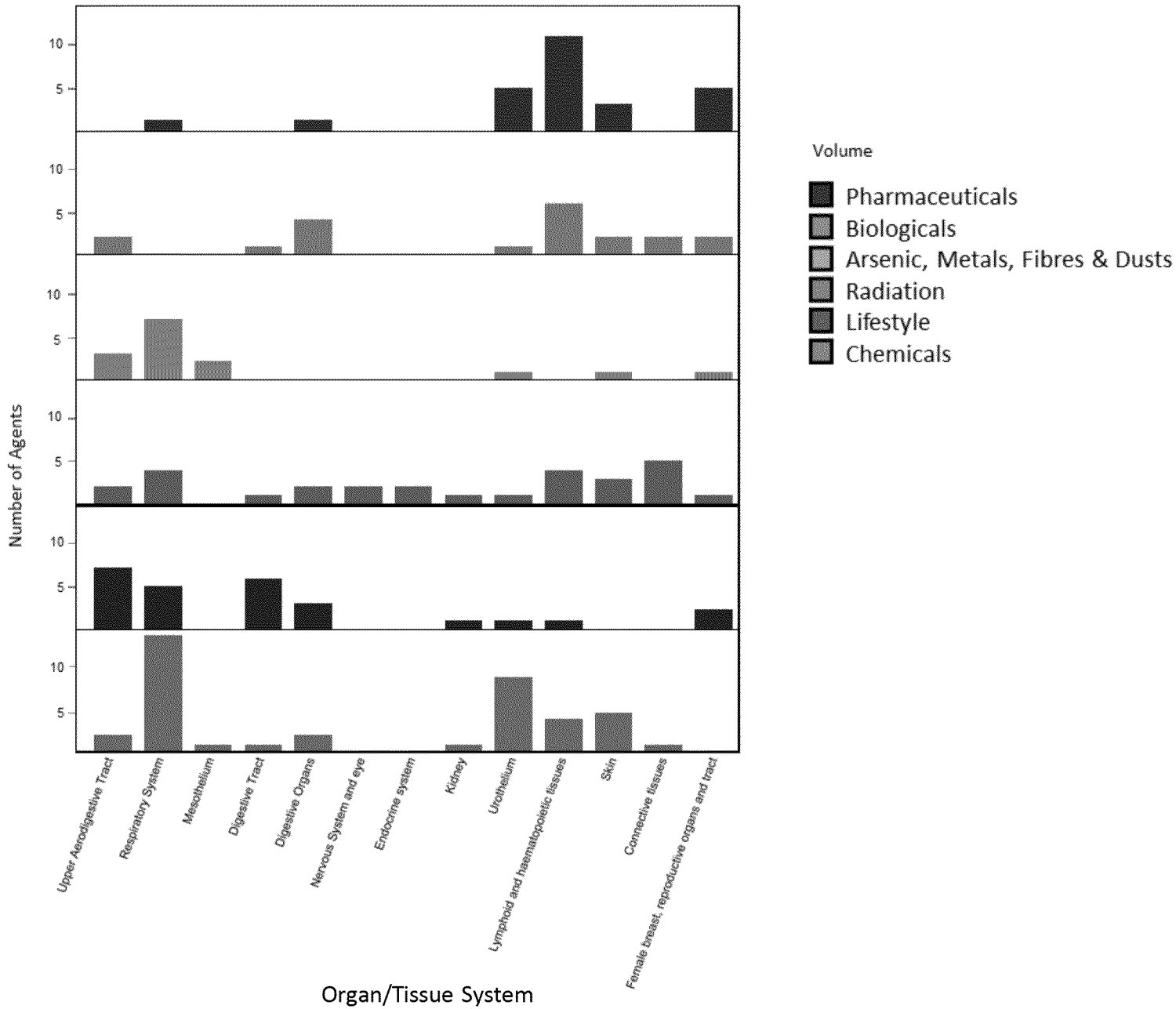
Volume

- Pharmaceuticals
- Biologicals
- Arsenic, Metals, Fibres & Dusts
- Radiation
- Lifestyle
- Chemicals

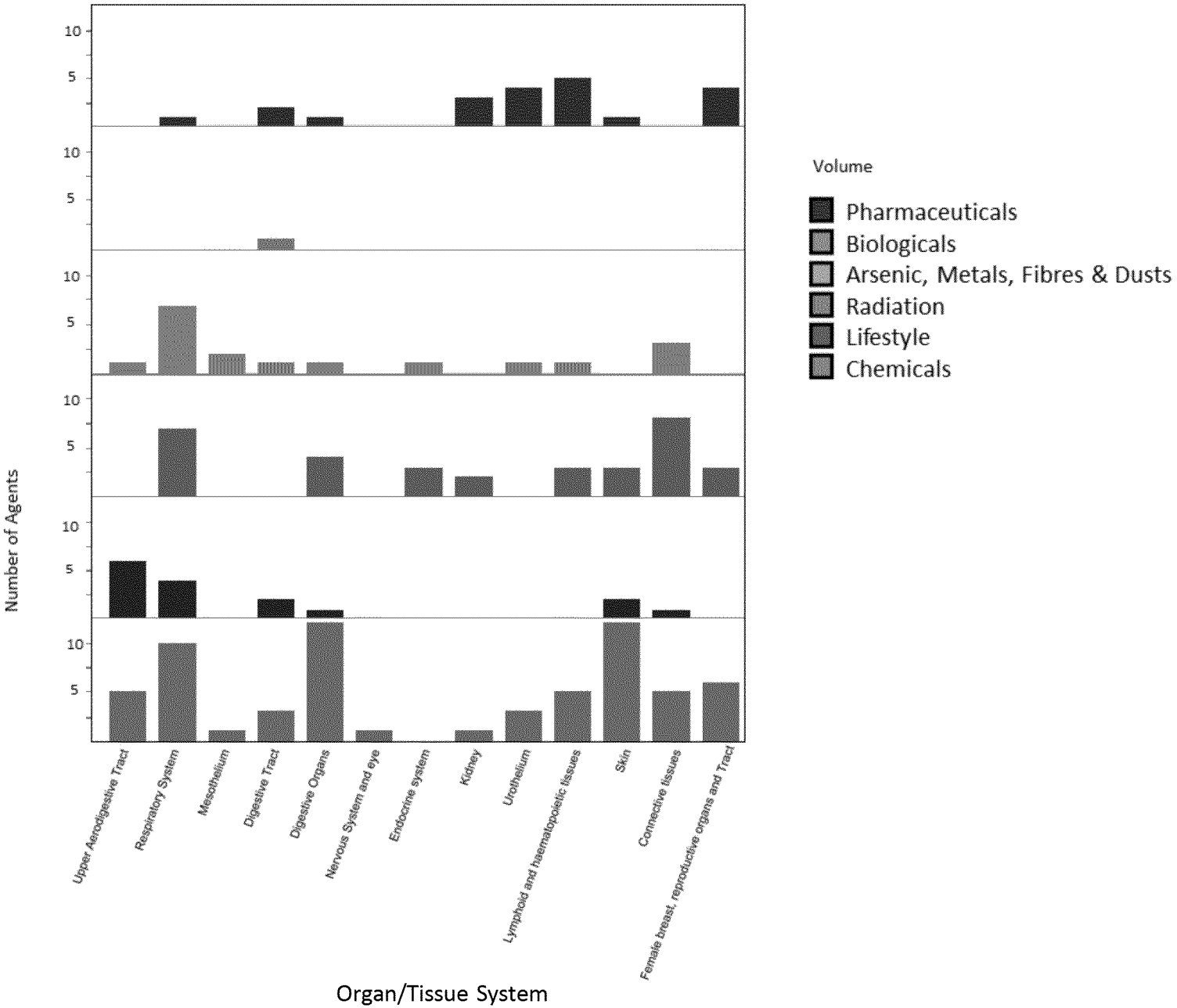
Organ System

- Upper aerodigestive tract
- Respiratory system
- Mesothelium
- Digestive tract
- Digestive organs
- Nervous system and eye
- Endocrine system
- Kidney
- Urothelium
- Lymphoid and haematopoietic tissue
- Skin
- Connective tissues
- Female breast, female reproductive organs and reproductive tract

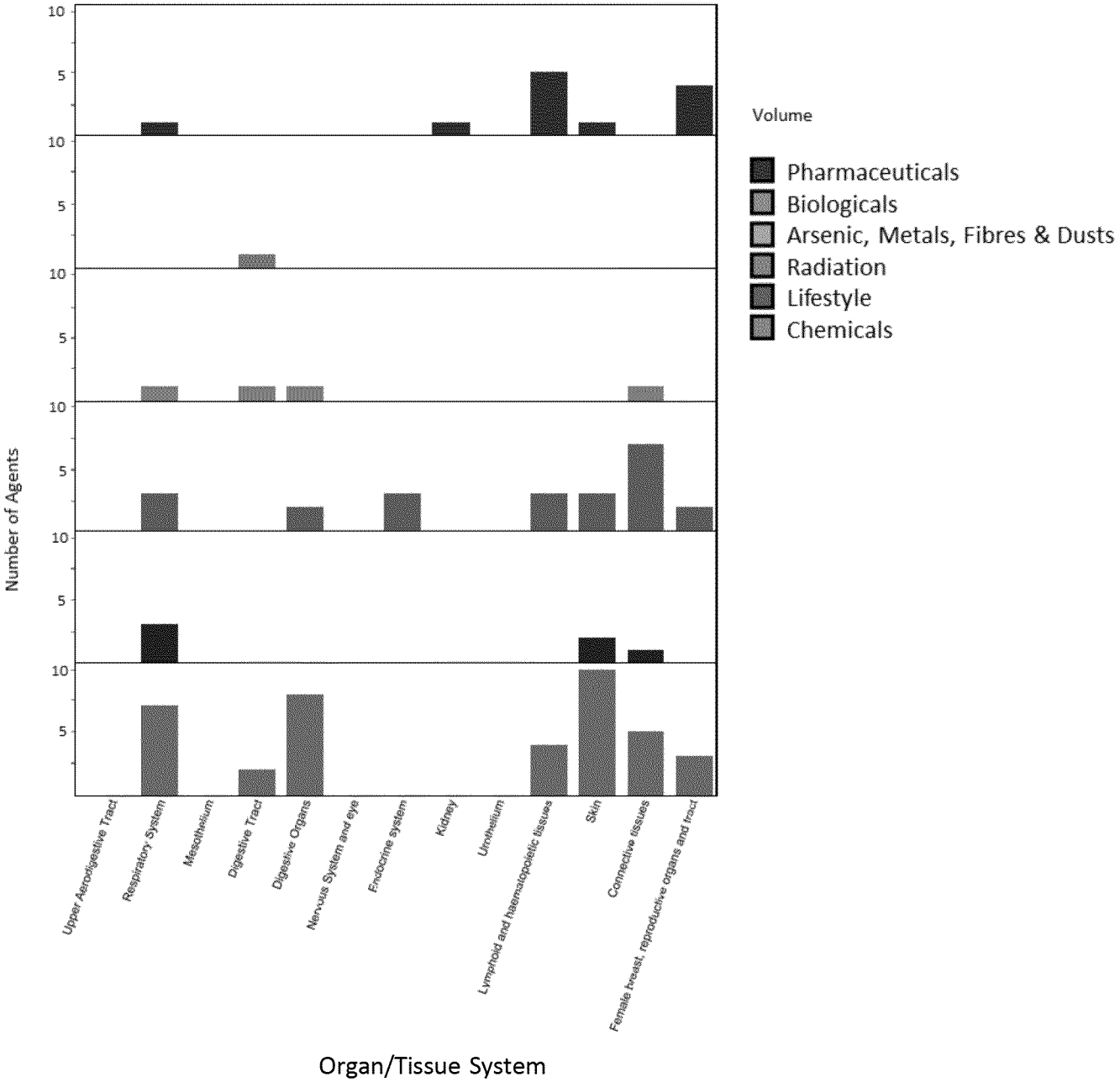
Supplemental Figure 4: Number of Agents Inducing Tumours in Rats in Each of 39 Tumour Sites by Type of Agent



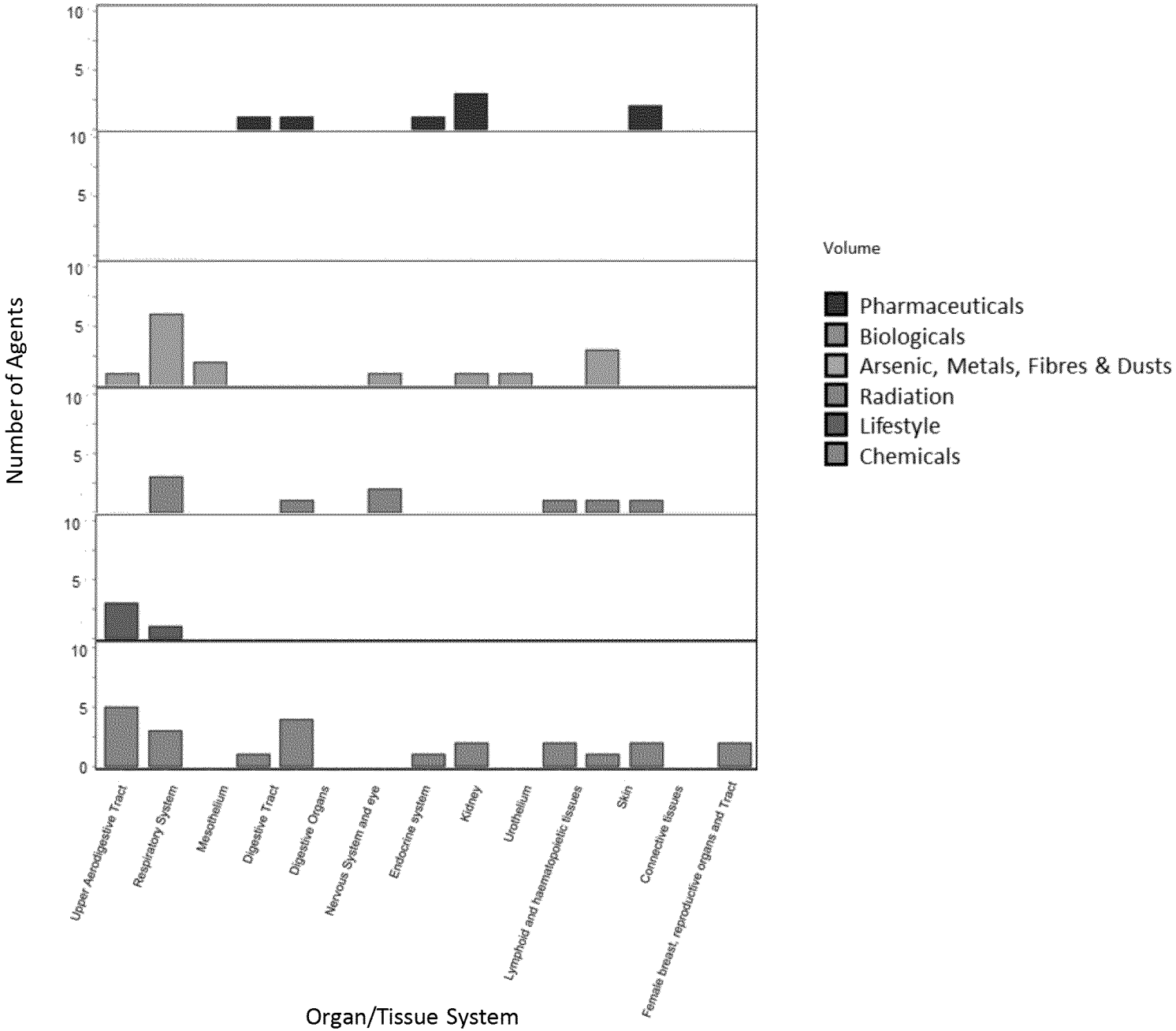
Supplemental Figure 5: Number of Agents Inducing Tumours in Humans in Each of 15 Organ/Tissue Systems by Type of Agent



Supplemental Figure 6: Number of Agents Inducing Tumours in Animals in Each of 15 Organ/Tissue Systems by Type of Agent



Supplemental Figure 7: Number of Agents Inducing Tumours in Mice in Each of 15 Organ/Tissue Systems by Type of Agent



Supplemental Figure 8: Number of Agents Inducing Tumours in Rats in Each of 15 Organ/Tissue Systems by Type of Agent

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

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

D. Krewski, J. M. Rice, M. Bird, B. Milton, B. Collins, P. Lajoie, M. Billard, Y. Grosse, R. Baan, V. Cogliano, K. Straif, J. Caldwell, I.I. Rusyn, C.J. Portier, R. Melnick, J. Little & J.M. Zielinski[1]

in collaboration with other participants in the IARC Workshop on
'Tumour-site Concordanceand Mechanisms of Carcinogenesis'
which convened in Lyon, April/November 2012[2]

Krewski et al. (2016) 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. (2016). Concordance analysis was based on the 60 agents with sufficient evidence of carcinogenicity both in humans and in animals, with at least one tumour site specified for humans and at least one tumour site specified for animals. For simplicity of presentation, analysis of concordance were based on the overlap between tumour sites expressed in animals and humans (Krewski et al., 2016, Table 7, Figure 9-10).

Concordance between animal and human tumour sites is based on the overlap between animal and human tumour sites, as shown in Supplemental Table 6 (all animals) and Supplemental Table 7 (mice and rats). Let N_h, N_a, and N_b denote the number of agents demonstrating a particular tumour site in humans, animals, or both humans and animals, respectively. The total number of agents demonstrating tumours at this site is then $N_t=N_h+N_a-N_b$. Concordance is measured by the percentage overlap, calculated as $(N_b/N_t)x100\%$. These results are shown in the column headed 'overlap' in Supplemental Tables 6 and 7. [The 'overlap' results in Supplemental Table 6 are the basis of the evaluation of concordance in Table 7 of Krewski et al. (2016)]

The workshop participants were also interested in the overlap between agents demonstrating tumours in animals at a particular site with agents demonstrating tumours in humans at that site, calculated as $(N_b/N_h)x100\%$. These results are shown in the column headed 'animal/human overlap' in Supplemental Tables 6 and 7, and reflect the percentage of agents demonstrating tumours at the site of interest in humans that have also been seen to cause tumours at that site in animals. [The 'animal/human overlap' results in Supplemental Table 6 are the basis of the analysis of overlap between animal and human tumours in Panel A of Figure 10 in Krewski et al. (2016).]

Conversely, the 'human/animal overlap' column in Supplementary Tables 6 and 7, calculated as $(N_b/N_a)x100\%$, reflects the percentage of agents demonstrating tumours at the site of interest in animals that have also been seen to cause tumours at that site in humans. [The 'human/animal overlap' results in

[1] Deceased.

[2] L. Banks, F.A. Beland, J.A. Bond, M.C. Bosland, J.R. Bucher, D.M. DeMarini, B. Fubini, B.D. Goldstein, S.S. Hecht, K. Hemminki, C.W. Jameson, A.B. Kane, R.J, Kavlock, P.F. Lambert, L. Stayner, B.W. Stewart, R.L. Ullrich, H. Vainio, P. Vineis, M.P. Waalkes, L. Zeise.

Supplemental Table 6 are the basis of the analysis of overlap between human and animal tumours in Panel B of Figure 10 in Krewski et al. (2016).]

More formal statistical analyses of concordance may be based on a comparison of animal and human tumours summarized in the form of the following 2x2 table.

	Humans		
Animals	Positive	Negative	Total
Positive	N_{11}	N_{12}	$N_{1.}$
Negative	N_{21}	N_{22}	$N_{2.}$
Total	$N_{.1}$	$N_{.1}$	N_t

Here, N_{11} denotes the number of agents for which the tumour site of interest was observed in both animals and humans, N_{22} denotes the number of agents for which the tumour site was seen in neither animals nor humans, N_{21} denotes the number of agents positive in humans and negative in animals, and N_{12} denotes the number of agents positive in animals and negative in humans. The total number of agents is given by $N_t = N_{11} + N_{22} + N_{12} + N_{21}$.

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

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

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

$$\kappa = (N_o-N_e)/(N_t-N_e),$$

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 $N_e = (N_{1.}N_{.1}/N_t) + (N_{2.}N_{.2}/N_t)$. 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). Since these two concordance measures are related by the formula

$$\kappa = (N_t\rho - N_e)/(N_t-N_e),$$

they provide equivalent information on concordance, albeit on a different scale of measurement.

Although the above statistical measures of concordance were considered by the workshop participants, the simpler measures of concordance in Supplemental Table 6 (all animals) and Supplemental Table 7 (mice and rats) were used as the basis for evaluating concordance between animal and human tumour sin the present analysis.

References

Gold,L.S., Bernstein,L., Magaw,R., & Slone,T.H. (1989) Interspecies extrapolation in carcinogenesis: prediction between rats and mice. *Environ.Health Perspect.*, **81**, 211-219.

Krewski, D., Rice, J.M., Bird, M., Milton, B., Collins, B., Lajoie, P, Billard, M., Grosse, Y., Baan, R., Cogliano, V., Straif, K., Caldwell, J., Rusyn, I.I., Portier, C.J., Melnick, R., Little, J. & Zielinski, J.M., in collaboration with other participants in the IARC Workshop on 'Tumour-site Concordance and Mechanisms of Carcinogenesis' which convened in Lyon, April/November 2012 (2016). Concordance between sites of tumour development in humans and in experimental animals for 111 agents that are carcinogenic to humans. [This volume.]

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

List of Tables

Supplemental Table 6. Concordance between Tumours seen in Humans and Animals for 60 Group-1 Agents by Organ and Tissue System/Tumour Site

Organ and Tissue System (Organ System No.)[1] *Tissue Site (Anatomical Site No.)* [1]	Humans	Animals[2]	Both	Overlap (%)[3]	Animal/Human Overlap (%)[4]	Human/Animal Overlap (%)[5]
Upper Aerodigestive Tract (1)	9	9	4	28.6	44.4	44.4
Nasal cavity and paranasal sinuses (1)	*3*	*3*	*0*	*0.0*	*0.0*	*0.0*
Nasopharynx (2)	*3*	*1*	*1*	*33.3*	*33.3*	*100.0*
Oral cavity (3)	*4*	*6*	*2*	*25.0*	*50.0*	*33.3*
Pharynx (4)	*2*	*0*	*0*	*N/A*	*N/A*	*N/A*
Tongue (5)	*0*	*1*	*0*	*N/A*	*N/A*	*N/A*
Salivary gland (7)	*1*	*0*	*0*	*N/A*	*N/A*	*N/A*
Respiratory System (2)	21	22	16	59.3	76.2	72.7
Larynx (9)	*3*	*1*	*1*	*33.3*	*33.3*	*100.0*
Lung (10)	*20*	*22*	*16*	*61.5*	*80.0*	*72.7*
Mesothelium (3)	2	2	2	100.0	100.0	100.0
Mesothelium (12)	*2*	*2*	*2*	*100.0*	*100.0*	*100.0*
Digestive Tract (4)	6	6	2	20.0	33.3	33.3
Oesophagus (14)	*5*	*0*	*0*	*N/A*	*N/A*	*N/A*
Stomach (15)	*3*	*5*	*1*	*14.3*	*33.3*	*20.0*
Intestine (including colon and rectum) (16)	*3*	*1*	*0*	*0.0*	*0.0*	*0.0*
Digestive Organs (5)	8	14	4	22.2	50.0	28.6
Liver parenchyma and bile ducts (17)	*7*	*14*	*4*	*23.5*	*57.1*	*28.6*
Pancreas NOS (18)	*2*	*0*	*0*	*N/A*	*N/A*	*N/A*
Gall bladder (19)	*1*	*0*	*0*	*N/A*	*N/A*	*N/A*
Nervous System and Eye (6)	2	0	0	N/A	N/A	N/A
Brain and spinal cord (CNS) (20)	*1*	*0*	*0*	*N/A*	*N/A*	*N/A*
Eye (22)	*1*	*0*	*0*	*N/A*	*N/A*	*N/A*
Endocrine System (7)	2	3	2	66.7	100.0	66.7
Thyroid, follicular epithelium (23)	*2*	*2*	*2*	*100.0*	*100.0*	*100.0*
Adrenal gland (medulla, cortex, NOS) (24)	*0*	*1*	*0*	*N/A*	*N/A*	*N/A*
Pituitary (25)	*0*	*1*	*0*	*N/A*	*N/A*	*N/A*
Kidney (8)	3	5	2	33.3	66.7	40.0
Kidney (renal cortex, renal medulla, kidney NOS) (26)	*3*	*5*	*2*	*33.3*	*66.7*	*40.0*
Urothelium (9)	10	7	7	70.0	70.0	100.0
Urothelium (renal pelvis or ureter or urinary bladder) (27)	*10*	*7*	*7*	*70.0*	*70.0*	*100.0*
Lymphoid and Haematopoietic Tissues (10)	12	10	7	46.7	58.3	70.0
Haematopoietic tissue (28)	*10*	*2*	*2*	*20.0*	*20.0*	*100.0*
Lymphoid tissue (29)	*2*	*10*	*1*	*9.1*	*50.0*	*10.0*
Skin (11)	11	16	7	35.0	63.6	43.8
Skin and adnexae (30)	*9*	*16*	*6*	*31.6*	*66.7*	*37.5*
Cutaneous melanocytes (31)	*3*	*0*	*0*	*N/A*	*N/A*	*N/A*
Connective Tissues (12)	6	14	6	42.9	100.0	42.9
Soft connective tissue (32)	*0*	*9*	*0*	*N/A*	*N/A*	*N/A*
Blood vasculature (endothelium) (33)	*1*	*0*	*0*	*N/A*	*N/A*	*N/A*
Hard connective tissue (bone, cartilage) (34)	*5*	*5*	*4*	*66.7*	*80.0*	*80.0*
Female Breast, Female Reproductive Organs and Reproductive Tract (13)	8	9	4	30.8	50.0	44.4
Breast (35)	*4*	*7*	*1*	*10.0*	*25.0*	*14.3*
Ovary (36)	*3*	*1*	*0*	*0.0*	*0.0*	*0.0*
Uterine cervix (37)	*3*	*3*	*2*	*50.0*	*66.7*	*66.7*
Uterus (38)	*2*	*3*	*1*	*25.0*	*50.0*	*33.3*
Vulva/vagina (39)	*1*	*0*	*0*	*N/A*	*N/A*	*N/A*
Other Groupings (15)	2	4	0	0.0	0.0	0.0
All cancers combined (43)	*1*	*0*	*0*	*N/A*	*N/A*	*N/A*
All solid cancers (44)	*1*	*0*	*0*	*N/A*	*N/A*	*N/A*
Exocrine glands NOS (47)	*0*	*4*	*0*	*N/A*	*N/A*	*N/A*

[1] Systems/sites in the anatomcially based tumour nomenclature system (see Supplemental Tables 1 and 4) lacking sufficient evidence in both humans and animals not shown. (For example, there was insufficient evidence of tumours of the male reportuctive tract in both humans and animals.)

[2] 'Animals' includes mice, rats, monkeys, dogs, and hamsters

[3] Percentage overlap calculated as $(N_b/(N_h+N_a-N_b))x100\%$, where N_h, N_a, and N_b denote the number of agents with sufficient evidence in humans, animals, or both humans and animals, respectively.

[4] Percentage overlap calculated as $(N_b/N_h)x100\%$.

[5] Percentage overlap calculated as $(N_b/N_a)x100\%$.

N/A: Calculation of overlap not possible when no agents demonstrate the tumour site of interest in either humans or animals (or both).

Supplemental Table 7. Concordance between Tumours seen in Humans and Rodents for 60 Group-1 Agents by Organ and Tissue System/Tumour Site

Organ and Tissue System (Organ System No.)[1] *Tissue Site (Anatomical Site No.)*[1]	Humans	Rodents[2]	Both	Overlap (%)[3]	Animal/Human Overlap (%)[4]	Human/Animal Overlap (%)[5]
Nasal cavity and paranasal sinuses (1)	*3*	*3*	*0*	*0.0*	*0.0*	*0.0*
Nasopharynx (2)	*3*	*1*	*1*	*33.3*	*33.3*	*100.0*
Oral cavity (3)	*4*	*6*	*2*	*25.0*	*50.0*	*33.3*
Pharynx (4)	*2*	*0*	*0*	*N/A*	*N/A*	*N/A*
Tongue (5)	*0*	*1*	*0*	*N/A*	*N/A*	*N/A*
Salivary gland (7)	*1*	*0*	*0*	*N/A*	*N/A*	*N/A*
Respiratory System (2)	21	22	16	59.3	76.2	72.7
Larynx (9)	*3*	*0*	*0*	*0.0*	*0.0*	*N/A*
Lung (10)	*20*	*22*	*16*	*61.5*	*80.0*	*72.7*
Mesothelium (3)	2	2	2	100.0	100.0	100.0
Mesothelium (12)	*2*	*2*	*2*	*100.0*	*100.0*	*100.0*
Digestive Tract (4)	6	5	1	10.0	16.7	20.0
Oesophagus (14)	*5*	*0*	*0*	*N/A*	*N/A*	*N/A*
Stomach (15)	*3*	*4*	*1*	*16.7*	*33.3*	*25.0*
Intestine (including colon and rectum) (16)	*3*	*1*	*0*	*0.0*	*0.0*	*0.0*
Digestive Organs (5)	8	13	3	16.7	37.5	23.1
Liver parenchyma and bile ducts (17)	*7*	*13*	*3*	*17.6*	*42.9*	*23.1*
Pancreas NOS (18)	*2*	*0*	*0*	*N/A*	*N/A*	*N/A*
Gall bladder (19)	*1*	*0*	*0*	*N/A*	*N/A*	*N/A*
Nervous System and Eye (6)	2	0	0	N/A	*N/A*	*N/A*
Brain and spinal cord (CNS) (20)	*1*	*0*	*0*	*N/A*	*N/A*	*N/A*
Eye (22)	*1*	*0*	*0*	*N/A*	*N/A*	*N/A*
Endocrine System (7)	2	3	2	66.7	100.0	66.7
Thyroid, follicular epithelium (23)	*2*	*2*	*2*	*100.0*	*100.0*	*100.0*
Adrenal gland (medulla, cortex, NOS) (24)	*0*	*1*	*0*	*N/A*	*N/A*	*N/A*
Pituitary (25)	*0*	*1*	*0*	*N/A*	*N/A*	*N/A*
Kidney (8)	3	2	1	25.0	33.3	50.0
Kidney (renal cortex, renal medulla, kidney NOS) (26)	*3*	*2*	*1*	*25.0*	*33.3*	*50.0*
Urothelium (9)	10	6	6	60.0	60.0	100.0
Urothelium (renal pelvis or ureter or urinary bladder) (27)	*10*	*6*	*6*	*60.0*	*60.0*	*100.0*
Lymphoid and Haematopoietic Tissues (10)	12	10	7	46.7	58.3	70.0
Haematopoietic tissue (28)	*10*	*2*	*2*	*20.0*	*20.0*	*100.0*
Lymphoid tissue (29)	*2*	*10*	*1*	*9.1*	*50.0*	*10.0*
Skin (11)	11	16	7	35.0	63.6	43.8
Skin and adnexae (30)	*9*	*16*	*6*	*31.6*	*66.7*	*37.5*
Cutaneous melanocytes (31)	*3*	*0*	*0*	*N/A*	*N/A*	*N/A*
Connective Tissues (12)	6	13	5	35.7	83.3	38.5
Soft connective tissue (32)	*0*	*9*	*0*	*N/A*	*N/A*	*N/A*
Blood vasculature (endothelium) (33)	*1*	*0*	*0*	*N/A*	*N/A*	*N/A*
Hard connective tissue (bone, cartilage) (34)	*5*	*4*	*3*	*50.0*	*60.0*	*75.0*
Female Breast, Female Reproductive Organs and Reproductive Tract (13)	8	9	4	30.8	50.0	44.4
Breast (35)	*4*	*8*	*2*	*20.0*	*50.0*	*25.0*
Ovary (36)	*3*	*1*	*0*	*0.0*	*0.0*	*0.0*
Uterine cervix (37)	*3*	*2*	*1*	*25.0*	*33.3*	*50.0*
Uterus (38)	*2*	*2*	*1*	*33.3*	*50.0*	*50.0*
Vulva/vagina (39)	*1*	*0*	*0*	*N/A*	*N/A*	*N/A*
Other Groupings (15)	2	4	0	0.0	0.0	0.0
All cancers combined (43)	*1*	*0*	*0*	*N/A*	*N/A*	*N/A*
All solid cancers (44)	*1*	*0*	*0*	*N/A*	*N/A*	*N/A*
Exocrine glands NOS (47)	*0*	*0*	*0*	*N/A*	*N/A*	*N/A*

[1] Systems/sites in the anatomcially based tumour nomenclature system (see Supplemental Tables 1 and 4) lacking sufficient evidence in both humans and animals not shown. (For example, there was insufficient evidence of tumours of the male reportuctive tract in both humans and animals.)

[2] 'Rodents' includes mice and rats.

[3] Percentage overlap calculated as $(N_b/(N_h+N_a-N_b))x100\%$, where N_h, N_a, and N_b denote the number of agents with sufficient evidence in humans, animals, or both humans and animals, respectively.

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To: dkrewski@uottawa.ca[dkrewski@uottawa.ca]
From: Ron Melnick
Sent: Thur 7/14/2016 5:09:58 AM
Subject: Re: Final Draft of Concordance Analysis Chapter

Dan,
If you think my comments and suggestions on previous drafts had a significant impact on the final version of the concordance chapter, then I would be happy to be listed as a co-author.

Best regards,
Ron

On Jul 13, 2016, at 5:48 PM, Daniel Krewski <dkrewski@uottawa.ca> wrote:

> Robert, attached is a slightly revised version of the concordance chapter, incorporating the final list of authors and collaborators that we agreed upon today here in Lyon. I've also changed 'Working Group' to 'Workshop Participants' where appropriate to reflect the final IARC designation of this expert group.
>
> I would like to thank both you and Bernard for the thorough editorial review that you conducted on the draft that I submitted on June 30.
>
> Ron, we would like to invite you to be a co-author on this chapter based on the valuable input that you provided during course of the concordance subgroup teleconferences calls earlier this year. Jane Caldwell, who designed and wrote up Tables 7 and 8, and Ivan Rusyn, who designed Figures 9 and 10, have already agreed to be co-authors on this paper, based on their input over the last few months. Your most recent suggestions are embodied in Figure 10 in the main paper and in Supplemental Tables 6 and 7 – please let us know if you are agreeable to being listed as a co-author, rather than in the list of other workshop participants in the footnote at the bottom of the title page.
>
> Ron, Robert is preparing a final set of materials on concordance and mechanisms for distribution to all workshop participants shortly after we hear from you.

Robert, I'll send you Word, Excel and PowerPoint files with all of the documents used in the preparation of the attached pdf file for use by the IARC editor in charge of this important Scientific Publication.

Please let me know if there is any additional information that I may provide.

With best regards.

Daniel Krewski, PhD, MHA

NSERC 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

Tel: 613-562-5381/Fax: 613-562-5380

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Administrative Assistant: Nicole Begnoche

Tel: 613-562-5381

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Project Coordinator: Shalu Darshan, PhD

Tel: 613-562-5800 X1949

Email: sdarshan@uottawa.ca

<2016 Krewski et al Concordance Analysis July 13 with Supplemental Material.pdf>

To: Bernard Stewart[Bernard.Stewart@health.nsw.gov.au]; Kurt Straif[StraifK@iarc.fr]; Robert Baan[BaanR@visitors.iarc.fr]; Vincent Cogliano[cogliano.vincent@gmail.com]
Cc: Cogliano, Vincent[cogliano.vincent@epa.gov]
From: Daniel Krewski
Sent: Tue 7/12/2016 2:45:44 PM
Subject: RE: Consensus statement Vol100WS

Robert, we should consider how best to identify the WG/WPs in the concordance and mechanisms chapters, as they are included as 'corporate' authors as noted below [on behalf of . . .].

The WG/WPs might be listed in the acknowledgements section by name, or as a footnote on the first page – you may have other ideas that we could talk about tomorrow . . . I do think that as these chapters include the 'on behalf of' authors, they should be listed by name somewhere [as a minimum, in the front material for the Scientific Publication] . . .

Dan K.

From: Daniel Krewski
Sent: July-12-16 4:58 AM
To: Bernard Stewart <Bernard.Stewart@health.nsw.gov.au>; Kurt Straif <StraifK@iarc.fr>; Robert Baan <BaanR@visitors.iarc.fr>; Vincent Cogliano <cogliano.vincent@gmail.com>
Cc: Vincent Cogliano <cogliano.vincent@epa.gov>
Subject: RE: Consensus statement Vol100WS

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'[on behalf of] participants in the IARC Workshop on 'Tumour-site Concordance and Mechanisms of Carcinogenesis', which convened in Lyon, April/November 2012'?

Given all of the (productive) interaction among the individuals involved in the two workshops in 2012 that occurred between then and now, this group might be seen more as a 'Working Group' rather than 'Workshop Participants'.

Food for thought . . .

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Sent: July-12-16 12:31 AM
To: Kurt Straif <StraifK@iarc.fr>; Robert Baan <BaanR@visitors.iarc.fr>; Vincent Cogliano <cogliano.vincent@gmail.com>
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Beyond those considerations, I was not seeking to reflect on the authority or character of the present Group. So, no problem with leaving terminology as proposed.

Regards

Bernard.

From: Kurt Straif [mailto:StraifK@iarc.fr]
Sent: Tuesday, 12 July 2016 2:23 AM
To: Robert Baan <BaanR@visitors.iarc.fr>; Bernard Stewart <Bernard.Stewart@health.nsw.gov.au>; Vincent Cogliano <cogliano.vincent@gmail.com>
Cc: Vincent Cogliano <cogliano.vincent@epa.gov>; Daniel Krewski <dkrewski@uottawa.ca>
Subject: RE: Consensus statement Vol100WS

Dear all,

I am not in favour of post-hoc calling this an AG, I support Roberts approach,

Kurt

From: Robert Baan
Sent: 11 July 2016 15:43
To: Bernard Stewart <Bernard.Stewart@health.nsw.gov.au>; Vincent Cogliano <cogliano.vincent@gmail.com>; Kurt Straif <StraifK@iarc.fr>
Cc: Vincent Cogliano <cogliano.vincent@epa.gov>; Daniel Krewski <dkrewski@uottawa.ca>
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I was not sure about the term 'Advisory Group' in this context. Initially, the participants in the two Vol100+ Workshops were not formally considered an Advisory Group, but we can of course adopt this name now.

I myself have been using the term 'Workshop participants'. Please advice.

I also drafted some text by way of Introduction to the consensus document.

I value comments,

Robert

From: Bernard Stewart <Bernard.Stewart@health.nsw.gov.au>
Sent: Monday, July 11, 2016 10:32 AM

To: Vincent Cogliano; Kurt Straif; Robert Baan
Cc: Vincent Cogliano
Subject: RE: Consensus statement Vol100WS

Greetings to all from 'down under' with Sydney gripped by winter; at 6am it was 7°C.

I take this opportunity to join others and offer my own congratulations to you, Vincent, in creating a meaningful statement.

It seemed prudent to delay my own input till other matters had been addressed. In the attached, I adopted all previous track changes in order to have a manageable text into which I have inserted a few suggestions. Obviously adopt, modify or discard as thought best.

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And Portugal did it in extra time.

Warmest regards

Bernard.

From: Vincent Cogliano [mailto:cogliano.vincent@gmail.com]
Sent: Sunday, 10 July 2016 6:35 AM
To: Kurt Straif <StraifK@iarc.fr>; BaanR@visitors.iarc.fr; Bernard Stewart <Bernard.Stewart@health.nsw.gov.au>
Cc: Vincent Cogliano <cogliano.vincent@epa.gov>
Subject: Re: Consensus statement Vol100WS

Hello everyone--I agree with Robert's plan. Yes/No, then Go! Attached are some more edits based on the additional comments sent last week by Kurt. I'm OK with all comments and changes, so you can convert the attached redline to a clean copy, then send to the Working Group. It might be best for it to come from Robert. He'll get better compliance than if it came from anyone else.

ALLEZ LES BLEUS !!!

Vincent

Begin forwarded message:

From: Kurt Straif <StraifK@iarc.fr>
Date: July 8, 2016 at 10:15:10 EDT
To: Robert Baan <BaanR@visitors.iarc.fr>, "Cogliano, Vincent" <cogliano.vincent@epa.gov>
Cc: Bernard Stewart <Bernard.Stewart@SESIAHS.HEALTH.NSW.GOV.AU>
Subject: RE: Consensus statement Vol100WS

Fine with me,

Kurt

PS As always, I'm for the underdogs, Portugal!

From: Robert Baan
Sent: 08 July 2016 16:06
To: Kurt Straif <StraifK@iarc.fr>; Cogliano, Vincent <cogliano.vincent@epa.gov>
Cc: Bernard Stewart <Bernard.Stewart@SESIAHS.HEALTH.NSW.GOV.AU>
Subject: Consensus statement Vol100WS

Dear Kurt, Bernard, Vincent,

Dan Krewski has kept the 30-June deadline for submitting the final version of his

chapters.

I will do my best to send the Concordance and Mechanistic Analyses, Yann's Concordance Data Set, and the Consensus Statement to all the participants this weekend, asking their approval. As we cannot engage in lengthy discussions about comments from 30+ participants, I propose that we ask for a Yes/No answer.

May I assume that you generally agree with this plan.

Bon weekend!

Robert

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(there is a chance that France will win the European Soccer Championship this coming Sunday!)

From: Kurt Straif
Sent: Wednesday, July 6, 2016 10:04 AM
To: Cogliano, Vincent
Cc: Bernard Stewart; Robert Baan
Subject: RE: Consensus statement Vol100WS

Dear Vincent,

Thank you for swift turn-around of the revised summary conclusions.

Please see some additional edits and comments – I think we are zeroing in on a clean draft to be shared with the v100+ WG.

Perhaps this should best come from Robert?

Kurt

From: Cogliano, Vincent [mailto:cogliano.vincent@epa.gov]
Sent: 05 July 2016 15:49
To: Robert Baan <BaanR@visitors.iarc.fr>
Cc: Kurt Straif <StraifK@iarc.fr>; Bernard Stewart <Bernard.Stewart@SESIAHS.HEALTH.NSW.GOV.AU>; dkrewski@uottawa.ca
Subject: RE: Consensus statement Vol100WS

Dear Robert et al—Attached is a revised set of possible consensus statements. Several have been revised, and there are three new statements.

I stayed away from factual descriptive statements that are covered well in Dan's papers (for example, lung cancer is the most common site and genotoxicity by far the most common key characteristic). Dan's papers cover these points well, and it saves the consensus statement for overarching principles and insights from the Advisory Group.

There are also responses to Kurt's queries in comments on his comments.

Thanks again, everyone, and I hope we can wrap this up soon in a couple of calls.

Vincent

From: Robert Baan [mailto:BaanR@visitors.iarc.fr]
Sent: Thursday, June 23, 2016 10:00 AM
To: Cogliano, Vincent <cogliano.vincent@epa.gov>; Cogliano, Vincent <cogliano.vincent@epa.gov>
Cc: Kurt Straif <StraifK@iarc.fr>; Bernard Stewart <Bernard.Stewart@SESIAHS.HEALTH.NSW.GOV.AU>; dkrewski@uottawa.ca
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Dear Vincent,

Some time ago you made a start drafting a 'consensus statement' that summarized the main points on which general agreement among the Workshop participants (Vol100WS) could be reasonably expected. An earlier email message of yours, and

a first-draft statement with Kurt's annotations, are attached. Also attached are the two key papers from Dan Krewski and his team on the analysis of the 'concordance' and 'mechanisms' data sets. The outcome of these analyses should be mentioned/summarized in the consensus document. May I ask you to prepare a second draft of the consensus statement on the basis of this material.

We received just recently the two chapters attached, and they are being edited right now. As soon as possible we will send these documents to the Workshop participants for their final approval. It would be nice to send your consensus document at the same time.

I hope you can give this priority on your 'to-do' list.

Best wishes,

Robert

This message is intended for the addressee named and may contain confidential information. If you are not the intended recipient, please delete it and notify the sender.

Views expressed in this message are those of the individual sender, and are not necessarily the views of NSW Health or any of its entities.

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Cc: Cogliano, Vincent[cogliano.vincent@epa.gov]
From: Daniel Krewski
Sent: Tue 7/12/2016 8:58:43 AM
Subject: RE: Consensus statement Vol100WS
2016 Krewski et al Concordance Analysis July 12 with Supplemental Material.pdf

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Thank you for swift turn-around of the revised summary conclusions.

Please see some additional edits and comments – I think we are zeroing in on a clean draft to be shared with the v100+ WG.

Perhaps this should best come from Robert?

Kurt

From: Cogliano, Vincent [mailto:cogliano.vincent@epa.gov]
Sent: 05 July 2016 15:49
To: Robert Baan <BaanR@visitors.iarc.fr>
Cc: Kurt Straif <StraifK@iarc.fr>; Bernard Stewart <Bernard.Stewart@SESIAHS.HEALTH.NSW.GOV.AU>; dkrewski@uottawa.ca
Subject: RE: Consensus statement Vol100WS

Dear Robert et al—Attached is a revised set of possible consensus statements. Several have been revised, and there are three new statements.

I stayed away from factual descriptive statements that are covered well in Dan's papers (for example, lung cancer is the most common site and genotoxicity by far the most common key characteristic). Dan's papers cover these points well, and it saves the consensus statement for overarching principles and insights from the Advisory Group.

There are also responses to Kurt's queries in comments on his comments.

Thanks again, everyone, and I hope we can wrap this up soon in a couple of calls.

Vincent

From: Robert Baan [mailto:BaanR@visitors.iarc.fr]
Sent: Thursday, June 23, 2016 10:00 AM
To: Cogliano, Vincent <cogliano.vincent@epa.gov>; Cogliano, Vincent <cogliano.vincent@epa.gov>
Cc: Kurt Straif <StraifK@iarc.fr>; Bernard Stewart <Bernard.Stewart@SESIAHS.HEALTH.NSW.GOV.AU>; dkrewski@uottawa.ca
Subject: Consensus statement Vol100WS

Dear Vincent,

Some time ago you made a start drafting a 'consensus statement' that summarized the main points on which general agreement among the Workshop participants (Vol100WS) could be reasonably expected. An earlier email message of yours, and a first-draft statement with Kurt's annotations, are attached. Also attached are the two key papers from Dan Krewski and his team on the analysis of the 'concordance' and 'mechanisms' data sets. The outcome of these analyses should be mentioned/summarized in the consensus document. May I ask you to prepare a second draft of the consensus statement on the basis of this material.

We received just recently the two chapters attached, and they are being edited right now. As soon as possible we will send these documents to the Workshop participants for their final approval. It would be nice to send your consensus document at the same time.

I hope you can give this priority on your 'to-do' list.

Best wishes,

Robert

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

Daniel Krewski[1,2,3], Jerry Rice[4], Michael Bird[1,2], Brittany Milton[2], Brian Collins[2], Pascale Lajoie[1,5], Mélissa Billard [1,], Yann Grosse[6], Robert Baan[6], Vincent Cogliano[7], Kurt Straif[6], Jane Caldwell[8], Ivan Rusyn[9], Christopher Portier[6], Julian Little[3] & Jan M. Zielinski[1,10,†]
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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[Affiliations] in List of Contributors >> remove superscript numbers >> leave footnote †deceased with Dr Zielinski

Abstract

Since its inception in the early 1970s, the *Monographs Programme* of the International Agency for Research on Cancer (IARC) has developed 116 *Monographs* on 990 agents for which there exists some evidence of human cancer risk; of these, 118 agents met the criteria for Group 1, *carcinogenic to humans*. Volume 100 (Vol 100) of the *IARC Monographs*, compiled in 2008-2009 and published in 2012, provided a review and update of the 107 Group-1 agents identified as of 2009. These agents have been 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 the data set developed by Grosse et al. (this Volume) for human and animal tumours and tumour sites associated with exposure to these agents – and five additional Group-1 agents defined in subsequent *Monographs* –, we analyzed the degree of concordance between the sites where tumours arise in humans and animals (mice, rats, hamsters, dogs, and primates). An anatomically-based tumour nomenclature system, representing 39 tumour sites and 15 organ and tissue systems for which there was *sufficient evidence* of carcinogenicity in human and/or animals, was developed and used as the basis for species comparison. The present analysis identifies 91 Group-1 agents with *sufficient evidence* (82

agents) or *limited evidence* (9 agents) of carcinogenicity in animals. The most common tumours observed in both humans and animals were those of the respiratory system, followed by the lymphoid and hematopoietic tissues, urothelium, skin, and digestive organs. Tumours of the upper aero-digestive tract and respiratory system were observed for 47 of the 111 distinct Group-1 carcinogens identified through Volume 109 of the *IARC Monographs*, comprising mostly chemical 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 were observed for 26 agents, tumours of the urothelium for 18 agents, and skin tumours for 14 agents. Exposure to radiation (particularly X- and gamma radiation) and tobacco smoking were associated with tumours at multiple sites in humans. Although the *IARC Monographs* do not focus on tumour-site concordance between animals and humans, substantial concordance was observed for a number of organ and tissue systems, even under the stringent criteria for *sufficient evidence* of carcinogenicity employed by the IARC. It should be noted that some caution is needed in interpreting concordance at sites where the sample size is particularly small: although perfect (100%) concordance was noted for agents causing tumours of the mesothelium, only two Group-1 agents meeting the criteria for inclusion in the concordance analysis caused tumours at this site. Concordance between the sites of tumour development seen in animals and humans is not perfect. However, the extent of concordance presented here supports the view that tumour sites in experimental animals should be considered with reference to possible or known tumorigenesis in humans, in order to possibly expand mechanistic understanding in relation to particular carcinogens.

Introduction

Since the establishment of the *IARC Monographs Programme* within the International Agency for Research on Cancer (IARC) in the early 1970s, a large number of agents have been evaluated for which there exists some evidence of a possible increased cancer risk to humans. The *Monographs Programme* has developed detailed criteria against which to evaluate the available scientific evidence on the carcinogenic potential of such agents. These criteria are described in the *Preamble* to the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* (Cogliano et al., 2004; IARC, 2006; see http://monographs.iarc.fr/ENG/Preamble/index.php), and used to weigh the evidence provided by human epidemiological studies, animal cancer bioassays, and information on possible biological mechanisms of action, to classify agents into one of the following 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 the data from both the human and the animal studies as providing *sufficient evidence of carcinogenicity*, *limited evidence of carcinogenicity*, *inadequate evidence of carcinogenicity*, or *evidence suggesting lack of carcinogenicity*, whereas 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 IARC has developed 116 *Monographs* on 990 agents for which there exists some evidence of human cancer risk; of these agents, 118 met the criteria for Group 1. Volume 100 of the *IARC Monographs* provided a review and update of the 107 Group-1 agents identified as of 2009. This Volume is conveniently separated into six parts, focusing on pharmaceuticals (Vol 100A; IARC, 2012a); biological agents (Vol 100B; IARC, 2012b); arsenic, metals, fibres, and dusts (Vol 100C; IARC, 2012c); radiation (Vol 100D; IARC, 2013d); personal habits and indoor combustions (Vol 100E; IARC,

2012e); and chemical agents and related occupations (Vol 100F; IARC, 2012f), respectively. Since the publication of Volume 100, five additional agents – diesel exhaust (Vol 105; Benbrahim-Tallaa et al., 2012), trichloroethylene (Vol 106; Guha et al., 2012), polychlorinated biphenyls (PCBs) and dioxin-like PCBs (Vol 107; Lauby-Secretan et al., 2013), outdoor air pollution and particulate matter from outdoor air pollution (Vol 109; 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 Volume 100, they would have been included in Vol 100F; for ease of reference, we will include these agents in an expanded group of chemicals and related occupations denoted by Vol 100F*.

The 113 agents classified 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 Vol 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 Vol 107. 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 Vol 100, there are 23, 11, 10, 18, 12, and 37 Group-1 agents in Vol 100A through Vol 100F*, respectively.

Because both animal and human data are considered in evaluating the weight of evidence for human carcinogenicity, the degree of concordance between species for tumour induction by carcinogenic agents is of importance. A high degree of site concordance between species supports the ability of experimental animal studies to predict not only a potential cancer risk for humans, but also the specific sites of cancer induction expected from human exposure to carcinogenic agents. On the other hand, lack of concordance may indicate the need for further research to make sure all cancer sites have been identified in sensitive human subpopulations or in appropriate experimental animal models, and to identify the underlying mechanisms that species may or may not have in common. This chapter uses the data set assembled by Grosse et al. (this Volume) derived from the available information on the agents classified by the IARC as being *carcinogenic to humans* (Group 1) in Volume 100 through Volume 109, the last *Monograph* for which final data were available at the time this analysis was conducted. This database includes all tumour sites identified in the *Monographs* for which there is *sufficient evidence* of carcinogenicity in humans and/or animals, and includes internationally peer-reviewed and published human and experimental animal data to support analyses of tumour sites seen in humans and animals. Although the database also includes human tumour sites for which there is *limited evidence* of carcinogenicity of the agent, human tumour sites were not systematically identified in the *Monographs* in the case of *limited evidence*. Animal tumour sites were generally not identified in the case of *limited evidence* in animals.

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

Methods

Tumour Nomenclature in Animals and Humans. Although human tumours can be coded in a standardized manner by use of the 'International Classification of Diseases' coding system (ICD9, 1977; ICD10, 2011), a comparable 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 Supplemental Material I, this taxonomy is anatomically based, and includes 47 tumour sites grouped within 15 organ and tissue systems. This includes 39 distinct animal and human tumour sites specified for Group-1 agents in Vol 100A-F*, as well as eight additional tumour sites that were considered to be of importance, even though they did not appear in the tumour-site concordance data set developed by Grosse et al. (this Volume). The 39 individual tumour sites seen in either animals or humans through Volume 109 of the *IARC Monographs* are listed in Table 2. The category 'other groupings' includes the three sites (all cancers combined; all solid cancers; and exocrine glands 'not otherwise specified', NOS) that do not fit in any of the other 14 groupings. All analyses reported in this chapter are based on the 39 individual tumour sites within the 15 organ systems in Table 2.

Aggregation of tumour sites within an organ system was guided by several factors including anatomical and functional relatedness. The individual specialized epithelia of the upper aero-digestive tract, respiratory system, digestive tract, and digestive organs occur for the most part in a single or a few anatomical sites, which are precisely captured by the available epidemiological and experimental data. In contrast, both kidney and urothelium are data-rich sites and carcinogenic agents for either site display little or no overlap in target organ. 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 anatomical location. Likewise, skin cancers are aggregated irrespective of anatomical location, with the exception that malignant melanoma as it occurs in humans is unknown in rats or mice; cutaneous melanocytes are thus included separately in the Table as a human tumour site only for the sake of completeness. Estrogen-producing and estrogen-responsive tissues are aggregated in the organ system 'female breast, female reproductive organs and 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 for the sake of completeness, despite the high prevalence in humans of prostate and testicular germ-cell cancers.

Retrieval of Data on Tumour Occurrence from the IARC Monographs. Grosse et al. (this Volume) extracted data from Volumes 100, 105, 106, 107 and 109 on tumour sites reported in humans or animals for the 111 distinct Group-1 agents considered here. This information is illustrated in Table 3, with one compound from each of Volumes 100A-F, as well as diesel exhaust (Vol 105), trichloroethylene (TCE) (Vol 106), PCBs (Vol 107) and air pollution (Vol 109). Table 3 gives the tumour sites for which the agents provide *sufficient evidence* of carcinogenicity in humans, as well as sites for which there is *limited evidence*. Tumour sites for which *sufficient evidence* of 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 agents show *limited evidence* of carcinogenicity in humans are included in Table 3, this information is not considered in the present analysis. In fact, although our original intent was to consider tumour sites

with *sufficient* or *limited evidence* in humans when evaluating concordance with animal tumour sites with *sufficient evidence*, there are only two Group-1 agents with *limited*, but not *sufficient*, evidence of carcinogenicity in humans.

Effects of Sex, Strain, and Route of Administration. The last column in Table 3 provides details on animal studies relevant to the evaluation of the agent of interest, including the sex and strain of the test animals, and the route of administration of the test agent. Although this information has been recorded where available, it is difficult to examine concordance with respect to these important factors for a variety of reasons.

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 sex-specific. Also, some animal experiments use only one sex, while 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. Indeed, in many cases information on strain is unavailable, precluding the possibility of strain-specific analyses.

Human exposure to carcinogens can occur by oral ingestion, inhalation, dermal absorption, as well as *via* other routes such as injection of pharmaceutical agents for therapeutic purposes. Animal experiments may involve other routes of exposure, such as intraperitoneal injection or intra-tracheal 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 lack of concordance between tumour sites observed in animals and humans. However, since data on cancer outcomes for a given 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 the concordance analyses, we examined the organ distribution of the 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 tumours caused by all 111 distinct Group-1 carcinogens considered here.

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.

Results

The concordance data set assembled by Grosse et al. (this Volume) summarized in Table 1 includes 111 distinct Group-1 agents identified in the *IARC Monographs* up to and including Volume 109. 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 on the basis of mechanistic upgrades according to the evaluation criteria outlined in the *Preamble* to the *IARC Monographs*. Benzo(*a*)pyrene (B*a*P), for example, was placed in Group-1 on the basis of epidemiological data on exposure to mixtures of PAHs containing B*a*P that provided *sufficient evidence* for lung or skin cancer in humans, coupled with extensive mechanistic data on B*a*P, suggesting that the mechanisms by which B*a*P causes tumours in animals would also be expected to operate in humans: no data in humans on B*a*P alone were available for evaluation (IARC, 2010). An important aspect of such mechanistic upgrades for purposes of the present analysis is the general lack of identification of a human tumour site: of the ten agents placed in Group-1 on the basis of a mechanistic upgrade, tumour sites in humans were specified only for phenacetin, which was determined to cause tumours of the renal pelvis and ureter, based on results of the evaluation of phenacetin as the active ingredient in analgesic mixtures.

Of the ten agents in Table 4 placed in Group-1 on the basis of mechanistic upgrades, all but one – etoposide – demonstrated *sufficient evidence* of carcinogenicity in animals. In the assignment of etoposide to Group-1 in the absence of *sufficient evidence* in animals, the *Monograph* noted the *limited evidence* of carcinogenicity in humans on the basis of the induction of acute myeloid leukaemias with distinctive chromosomal translocations by drugs, including etoposide, that target topoisomerase II. One agent (phenacetin as present in an analgesic preparation, mentioned above) demonstrated *sufficient evidence* of carcinogenicity in humans, three showed *limited evidence* in humans, and four had in*adequate evidence* in humans; no epidemiological data were available for two agents (B*a*P and PeCDF).

Apart from the nine Group-1 mechanistic upgrades for which no human tumour sites were identified, there are four other agents for which the same is true (Table 5): 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). These were generic evaluations across a range of agents falling in these categories. In addition, no human tumour site was specified for the lifestyle agents, areca nut and ethanol in alcoholic beverages, as no epidemiological data were available for areca nut alone or for ethanol in alcoholic beverages alone (Grosse et al., this Volume).

No animal tumour sites were identified for 38 of the 111 agents considered here (Table 6). These included 20 agents with *inadequate evidence* in animals: seven agents representing occupational exposures that would be difficult to replicate in the laboratory; two pharmaceutical agents used in combination for which no animal data were available on the mixture; seven biological agents (all viruses) for which the selection of an appropriate animal model was problematic; two agents, etoposide and wood dust, for which the available animal tests were considered inadequate; and two agents, treosulfan and leather dust, for which no animal data were available. Although the latter two agents, lacking any animal test data, 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 discussion 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 are largely uninformative because of inadequate testing.

IARC Monographs 76 (IARC 2000) and 100A (IARC 2012a) noted that etoposide was tested in only one experiment with wild-type and heterozygous *Nf1* (neurofibromatosis type 1 gene) knock-out mice treated by gastric intubation for six weeks with etoposide at 100 mg/kg body weight/week (Mahgoub *et al.*, 1999). This single short-duration study was

judged as providing *inadequate evidence* of carcinogenicity in animals. The available studies with wood dust originally considered in *IARC Monograph* 62 (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. Upon re-evaluation of wood dust in *Monograph* 100C (IARC 2012c) it was concluded that most of the studies conducted with wood dust (nearly all with beech wood dust) had small numbers of animals or were of short duration, thus providing *inadequate evidence* of carcinogenicity in animals. These considerations suggest that neither etoposide nor wood dust have been subject to adequate animal testing, therefore precluding a determination of their carcinogenic potential in animals.

Ten agents, including six pharmaceutical products (busulfan; chlornaphazine; cyclosporine; combined estrogen-progestogen menopausal therapy; methyl-CCNE; 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. As mentioned above, 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. Treatment with busulfan, for example, resulted in a significant increase in the incidence of thymic and ovarian tumours in BALB/c mice, which was found difficult to interpret, while in another study busulfan, when given to rats during gestation, affected the incidence of uterine adenocarcinomas in the offspring upon intra-uterine treatment 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, and of pulmonary tumours (not otherwise specified) in mice following intravenous injection; a significant increase in the incidence of mammary tumours was seen following subcutaneous injection of sulfur mustard in rats, relative to an external control group, while fore-stomach tumours were numerically, but not significantly, elevated in rats treated by oral gavage (IARC, 2012f). The exposure by subcutaneous and intravascular injection was considered to be of limited relevance to the most common human routes of exposure. Although not meeting the stringent criterion for *sufficient evidence* of carcinogenicity in animals, the *limited evidence* provided by busulfan, as well as by the other six 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 eight agents demonstrating *sufficient evidence* of carcinogenicity in animals, as reproducible results were unavailable in two or more studies of adequate design in the same species for any of these agents. Although melphalan showed evidence of a statistically significant increase in the incidence of tumours of the forestomach, skin and lung in mice, as well as lymphosarcoma, these results were not replicated in two or more independent studies (IARC, 2012f). In the rat, melphalan also produced mammary gland tumours and peritoneal sarcoma, but these findings were again not replicated in independent studies. Phosphorous-32 caused leukaemia in mice and osteogenic sarcomas in rats in single studies. Similarly, acetaldehyde in drinking-water induced pancreatic adenomas, combined lymphomas and leukaemias, uterine and mammary gland adenocarcinomas, and head osteosarcomas in 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 aluminium refining in animals was based on a single limited mouse skin-tumour study with PAH-containing particulates from aluminium-production

plants, in conjunction with *sufficient evidence* of carcinogenicity in experimental animals for many of the PAHs detected in air samples from such plants and previously evaluated in *IARC Monograph* Volume 92 (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 aero-digestive tract in hamsters and humans for betel quid with tobacco.

While 2,3,4,7,8-pentachlorodibenzofuran (PeCDF) provided *sufficient evidence* of carcinogenicity in animals, no animal site was identified. PeCDF was tested by the U.S. National Toxicology Program in a two-year animal bioassay (female rats only) with exposure by oral gavage (NTP, 2006). There was some evidence of carcinogenic activity of PeCDF, based on increased incidences of hepatocellular adenoma and cholangiocarcinoma of the liver and gingival squamous cell carcinoma of the oral mucosa. 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 (Vol 100F; IARC, 2012f). These observations led to the conclusion that there is *sufficient evidence* for the carcinogenicity of PeCDF in animals, although there is no specific organ site that can be designated as responsible for this *sufficient evidence.* Because of the absence of a specific tumour site in animals, PeCDF is not included in the concordance analyses.

A component of four Group-1 agents, but not the agent itself, demonstrated *sufficient evidence* of carcinogenicity in animals. These are: fission products including Sr-90, where strontium-90 demonstrated *sufficient evidence* of carcinogenicity in animals (Vol 100D, pg 297; IARC, 2012d); haematite mining with exposure to radon (underground), where radon demonstrated *sufficient evidence* of carcinogenicity in animals (Vol 100D, pg 274; IARC, 2012d); acetaldehyde associated with consumption of alcoholic beverages, where acetaldehyde demonstrated *sufficient evidence* of carcinogenicity in animals (Vol 100E, pg 472; IARC, 2012e); and occupational exposures during aluminium production, where airborne particulate polynuclear organic matter from aluminium-production plants demonstrated *sufficient evidence* of carcinogenicity in animals (Vol 100F, pg 221; IARC, 2012f). 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.

Excluding the 20 agents in Table 5 lacking appropriate animal data, i.e. seven occupational exposures not reproducible in the laboratory, two agents used in combination with no animal data available on the mixture, seven agents where the use of animal models is problematic due to species-specificity or other limitations, and four 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 correspondence between sites where tumours are 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 an evaluation of concordance between tumour sites seen in animals and humans. Results are presented

first for the 39 tumour sites included in the anatomically based tumour nomenclature system seen in either animals or humans, followed by the 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; biological agents; arsenic, metals, fibres, and dusts; radiation; personal habits and indoor combustions; and chemical agents and related occupations). Lung tumours represent the most common tumour seen in humans, with 28 of the 111 known human carcinogens inducing lesions at this site; of these, thirteen are associated with exposure to chemical agents and related occupations, and seven are in the category of arsenic, metals, fibres, and dusts. Tumours of the haematopoietic tissues are associated with exposure to 18 agents, urothelial tumours with 18, skin tumours with 12, and liver and bile duct tumours with 11 agents; chemicals and related occupations account for the largest number of agents causing these lesions. This category also accounts for half (9/18) of the urinary tract/urothelial tumours, with pharmaceuticals accounting for half (9/18) of the 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, i.e. caused by 29 of the 111 known human carcinogens, with the categories of chemicals (10), arsenic, metals, fibres, and dusts (7), and radiation (7) accounting for the majority. After the lung, the animal sites associated with the largest number of agents are the skin and adnexae (18 agents), liver parenchyma and bile ducts (19), lymphoid tissue (14), soft connective tissue (11) and breast (11). Separate tumour profiles are shown for agents causing tumours in mice (62 agents) and rats (64 agents) in Figures 3 and 4, respectively. In rodents (mice and rats combined), the lung is the site associated with the largest number of carcinogens.

Organ- and Tissue-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 aero-digestive tract and respiratory system are caused by 47 of the 111 human carcinogens, comprised mostly of chemicals agents and related occupations (16), arsenic, metals, fibres, and dusts (10), and personal habits and indoor combustions (12). After the upper aero-digestive tract and respiratory system, the organ systems associated with the largest number of agents are the lymphoid and haematopoietic systems (26 agents), the skin and connective tissues (22), and the urothelium (18). The category chemical agents and related occupations represents the largest group of carcinogens 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 aero-digestive tract and respiratory system are caused by 41 of the 111 agents under study, with chemical agents and related occupations (15 agents), 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, comprising mostly 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 aero-digestive 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

Of the 111 distinct Group-1 agents identified through Volume 109, there are 60 for which both a human tumour site and an animal tumour site have been identified. Of the 111 Group-1 agents in Table 1, 15 had no human tumour site specified (Table 5) and 38 agents had no animal tumour site identified (Table 6). With two agents—aristolochic acid, and plants containing aristolochic acid—having neither a human nor an animal tumour site specified, there are 111 – 15 – 38 + 2 = 60 agents with at least one tumour site identified in both humans and animals. These 60 agents may be used to evaluate concordance between tumour sites seen in animals and humans, as at least one tumour site has been identified in both.

The overlap between human and animal tumour sites targeted by these 60 agents is summarized in Table 7 by organ and tissue system/tumour site. The category 'other groupings' of tumours – which comprises all cancers combined, all solid cancers, and exocrine glands (NOS) – was created to accommodate tumour sites reported in the *IARC Monographs* that did not fall into any of the other categories in Table 2. Because this category lacks biological cohesiveness, 'other groupings' of tumours were not considered in the concordance analysis.

Nine agents cause tumours in the upper aero-digestive tract in humans, and nine agents demonstrate tumours in this organ and tissue system in animals; four agents demonstrate tumours in this system in both humans and animals. There are 9+9-4=14 distinct agents that demonstrate tumours in this system in either humans or animals, for an overlap of 4/14, or 28.6%. Within the upper aero-digestive tract, there are three agents that demonstrate tumours in the nasal cavity and paranasal sinuses in humans and three agents that demonstrate tumours at this site in animals, with no overlap. Of the three agents inducing tumours in the nasopharynx, one agent caused tumours in both humans and animals, for an overlap of 33.3%. In the oral cavity, overlap is 25%. Overlap is not calculated when there are no agents demonstrating tumours in either humans or animals, as in the pharynx, tongue, and salivary gland.

The lung is the most common site at which tumours are observed, with 61.5% overlap among the 26 agents causing lung tumours in humans or animals. Among the 10 agents causing tumours in the urothelium (renal pelvis, ureter or urinary bladder), there is 70% overlap between agents causing tumours in humans or animals.

As results for individual tumour sites are often based on small numbers, emphasis is placed on interpretation of results at the organ and tissue system level where the sample size is generally larger than for individual tumour sites within organ and tissue systems. Overlap varies among the organ and tissue systems, ranging from 20% (based on 10 agents) in the digestive tract to 100% in the mesothelium. Overall, high overlap is seen for some organ and tissue systems, but not for others. Some caution is needed in interpreting concordance at sites where the sample size is particularly small: although 100% concordance was noted for agents causing tumours of mesothelium, only two Group-1 agents – asbestos and erionite - meeting the criteria for inclusion in the concordance analysis caused tumours at this site.

The results in Table 7 are depicted in graphical form in Figure 9. Of the 14 Group-1 agents causing tumours of the upper aero-digestive tract in either humans or animals, nine cause tumours in the upper aero-digestive tract in humans, 22 cause upper aero-digestive tract tumours in animals, and 16 agents cause such tumours in both humans and animals, for an overlap of 28.6%. Of the 27 agents causing tumours of the respiratory system in either humans or animals, 21 cause respiratory tumours in humans, 22 cause respiratory tumours in animals, and 16 agents cause respiratory tumours in both humans and animals, for an overlap of 59.3%. While presenting the same data as shown in Table 7, the graphical representations of these results in Figure 9 for all organ and tissue systems also illustrate the large variation in sample size among the organ/tissue systems, with the area of the circles being proportional to sample size.

The results presented in Table 7 are based on concordance between tumour sites seen in humans and all animal species, reflecting our interest in evaluating the extent to which tumours caused by Group-1 agents occur in similar organs or organ systems in humans and animals. The animal data included in this analysis are dominated by results obtained in studies with rats and mice: of the 60 Group-1 agents included in the analysis, 40, 38, 8, 7, and 3 agents demonstrated tumours in mice, rats, hamsters, dogs, and monkeys, respectively. As a consequence, including only mice and rats in the analysis yielded results similar to those in Table 7 (see details in Supplemental Material II, where Supplemental Table 6 presents results for all animals and Supplemental Table 7 presents results for mice and rats only).

Figure 10 shows the percentage of Group-1 agents causing tumours in specific organ and tissue systems in humans that are also associated with tumours in animals (Panel A), as well as the percentage of agents causing tumours in specific organ and tissue systems in animals that are also associated with tumours in humans (Panel B).

As detailed in Supplemental Material II, it is important to note that the measures of concordance presented in Figure 10 differ from those in Table 7. The percentage overlap in Table 7 (and Figure 9) reflects the number of agents causing tumours in a specific organ/tissue system in *both* humans *and* animals, relative to the number of agents causing tumours in that system in *either* humans *or* animals, providing an overall measure of overlap between animal and human carcinogens in a specific organ/tissue system. The percentage overlap in Panel A of Figure 10 provides a measure of the overlap between agents causing tumours in a specific organ/tissue system in animals with agents causing tumours in that system in humans. Conversely, the percentage overlap in Panel B of Figure 10 provides a measure of the overlap between agents causing tumours in a specific organ/tissue system in humans with agents causing tumours in that system in animals. Note that unless the numbers of agents causing tumours in humans and animals in a specific organ/tissue system are the same (as is the case for tumours of the upper aero-digestive tract), the results in Panel A, where human Group-1 agents constitute the reference set against which animal Group-1 agents are compared, will differ from those in Panel B, where animal Group-1 agents constitute the reference set for comparison with human Group-1 agents.

As indicated in Panel A of Figure 10, all agents (100%) causing tumours of the mesothelium, endocrine system, and connective tissues also cause tumours in those organ and tissue systems in animals. Overlap of at least 50% is observed for all other organ and tissue systems, with the exception of the upper aero-digestive tract (44%) and the digestive tract (33%). Conversely, there is less overlap between agents causing tumours in specific organ and tissue systems in animals with results in humans (Figure 10, panel B), possibly reflecting either a greater spectrum of tissue sites expressed in animal studies than in human studies, or the greater number of studies conducted in animals as compared to humans.

As is the case with the concordance results focusing on overall overlap presented in Table 7, caution is required when interpreting results where there are few agents for comparison in Figure 10 (both Panels A and B).

The 60 agents included in the present concordance analysis are listed in Table 8 in boldface type. This table presents the tumour site data for humans and animals at the organ and tissue system level only, as results for individual tumour sites are too sparse to support meaningful comparisons of this type. The human data are presented in the column on the left, the animal data in the column on the right, and overlap in the middle column. Using this display, potential relationships among agents causing tumours within the same organ/tissue system can be examined. Overlap between human and animal carcinogens acting within the same organ and tissue system can also be examined both for individual agents and for groups of agents.

In order to permit a more complete comparison between animal and human tumour sites, tumour sites with only *limited evidence* in humans are included in Table 8 in light grey font. For agents such as diethylstilbestrol (a synthetic non-steroidal estrogen widely used in the US between the 1940s and 1970s, but now rarely used), there is difficulty in generating newer data regarding human exposure. Because men exposed to diethylstilbestrol *in utero* have passed the age of highest risk for testicular cancer, further study cannot clarify the association between this exposure and testicular cancer (Vol 100A; IARC, 2012a). Human data for this agent will remain limited for this endpoint, although supported by the induction of testicular tumours in rodents.

With ongoing studies, more evidence can be gathered that provides increasing certainty about potential human cancer risks. Although IARC had previously evaluated trichloroethylene (TCE) in 1979, 1987, and 1995, this substance was not declared to be *carcinogenic to humans* – causing kidney cancer – until 2012 due to the emergence of new data (Vol 106; IARC, 2014). Although it was noted that a positive association had been observed between liver cancer and exposure to TCE, the lack of data was cited as the rationale for its designation as having only *limited evidence* of carcinogenicity in humans in the previous evaluations. In 2013, an updated pooled analysis of three Nordic studies with 10-15 years of additional follow-up demonstrated that human exposure to TCE was associated with a possibly increased risk of liver cancer (Hansen et al. 2013). Inclusion of the limited human data for TCE-induced liver cancer in humans allows for the observation of overlap between animals and human for this endpoint.

This example illustrates that the inclusion of agents with *limited evidence* of carcinogenicity in humans enhances the ability to identify concordance relationships. Comparisons between Table 7, which includes only sites with *sufficient evidence* in humans, and Table 8, which includes sites with *limited evidence* in humans, illustrates increased coherence among agents that have similar chemical and mechanistic characteristics when limited human data are considered.

There are also examples of increased site concordance if less stringent criteria are applied than are used by the IARC for determining *sufficient evidence* of carcinogenicity. Although no human tumour site with *sufficient evidence* of carcinogenicity in humans is identified for ethylene oxide, there is *limited evidence* of breast cancer and non-Hodgkin lymphoma in humans (see Supplemental Table 2). In evaluating the available animal data on estrogen and progestogen oral contraceptives (Vol 100A; IARC 2012a) it was concluded that 'The data evaluated showed a consistent carcinogenic effect of several estrogen-progestogen combinations across different animal models in several organs.' Similarly, the synthesis statement in the evaluation of diethylstilbestrol notes:

> "The oral administration of diethylstibestrol induced tumors of the ovary, endometrium and cervix, and mammary adenocarcinomas in female mice. Osteosarcomas and Leydig cell tumors were induced in rasH2 and Xpa/p53 male mice, respectively. Subcutaneous implantation of diethylstilbestrol induced mammary tumors in female Wistar rats. Perinatal exposure to diethylstilbestrol induces lymphoma, uterine sarcomas, adenocarcinomas and pituitary, vaginal, and ovarian tumours in female mice. Uterine adenocarcinomas and mammary and vaginal tumors were also induced in female rats. In hamsters, diethylstilbestrol perinatal exposure induced kidney tumour." [Vol 100A; IARC, 2012a]

Agents affecting male reproductive organs are also included in Table 8, although they are not part of the concordance analyses in Table 7 due to a lack of *sufficient evidence* in either humans or animals. TCDD (2,3,7,8-tetrachlorodibenzo-para-dioxin) is included in Table 8, but its designation as an agent affecting 'all cancers combined' in humans precludes site-specific tumour concordance analyses. These examples illustrate increased site concordance by applying less stringent criteria than those applied for the concordance analysis presented in Table 7.

Table 8 shows human data indicating biological plausibility for the upper aero-digestive tract and lung to be targets for agents for which the portal of entry is the lung (as with dusts, particles, and particles that serve as a vehicle for a mixture of other carcinogens such as during tobacco smoking and coke production). Lympho-haematopoietic cancers are a consistent endpoint for antineoplastic alkylating agents that induce these cancers after their use in chemotherapy for the eradication of other neoplasms (Vol 100A; IARC, 2012a), radioactive materials (Vol 100D; IARC, 2012d), and a number of chemical agents and related compounds that are metabolized to or are in themselves agents that are reactive with DNA (Vol 100F; IARC, 2012f).

Table 8 also illustrates some of the potential relationships between agents that may act in a similar fashion in humans. Tobacco smoke and its related agents (smokeless tobacco and second-hand tobacco smoke) affect a number of similar organ/tissue systems. For radioactive materials, almost all organs/sites are affected by ionizing radiation: these agents affect multiple target tissues because they are able to reach the nucleus and cause a variety of DNA lesions and other effects reflected by the key characteristics of human carcinogens (Smith, this Volume; Krewski et al., this Volume; see also Smith et al., 2016). Radioactive materials also do not require metabolism in order to induce cancer. Several dyes are associated with urothelial cancer in humans and act through a similar mechanism (Vol 100F; IARC, 2012f). Agents that disrupt the endocrine system and related organs (e.g., polychlorinated biphenyls, diethylstilbestrol, estrogen-only menopausal therapy, estrogen-progestogen oral contraceptives (combined), and tamoxifen) induce cancer at similar sites, including female reproductive organs and breast. Metals appear to have many target sites in common, including the upper aero-digestive tract, respiratory system, kidney, and prostate.

As noted previously, the animal database is predominantly populated by results from studies in rodents. Respiratory tract tumours are induced in rodents by many of the same agents that cause such tumours in humans. For the mesothelium, a rare tumour in humans or animals and one specifically induced by a small number agents, there is good agreement between the human and animal databases. Many agents metabolized in the liver to reactive compounds induce liver cancer in animal models, with less apparent overlap with the human data (see digestive organs, Table 8). Susceptibility of rodent liver to cancer induction is species-, sex-, and strain-specific, and varies widely. Nonetheless, all

agents that induce liver cancer in rodents induce cancer at some other site in humans. In some instances the apparent lack of overlap between animal and human databases can still reflect mechanistic concordance for similar agents. Dyes such as magenta, 4-amino biphenyl, benzidine, 2-napthylamine all cause liver cancer in rodents and urothelial cancers in humans. 2,3,7,8-Tetrachlorodibenzo-paradioxin and polychlorinated biphenyls are both associated with liver cancer in rodents and lymphoid and haematopoietic tissue cancers in humans.

Human exposures to diethylstilbestrol, estrogen-only menopausal therapy, and combined estrogen-progestogen oral contraceptives are all associated with cancers of the female breast, female reproductive organs and reproductive tract. Kidney cancer is induced in male hamsters upon exposure to either diethylstilbestrol or estrogen-only menopausal therapy. Estrogen-only data presented in the *Monograph* on combined estrogen-progestogen oral contraceptives indicate a similar result (Vol 100A; IARC, 2012a). Although there appears to be concordance within species for the tumours these agents induce, there does not appear to be overlap in rodent kidney and human female sites. However, there may be mechanistic concordance between these two endpoints, as both diethylstilbestrol and estrogen may damage DNA through oxidative damage, formation of unstable adducts, and induction of apurinic sites. In male Syrian hamsters the major metabolites of diethylstilbestrol are catechols that easily oxidize to catechol *o*-quinones, which are DNA-reactive. Implantation of estrone or estradiol in male hamsters results in the induction of renal carcinomas exclusively (Li et al., 1983). Metabolic activation of estrogens by cytochrome P450 may also be related to a mechanism similar to that for PAHs (Cavalieri and Rogan, 2014). Thus, diethylstilbestrol and estrogen may have mechanistic similarities that result in an apparent lack of organ/tissue system overlap, with the hamster kidney being indicative of human risk.

Discussion

Since the early 1970s, the *Monographs Programme* at the International Agency for Research on Cancer has been evaluating potential cancer risks to humans (Saracci & Wild, 2015). Separate evaluations of the available animal and human evidence are made, and then combined to make an overall evaluation of the strength of evidence for human carcinogenicity. As of the time of this analysis, 118 distinct agents have met the IARC criteria for determining causality, and designation of these agents as being in Group 1: *Carcinogenic to humans*, with 111 distinct Group-1 agents available for inclusion in the data set of tumours and tumour sites in animals and humans developed by Grosse et al. (this Volume).

The well-established weight-of-evidence criteria for the evaluation of the available human, animal, mechanistic, and exposure data used by IARC are detailed in the *Preamble to the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* (IARC, 2006; see http://monographs.iarc.fr/ENG/Preamble/index.php) and provide clear guidance to the Working Groups convened to review agents. Satisfying the criteria for *sufficient evidence* of carcinogenicity in both animals and humans reasonably infers causality, which can be strengthened by mechanistic considerations. However, an immediate challenge in making comparisons for tumour-site concordance between species 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; tumours at 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, 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. This tool, developed for tumour comparisons across and within species, included 39 individual tumour sites for which agents showed *sufficient evidence* of carcinogenicity in humans and/or animals, which were further aggregated into 15 organ and tissue systems. This aggregation allows comparisons to be made at a higher level of organization and a portal of entry that may reflect anatomical and physiological similarities, with, for example, the lung and lower respiratory tract being considered together as the respiratory system. Aggregation also allows more data to be considered for analyses, which increases the robustness of the ensuing conclusions. For our concordance analyses, data at both the individual site level as well as at the organ system level were examined.

Although the present analysis demonstrates generally good agreement between animal and human tumour sites after exposure to Group-1 carcinogens, concordance was not demonstrated with every agent and tumour site. There are several factors and important limitations that may result in lack of tumour concordance based on these data. Relevant and reliable data to support a complete analysis of concordance are unavailable for either animals or humans for many of the 111 agents. Some agents, notably the human papillomaviruses, 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 in combined estrogen-progesterone menopausal therapy may also not have been evaluated in animals, particularly if the components of the mixture had been previously evaluated separately. Relevant animal tests may still provide only *limited* or *inadequate* evidence of carcinogenicity through limitations in study design or conduct, or if the mechanism of action of the agent of interest was specific to human exposures and not easily replicated in an experimental animal model. Animal studies may also show tumours that are species- and/or sex-specific.

As part of the determination of weight of evidence, agents that induce tumours at multiple sites and across multiple species are considered to present a more robust cancer hazard to humans. However, the experimental animal database used for our analysis consists primarily of rodent data. It is notable that of the 111 Group-1 agents examined here, three agents caused tumours in humans and 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 inter-species tumour-site concordance.

Our analyses exclude the 11 biological agents in Vol 100B, 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 (see Vol 100B, pp 41–42; IARC, 2012b). 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