

The Vital Contribution of Independent, Ethically Grounded Research to the Global Health Agenda

Kurt Straif

THE GLOBAL BURDEN OF CANCER IS HIGH and continues to increase. The annual number of new cases was estimated at 18 million in 2018 and is expected to increase to almost 30 million by 2040.³⁵ With current trends in demographics and exposure, much of the increase in cancer burden is expected in low- and medium-income countries. These countries often do not have the necessary resources to adequately treat all cancer patients. Cancer is already the leading underlying cause of death in many countries, and no country can treat its way out of the cancer problem. Therefore, prevention is the most effective response to this increasing challenge. The first step in cancer prevention is to identify the causes of human cancer.

THE IARC MONOGRAPHS PROGRAMME AND TRANSPARENCY

Through the Monographs Programme, the International Agency for Research on Cancer (IARC) seeks to identify the causes of cancer in the human environment.³⁶ The IARC Monographs Programme is an international, interdisciplinary approach to carcinogenic hazard identification. Soon after the Agency was established in 1965 as the specialized cancer research arm of World Health Organization (WHO), it received frequent requests for advice on the carcinogenic risk of chemicals, including inquiries about lists of known and suspected human carcinogens. In response to these requests, the IARC Monographs was initiated in 1971. Reviews and evaluations of nominated agents and exposures are carried out by Working Groups of scientific experts who are invited to participate on the basis of their expertise and their contributions to the relevant areas of science. Over

³⁵ See Freddie Bray et al., “Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries,” *CA: A Cancer Journal for Clinicians* 68, no. 6 (2018): 394–424.

³⁶ See International Agency for Research on Cancer (IARC), “Preamble to the IARC Monographs,” last updated January 2019, monographs.iarc.fr/iarc-monographs-preamble-preamble-to-the-iarc-monographs/.

the decades, the IARC Monographs are a worldwide endeavor that has involved over a thousand scientists from more than fifty countries. The scientific reviews and evaluations are published as the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. In addition, and since volume 88 (2004), concise summaries of the evaluations and the rationale of each Monograph are published shortly after the meeting in the journal *Lancet Oncology*.

The Preamble to the IARC Monographs opens each volume.³⁷ The Preamble describes the objective and scope of the Programme, the scientific principles and procedures used in developing a Monograph, the types of evidence considered, and the scientific criteria that guide the evaluations. The Preamble promotes consistency of evaluations developed by different Working Groups on different topics. The evaluations are unique in representing the scientific consensus of an international Working Group of leading scientific experts. The carcinogenicity evaluation process used for the Monographs is widely recognized for its rigor and transparency (see Table 1). The Preamble also specifies strong measures to avoid conflicts of interest and interference by special interests.

Table 1: Measures to assure full transparency of the IARC Monograph Evaluations

Public announcements:	- Methods (published online, in advance)
	- Topic and timing (1 year in advance)
	- Working Group and all other participants (2 months in advance)
	- Results (<i>Lancet Oncology</i> , full <i>Monograph</i>)
Public process open to scientific observers	
Fully referenced <i>Monograph</i> is published online for free download:	- It cites only peer-reviewed, published, and publicly available data (for independent scientific scrutiny).
	- All studies (positive and negative) are described.
	- Rationale for conclusions is given.

³⁷ See International Agency for Research on Cancer (IARC), "Preamble to the IARC Monographs."

SELECTION OF PARTICIPANTS AND MANAGEMENT OF CONFLICT OF INTERESTS

The Monographs have a strong record of recruiting a diversity of international experts to form Working Groups that are authoritative, scientifically insightful, and highly regarded internationally. The Monographs identify leading experts from systematic searches of the literature and from public responses to the Call for Experts via the Monographs's website. Subject-matter experts are selected based on demonstrated knowledge and experience and careful screening to eliminate conflict of interests, and highly specific subject-matter expertise can be supplemented with broader subject expertise. Consideration is also given to demographic diversity and balance of scientific findings and interpretations. Each expert critically reviews an assigned portion of the scientific literature. The Working Group then meets at IARC for eight days to discuss the evidence, develop consensus, and arrive at an overall evaluation on the strength of the evidence.

The Monographs conduct open and transparent evaluations, strictly managing conflicts of interest of potential participants. Scientists with real or apparent conflicts of interest can be included as Invited Specialists. These scientists draft text on topics with no impact on carcinogenicity evaluation, but do not serve as meeting or subgroup chair and do not participate in the evaluation. Representatives from national and international public health institutions often participate in Monographs meetings because their agencies sponsor the Programme or are interested in the subject of the meeting. Stakeholders with potential conflicts of interest may be granted Observer status, in the interest of transparency, permitting them to observe the meeting but not influence the outcome. These clearly defined roles are an important mechanism by which subject-matter experts from different perspectives, including those who may have a real or apparent conflict, may contribute critical knowledge.

SYSTEMATIC REVIEW AND EVALUATION

The IARC Monographs are published as a series of volumes. Generally, three volumes are developed every year. Each volume contains one or more Monographs, which can cover either a single agent or a group of related agents. Each Monograph consists of a comprehensive, systematic review of the published scientific literature. Each Monograph contains a critical review of the openly available scientific literature, followed by an evaluation of the strength of the evidence that the agent can cause cancer. Over time, the structure of a Monograph has evolved to include the following sections: 1) Exposure data, 2) Studies of cancer in humans, 3) Studies of cancer in experimental animals, 4) Mechanistic and other relevant data, 5) Summary of sections 1-4, 6) Evaluation and rationale.

The process of systematic review and evaluation used for IARC's evaluations is laid out in the Preamble to the Monographs. International working groups of invited experts evaluate human, animal, and mechanistic evidence and reach a consensus evaluation of carcinogenicity for each agent. Initially, human and animal cancer data are evaluated separately according to causal criteria established in the Preamble. The strength of the evidence is categorized as Sufficient, Limited, Inadequate, or Suggesting lack of carcinogenicity. Mechanistic evidence can also be invoked to upgrade an evaluation. Alternatively, strong mechanistic evidence for the absence of a relevant mechanism in humans can downgrade an evaluation based on animal cancer data. For the overall evaluation of carcinogenicity, the Working Group considers the totality of the evidence and assigns agents to one of four causal groups following a well-defined evaluation matrix that evolved over time: 1) Carcinogenic to humans; 2A) Probably carcinogenic to humans; 2B) Possibly carcinogenic to humans; 3) Not classifiable as to its carcinogenicity to humans.

Consistent with the precautionary principle, sufficient animal cancer evidence can be used to classify an agent as potentially carcinogenic to humans in the absence of adequate human data. The evaluations undertaken for the Monographs constitute hazard identification, but the Preamble also aims at characterizing risk quantitatively.

Since its inception in 1971 the Monographs Programme has evaluated more than one thousand agents. Initially the Monographs focused on environmental and occupational exposures to chemicals, but their scope has expanded to include other factors and complex mixtures. Moreover, physical agents, biological agents, personal habits, and household exposures have been reviewed, some of them several times as new information became available in the published scientific literature. About 120 of these agents have been identified as carcinogenic, and about four hundred as probably carcinogenic, or possibly carcinogenic to humans (Groups 1, 2A and 2B, respectively).

VOLUME 100 OF THE IARC MONOGRAPHS

Volume 100 of the IARC Monographs comprises a reassessment and update of the more than one hundred agents classified by the IARC as carcinogenic to humans (Group 1) in Volumes 1-99. During 2008-2009, the IARC Monographs Programme organized six international Working Group meetings of experts in carcinogenesis and public health. A review article summarizes all evaluations of the volume 100 series, including cancer site-specific evidence (also covering agents currently evaluated as probably or possibly carcinogenic to humans), now allowing scientists to search the

evidence on carcinogenic risks not only by agent, but also by cancer site.³⁸

IMPACT OF THE IARC MONOGRAPHS

The international character of the IARC Monographs is unique. Moreover, as the specialized cancer agency of the World Health Organization, IARC has a strategic position within the United Nations. This status not only accords IARC a level of independence beyond that of most national agencies but elevates the impact of its work and facilitates the translation of Monograph findings to public health recommendations, guidelines, and policy worldwide.

The Monographs have been called the WHO's encyclopedia of carcinogens. National and international health agencies use the Monographs as a source of scientific information on known, probable, and possible carcinogens and as scientific support for their actions to prevent exposure to these agents. In high-income countries national agencies make frequent reference to the IARC Monographs. In developing countries, the IARC Monographs provide information about carcinogens to countries whose health ministries do not have the resources and experience in evaluating cancer hazards. Several Monographs have addressed cancer hazards that disproportionately affect developing countries, for example malaria (caused by infection with *Plasmodium falciparum* in holoendemic areas), betel quid chewing, and indoor emissions from household combustion of solid fuels (i.e., coal and biomass). In addition, as developing countries become more industrialized, exposure to some hazardous chemicals evaluated by the Monographs has increased, especially in countries where workplace and environmental standards are not adequate or are not enforced.

Individuals also use the information and conclusions from the Monographs to make better choices that reduce their exposure to potential carcinogens and their risk of developing cancer. In this way, the IARC Monographs contribute to cancer prevention and the improvement of public health.

SERIES OF IARC MONOGRAPHS ON AIR POLLUTION

In February 2003, the IARC Monographs Advisory Group on Priorities for Future Evaluations recommended that IARC develop a series of Monographs on air pollution. Emissions from motor vehicles, industrial processes, power generation, the household combustion of solid fuel, and other sources pollute the ambient air across the globe. The precise chemical and physical features of ambient air pollution, which comprise a myriad of individual chemical constituents, vary

³⁸ See Vincent James Coglian et al., "Preventable Exposures Associated with Human Cancers," *Journal of the National Cancer Institute* 103, no. 24 (2011): 1827–1839.

around the world due to differences in the sources of pollution, climate, and meteorology, but the mixtures of ambient air pollution invariably contain specific chemicals known to be carcinogenic to humans.

Given the complexity of the topic, the multiplicity of environments where exposures to airborne carcinogens take place, the diversity of the sources, and the multiple components of the air pollution mixture that may contribute to its carcinogenicity, the 2003 Advisory Group recommended to convene a special Advisory Group for the planning of a series of IARC Monographs on air pollution.

A multidisciplinary Advisory Group³⁹ that included epidemiologists, toxicologists, atmospheric scientists, cancer biologists, and regulators first provided a state-of-the-art overview on topics related to exposure characterization, atmospheric and engineering sciences, epidemiological studies on cancer, results of pertinent cancer bioassays and data elucidating potential mechanisms of carcinogenicity of compounds related to air pollution, then discussed and made recommendations for the development of a series of Monographs on air pollution. Following these recommendations IARC developed a series of six Monographs meetings (see Table 2).

Table 2: Series of IARC Monographs on air pollution

<i>Volume 92</i>	<i>Some Non-heterocyclic Polycyclic Aromatic Hydrocarbons and Some Related Exposures</i>	October 2005
<i>Volume 93</i>	<i>Carbon Black, Titanium Dioxide, and Talc</i>	February 2006
<i>Volume 95</i>	<i>Household Use of Solid Fuels and High-temperature Frying</i>	October 2006
<i>Volume 103</i>	<i>Bitumens and Bitumen Emissions, and Some N- and S-Heterocyclic Polycyclic Aromatic Hydrocarbons</i>	October 2011
<i>Volume 105</i>	<i>Diesel and Gasoline Engine Exhausts and Some Nitroarenes</i>	June 2012
<i>Volume 109</i>	<i>Ambient Air Pollution</i>	October 2013

IARC MONOGRAPH ON DIESEL AND GASOLINE ENGINE EXHAUST

As part of this series of Monographs on air pollution, an IARC Monographs Working Group re-evaluated the carcinogenic hazards to humans of diesel and gasoline engine exhaust. Diesel engine exhaust

³⁹ See Kurt Straif et al., ed., *IARC Scientific Publication No. 161: Air Pollution and Cancer* (Lyon: International Agency for Research on Cancer, 2013).

was classified as “carcinogenic to humans” (Group 1) and gasoline engine exhaust as “possibly carcinogenic to humans” (Group 2B).⁴⁰

Exposure is characterized in Section 1 of the Monograph. Diesel engines are used for on-road and non-road transport (e.g., trains and ships) and (heavy) equipment in various industrial sectors (e.g., mining and construction), and in electricity generators, particularly in developing countries. Emissions from these engines are complex with varying composition. The gas phase consists of carbon monoxide, nitrogen oxides, volatile organic compounds such as benzene and formaldehyde, and particles consist of elemental and organic carbon, ash, sulfate, and metals. Polycyclic aromatic hydrocarbons and nitroarenes are distributed over the gas and the particle phase.

Section 2 reviews the evidence on cancer in humans, typically derived from analytical studies of cancer epidemiology. A large US miners’ study quantified diesel engine exhaust via estimated elemental carbon as a proxy of exposure and reported a cohort analysis and a nested case—control analysis adjusted for tobacco smoking. Both showed positive trends in lung cancer risk with increasing exposure, with a two- to three-fold increased risk in the highest categories of cumulative or average exposure. A 40 percent increased risk for lung cancer was observed in US railroad workers exposed to diesel engine exhaust. Indirect adjustment for smoking and a more accurate exposure assessment strengthened the validity of the results. A large cohort study reported a 15-40 percent increased lung cancer risk in US truck drivers and dockworkers with exposure to diesel engine exhaust, with a significant trend of increasing risks with longer duration of employment, adjusted for tobacco smoking. Findings of the above cohort studies were supported by those in other occupational groups and by case-control studies including various occupations involving exposure to diesel-engine exhaust supported the Working Group’s conclusion of “sufficient evidence” in humans for the carcinogenicity of diesel engine exhaust.

Studies on cancer in experimental animals are summarized in Section 3. The Working Group concluded that there was “sufficient evidence” in experimental animals for the carcinogenicity of whole diesel engine exhaust, diesel engine exhaust particles, and extracts of the particles.

Section 4 summarizes evidence regarding mechanisms of carcinogenicity. Diesel engine exhaust, diesel engine exhaust particles, diesel engine exhaust condensates, and organic solvent extracts of diesel engine exhaust particles induced *in vitro* and *in vivo*

⁴⁰ See International Agency for Research on Cancer (IARC), *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 105: Diesel and Gasoline Engine Exhausts and Some Nitroarenes* (Lyon: International Agency for Research on Cancer, 2013).

various forms of DNA damage. Increased expression of genes involved in xenobiotic metabolism, oxidative stress, inflammation, antioxidant response, apoptosis, and cell cycle regulation in mammalian cells was observed. Positive genotoxicity biomarkers of exposure and effect were also observed in humans occupationally exposed to diesel engine exhaust. The Working Group concluded that there is “strong evidence” for the ability of whole diesel engine exhaust to induce cancer in humans through genotoxicity.

The Sections 5 and 6 summarize the evidence and conclude with the domain-specific and overall evaluations by the Working Group (see Table 3).

Table 3: Monograph evaluations on the carcinogenicity of diesel engine exhaust

• There is sufficient evidence for the carcinogenicity in humans of diesel engine exhaust. Diesel engine exhaust causes lung cancer. Also, a positive association between diesel engine exhaust and bladder cancer has been observed.
• There is sufficient evidence for the carcinogenicity in experimental animals of whole diesel engine exhaust.
• There is inadequate evidence in experimental animals for the carcinogenicity of gas-phase diesel engine exhaust.
• There is sufficient evidence in experimental animals for the carcinogenicity of diesel engine exhaust particulate matter. There is sufficient evidence in experimental animals for the carcinogenicity of extracts of diesel engine exhaust particles.
• Overall evaluation: Diesel engine exhaust is carcinogenic to humans (Group 1).

Gasoline engine exhaust and cancer risk was investigated in only a few epidemiological studies and, because of the difficulty to separate the effect of diesel engine exhaust and gasoline engine exhaust, evidence for carcinogenicity was evaluated as “inadequate.” Organic extracts of gasoline engine exhaust condensate induced cancer in mice and in rats; gasoline engine exhaust condensate also induced cancer. The Working Group concluded that there was “sufficient evidence” in experimental animals for the carcinogenicity of condensates of gasoline engine exhaust. Overall, gasoline engine exhaust was classified as “possibly carcinogenic to humans” (Group 2B).

IARC MONOGRAPH ON GLYPHOSATE

The second example of IARC Monograph evaluations is on glyphosate. Its description here is more condensed and serves primarily as background for the concluding thoughts on interference from vested interest groups. Glyphosate was nominated for consideration by the 2014 Advisory Group (AG) to recommend priorities for IARC Monographs during 2015-2019, recommended for priority evaluation by that AG and included by the IARC Monographs scientific secretariat as one of the pesticides for evaluation by the Volume 112 Working Group.⁴¹

Glyphosate is currently the most heavily used broad-spectrum herbicide. It is used in more than 750 different products and its use has increased substantially with the marketing of genetically modified glyphosate-resistant crop varieties. In humans, there was limited evidence for the carcinogenicity of glyphosate. Case-control studies of occupational exposure in the US, Canada, and Sweden reported increased risks for non-Hodgkin's lymphoma that persisted after adjustment for other pesticides. The cohort of the US Agricultural Health Study did not show a significantly increased risk of non-Hodgkin's lymphoma. In experimental animals, in male CD-1 mice, glyphosate induced a positive trend in the incidence of renal tubule carcinoma, a rare tumor. Another study reported a positive trend for hemangiosarcoma in male mice. A glyphosate formulation promoted skin tumors in an initiation-promotion study in mice. Glyphosate has been detected in the blood and urine of agricultural workers, indicating absorption. Glyphosate and glyphosate formulations induced DNA and chromosomal damage in mammals, and in human and animal cells *in vitro*. One study reported increases in micronuclei in residents of several communities after spraying of glyphosate formulations. Bacterial mutagenesis tests were negative. Glyphosate, glyphosate formulations, and aminomethylphosphonic acid (AMPA, a metabolite) induced oxidative stress in rodents and *in vitro*.

Based on limited evidence in humans, sufficient evidence in experimental animals, and further corroborated by strong mechanistic evidence the Working Group classified glyphosate as "probably carcinogenic to humans" (Group 2A).

VESTED INTEREST

There is a long history of interference with science of occupational and environmental carcinogens by vested interest groups. Asbestos is probably the best-known example, and asbestos lobbyists followed

⁴¹ See International Agency for Research on Cancer (IARC), *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 112: Some Organophosphate Insecticides and Herbicides* (Lyon: International Agency for Research on Cancer, 2017).

successful strategies developed by the tobacco industry: 1) creating doubt, 2) attacking science, 3) intimidating scientists, 4) lobbying policymakers, and 5) delaying action. Detailed case studies on global warming, second-hand smoke, asbestos, lead, plastics, and many other toxic materials are revealed in the thoroughly researched book by David Michaels, *Doubt Is Their Product: How Industry's Assault on Science Threatens Your Health*.⁴²

Industry's reaction to the IARC Monograph on glyphosate is another stark case study. IARC and WHO were faced with an unprecedented, "orchestrated campaign" from industry. These reactions included:

- Demands to Directors of IARC and WHO to withdraw the *Monograph's* evaluation
 - Lobbying politicians, agencies, WHO, and member states
 - Paid consultants criticize methods and findings
 - Re-evaluation by an industry-funded committee
 - Ghost-written scientific papers and press articles
 - Legal demands aimed to harass US scientists
 - Intimidating letters to international scientists
 - Inquiries by the US Congress into the scientific rigor of the Monographs.

Activities from industry and IARC's careful, but firm, responses are documented on IARC's Governance website.⁴³ Further, several books—like *Whitewash: The Story of a Weed Killer, Cancer, and the Corruption of Science*⁴⁴—and dossiers—like "The Monsanto Papers"⁴⁵—are providing in depth details and background information, including from previously secret documents revealed during the discovery phase of ongoing litigation.

During these challenging times, the IARC Monographs have been strongly supported by the vast majority of the scientific community⁴⁶ and by civic society. With the increasing global burden of cancer and the urgent need for a stronger focus on prevention on one side and, on the other side, a general political climate of deniers of science in general and specifically of pollution and its nexus with the global

⁴² See David Michaels, *Doubt Is Their Product: How Industry's Assault on Science Threatens Your Health* (Oxford: Oxford University Press, 2008).

⁴³ See International Agency for Research on Cancer (IARC), "Information for IARC Councils," governance.iarc.fr/ENG/infocouncils.php.

⁴⁴ See Carey Gillam, *Whitewash: The Story of a Weed Killer, Cancer, and the Corruption of Science* (Washington, DC: Island Press, 2017).

⁴⁵ See Stéphane Horel and Stéphane Foucart, "The Monsanto Papers," last modified November 20, 2017, *Environmental Health News*, www.ehn.org/monsanto-glyphosate-cancer-smear-campaign-2509710888.html.

⁴⁶ See Neil Pearce et al., "IARC Monographs: 40 Years of Evaluating Carcinogenic Hazards to Humans," *Environmental Health Perspectives* 123, no. 6 (2015): 507–514.

climate crisis and related massive adverse effects on human and planetary health, a strong and independent Monographs Programme is needed more than ever. Lessons learned from the exposed massive interference may help to strengthen authoritative and independent scientific consensus as the scientific basis for local, national, and global actions to prevent cancer. **M**

Kurt Straif, MD, is visiting scholar, Professor of Epidemiology, Co-Director of the Global Observatory on Pollution and Health of the Schiller Institute for Integrated Science and Society, at Boston College. After medical studies in Liège (Belgium), Heidelberg and Bonn (Germany), he started his career in internal medicine in Bonn. With a fellowship of the German Academic Exchange Office, he pursued an MPH at University of California Los Angeles (UCLA). Later, in Germany, he was assistant professor at the University of Giessen, focusing on occupational, environmental, and social medicine, and an assistant and associate professor in epidemiology and social medicine at the University of Münster. At the same time, he completed a PhD in epidemiology at the UCLA, with a focus on cancer epidemiology and epidemiologic methods. Since 2001, he had leading positions at the International Agency for Research on Cancer (IARC), first as a senior epidemiologist, Head of the IARC Monographs program, to classify carcinogenic hazards of all kinds of environmental exposures (chemical, biological, physical agents, and personal habits); Acting Head of a large epidemiological research group; and initiator of large international projects. In 2014, he relaunched the *IARC Handbooks of Cancer Prevention* with a broad perspective on prevention (breast cancer screening, avoidance of obesity, and colorectal cancer screening). Since 2017 he also supervises the World Health Organization Classification of Tumors (“Blue Books”). In 2016, he received the Champion of Environmental Health Research Award in commemoration of fifty years of Environmental Health Research by the National Institutes of Health. In 2018, he presented the Distinguished Lecture in Occupational and Environmental Cancer at the US National Cancer Institute.