Chapter 1. The role of epidemiology in cancer hazard identification by the *IARC Monographs* programme

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In the *IARC Monographs* programme, epidemiological evidence is typically synthesized according to precepts that take into account whether the design, conduct, and interpretation of such studies supports a causal interpretation of their findings. Evidence syntheses can in turn be used to support various public health measures, including hazard identification, risk assessment, intervention development, and impact assessment.

Since its inception, the aim of the *IARC Monographs* programme has been to identify carcinogenic hazards for humans, by integrating, for each agent under investigation, all available evidence from studies in humans, animals, and in vitro systems. Therefore, it is important that reviewers of the evidence on cancer in humans are acquainted with the wider context of their review work. For this purpose, Section 1.1 provides an overview of the working methods and procedures used in producing the *IARC Monographs*, as applied today (Annex 1 outlines their evolution since the programme's origins), Sections 1.2 and 1.3 deal specifically with cancer epidemiology, discussing the use and evaluation of studies on human cancers with actual examples from the *IARC Monographs* programme. Section 1.4 discusses issues related to conflicts of interest (COIs). Section 1.5 examines the cancer hazard classification of all agents hitherto evaluated by the *IARC Monographs* programme from the perspective of false-positive and false-negative conclusions. Approaches for further enhancing the incorporation of bias assessments in the context of cancer hazard identification are described in the Preface and Chapter 6.

1.1 Overview of cancer hazard identification in the *IARC Monographs* programme

As the cancer research arm of the World Health Organization (WHO), IARC has estimated that there were 19.3 million new cases of cancer globally in 2020, with a projected increase of nearly 50% by 2040 (Sung et al., 2021). While part of this increase is attributable to the ageing of global populations and increasing capabilities for and access to diagnosis, particularly in low- and middle-income countries, a growing prevalence of exposure to external causes of cancer – both known and unknown – has also been postulated. Primary prevention requires identification of the causes of cancer. Since 1971, the *IARC Monographs* programme has

convened experts in cancer epidemiology, cancer bioassays, and mechanistic studies to review and evaluate the evidence on carcinogenicity of a diverse set of agents, including chemicals, particles and fibres, physical and biological agents (e.g. ionizing radiation, viruses), pharmaceuticals, complex mixtures (e.g. air pollution), personal behaviours (e.g. tobacco smoking, opium consumption), and occupational exposure circumstances (e.g. occupational exposure as a painter or as a firefighter).

Over the course of 52 years, 136 meetings have been convened of expert Working Groups to deliberate on the evidence, resulting in the publication of detailed evidence evaluations that have identified 546 agents as *carcinogenic to humans*, *probably carcinogenic to humans*, or *possibly carcinogenic to humans*. The available literature is summarized and synthesized into *IARC Monographs* volumes using an approach documented in each volume in a Preamble (IARC, 2019), which has been included since the first volume was published in 1972. As scientific methods have evolved, the Preamble has been updated accordingly (Baan and Straif, 2022), 10 times between 1977 and 2019 (see Annex 1). The Preamble lays out the steps for selecting meeting participants, for the prevention and management of COIs, and for the conduct of the meeting, as well as the methods to be used for the evidence synthesis and integration. The most recent update to the Preamble emphasizes increased transparency and scientific rigour of the review, as well as modernized methods for literature searching and screening (Samet et al., 2020), as described in Section 1.2. Side Box 1.1 provides an overview of the current evidence synthesis and integration approach.

The *IARC Monographs* programme is a process of cancer hazard identification. Working Groups ascertain whether evidence supports a causal interpretation of any observed associations between an agent and one or more types of cancer; however, they do not conduct a full risk assessment, in which the quantification of the risk of cancer associated with specific routes and levels of exposure is carried out (Samet et al., 2022). Given this focus on hazard identification, the key question faced by Working Groups is whether associations that are observed support a causal interpretation, rather than being an artefact of poor study design, the result of incorrect analysis or interpretation, or due to confounding or biases such as information bias or selection bias. The approaches by which Working Groups judge cancer epidemiology studies, individually and collectively, are described in detail in Sections 1.2–1.3. For cancer in humans, there are prespecified categories for classifying the evidence evaluation: *sufficient*, *limited*, *inadequate*, and *evidence suggesting lack of carcinogenicity* (*ESLC*). The cancer sites for which there is judged to be *sufficient* evidence have been specifically identified for each agent since *IARC Monographs* Volume 98 (IARC, 2010), while the cancer sites for which there is judged to be *limited* evidence or *ESLC* have been identified since *IARC Monographs* Volume 100 (IARC, 2012a, b, c, d, e, f). For agents suspected to cause cancer, it is not possible to design ethical experiments in humans. Consequently, most of the epidemiological evidence evaluated in the *IARC Monographs* derives from observational studies. In order to reach a determination that there is *sufficient* evidence that an agent causes cancer in humans, the Working Group judges that a causal relation has been established for one or more cancer sites, in that a positive association has been observed in the body of evidence, and that chance, bias, and confounding can be ruled out with reasonable confidence as an explanation for these positive findings. When a determination is made that the evidence is *limited*, this implies that a causal interpretation is credible, in that a positive association between exposure and cancer has been observed in the body of evidence, but chance, bias, or confounding, or some combination thereof, could not be ruled out with reasonable confidence. When it is determined that the evidence is *inadequate*, this implies that the ensemble of research does not permit a conclusion about a causal association. This usually reflects one of the following reasons: no data or sparse data were available, or a positive association was not observed in the body of evidence, or findings were positive but were judged to be entirely explained by chance, bias, or confounding.

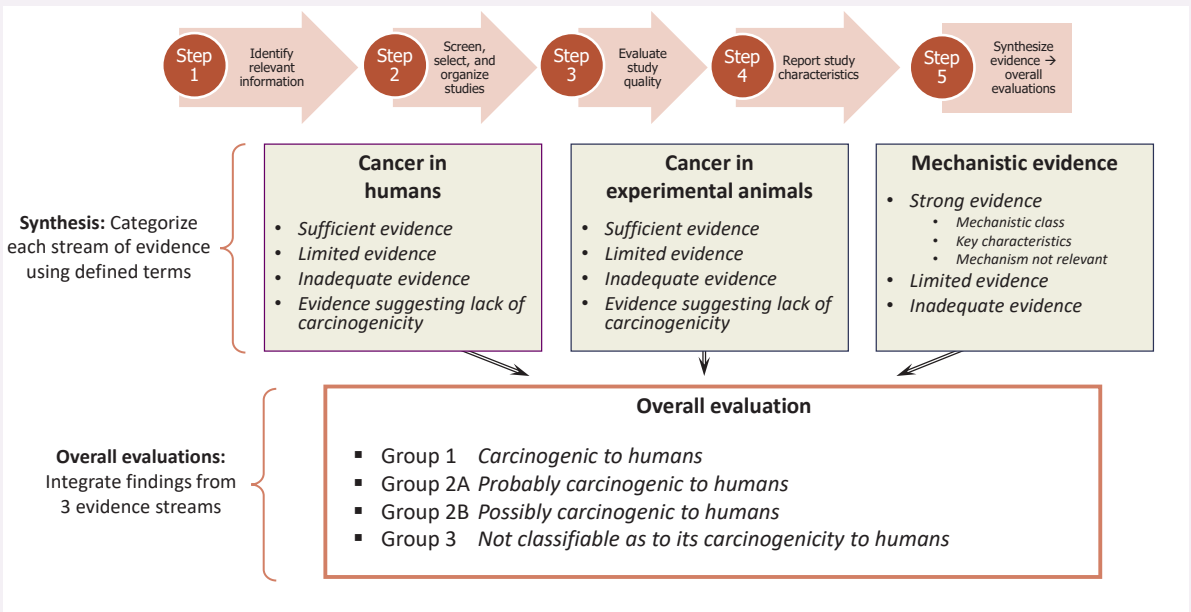
These classification categories have been largely unchanged since the revision of the *IARC Monographs* Preamble in Volume 30 in 1982 (IARC, 1983), when the phrase “chance, bias, and confounding” was introduced to differentiate between *sufficient* and *limited* evidence (see Annex 1). For a determination of *ESLC*, a judgement is made that no positive findings

Side Box 1.1. Evidence synthesis and integration in the *IARC Monographs*

As laid out in the current Preamble, adopted in 2019, the *IARC Monographs* evaluations are carried out in a five-step systematic review process (Fig. 1.1). Step 1 is the identification of relevant studies, by conducting extensive literature searches. Step 2 involves screening, selecting, and organizing the identified studies. Study quality (including consideration of potential biases) is evaluated in Step 3, and study characteristics are reported in Step 4. Step 5 of the review process, evidence synthesis and integration, is conducted at an 8-day meeting held at IARC in Lyon, France.

Three streams of evidence are considered in the *IARC Monographs* evaluation process: cancer in humans, cancer in experimental animals, and mechanistic evidence. The evidence is first synthesized individually by stream using well-defined criteria. Then the evidence is integrated across the streams, using guidelines established in the Preamble, into one of four groups: Group 1, *carcinogenic to humans*; Group 2A, *probably carcinogenic to humans*; Group 2B, *possibly carcinogenic to humans*, and Group 3, *not classifiable as to its carcinogenicity to humans* (Fig. 1.1). (text continues on page 7)

Fig. 1.1. Overview of the *IARC Monographs* evidence synthesis and evaluation process. Source: Compiled from Samet et al. (2020).



were seen in adequately powered and well-conducted studies at any exposure level and that bias could be ruled out as an explanation for the absence of an association. For example, for coffee drinking, there was deemed to be *ESLC* for cancers of the pancreas, liver, female breast, uterine endometrium, and prostate (IARC, 2018a). In practice, a designation of *ESLC* is often used when an inverse association is observed for a cancer site (e.g. such an inverse association was noted for coffee drinking and cancers of the liver and endometrium). Typically, *ESLC* for one or more cancer sites may occur together with *sufficient* or *limited* evidence of carcinogenicity for other sites (e.g. the agent tamoxifen exhibited *sufficient* evidence for causation of endometrial cancer and *ESLC* for breast cancer; IARC, 2012a).

The evidence for the two other streams, cancer in experimental animals and carcinogen mechanisms, is synthesized using different approaches from that used for cancer in humans (Samet et al., 2020). Once an evaluation is made regarding the evidence synthesis for each individual evidence stream, the three streams

Fig. 1.2. Possible combinations leading to overall evaluations during evidence integration in the *IARC Monographs* programme of cancer hazard identification.

Evidence of cancer in humans	Evidence of cancer in experimental animals	Mechanistic evidence	Evaluation
Sufficient	Irrelevant	Irrelevant	*Carcinogenic* (Group 1)
Limited or *inadequate*	*Sufficient*	*Strong* (exposed humans)	
Limited	*Sufficient*	*Limited* or *inadequate*	*Probably carcinogenic* (Group 2A)
Limited	*Limited* or *inadequate*	*Strong*	
Inadequate	*Sufficient*	*Strong* (human cells or tissues)	
Limited or *inadequate*	Irrelevant	*Strong* (mechanistic class)	
Limited	*Limited* or *inadequate*	*Limited* or *inadequate*	*Possibly carcinogenic* (Group 2B)
Inadequate	*Sufficient*	*Limited* or *inadequate*	
Inadequate	*Limited* or *inadequate*	*Strong*	
Inadequate	*Sufficient*	*Strong* (does not operate in humans)	*Not classifiable* (Group 3)
All other situations			

are integrated by the Working Group into an overall synthesis leading to one of the four classification groups (Fig. 1.2).

The overall evaluation reflects the degree of certainty about the strength of evidence regarding the carcinogenicity of the agent to humans. A determination of *sufficient* evidence regarding one or more cancer sites in humans leads directly to a Group 1 classification, regardless of the evidence in the other two streams. If *sufficient* evidence for cancer in humans is not shown for any cancer site but there is *limited* evidence regarding one or more cancer sites, then evaluations from the other two streams may inform the overall classification: a determination of either *sufficient* evidence for cancer in experimental animals or *strong* mechanistic evidence (or both) combines with the *limited* evidence for cancer in humans to give a Group 2A classification. Recent examples include night shift work and 1,1,1-trichloroethane: for night shift work, human cancer evidence was *limited* for cancers of the breast, prostate, and colorectum (IARC, 2020); for 1,1,1-trichloroethane, evidence was *limited* for multiple myeloma (IARC, 2022). In both instances, there was *sufficient* evidence for cancer in experimental animals, and for night shift work there was also *strong* mechanistic evidence in experimental systems. However, in most instances, particularly for environmental or occupational exposures, a determination of *sufficient* evidence for cancer in humans is accompanied by *sufficient* evidence in experimental animals, *strong* mechanistic evidence, or both (Cogliano et al., 2011; IARC, 2012b, c, d, e, f). It is possible to arrive at a Group 1 classification with *limited* or even *inadequate* evidence regarding cancer in humans if there is *sufficient* evidence for cancer in experimental animals and *strong* mechanistic evidence in exposed humans. Three examples are ethylene oxide (IARC, 1994), neutron radiation (IARC, 2000), and perfluorooctanoic acid (PFOA; Zahm et al., 2024).

1.2 Methods for evaluating human cancer studies in cancer hazard identification

1.2.1 The IARC Monographs *approach*

Section B.2 of the *IARC Monographs* Preamble (IARC, 2019) presents two parts specifically devoted to human cancer studies: the first details considerations in the evaluation of individual studies, and the second addresses considerations for evaluation of the overall body of evidence. The first part (Sections B.2a–B.2c) addresses the types of study to be considered for the evaluation of human cancer

evidence, indicating that high-quality case–control and cohort studies usually provide the most suitable data for such an exercise; it then mentions the procedures to be followed for the identification of eligible studies of cancer in humans and outlines the key aspects of assessment of an individual study's quality and informativeness (the latter term designating the overall ability of a study to identify an effect when one exists, or to identify the lack of an effect when none exists). Four cardinal aspects of each study should be examined: the study description and design, the study population (including subpopulations, such as people potentially susceptible to cancer), the outcome measurement, and the exposure measurement. Furthermore, in evaluating the adequacy of statistical methods of analysis, which have evolved considerably in scope and sophistication in recent decades, the role of random and systematic errors, collectively designated as chance, bias, or confounding, should be considered. The *IARC Monographs* Preamble (IARC, 2019) notes, "For the sake of economy and simplicity, in this Preamble the list of possible sources of error is referred to with the phrase 'chance, bias, and confounding', but it should be recognized that this phrase encompasses a comprehensive set of concerns pertaining to study quality." The Preamble emphasizes, "These sources of error do not constitute and should not be used as a formal checklist of indicators of study quality. The judgement of experienced experts is critical in determining how much weight to assign to different issues in considering how all of these potential sources of error should be integrated and how to rate the potential for error related to each of these considerations." As a transition to the second part, the combination of studies via meta-analysis and pooled analyses is sketched (in Section B.2d) as a valuable, albeit not prescriptive, tool to check the consistency of results across studies.

The second part of Section B.2e presents a range of considerations in assessing the body of epidemiological evidence, stating in the opening paragraph, "There is no formulaic answer to the question of how many studies of cancer in humans are needed from which to draw inferences about causality, although more than a single study in a single population will almost always be needed. The number will depend on the considerations relating to evidence described." This part carries an obvious footprint of the viewpoints presented by Hill (1965), from which the available epidemiological evidence needs to be critically scrutinized. Although formulated to assist causal inference on environmental exposures of various kinds, the Hill perspective has become more generally influential in discussions on causal inference from observational studies. Set aside from these viewpoints is the issue of ruling out chance, namely the effects of sampling errors, estimated by tests of significance and confidence limits, on which Hill takes a firm position (Hill, 1965): "No formal tests of significance can answer [causal] questions. Such tests can, and should, remind us of the effects that the play of chance can create, and they will instruct us in the likely magnitude of those effects. Beyond that they contribute nothing to the 'proof' of our hypothesis." This position remains, in essence, valid today (Savitz et al., 2024).

Each of these viewpoints focuses on a feature of the epidemiological data that, if present, supports a causal interpretation of an observed association between an exposure and a risk of cancer. The nine features, as labelled by Hill (but in a different order), are reported in Table 1.1. With the exception of temporality, which is, in fact, an absolute requirement, the relative weight of each feature is not fixed, and the absence of a feature does not automatically detract from a causal interpretation. However, consistency – which reflects, within an observational context, the important concept of reproducibility in science – ranks generally high in weight but must be balanced by consideration of the relative informativeness and potential for bias of the different studies contributing evidence to the evaluation.

The evaluation of several of the features in Table 1.1 to infer the causal nature of an observed association evolved early in the *IARC Monographs* programme; it has been maintained for the past 40 years, unchanged at its core, and has been accompanied by several specifications and explicit indications, outlined in Annex 1. For example, consideration number 5, consistency (which has always had a prominent role for causal inference), has recently been better specified in terms of triangulation methods (e.g. Lawlor et al., 2016; for additional information, see Chapter 6). As further examples, the Preamble now advises Working Groups to explicitly consider the direction and magnitude of biases (e.g. as arising from exposure misclassification or unmeasured confounding), not simply their presence, and discusses the possibility of *ESLC* of an exposure.

Table 1.1. Features of an association between exposure and cancer risk that support a causal interpretation within the *IARC Monographs* programme

Feature	Evaluation within *IARC Monographs*
1. Temporality	There should be unequivocal evidence that the onset of exposure has preceded the onset of a detectable cancer.
2. Strength	Once all feasible adjustments for confounding and biases have been implemented, a strong resulting association (e.g. with high relative risk) is less likely than a weak one to be fully explained by residual or unknown confounding and biases, and therefore is more likely to be of causal nature.
3. Specificity	This consideration, suggesting that evidence is stronger when carcinogenicity is observed in only one or a few organs or tissues (rather than in many), has been variably invoked by Working Groups. For agents that exhibit systemic exposure (e.g. ionizing radiation), specificity is not highly valued. For other agents, where exposure is not systemic (e.g. some lung carcinogens), a finding of specific effects only in organs where exposure occurs strengthens a causal interpretation. Furthermore, an association may sometimes be judged as much stronger when exposure is redefined by restriction to specific subgroups (e.g. people with a particular genetic polymorphism or exposed to a single chemical) or the outcome is restricted to specific histological or molecular subtypes of a cancer.
4. Biological gradient	In carcinogenesis, an all-or-none response to a carcinogen very rarely, if ever, occurs. Hence, finding that an increasing exposure level is associated with an increasing cancer risk is in accordance with established biological knowledge on cancer causation.
5. Consistency	A causal interpretation of an association receives considerable support when findings are consistent between studies carried out in different populations, with possibly different exposure and confounding patterns or effect modification, or with different study designs and methods (accounting for differences in study informativeness, e.g. exposure contrast or latency considerations). Study informativeness is an important consideration here. A study is informative to the extent that it is capable of detecting an increased risk when it truly exists; this goes beyond study power and depends on the availability of the right population with the right exposures and the right design with the right cancer type. Fully informative studies permit sounder interpretation of results than do minimally informative studies.
6. Experiment	A reduction of risk after reduction or cessation of an exposure points to the exposure as the causative agent of the risk; this indication carries particular weight if the reduction or cessation occurs in the framework of a purposely designed intervention (e.g. a regulatory measure to reduce the level of an air pollutant).
7. Plausibility	Firmly established biological mechanisms (e.g. a precursor lesion well documented as entailing a high risk of subsequent cancer) speak in favour of the causal nature of the association between an exposure and a cancer if, for example, the same exposure is also found to be associated with the precursor lesion. Biological mechanisms still under investigation do not contribute to the evaluation of the evidence in humans and are examined separately, within the mechanistic evidence stream of an *IARC Monographs* evaluation process.
8. Coherence	In Hill's words, the causal interpretation "should not seriously conflict with the generally known facts" (Hill, 1965) about the disease and – it can be added – the exposures, such as their respective distributions, patterns, and trends within and between populations. Coherent findings across related cancer sites with respect to exposure to the target organ (e.g. as for cigarette smoking or alcohol consumption) can support a causal interpretation.
9. Analogy	This weak feature is not usually considered, except in the strict sense of regarding as analogous certain chemicals with very close structural and activity properties; this consideration would occur in the mechanistic evidence stream evaluation for the *IARC Monographs*.

Side Box 1.2. Examples of other programmes of cancer hazard identification

Since 1978, the United States Department of Health and Human Services has had the legislative mandate to publish a cancer hazard report (prepared by the National Toxicology Program), known as the Report on Carcinogens (RoC), which lists substances (defined as "agents, substances, mixtures, exposure scenarios") that are "either known or reasonably anticipated to be a human carcinogen" (Lunn et al., 2022). Evaluation by the RoC requires that a significant number of people be exposed in the USA. Like the *IARC Monographs* programme, the National Toxicology Program RoC adheres to a well-defined and structured process for evaluating substances for their carcinogenic hazard. This process also includes consideration of human cancer, animal bioassay, and mechanistic evidence streams. Considerations in the evaluation of human cancer studies are similar to those used in the *IARC Monographs* (Lunn et al., 2022). Study informativeness (identified from assessments of risk of bias and study sensitivity) is emphasized for human cancer evaluations. One major difference between the programmes is that the RoC is drafted by scientific staff within the National Institute of Environmental Health Sciences programme, rather than external expert Working Groups, and goes through external expert peer review and public comment before finalization. A detailed comparison of cancer classification methods and results has been published by Lunn et al. (2022), but it is worth noting that there is generally high concordance between the agents classified in Group 1 in the *IARC Monographs* and those classified by the RoC as "known to be carcinogenic to humans".

Other major programmes that undertake hazard identification do so within the context of a formalized risk assessment, for example the Integrated Risk Information System (IRIS) programme of the United States Environmental Protection Agency (U.S. EPA, 2022), the Dutch Expert Committee on Occupational Safety (DECOS; Health Council of the Netherlands, 2012), the European Food Safety Agency, and many others. These programmes evaluate human cancer evidence in a variety of ways, often using evaluation approaches (e.g. IRIS and DECOS) similar to those of the *IARC Monographs* programme, with careful consideration of study quality and potential for bias. (text continues below)

1.2.2 Other major programmes of cancer hazard identification

While the *IARC Monographs* programme is the world's oldest cancer hazard identification programme, other health organizations worldwide have been engaged in the conduct of cancer hazard identification, some for decades. Side Box 1.2 briefly mentions a few such programmes, emphasizing the extent to which their evaluation approaches differ from those of the *IARC Monographs*.

1.3 Examples of current approaches to bias consideration in *IARC Monographs* evaluations

Historically, and specifically since the implementation of the Preamble revision in 1987 (IARC, 1987), Working Groups have used a variety of approaches to determine whether chance, bias, and confounding can be ruled out with reasonable confidence, as a delimiter between evaluations of *sufficient* and *limited* evidence, or whether a causal interpretation is even credible, in distinguishing between *limited* and *inadequate* evidence. Working Groups closely scrutinize the adequacy of study design and analysis methods and of reporting of results, noting detailed strengths and limitations of the studies evaluated. The evidence triangulation principle has long been applied in considering whether different studies that have diverse types of bias point to the same conclusion. For example, ecological and case–control studies of arsenic in drinking-water had different bias potentials from each other and from cohort studies of inhalation exposure to arsenic in workers; however, all three types of study strongly pointed to an excess risk of lung cancer (IARC, 2012c). Case–control studies of low-level radon exposure in the general population (which had some potential for recall bias and non-differential exposure misclassification) complemented cohort studies of uranium miners exposed to high-dose radiation levels, lending confidence to a causal interpretation of the association between radon progeny and lung cancer (IARC, 2012d).

Negative control outcomes, i.e. outcomes that are plausibly related to confounders but not to the agent of interest, can help elucidate whether confounding exists. As an example,

the association between an agent and chronic obstructive pulmonary disease (COPD) is often examined by Working Groups in conjunction with that observed for the agent in question and lung cancer. Because COPD is related strongly to tobacco smoking but less strongly, or not at all, to many other lung carcinogens, the absence of an association between an agent and COPD provides reassurance that smoking is not a confounder of the association observed between the agent and lung cancer. More quantitative approaches when information about the confounder is available for only some subjects (or is not available for any subject), such as the use of indirect adjustments, and worst-case assumptions about confounder–exposure distributions, have been rarely used by Working Groups but are explicitly mentioned in the Preamble (IARC, 2019, p. 17).

The current Preamble (IARC, 2019, pp. 15–16) emphasizes the explicit evaluation of exposure assessment quality, including the expected impact of any related biases on the direction and magnitude of measures of association between exposure and cancer.

To illustrate the approaches used by Working Groups, we draw examples from the four topics of interest that will be discussed throughout the rest of this volume (as noted in the Preface): radiofrequency electromagnetic field (RF-EMF) radiation (Example 1.1), consumption of red meat (Example 1.2), night shift work (Example 1.3), and consumption of opium (Example 1.4). It is important to note that, in addition to concerns about bias and confounding, study

Example 1.1. Evaluation of radiofrequency electromagnetic field (RF-EMF) radiation by the *IARC Monographs*

Radiofrequency electromagnetic fields, as generated in mobile phone use, were evaluated in *IARC Monographs* Volume 102 as *possibly carcinogenic to humans* (Group 2B), on the basis of *limited* evidence for cancer in humans and *limited* evidence of carcinogenicity in experimental animals (IARC, 2013). The Working Group noted in their rationale that the human epidemiological evidence was mixed. Some small case–control studies, several studies of occupational exposure, and a large cohort study, all investigating brain tumours (particularly gliomas) were regarded as uninformative because of several potential sources of exposure misclassification and insufficient control for possible confounding. The bulk of the evidence came from reports of the Interphone study – a very large international, multicentre case–control study – and a separate large case–control study in Sweden on acoustic neuroma and glioma and meningioma of the brain. Both studies showed an association between mobile phone use and glioma and acoustic neuroma. However, each study presented non-negligible limitations. In the Interphone study, an increased risk of glioma was found only for the highest levels of estimated cumulative exposure (cumulative call time). However, differential participation rates between participants in the case and control groups – compounded with lower participation rates of control participants who were non-regular mobile phone users than of control participants who were regular users – could have resulted in a lower estimated risk of brain cancer among regular mobile phone users than the true risk for the participating centres. This is one of the reasons given that chance and bias could not be excluded as possible explanations for the increased risk at the highest levels of exposure. The study in Sweden revealed an increased risk of glioma, with a gradient with increasing cumulative call time. The sequential approach, using a self-administered questionnaire followed by a phone interview to collect exposure and confounder information, raised the possibility of information bias, with validation studies not having been carried out in the pertinent population. There were also concerns about recall bias, which were somewhat tempered by the specificity of the positive associations for two tumour subtypes (glioma and acoustic neuroma) but not others. The limitations of the two studies led the Working Group to the evaluation that there was *limited* evidence for cancer in humans; it appears that the reviewers had made full use of the published results in the main and ancillary publications of all studies, and especially of the Interphone study and the study in Sweden, to probe the existence and direction of biases without, however, formally estimating the overall impact of biases for each study. (text continues above)

Example 1.2. Evaluation of red meat consumption by the *IARC Monographs*

Red meat consumption was evaluated as *probably carcinogenic to humans* (Group 2A), on the basis of *limited* evidence for cancer in humans and *strong* mechanistic evidence (IARC, 2018b). The Working Group identified a large number of cohort and case–control studies, conducted across five continents. They noted substantial variation in the quality of study design and exposure assessment instruments, as well as in the definition of red meat consumption. Cohort studies with quantitative information on red meat consumption derived from validated dietary questionnaires and with good control for confounding were deemed most informative, together with a small subset of case–control studies, in examining risk of colorectal cancer. The main determinant in reaching a conclusion of *limited* evidence for cancers of the colorectum and pancreas in humans was the inconsistency of results in some of the larger, higher-quality studies. For prostate cancer, concerns about reporting bias and outcome misclassification for aggressive forms of disease were additionally mentioned. No formal appraisal of bias was carried out for these or other cancer sites in relation to red meat consumption. (text continues on page 13)

Example 1.3. Evaluation of night shift work by the *IARC Monographs*

Night shift work (IARC, 2020) was evaluated as *probably carcinogenic to humans* (Group 2A), on the basis of *limited* evidence for cancer in humans, *sufficient* evidence for cancer in experimental animals, and *strong* mechanistic evidence in experimental systems. There were two types of human cancer study, with different bias concerns: cohort studies of night shift workers in the general population as well as among nurses and flight crew, and population-based case–control studies. Most cohort studies did not show positive findings, but most could not detect associations for specific time windows of sensitivity for induction of breast cancer (e.g. premenopausal breast cancer after recent or non-recent night shift work). Others had short follow-up periods, leading to concerns about study power or the ability to detect cancer risk with long latency. In addition, non-differential exposure misclassification was a serious concern, but the Working Group did not attempt to quantify the magnitude of this bias. A large and informative pooled case–control study (Cordina-Duverger et al., 2018) showed positive associations between night shift work and breast cancer overall, with a positive exposure–response association observed for only one of several exposure metrics. Here, differential exposure misclassification (due to recall bias) and selection bias were of primary concern, with bias away from the null (i.e. a no-association measure) being thought most likely, but the Working Group did not estimate the magnitude of the bias or whether it could explain the magnitude of risk elevation found in the case–control studies. The Working Group concluded that there was *limited* evidence for breast cancer (as well as cancers of the prostate and colorectum) in humans. (text continues on page 13)

Example 1.4. Evaluation of opium consumption by the *IARC Monographs*

In 2020, opium consumption was evaluated as *carcinogenic to humans* (Group 1), with *sufficient* evidence for cancer in humans (IARC, 2021). The evidence regarding an association between opium consumption and cancer consisted of one large well-conducted cohort study and several dozen case–control studies. All were population-based or hospital-based, and most were conducted in the Islamic Republic of Iran. In the Working Group's evaluation, the use of causal diagrams helped to elucidate which covariates might be confounders. The Working Group used directed acyclic graphs (DAGs) to identify the main concerns regarding bias; these included residual confounding (primarily by tobacco smoking), selection bias, and recall bias for case–control studies, and non-differential exposure misclassification, reverse causation, and protopathic bias for all study designs.

The cohort study was subject to non-differential exposure misclassification, and exposure history was captured at one time point and was not further updated. However, the use of biomarkers of opium metabolites was thought to provide good validation for the questionnaire-based exposure assessment method. Residual confounding by tobacco smoking was a second concern, although the cohort study had detailed estimates of several smoking measures, which were used to adjust for tobacco smoking. Opium-related risk was also examined in never-smokers of tobacco.

In the population-based case–control studies, the main concern was recall bias, and there was some evidence that the choice of control group influenced the estimated odds ratios. Selection bias due to differential participation rates of case and control participants was a potential concern, as were protopathic bias and reverse causation. However, the latter two sources of bias were thought to have been adequately dealt with by investigators during the analyses. A formal assessment of the impact of some of these sources of bias was evaluated in an annex (IARC, 2021), and this work was important to the Working Group's evidence synthesis, which concluded that there was *sufficient* evidence in humans that opium consumption causes cancers of the lung, larynx, and bladder, and *limited* evidence that opium consumption causes cancers of the oesophagus, pancreas, pharynx, and stomach. However, the different sources of potential bias were evaluated individually and were not combined in any quantitative analysis. (text continues on page 13)

informativeness is used to evaluate reasons for consistency (or not) of findings, one of the key principles of causal inference used in the *IARC Monographs*.

1.4 Minimizing conflicts of interest in cancer hazard identification

In contemporary research, COI is a widespread phenomenon, but its structural social aspects and causes are beyond the scope of this volume. The relevance of COIs here stems from the potential for inducing erroneous scientific judgements in cancer hazard identification, hampering and delaying the attainment of scientifically valid evidence, with the consequence of increased health and economic costs to society. The United States Institute of Medicine defines a COI as "a set of circumstances that creates a risk that professional judgement or actions regarding a primary interest will be unduly influenced by a secondary interest" (Lo and Field, 2009). Of these circumstances, research funding, including employment support, and personal financial interests have been well documented after surveys of published studies as having the potential to distort scientific judgements in several areas of epidemiology, including studies for cancer hazard identification (Michaels, 2008; Mandrioli et al., 2016; Lundh et al., 2017). Reviewers of the evidence pertinent to cancer hazard identification are at times confronted with the situation where the influence of an identified COI on the aims, overall informativeness, design, results, and interpretation of a study cannot be directly evaluated. In such instances, separate consideration and comparison of results can be made of studies involving clear COIs and studies not so affected, with full reports on whether and why this examination leads to equal or different treatment of the results of the two types of study when drawing interpretative conclusions.

Of course, reviewers themselves may have COIs, and in evidence evaluation and synthesis COI avoidance is no less important than methodological correctness. In the *IARC Monographs* programme, IARC has developed and applies a COI prevention and control policy. Before a Working Group meeting, each potential participant, including the IARC Secretariat, fills in a WHO declaration of interests form to report financial interests, employment and consulting work (including remuneration for serving as an expert witness), individual and institutional research support, and non-financial interests, such as public statements and positions related to the meeting. The declared interests are then assessed to determine whether there is a COI barring participation in the Working Group in question. Meeting participants occupy one of five positions: Working Group full member, Invited Specialist, Representative (of a national or international health agency), Observer, or IARC Secretariat member. Only Working Group full members, assessed as having no COI, can take part in all phases of the evidence evaluation, while other participants have different limitations (Table 2 of IARC, 2019) to formally control for potential COI effects arising from their positions.

It is important for a reader of an *IARC Monograph*, papers cited in it, and published commentaries on it, to consider the possible presence of COIs by carefully examining COI and funding statements and, when in doubt, even an author's body of work beyond the single paper being consulted. The mere presence of COIs may indeed be difficult, if not impossible, to detect if no information at all is provided or when authors declare no COI despite, for instance, funds for the work being provided by the producer or user of the agent under evaluation.

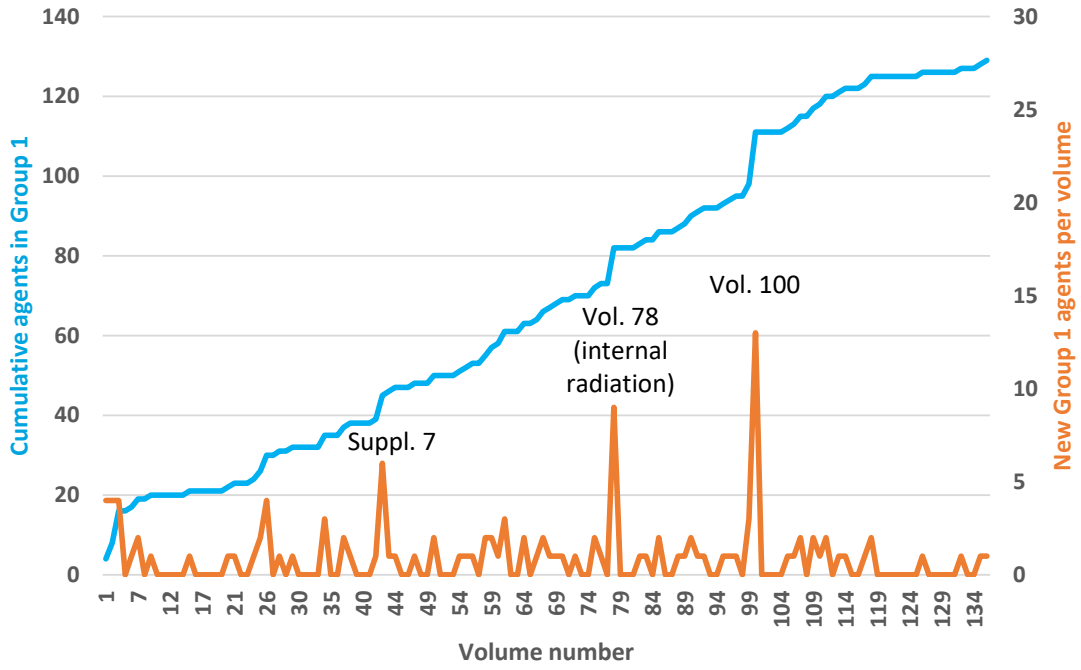
Different competent and COI-free researchers may legitimately take varying viewpoints on the same body of evidence. The Preamble instructs the IARC Secretariat to include a representation of diverse credible viewpoints when assembling a Working Group. Such diversity of viewpoints can be essential in ensuring that all aspects of study quality, informativeness, and potential for bias are brought forward for deliberation and evaluation by the Working Group; this also minimizes any risk of bias that may derive from the viewpoints of Working Group participants themselves as authors of studies of the agent being evaluated.

1.5 False-positives and false-negatives in cancer hazard identification: the *IARC Monographs* experience over more than 50 years

Agents are prioritized for evaluation in the *IARC Monographs* programme if there is evidence for human exposure and some evidence for or suspicion of carcinogenicity (IARC, 1998), based on studies in humans or animals (Samet et al., 2020). Thus far, in the *IARC Monographs* programme, 129 agents have been identified as *carcinogenic to humans* (Group 1). There has been a steady growth in the identification of these carcinogenic agents over the life of the programme (Fig. 1.3), with step changes at particular points when certain agents with an abundance of human cancer evidence were considered eligible for evaluation (e.g. biological agents in the mid-1990s, ionizing radiation in the late 1990s), and in the re-evaluations of all agents, published in *IARC Monographs* Supplement 7 (IARC, 1987), and of all Group 1 agents, published in *IARC Monographs* Volume 100 (Cogliano et al., 2011). (In *IARC Monographs* Volume 100, some broad agent groupings were divided to better denote the different cancer sites in humans with *sufficient* or *limited* evidence.)

In evaluating the human cancer evidence, as noted in Section 1.2, expert Working Groups judge whether the evidence at hand supports a causal interpretation with reasonable confidence. The question may arise about to what extent this process of judgement is likely to result in false-positives (e.g. a declaration that there is *sufficient* evidence for a causal association between the agent and a given cancer site when the association is actually not causal) or false-negatives (e.g. a failure to identify a truly causal association). Several critics have argued that expert judgement of human cancer observational data has the potential to produce many false-positives (Taubes, 1995; Ioannidis, 2005; Boffetta et al., 2008). Other authors have suggested that such concerns lack foundation, in part based on the experience of the *IARC Monographs* programme (Cogliano et al., 2004; Blair et al., 2009; Pearce et al., 2015; Saracci, 2017; McCullough et al., 2022). Over the 52-year history of the programme, there have been many opportunities to examine this question in detail. During this time, a determination that there is *sufficient* evidence of carcinogenicity in humans for at least one cancer type has almost

Fig. 1.3. Time series showing the addition of new agents in Group 1 over the 52-year history of the *IARC Monographs* programme.

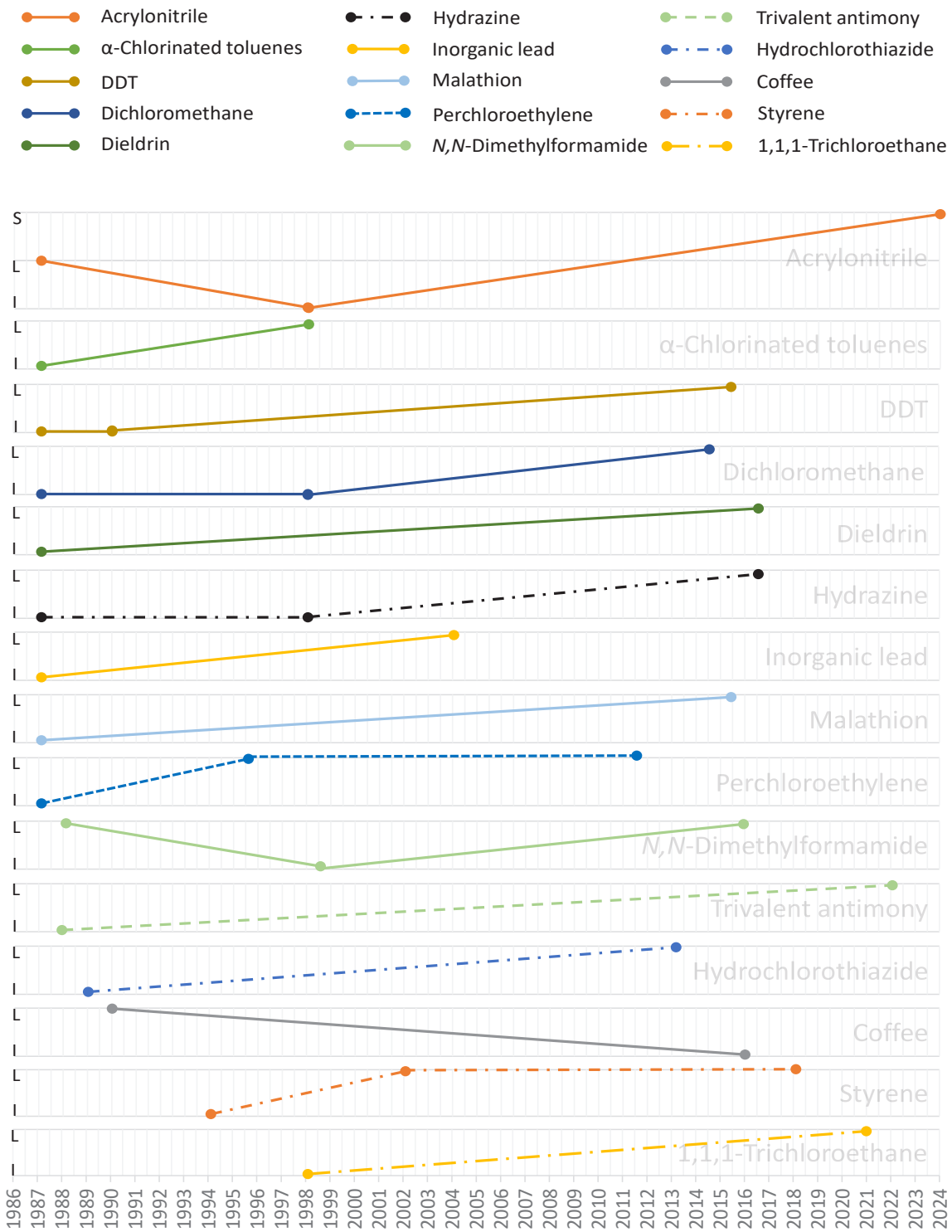


never been reversed. For example, as published in *IARC Monographs* Volume 100 (IARC, 2012a, b, c, d, e, f), different Working Groups re-evaluated the evidence for all the (more than 100) agents then classified in Group 1. With the exception of human papillomavirus (HPV) type 66, all of these re-evaluated agents were reaffirmed as Group 1. For many, if not most, of the agents, the human cancer evidence had strengthened since the previous evaluation, and additional cancer sites with *sufficient* or *limited* evidence were identified. There is also broad concordance between classifications of *sufficient* evidence in the *IARC Monographs* and those in other hazard identification programmes (Lunn et al., 2022). These findings suggest that there is a low false-positive rate for a determination that there is *sufficient* evidence of carcinogenicity in humans.

The category of *limited* evidence is characterized by some uncertainty, in which new evidence from informative studies might be expected to shift the evaluation to either *sufficient* or *inadequate* (or even *ESLC*). However, in practice, agents have more often moved upwards in classification than downwards. For agents with *limited* evidence in humans, in many cases (e.g. arsenic, dioxin, polychlorinated biphenyls, trichloroethylene) the evaluations have advanced, over time, to *sufficient*. Other agents that have moved between classifications over time were much more likely to move up from *inadequate* to *limited* than down from *limited* to *inadequate* (Fig. 1.4). Examples of such agents that have moved up include industrial chemicals, such as α-chlorinated toluenes, dichloromethane, styrene, and 1,1,1-trichloroethane, and pesticides, such as dichlorodiphenyltrichloroethane (DDT), dieldrin, and malathion. Coffee is an example of an agent that has moved down from *limited* to *inadequate*. *N,N*-dimethylformamide moved from *limited* to *inadequate* in 1998 and back to *limited* in 2016. Acrylonitrile moved from *limited* to *inadequate* in 1998 and then to *sufficient* in 2024.

In 1983, a workshop held in Oxford, United Kingdom, discussed interpretations of so-called negative evidence in human studies (i.e. evidence deriving from studies in humans that was deemed to be unconvincing) for 10 agents with *sufficient* evidence from cancer bioassays (Wald and Doll, 1985). For most of the 10 agents, the workshop attendees concluded that the evidence was

Fig. 1.4. Agents whose classification has shifted between categories of *inadequate* and *limited* regarding human cancer over the life of the *IARC Monographs* programme (excluding most agents that were eventually classified as *sufficient*). I, *inadequate*; L, *limited*; S, *sufficient*.



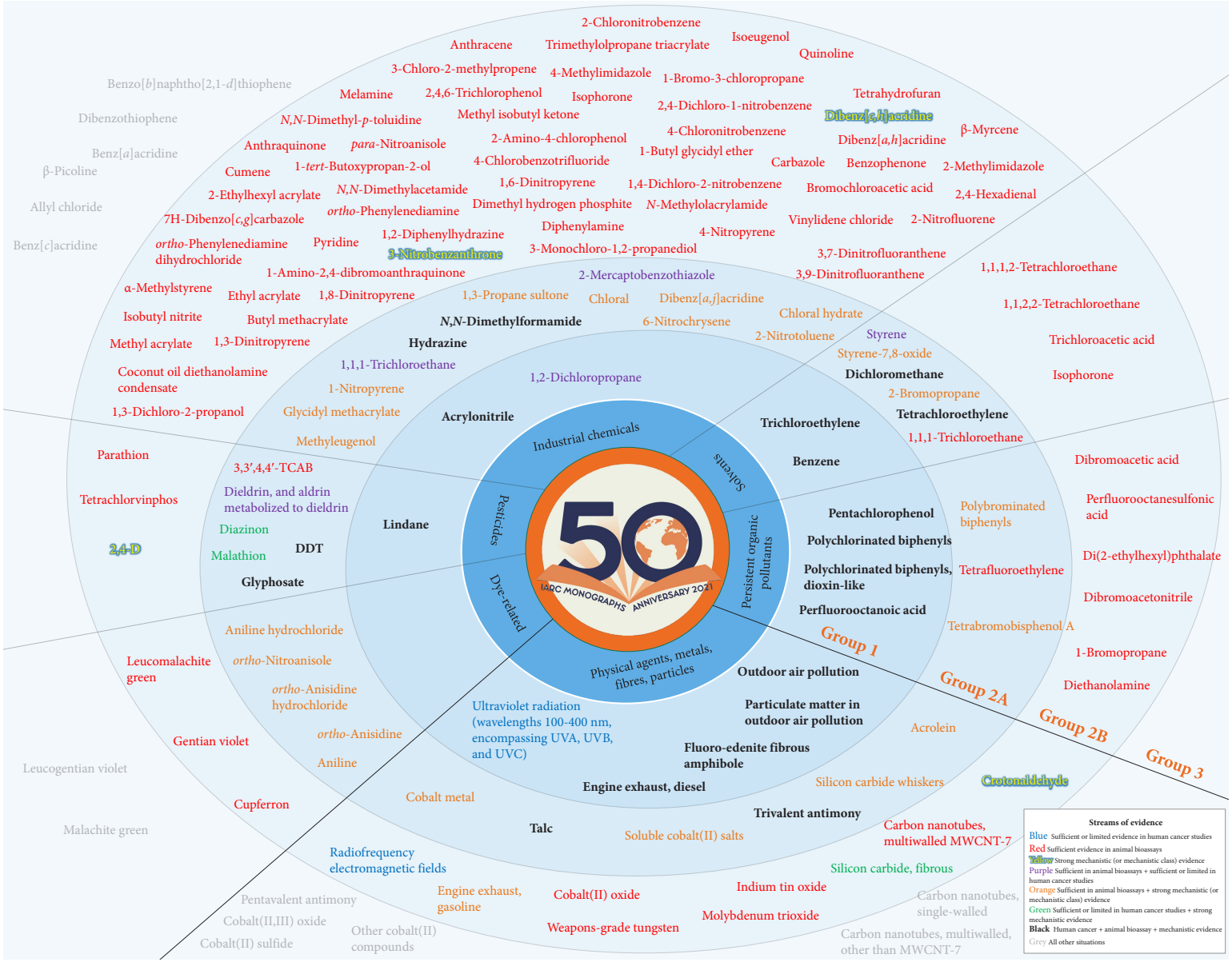
likely to remain classified as *inadequate* or even as *ESLC* in humans. Notably, in the 40 years since this workshop, 3 of the 10 agents (beryllium, formaldehyde, and oral contraceptives) were found to have *sufficient* evidence for cancer in humans, and another 4 (DDT, hydrazine, nitrites, and hairdresser exposures to dyes) to have *limited* evidence in humans. Improvements in the number, quality, and informativeness of epidemiological studies were key to these changes for these agents, whose previous evaluations could be viewed as false-negatives. A similar analysis of the agents for which there had been *inadequate* evidence regarding cancer in humans, published in *IARC Monographs* Supplement 7 (IARC, 1987), found that many of these had advanced in classification since then (Cogliano et al., 2004). Such patterns suggest that many epidemiological biases in the literature on carcinogenicity (e.g. exposure misclassification, selection biases, and even confounding) are operating in a downward direction or towards the null.

One potential reason for the relatively low false-positive rate in the classification of agents in Group 1 is the fact that several lines of evidence contribute to the nomination of agents for evaluation; in other words, potential carcinogenicity in humans is often preceded by evidence of cancer in experimental animals or of carcinogen mechanisms. For nearly all the Group 1 agents re-evaluated in *IARC Monographs* Volume 100 (IARC, 2012a, b, c, d, e, f), there was persuasive evidence of carcinogenicity in experimental systems. Since then, 150 environmentally relevant agents have been evaluated (or re-evaluated) in the *IARC Monographs* programme. Fig. 1.5 shows their classifications (moving outwards from Group 1 in the centre to Group 3 at the periphery), grouped by agent type and coloured by the evidence stream contributing to the evaluation. Notably, there have been contributions from several evidence streams for nearly all Group 1 agents. It is quite rare for human cancer evidence (either *sufficient* or *limited*) to form the sole basis for an evaluation (one example is radiofrequency electromagnetic field [RF-EMF] radiation). In Group 2A, there are numerous instances of *limited* human cancer evidence combined with either mechanistic or bioassay evidence. It is worth noting that nearly all these evaluations were based on occupational cancer epidemiology studies; this may be due to the generally higher exposure contrasts and well-characterized exposure information (leading to enhanced informativeness) in occupational settings (Loomis et al., 2018).

1.6 Conclusion

Cancer epidemiology studies have formed a crucial part of the evidence base for hazard identification since the early 1970s. Observational studies in which bias and confounding have been reasonably ruled out have been the main source of *sufficient* evidence leading to a determination that an agent is *carcinogenic to humans* – a process that has proven relatively conservative over the decades. The Preamble to the *IARC Monographs* calls for explicit examination of the potential for sources of bias (including confounding) to explain observed findings. This chapter provides examples of how such biases have been considered in recent *IARC Monographs* evaluations for agents found to have *limited* evidence (RF-EMF radiation, night shift work, and consumption of red meat) or *sufficient* evidence (opium consumption) of carcinogenicity in humans. Subsequent chapters explain concepts for explicitly evaluating the roles of confounding, information bias, and selection bias using these agents as examples, and demonstrate how these concepts may be incorporated into evidence synthesis.

Fig. 1.5. Environmentally relevant agents classified by the *IARC Monographs* in Volumes 101–136.



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