Annex 1. Evolution of the *IARC Monographs* Preamble from early investigations and reviews in the 1960s until the present day

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A1.1 The beginnings: cancer in occupational groups

Observations in humans pointing to life circumstances linked to the appearance of tumours go far back in history. Significant examples based on accurate observation of special population groups, rather than isolated clinical cases, have been quoted (Clemmesen, 1965): the reporting in the 16th century of a frequent respiratory disease, later identified as cancer in 1879 by Härting and Hesse, among miners in the Erzgebirge (Ore Mountains) of central Europe; the description of scrotal cancer in chimney sweepers by Pott in 1775; and the statistical evidence of an increased frequency of breast cancer in nuns presented by Rigoni-Stern in 1844, with Ramazzini's observations predating this by nearly 150 years (Franco and Franco, 2001).

However, it is since the burgeoning industrialization of the 18th century that humans have come into contact with a constantly expanding number of artificial and synthetic substances, i.e. natural substances that have been highly transformed and mixed. Specific industries or sections within industries came to represent nearly experimental situations of often prolonged and high-concentration exposure of workers to a variety of chemicals and chemical mixtures. Wilhelm Hueper, the first director of the Environmental Cancer Section at the United States National Cancer Institute, collected in a massive textbook, *Occupational Tumors and Allied Diseases* (Hueper, 1942), the accumulated evidence in humans and, through experiments in animals, on occupational exposures as causes of cancers. The documentation on cases in humans was often based on fragmentary and incomplete clinical and pathological data, and Hueper himself, not to mention his numerous critics (Sellers, 1997), regarded it as mostly circumstantial evidence of carcinogenicity, which, however, in favourable situations could justify medicolegal recognition of an occupational cause of a cancer (throughout his professional life, Hueper was a strong advocate of workers' health protection). The ultimate proof of occupational etiology of a chemical agent had to come through successful reproduction of the neoplasms in animals.

A1.2 Tobacco smoking and the emergence of new epidemiological methods

The criterion of reproduction in animals, which was in itself problematic, later proved to be a hurdle in

identifying as a cancer hazard the exposure to tobacco smoking, which after centuries of use in various forms had become widespread with the industrial production of cigarettes in the first half of the 20th century. During the same period, mortality and morbidity statistics, as well as clinical reports in several countries, indicated a marked increase of several cancers, especially of the respiratory tract, among men, suggesting a link to the spreading habit, also among men, of regular cigarette smoking. To probe this hypothesis, several studies were conducted, particularly in Germany in the years between the two World Wars (Davey Smith and Egger, 2005). A remarkable short paper by Pearl (1938) clearly showed a sizeable curtailment of the life expectancy of smokers compared with that of non-smokers.

The investigation of carcinogenicity in humans of occupational and environmental exposures and of tobacco smoking gained a renewed impetus after the Second World War. In 1950, three well-conducted case–control studies on lung cancer and cigarette smoking were published (Doll and Hill, 1950; Levin et al., 1950; Wynder and Graham, 1950); studies of worker populations accrued in the following years (Case et al., 1954; Doll, 1955). Later, the first results from cohort investigations of smoking were published (Doll and Hill, 1956; Hammond and Horn, 1958). A range of methodological issues emerged, which were unclear or even poorly understood at the time, prompting the fast development of new conceptual insights and methods of epidemiological study planning and analysis. The contributions of Cornfield are still particularly remarkable: as early as 1951, he had pointed out the essential link to risk as estimable from both cohort and case–control studies (Cornfield, 1951); in 1959, he provided a decomposition of crude risk into a net (adjusted) risk component and a component ascribable to confounding variables (Cornfield et al., 1959); and in 1962, he first used logistic regression (via discriminant analysis) to relate a dependent variable to several independent variables (Cornfield, 1962).

The time was soon ripe for two landmark publications in epidemiology: *Smoking and Health*, commissioned by the United States Surgeon General (U.S. Public Health Service, 1964), which in its conclusions indicted cigarette smoking as a cause of lung and laryngeal cancer and pipe smoking as a cause of oral cancer, and Hill's paper *The environment and disease: association or causation?* (Hill, 1965). Both publications addressed thorny issues on, and provided guidelines for, the establishment of the causal role of an exposure solely on the basis of observational studies in humans in the absence of both randomized studies in humans and reproduction of carcinogenesis in animals. The latter was the missing piece in the evidence linking tobacco smoking to cancer; both the United States Surgeon General's report and Hill's paper downplayed its role relative to epidemiological evidence, which was regarded as potentially capable of standing on its own feet. This represented a significant departure, which was bound to influence epidemiological thinking for several decades, from Hueper's criterion of reproducibility in animals, which, in turn, reflected the time-honoured etiological criteria in bacteriology (called Koch's postulates), the field of medicine in which most disease causes known at that time had been successfully identified.

Against this backdrop, two publications stand out that summarized the epidemiological evidence on cancer hazards existing by the mid-1960s: the scholarly *Statistical Studies in the Aetiology of Malignant Neoplasms* (Clemmesen, 1965) and the narrative critical review *The Prevention of Cancer: Pointers from Epidemiology* (Doll, 1967).

A1.3 1972: the first *IARC Monographs*

IARC started operating in Lyon, France, in 1967. Soon, requests were received from different public health quarters to provide an authoritative list of carcinogens for humans. Lorenzo Tomatis, who was at that time the head of the Unit of Chemical Carcinogenesis at IARC, realized that no such list could be provided without the ad hoc systematic work of assembling and evaluating all available evidence for carcinogenicity of an agent, integrating results from studies in humans and in experimental animals. The *IARC Monographs* programme was born, with the title of *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man* ("man" became "humans" in 1978), and the first volume was published in 1972. The title specified "chemicals" because this was the class of agents within which the largest number of exposures suspected to be cancer hazards were found at that time.

The first volume of the *IARC Monographs* (IARC, 1972) presented the evaluation, by a Working Group

composed of 12 scientists external to IARC, of 19 chemicals in the categories of inorganic substances, chlorinated hydrocarbons, aromatic amines, *N*-nitroso compounds, and natural products. The Working Group had met for 5 days (later to become 8 days for most *IARC Monographs* meetings) with the support of a Secretariat of IARC staff members; also attending were technical advisors, Observers, and WHO Representatives. The consensus-making body for the evaluations comprised only the Working Group members. An opening note to the reader stressed that no guiding principles were generally accepted to extrapolate results in experimental animals to humans when no data in humans were available; such principles might be developed only on the basis of some definite cases, and hence the *IARC Monographs* would continue in the initial format until sufficient background material had been accumulated. More generally, the same applied to the integration of results from human and animal studies, which for the time being could only be summarized separately, and to defining principles to weigh the evidence on carcinogenicity. For instance, the human evidence for lead and lead salts read, "There is no evidence to suggest that exposure to lead salts causes cancer of any site in man", but there was no indication of how this conclusion was reached by the Working Group. During the next 5 years, the introductory section of each *Monographs* volume was enriched by an increasingly detailed description of key points to be considered by the Working Group in reviewing and assessing the evidence. In addition to data on the chemical and physical characteristics of an agent, its uses and occurrence in the human environment, and results from cancer studies in humans and animals, other relevant biological data, in particular on mutagenicity and genotoxicity, came to be included.

A1.4 1972–1980: *IARC Monographs* Volume 17 and Supplement 1

Volume 17 of the *IARC Monographs* (IARC, 1978) had two features arising from the first years of experience. First, all introductory remarks were grouped into a Preamble, which described the *IARC Monographs* methodology and the Working Groups' operational procedures. Second, the predefined terms *sufficient evidence of carcinogenicity* and *limited evidence of carcinogenicity* were adopted, separately for animals and humans, accompanied by an outline of what types of result would support each definition.

A major advance in the evolution of the *IARC Monographs* followed 2 years later, with a Supplement to the series (IARC, 1979); a special Working Group provided some guidance for rating the evidence, separately, for studies in animals and in humans. For the latter, *sufficient* evidence indicated a causal association, *limited* evidence suggested a possible effect but was not sufficient to demonstrate a causal association, and *inadequate* evidence was considered to be qualitatively or quantitatively insufficient to permit any conclusions. As a final evaluation step, on the basis of the combined evidence from studies in animals and in humans, an agent was to be classified in one of three groups.

- Group 1: the agent is *carcinogenic to humans*. This classification was to be applied only if there was *sufficient* evidence for cancer in humans.
- Group 2, subdivided into two subcategories: Group 2A, the agent is *probably carcinogenic to humans*; Group 2B, the agent is *possibly carcinogenic to humans*. These subcategories indicate different degrees of confidence in judging the evidence as supportive of carcinogenicity.
- Group 3: the agent *cannot be classified as to its carcinogenicity to humans*.

With the introduction of this overall classification, the basic layout of the *IARC Monographs* evaluation was established. It is still maintained (see Section 1.1) as a framework suitable for incorporating updates as required by advances in cancer research.

A1.5 1981–1990: *IARC Monographs* Supplements 4 and 7

Two important steps in the evolution of the *IARC Monographs* took place in 1982 (IARC, 1982) and 1987, leading to a Preamble structure and contents that proved subject only to marginal additions for several decades. In the formulation of Supplement 7 (IARC, 1987), several types of study were enlisted to investigate cancer hazards in humans: case reports, descriptive studies of cancer occurrence in populations, and analytical case–control and cohort studies (possible intervention studies also fall into this category). On the basis of a review of findings from such studies, the evidence of carcinogenicity could be placed into one of three categories. A declaration of *sufficient* evidence of carcinogenicity indicates: "The

Working Group considers that a causal relation has been established between exposure to the agent and human cancer. That is, a positive relation has been observed between exposure to the agent and cancer in studies in which chance, bias, and confounding could be ruled out with reasonable confidence." Without this reasonable confidence, the evidence is to be rated as *limited*. If the studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of a causal association, the evidence is to be rated as *inadequate*. A fourth category, *evidence suggesting lack of carcinogenicity* (*ESLC*), as derivable from negative studies, was included with a concluding remark: "the possibility of a very small risk at the levels of exposure studied can never be excluded."

It is not coincidental that the clear and concise formulation of the criteria concerning the evidence in humans came in the years when epidemiological methods and statistical methods for epidemiology underwent in-depth revision and innovative expansion. At IARC itself, Breslow and Day began in 1976 to prepare two volumes in the Statistical Methods in Cancer Research series – to which this volume belongs – devoted, respectively, to the analysis of case–control studies (Breslow and Day, 1980) and cohort studies (Breslow and Day, 1987). As Breslow and Day (1980) stated, "The theme is, above all, one of unity. While much of the recent literature has focused on the contrast between cohort and case–control approaches to epidemiological research, we emphasize that they in fact share a common conceptual foundation, so that, in consequence, the statistical methodology appropriate to one can be carried over to the other with little or no change." The books, extensively illustrated by actual analyses of data sets from epidemiological studies, offered the best presentation, at once theoretically rigorous and practically applicable, of statistical methods in epidemiology available at the time. They became a popular reference for epidemiologists well outside the cancer field.

A1.6 1991–2010

Until 1992, the classification of an agent in Group 1 (*carcinogenic to humans*) had been strictly dependent on the existence of *sufficient* evidence from studies of cancer in humans. In 1991, in view of the continuously accruing knowledge of a variety of carcinogenesis mechanisms, a Working Group introduced a critical addition. As recorded in *IARC Monographs* Volume 54 (IARC, 1992), this reads: "Exceptionally, an agent (mixture) may be placed in this category when evidence in humans is less than sufficient but there is *sufficient* evidence of carcinogenicity in experimental animals and *strong* evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity."

In subsequent years, the *IARC Monographs* included three important new features. First, Volume 88 of the *IARC Monographs* (IARC, 2006) carried for the first time, in an introductory note to the reader, a much-needed terminology clarification: "The term 'carcinogenic risk' in the *IARC Monographs* series is taken to mean that an agent is capable of causing cancer under some circumstances. The *IARC Monographs* evaluate cancer hazards, despite the historical presence of the word 'risks' in the title."

Second, emphasis had constantly been placed by IARC not only on the methodological procedures used to evaluate carcinogenicity to humans but also on the objective conditions within which such evaluations were to take place. The Preamble to *IARC Monographs* Volume 94 (IARC, 2010), stemming from a review by an ad hoc advisory group, codifies in a detailed description, aimed at preventing conflicts of interest, the role of each of the five different components of participants in a *Monographs* meeting: voting Working Group members, non-voting Invited Specialists, Representatives (of national and international health agencies), scientific Observers, and the IARC staff Secretariat.

Third, in 2008 and 2009, a massive review of human carcinogens was undertaken for Volume 100 (IARC, 2012a, b, c, d, e, f), in which the data on all the agents previously classified in Group 1 (*carcinogenic to humans*) were updated and the evaluations reviewed, adding specifications of target organs. On the basis of the newly accumulated evidence, only one of the agents (human papillomavirus type 66) was moved downwards from Group 1 by the six Working Groups conducting the review.

A1.7 2011 until today

It was already apparent in the Volume 100 review (IARC, 2012a, b, c, d, e, f) that mechanistic and other relevant biological data had a steadily growing role in carcinogenicity evaluation. This promoted an overall revision of the Preamble, in 2019

(IARC, 2019a, b; Samet et al., 2020), alongside a transformation of the title to *IARC Monographs on the Identification of Carcinogenic Hazards to Humans*, which clearly defines in today's accepted terminology the programme's activity as actually implemented since the very beginning. The revision of the Preamble took into account advances in the assessment of mechanistic data, including, in particular, the identification of key characteristics of carcinogens, which provide a framework for the organization of mechanistic data and the assessment of strengths as well as gaps in evidence. The current Preamble reflects these advances and describes a process to reach a carcinogenicity classification by integrating, along parallel and harmonized lines, the three streams of evidence: experimental animal bioassays, mechanistic investigations, and epidemiological studies.

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