GENERAL REMARKS

1. Introduction

This one-hundred-and-eighth volume of the *IARC Monographs* includes evaluations of the carcinogenic hazard to humans of exposure to 14 herbal products or pharmaceutical drugs. None of these, except hydrochlorothiazide, have been previously evaluated by the Working Group.

Hydrochlorothiazide – a pharmaceutical drug – was considered in 1989 by an *IARC Monographs* Working Group (IARC, 1990), and was evaluated as *not classifiable as to its carcinogenicity to humans (Group 3)* based on *inadequate evidence* for carcinogenicity in humans and in experimental animals.

A summary of the findings of this meeting appears in *The Lancet Oncology* (Grosse *et al.*, 2013).

Among the agents that are known to cause cancer in humans specifically, there are several pharmaceuticals and other drugs. Volume 100A of the *IARC Monographs* (IARC, 2012) reviewed pharmaceuticals that in previous evaluations had been categorized as *carcinogenic to humans (Group 1)*, primarily on the basis of epidemiological evidence for causation. In respect of specific chemical carcinogens, the number of agents classified as *carcinogenic to humans* that are therapeutic drugs is second only to the number of agents that have been identified in the context of occupational exposures.

Apart from pharmaceutical drugs that are industrially produced agents identified with a specific therapeutic usage, a major aspect of the use of drugs worldwide involves herbal products. Estimates from WHO indicate that 80% of the world's population has used herbal products as medicines. Use of the term "herbal medicine" is arbitrary in many contexts. In particular, a wide variety of pharmaceutical drugs, that is, agents recognized as having a particular pharmacological mode of action and associated clinical benefit, are derived from plants or other natural sources. This category of agent is likewise represented in previous *IARC Monographs*; and one – aristolochic acid – has been classified as a Group 1 agent (IARC, 2012).

Pharmaceutical drugs are subject to strict regulation in most countries, and their availability is highly restricted. This may not be the case with materials used in the preparation of herbal medicines. The therapeutic benefit of such herbal products may have been recognized in certain communities for centuries. Moreover, herbal products are available in several regulatory paradigms, ranging from foods and dietary supplements to cosmetics and over-the-counter (non-prescription) and prescription drugs. Worldwide, this means that product quality and composition may vary from country to country and within countries, even when different products bear the same name. In addition, the use of particular herbal products may vary markedly between countries and between communities within a country.

2. Exposure to herbal products and pharmaceuticals

Herbal products are complex mixtures that originate from biological sources. Unlike single-entity pharmaceuticals, plants contain thousands of primary and secondary metabolic constituents. In addition, raw materials are inherently variable because their chemical composition depends on factors such as geographical origin, weather, harvesting practices, while the chemical composition of the finished herbal products may not match that of the parent plants, and products frequently contain multiple botanical ingredients.

Discussions of exposure to natural products can be complicated by several factors. The first is the market category in which the product falls. Herbal products can be sold as conventional foods or food additives (e.g. flavouring or colouring agents), as dietary supplements, as cosmetic ingredients, or as herbal medicines (various national regulatory schemes may classify these as natural health products, therapeutic goods, phytomedicines, herbal medicinal products, traditional medicines, or conventional drugs). There may also be use of self-collected plants that are not marketed products.

Herbal medicine preparations are herbal products and consequently constitute complex mixtures. The biological impact, and specifically the carcinogenicity of complex mixtures, may be addressed by consideration of information concerning the mixture, and its variability in different contexts, and also by consideration of information concerning biologically active components within such mixtures. Information relevant to possible carcinogenicity may be most adequately addressed with reference either to the mixture or to the active component(s). Therefore, some *Monographs* in the present volume are specified with reference to the plant itself, i.e. *Aloe vera*, *Ginkgo biloba*, goldenseal, or kava. Other *Monographs* are specified with reference to individual components known to occur in particular plants, as is the case for pulegone and digoxin. Certain previous *IARC Monographs* evaluations are immediately relevant to the present evaluations to the extent that they involve components (e.g. quercetin for *Ginkgo biloba*, anthraquinones for *Aloe vera*) or metabolites (e.g. phenobarbital for primidone) of agents considered in the present volume.

Over the past several decades, there has been a revolution in the production, sale, and use of herbal products. In the 1970s, botanicals were largely sifted, cut, or powdered plant material in the form of a tablet, capsule, tea, or tincture. More recently, herbal products are often derived from intensely processed, carefully controlled organic extracts of plant material that have been spray-dried onto a solid carrier or diluent and then formed into a hard or soft capsule or tablet. The goal of many such processes is to create "standardized" extracts adjusted to contain consistent amounts of selected compounds of interest. Unfortunately, most standardized extracts focus on one or a handful of the thousands of constituents of the whole plant, so that even standardized extracts that are created using different processing techniques (e.g. different solvents, different ratios of plant to solvent) may achieve the desired levels of the desired chemical constituents while being otherwise chemically dissimilar. Attempts to compare herbal products by viewing the entire phytochemical fingerprint are beginning to appear, but these techniques have not yet had time to have an impact on the market or the publicly available scientific literature (van Beek & Montoro, 2009).

There are several advantages to using such highly processed raw materials. These include the ability to produce dosage forms that are more uniform in their composition, and the ability to preferentially concentrate the desirable constituents of a plant while leaving behind undesirable constituents. Because products are frequently

referred to generically by the name of the plant in marketing and consumer-use surveys, it is difficult to differentiate between exposure to the crude plant material or to unique, highly processed proprietary extracts that differ significantly from both the plant source and from other proprietary products. In countries where there is pre-market review and product licensing, products must often conform to published compositional standards, such as those in the United States Pharmacopoeia or the European Pharmacopoeia; and similarly named products marketed in this regulatory environment are likely to be relatively similar to each other in composition, but may be very dissimilar from products that do not meet such standards.

In addition to the broad variability in composition of herbal products that are available to consumers, problems in interpreting published scientific studies of herbal products have been reported. Wolsko *et al.* (2005) performed a systematic review of the "Materials and Methods" sections of 81 published studies on herbal products. They noted that only 12 (15%) of the studies reported any kind of quantitative chemical analysis of the study material, and that only 8 (10%) of those reporting analysis reported results of the analysis. In addition, only 40 of the studies (49%) provided the Latin binomial name of the study material, only 8 (10%) identified the part of the plant used, and only 23 (28%) described the extraction/processing method used to create the product. A larger review by Gagnier *et al.* (2011) reported similar findings. To prevent such problems in future studies, Swanson (2002) and Gagnier *et al.* (2006) have published guidelines for the reporting of studies on natural products.

While some organizations that conduct safety studies adhere to or surpass the above guidelines when selecting test articles or designing studies, it would be useful if these guidelines became standard practice, as the reproducibility and reliability of safety studies would be greatly enhanced. Unfortunately, while such recommendations are useful, selecting the article to be tested from among dozens or hundreds of products with similar or identical names but widely divergent compositions remains a major obstacle.

As with most herbal products, there may be some controversy surrounding generalizability of conclusions for a commercial entity, because commercial products are very diverse in terms of processing, composition, and intended use. Attempts to identify the predominant form of an herbal product in the market place are pure conjecture in the absence of data. This is a recurring theme for all discussions on herbal products.

The ability of the Working Group to gauge the extent of global exposure to herbal products was very limited, since the quality and quantity of data available were inconsistent across countries. Having better information on patterns of use and on product composition would provide a means to prioritize the herbal products considered in this volume for such activities as policy formulation or further research needs.

While the available information on exposure to pharmaceuticals was more abundant and accessible than that on herbal products, limitations remain. For the most part, information on prescribing patterns outside the USA was not available to the Working Group. In addition, published studies indicated that patterns of adherence and persistence are suboptimal for medications used to manage or treat chronic conditions. And while prescribing patterns are available for some drugs, such data do not exist for over-the-counter drugs; consequently, exposure estimates must be made using means similar to those used to estimate exposure to herbal products (e.g. *Aloe vera*, for which over-the-counter use is difficult to quantify), namely sales data and consumer use surveys. Although not widely available or widely accessible, such data for over-the-counter drugs is more informative than for herbal products sold as foods or dietary supplements because drug products with similar names are required to be similar in composition.

As indicated above, exposure can generally be much more accurately measured for pharmaceuticals than for other agents, and therapeutic doses used in humans are often closer to those tested in experimental animals. Nonetheless, characterizing the true nature of exposure to drugs in relation to carcinogenicity is complicated by the variability in adherence to drugs and their varying patterns of use – intermittent versus continuous.

Exposure to herbal products or pharmaceutical drugs may occur as a consequence of occupational exposure of people involved in production or manufacture of these agents. Exposure may also occur as a result of water pollution by these agents. Generally, levels of occupational or environmental exposure are much lower than levels of exposure experienced by people using the respective herbal products or drugs. Almost no information was available to the Working Group concerning occupational or environmental circumstances of exposure to the agents evaluated in this volume.

3. Epidemiological studies of populations using drugs

The *Monograph* on digoxin exemplifies the complications in drug nomenclature that may arise due to differences in professional practice and disciplines (e.g. manufacturer, medical professional). As explained therein, the term "digitalis" as used with reference to chemical specifications may refer to a plant extract, while the same word in a medical therapeutic context may refer to a particular category of agents (e.g. digoxin, digitoxin). Such incongruities not only contribute to potential misunderstanding of data; in an immediate sense, they may complicate adoption of a particular term as the appropriate identification of the subject of a *Monograph* and/or the subject of evaluation statements adopted within a particular *Monograph*. In some instances, studies may generate epidemiological data that refer to the use of particular classes of drug, rather than particular individual drugs. Interpretation of such data to infer effects attributable to particular drugs, such as pioglitazone, rosiglitazone and hydrochlorothiazide, and the small number of available epidemiological studies, may render this task difficult or almost impossible.

Historically, in *IARC Monographs* evaluations for which relevant epidemiological data were available, determination of causality on the basis of associations reported in epidemiological studies has always been recognized as both challenging and of critical importance. In general terms, this subject is addressed in the Preamble to the *IARC Monographs*, and the matters raised in that context are fundamental to all such epidemiological data. In the specific case of epidemiological findings in relation to pharmaceutical drugs, it is self-evident that the exposed individuals are not a representative sample of the community, but rather are individuals identified by a diagnosis in consequence of which they have received the drug in question. At one extreme, increased risk of cancer in such individuals may be caused by the drug they have received. At the other extreme, an association between increased risk of cancer and use of a particular drug may be totally independent of causality and arise for several reasons: because patients with a particular disease are at greater risk of malignancy; because patients with a particular disease are more liable than the community in general to be exposed to an independent factor that causes or is correlated with increased risk of cancer; or because the symptoms of an undiagnosed cancer may also prompt the use of a drug, which can subsequently be suspected as its cause. An additional problem is that patients commonly receive more than one drug, and determination of the carcinogenicity of any single drug may be difficult.

4. Extrapolating from specific scientific findings

While historically, multiple studies of carcinogenicity in experimental animals may have been conducted on a single test agent in several independent laboratories, today the massive expense involved in rigorous testing for carcinogenicity in experimental animals often means that only one or two well conducted studies of carcinogenicity (often in one strain of rat and/or one strain of mouse, and typically involving males and females) may be available in the peer-reviewed literature or from government agency reports that are publicly available. As indicated in the Preamble, such studies, ideally conducted under good laboratory practice, may be able to establish *sufficient evidence* of carcinogenicity in experimental animals, depending upon the nature of results obtained.

Again, in relation to "single studies" as outlined above, when the test agent is a complex mixture, exemplified, for example, by an herbal product, it may not be possible to assume that the agent being tested is identical to either the material marketed under the same name and/or material tested in other studies that might otherwise be understood to indicate possible mechanism(s) of carcinogenesis or to exclude particular mechanism(s) of carcinogenesis.

As indicated in the Preamble, the *IARC Monographs* evaluations are wholly dependent on publicly available data that are exemplified by published research results in the peer-reviewed literature. This information comprises only a subset of data on pharmaceutical drugs, specifically excluding "commercial in-confidence" findings of the type provided by industry to national or multinational regulatory authorities in the context of applications to market particular drugs. The initiatives of the European Medicines Agency and other organizations to make such data publicly available are properly noted in this context.

5. Considerations beyond hazard identification

Many (if not most) regulatory decisions concerning putative carcinogens necessitate consideration not only of perceived hazard, but also of potential benefit. It is crucial, therefore, that regulatory decisions affecting drug availability include assessment not only of potential carcinogenicity (and other adverse effects), but also of the health benefits derived from their usage.

References

Gagnier JJ, Boon H, Rochon P, Moher D, Barnes J, Bombardier C; CONSORT Group(2006). Recommendations for reporting randomized controlled trials of herbal interventions: Explanation and elaboration. *J Clin Epidemiol*, 59(11):1134–49. doi:10.1016/j.jclinepi.2005.12.020 PMID:17027423

Gagnier JJ, Moher D, Boon H, Beyene J, Bombardier C (2011). Randomized controlled trials of herbal interventions underreport important details of the intervention. *J Clin Epidemiol*, 64(7):760–9. doi:10.1016/j.jclinepi.2010.10.005 PMID:21208777

Grosse Y, Loomis D, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L *et al.* International Agency for Research on Cancer Monograph Working Group (2013). Carcinogenicity of some drugs and herbal products. *Lancet Oncol*, 14(9):807–8. doi:10.1016/S1470-2045(13)70329-2 PMID:24058961

IARC (1990). Hydrochlorothiazide. *IARC Monogr Eval Carcinog Risks Hum*, 50:293–305. PMID:2292804

IARC (2012). Pharmaceuticals. Volume 100 A. A review of human carcinogens. *IARC Monogr Eval Carcinog Risks Hum*, 100:Pt A: 1–401. PMID:23189749

Swanson CA (2002). Suggested guidelines for articles about botanical dietary supplements. *Am J Clin Nutr*, 75(1):8–10. PMID:11756054

van Beek TA, Montoro P (2009). Chemical analysis and quality control of *Ginkgo biloba* leaves, extracts, and phytopharmaceuticals. *J Chromatogr A*, 1216(11):2002–32. doi:10.1016/j.chroma.2009.01.013 PMID:19195661

Wolsko PM, Solondz DK, Phillips RS, Schachter SC, Eisenberg DM (2005). Lack of herbal supplement characterization in published randomized controlled trials. *Am J Med*, 118(10):1087–93. doi:10.1016/j.amjmed.2005.01.076 PMID:16194636