Toxicology Reports 5 (2018) 504–511

Contents lists available at ScienceDirect

Toxicology Reports

journal homepage: www.elsevier.com/locate/toxrep

What is the meaning of 'A compound is carcinogenic'?

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ARTICLE INFO

Keywords:
Carcinogenesis
Chemicals
Genotoxic
Risk assessment

ABSTRACT

Chemical Carcinogens are compounds which can cause cancer in humans and experimental animals. This property is attributed to many chemicals in the public discussion, resulting in a widespread perception of danger and threat. In contrast, a scientific analysis of the wide and non-critical use of the term ‚carcinogenic' is warranted. First, it has to be clarified if the compound acts in a genotoxic or non-genotoxic manner. In the latter case, an ineffective (safe) threshold dose without cancer risk can be assumed. In addition, it needs to be investigated if the mode-of-action causing tumors in laboratory animals is relevant at all for humans.

In case the compound is clearly directly genotoxic, an ineffective threshold dose cannot be assumed. However, also in this case it is evident that high doses of the compound are generally associated with a high cancer risk, low doses with a lower one. Based on dose-response data from animal experiments, quantification of the cancer risk is carried out by mathematical modeling. If the safety margin between the lowest carcinogenic dose in animals and the relevant level of exposure in humans exceeds 10,000, the degree of concern is classified as low. Cases, where the compound turns out to be genotoxic in one study or one test only but not in others or only *in vitro* but not *in vivo*, are particularly difficult to explain and cause controversial discussions. Also for indirectly genotoxic agents, an ineffective (threshold) dose must be assumed. The situation is aggravated by the use of doubtful epidemiological studies in humans such as in the case of glyphosate, where data from mixed exposure to various chemicals were used. If such considerations are mixed with pure hazard classifications such as 'probably carcinogenic in humans' ignoring dose-response behavior and mode-of-action, the misinformation and public confusion are complete. It appears more urgent but also more difficult than ever to return to a scientifically based perception of these issues.

1. Introduction

Toxicological risk assessment is a science-based approach aimed at describing the quantitative risk of adverse effects of chemicals, preferentially in humans. It is the final goal of toxicological risk assessment to provide a rational basis for eventual regulatory measures in order to avoid or exclude such adverse outcome. The methods and results are not only discussed among scientists and regulatory bodies but also in the public.

Likewise, there are frequently reports in the press about the occurrence of chemicals or pollutants in the environment, in food or in the human body. For the author, the editor *etc.* the question is at hand, if this news is worthwhile being published. A common denominator of such reports is the issue that a vulnerable target such as ‚the environment, nature, plants, animals or humans may be at risk of being harmed. If officials such as representatives of a government, an authority *etc.* comment such news, they often claim that a risk cannot be excluded completely. Such a notion is often misunderstood, *i.e.*, it seems to indicate that a realistic risk in fact exists. The novelty of the news increases dramatically if it can be made plausible that the occurrence of the, chemical may or will cause a real danger including damage to the vulnerable target.

If an agency, authority or another official body has made such a vague statement, this will be mentioned in the report. If the scientific analysis reveals a more or less equivocal picture, *i.e.*, some reports underpin a risk whereas others dismiss it, the report will in many instances tend to give more weight to the concerns than to the reliefs.

This way of communicating the facts follows an idea similar to the so-called ‚precautionary principle since it tends to be more ‚on the safe side and has the positive side effects that the news gains more attention. A common way to illustrate such concerns is the notion that the, chemical is 'suspected to cause cancer'. Such a comment reads much easier than the notion that, the institution X has expressed such concerns whereas institutions Y and Z have dismissed them.

Exactly the same situation occurred, *e.g.*, in the case of the herbicide glyphosate which was classified as ‚probably carcinogenic in humans 'by the International Agency for Research on Cancer, an institution of the World Health Organization (WHO) [1], whereas other institutions

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https://doi.org/10.1016/j.toxrep.2018.04.002
Received 17 January 2018; Received in revised form 14 March 2018; Accepted 6 April 2018
Available online 07 April 2018

in the field such as the European Food Safety Authority [2], the Joint Meeting on Pesticide Residues (JMPR, also a WHO expert group) [3] and the German Federal Institute for Risk Assessment (BfR) [4] decided that it was, not relevant carcinogenic (or a similar wording). Nevertheless, several press releases added the attribute 'suspected to be carcinogenic' thus using the 'most negative' classification available. The latter isn't even wrong since there is one well-known institution having this point of view. However, it raises the general question how scientific institutions (two under the same umbrella of WHO) can come to such divergent conclusions in particular since they based them on the same publically available information. Thus, the question is what a classification as 'carcinogenic' is based upon and what the meaning of such a statement is. To get closer to an answer, it will be discussed first what our current understanding is on how a chemical can cause cancer.

2. Mechanisms of carcinogenicity of chemicals

In 1771, John Hill, a physician of London described a correlation between the use of tobacco (snuff) and nasal tumors [5], and 1775, the English physician Persival Pott observed that lean boys, so-called ‚chimney sweeps' crawling up the chimneys of to clean them with their bodies frequently suffered from skin cancer of the scrotum (described in [6]). About two hundred years later it was discovered that certain polycyclic aromatic hydrocarbons (PAHs) isolated from tar and soot caused similar types of skin cancer in laboratory animals. Probably, such PAHs had contributed to the tumors observed by Pott in the London chimney sweeps. Subsequently, the groundbreaking work by Elizabeth and James Miller [7], Jerina [8] and other researchers [9] showed that PAHs cannot cause cancer directly but need metabolic activation by cytochrome P450 (CYP) mono-oxygenases to do so. These enzymes are preferentially found in the endoplasmic reticulum of cells, *e.g.* in the liver cell, and are able to catalyze an enormous spectrum of chemical reactions most prominently the insertion of an oxygen atom in to organic substrates. Since the CYP enzymes are mainly located in the so-called microsomal fraction (mostly containing the endoplasmic reticulum) obtained by differential centrifugation of a tissue homogenate, they are also called microsomal mono-oxygenases. Their major function is the detoxification of a very broad spectrum of exogenous (and also endogenous) compounds by modifying their structure, *i.e.*, making them more hydrophilic and/or preparing them for further conjugation reactions (reviewed in [10]). Several chemical carcinogens such as carcinogenic polycyclic aromatic hydrocarbons, *e.g.* benzo(a)pyrene, are converted by CYP enzymes, however, into highly reactive unstable products. Due to their electrophilic properties, these are able to react with nucleophilic targets under formation of covalently bound adducts (Fig. 1). These targets are nucleophiles, *e.g.* proteins but also the genomic information, *i.e.* the nuclear DNA. If nuclear DNA is modified covalently a permanent change in the sequence of DNA bases called mutation or other changes in DNA structure may finally result [11,12].

Events of this type may lead to alterations in some cells not resulting in cell death but putting these cells on a 'track towards malignancy'. Such so-called 'initiated' cells bear genetic changes making them vulnerable to further steps or lesions. Furthermore, it is assumed that the process of malignization takes time and is subject to a variety of influencing factors. Since a single 'hit' is highly unlikely to result in a malignant cancer cell it is widely accepted that several genetic alterations have to occur before a malignancy develops, originating from the clonal expansion of a malignant cell [13]. On several (earlier) stages the process can be stopped or possibly even reversed. It is evident that all steps including the fate of the initial genetically altered cells are subject to a variety of responses of the host such as programmed death of the affected cell [14], repair of the DNA damage [15], attack by the immune system [16] *etc.*

Chemical carcinogenesis was recognized early as proceeding *via* distinct steps. Thus, an experimental two-stage skin carcinogenesis model was developed [17]. Chemicals which can facilitate or accelerate early steps in multi-stage carcinogenesis are called tumor promoters [18]. while compounds which enhance the growth and conversion of later stages such as precancerous hyperplasia are called tumor progressors [19]. It is not completely clear if such chemicals supporting the pathway towards malignancy do so only by modifying the survival and growth conditions of the cell or by helping to selects cells with a certain growth advantage within a mixed population of a tumorous lesion. Compounds acting as tumor promoters usually do not form reactive metabolites but act by modulating growth or cell death ('apoptosis') *via* receptor-mediated or other mechanisms [20,21]. It has to be kept in mind, however, that the available initiation-promotion regimens are simplified models which cannot reflect all facettes of chemical carcinogenicity [22].

Direct interaction of a chemical with the genome not necessarily requires metabolic activation. In fact some highly reactive chemicals used as chemical weapons but also certain drugs used in cancer chemotherapy are DNA-reactive in itself [23].

However, those chemicals which are relatively stable in the environment but require metabolic activation in the body are of much greater importance since they occur in food, environmental samples *etc.*

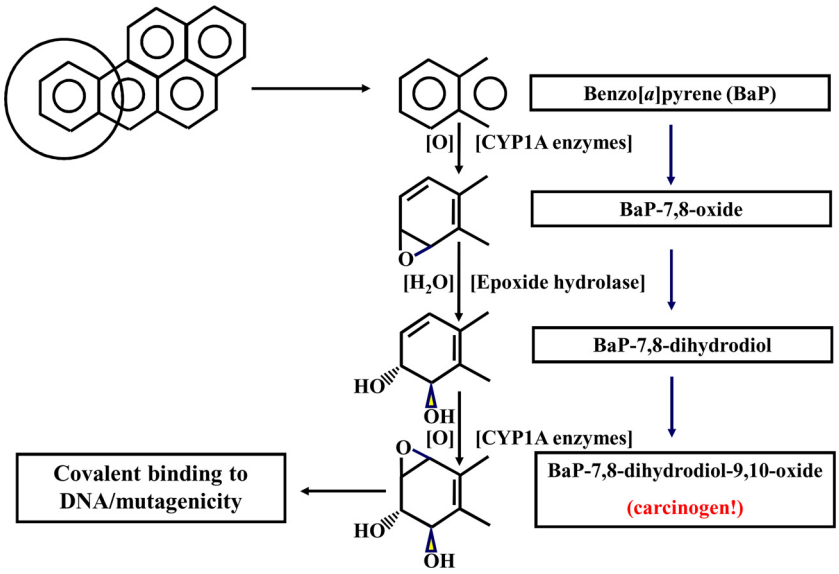

Fig. 1. Metabolic activation of benzo(a)pyrene into a directly genotoxic metabolite.