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Evaluating Cancer Risks Using Scientific Data: Glyphosate as an example

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The evaluation of whether a pesticide can cause cancer in humans requires the review and synthesis of scientific evidence from studies of human populations (epidemiology), animal cancer studies, and studies investigating cancer mechanisms.

Different approaches [1, 2] are used to answer the question «Does this chemical cause cancer in humans?»

Gathering the Scientific Evidence

The first step in any evaluation of the scientific literature is to make certain all of the literature is available for the review. Most organizations use some form of "systematic review" [3–6] where an explicit, prespecified approach is used to identify, select, assess, and appraise the data.

The quality of the individual studies must be assessed and summarized so the studies included in the assessment are appropriate. Different types of studies have different quality measures.

Studies of human populations

In studies of human populations (epidemiology), the quality of the study will depend on the type of study, the size of the study, the population being studied, etc. The two most common types of epidemiology studies for pesticides are cohort studies and case-control studies.

In a cohort study, researchers follow a population, like farmers, for an extended period of time and examine whether their cancer risks are greater in cohort members with exposures to pesticides than in those without the exposures. In a case-control study, people with a specific disease (cases) are matched to people without the disease (controls) and both groups are asked about their past exposures. A positive association is seen when cases have greater pesticide exposure than the controls. The major disadvantage of case-control studies is that cases may be more likely to blame their cancers on pesticides which could lead to what is called exposure bias.

Animal cancer bioassays

Typical animal cancer bioassays expose animals (generally rats or mice) to a chemical for a substantial proportion of the animal's life (generally 2 years) then kill the animal and examine its organs and tissues for tumors. Chemical registrants conduct cancer bioassays for pesticide approval pursuant to guidelines developed under the guidance of the Organization for Economic Cooperation and Development (OECD [7]). Other groups [8–10] provide guidance on how to analyze these studies based upon methodology papers from the published literature. These studies are conducted in a way that controls for everything in the animal's environment (e.g., food type, water quality, how often the animals are handled) leaving only the exposure to explain differences in tumor formation between control and exposed animals.

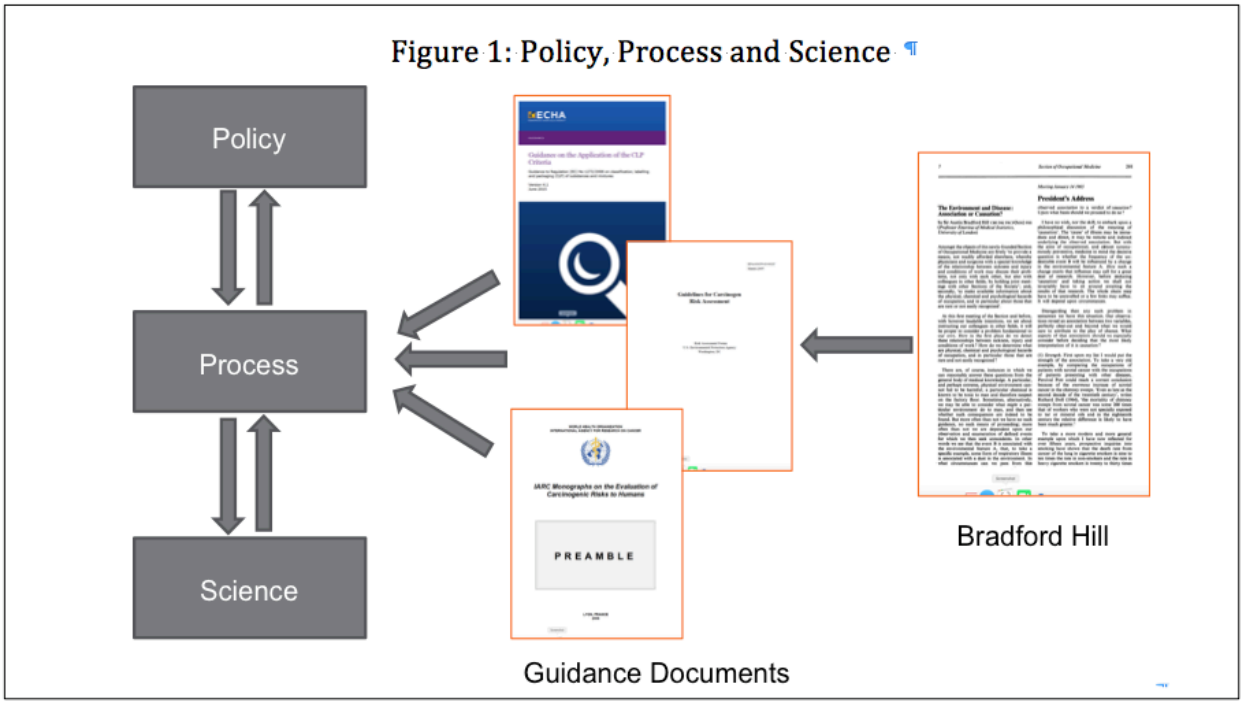
Studies generally use four groups of animals, one group receiving no exposure (control) and the remaining three groups receive different dose exposures to the chemical [11]. Doses are generally above human experience. By exposing animals to the highest dose possible, you increase the ability of the study to identify a risk if one is present. To avoid doses that are too high, studies are designed around a maximum tolerated dose (MTD). This dose is generally determined based upon a short study (90 days) in the same animals and is usually the maximum dose that can be tolerated by the animals without any signs of toxicity (e.g., weight loss). The OECD and EPA provide guidelines [7, 10] on how to choose this top dose.

Studies investigating cancer mechanisms

Many human carcinogens act via a variety of mechanisms causing various biological changes, taking cells through multiple stages from functioning normally to becoming invasive with little or no growth control (carcinogenic). Systematic review methods can be used for identifying and using key information from the literature to characterize the mechanisms by which a chemical causes cancer [12].

Evaluation of the Evidence

Once the quality of the individual studies has been assessed, a judgment needs to be made concerning the degree to which the studies support a finding of cancer in humans. To do this, the European Food Safety Authority (EFSA), the International Agency for Research on Cancer (IARC), and many others use guidelines [8–10, 13] that rely upon aspects of the criteria for causality developed by Hill [14]. This is depicted in Figure 1 where the Hill publication provides input into the development of guidance documents that then feed into the process. Policy refers to the laws and regulations that outline safety requirements. For example, in the European Union, pesticides that pose a carcinogenic hazard are banned; this is a policy statement and not a scientific statement. Process refers to the steps taken by regulators to meet the policy requirements imposed upon them by society's laws and regulations using the available science.



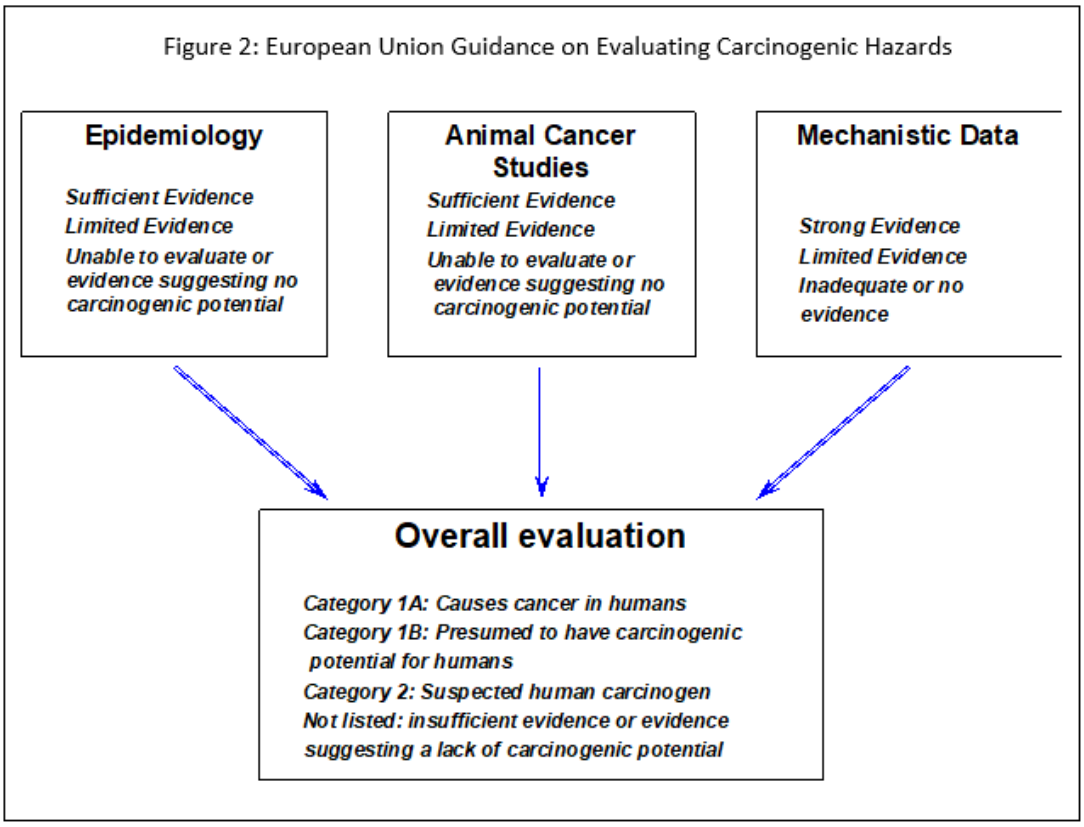
From a practical standpoint, most reviews break the literature up into three specific areas for evaluation; human studies, animal cancer studies, and mechanism studies. Figure 2 illustrates the classification scheme used by the European Union for cancer-causing agents [8]. Once the individual three areas of science have been evaluated, they are combined into an overall classification for the pesticide.

Classification

For the human epidemiological evidence, the EU guidance document provides explicit definitions for «sufficient evidence» and «limited evidence»; failure of a pesticide to fall into either of these two categories places the pesticide into the third category. These definitions are identical to the definitions used by the International Agency for Research on Cancer (IARC) [9] and, in fact, the EU guidance document references the IARC guidance document as the source of the definition.

In simple language, «sufficient evidence» means that the epidemiology literature is very strong and supports the idea that a pesticide causes cancer in humans without considering any other evidence. On the other hand, «limited evidence» means the epidemiology literature shows an association between a pesticide and cancer, but there is some uncertainty in these data that could have resulted in the association being due to chance or some other problem.

The same names for categories are used when evaluating the animal carcinogenicity evidence, however, the definitions change. In simple language, «sufficient evidence» means that the pesticide has caused cancer in animals and that the finding has been seen in more than one study or is so unusual that it cannot be due to chance. «Limited evidence» means there is data supporting a carcinogenic effect in animals, but it has not been replicated, the tumors are not malignant (meaning life-threatening) or there are problems with the studies being used.



The categories for mechanistic data are not explicitly defined in the EU guidance, but are explicitly defined in the IARC guidance [15]. «Strong evidence» means that the mechanism has been carefully studied and the results show a clear effect of the pesticide for this key characteristic while «limited evidence» means the evidence is somewhat inconsistent or covers only part of the overall mechanism.

Overall Evaluation

As seen in Figure 2, the EU classification system for carcinogens classifies a chemical into one of three categories or does not classify the chemical (fourth category). Category 1A means the chemical causes cancer in humans and, in most cases, this would mean there is «sufficient evidence» in humans from the epidemiology data. In rare cases, «limited evidence» in humans, «sufficient evidence» in animals and «strong evidence» of a cancer mechanism could result in a pesticide being placed into Category 1A.

The definition for Category 1B is a bit more complicated but basically derives from «sufficient evidence» in animals and «limited evidence» or «no evidence» in humans. On some occasions, «limited evidence» in humans and «limited evidence» in animals could also lead to the pesticide being placed into Category 1B, but this would likely require «strong evidence» of a carcinogenic mechanism.

Category 2 is for pesticides for which there is evidence of a carcinogenic effect of the pesticide, «*but which is not sufficiently convincing to place the substance in Category 1A or 1B*» [8].

The IARC uses very similar groupings for labeling carcinogens with the IARC Group 1 basically matching Category 1A, IARC Group 2A matching Category 1B and IARC Group 2B matching Category 2.

Important role of Mechanistic data

Mechanistic data plays an important role in determining the final category into which a pesticide will be placed. For example, if a pesticide causes a cancer in rats that the mechanistic data shows cannot occur in humans, then that pesticide would not be classified into Categories 1A, 1B or 2. On the other hand, if the pesticide under review has only «limited evidence" or no evidence in humans and animals, but the mechanistic data shows it acts identically to a pesticide already in Category 1A, that may be sufficient to classify the pesticide under review into Category 1A or 1B.

Glyphosate as an Example

Glyphosate is the most commonly used herbicides worldwide; most people would recognize the most common commercial form, ‹Round-Up›.

The carcinogenicity of glyphosate has been reviewed by numerous regulatory agencies including the EFSA [16], and all of them have concluded it is not carcinogenic. In the case of the EFSA, this would mean it does not fall into any of their Categories 1A, 1B or 2. In contrast, the IARC has also reviewed the literature on glyphosate and has categorized it as Group 2A (EU Category 1B).

There are many differences in the logistics of how EFSA and IARC reviewed glyphosate. EFSA requested a literature review from industry and rapporteur member state Germany (RMS) drafted the Renewal Assessment Report (RAR). IARC recruited independent, outside scientists to join a Working Group (WG) to evaluate the carcinogenicity of glyphosate. A substantial portion of the draft RAR contained text and tables that were copied and pasted from the industry submission including some evaluations [17]. The WG drafted the review from their home locations and then met at IARC headquarters for 8 days to finalize the draft and complete their evaluation. EFSA convened a peer-review committee (PRC) made up of representatives from the member states to evaluate the RAR and work with the RMS to get a satisfactory review. EFSA did not re-analyze any of the data, whereas the WG reanalyzed the animal cancer data and did a meta-analysis (combined analysis) of the epidemiology data. Following the IARC review EFSA reanalyzed the same data IARC had reanalyzed and went on to analyze some additional select data.

IARC and EFSA evaluated the same epidemiology studies in their evaluations. EFSA concluded the data was «very limited evidence» of carcinogenicity (not one of their categories) whereas IARC classified the epidemiological data as «limited evidence» due to associations with non-Hodgkins lymphoma (NHL). Thus, the two groups came to similar conclusions.

EFSA gave more weight to the one cohort study [18] and very little weight to the remaining studies which were all case-control studies. The IARC WG did their own meta-analysis demonstrating a strong association and concluded the cohort study was in the same direction as the other studies and of similar magnitude.

EFSA concluded there was «no evidence» of carcinogenicity in either rats or mice from the 12 animal cancer studies they reviewed. IARC concluded there was «sufficient evidence» of carcinogenicity from the 7 animal studies they reviewed. Thus, the two groups reached opposite conclusions on the animal data.

IARC reviewed publicly available information on 5 rat studies and 2 mice studies and saw increases in kidney tumors and hemangiosarcomas in mice and in benign tumors of the pancreas, liver and thyroid in rats; this matches their 2A classification. EFSA reviewed 7 rat studies and 5 mice studies and, even though, after their reanalysis, there were 17 positive findings in these studies, all were dismissed as not due to glyphosate.

EFSA has given seven reasons why the animal evidence is uniformly negative: a lack of dose-response; no consistency across studies; differences between the sexes; a lack of preneoplastic lesions (damage showing before cancer); data is within the range of the historical controls; results are due to a single high dose potentially at or above the maximum-tolerated dose; and trend tests and pairwise comparisons do not agree. Many of these reasons violate their guidelines and do the exact opposite of what the guidelines propose (historical controls, trend test) [19]. They did not test for consistency across studies (a simple statistical procedure) and trend tests account for a lack of dose-response. Males and females routinely have differing tumor responses and there is no biological reason why one would expect to see the same tumor in both sexes. Finally, while preneoplastic findings are important to aid in understanding a tumor response, there is no guarantee such findings will be present and several of the more important tumors have no preneoplastic state (e.g. malignant lymphoma).

For mechanisms, IARC concluded there is strong evidence for genotoxicity and oxidative stress while EFSA concluded there was no indication of genotoxicity and some evidence of oxidative stress. The main difference is the weight EFSA put on the negative industry studies of genotoxicity which IARC did not have access to.

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