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COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Chemical carcinogenicity revisited – series of papers of interest

1. Recently a series of commentary papers on knowledge of carcinogenesis and the assessment of chemical carcinogenicity has been published in Regulatory Toxicology and Pharmacology. These three papers are relevant to the COC guidance statement series, some of which will be discussed at the present meeting, and appropriate aspects can be incorporated in these as part of the rolling update and revision process.

2. A summary of the three papers has been prepared by one of the authors.

"*Chemical Carcinogenicity Revisited*

Developments in the understanding of the etiology of cancer have profound implications for the way the carcinogenicity of chemicals is addressed. In the last four decades, we have come to understand that for a cell and a group of cells to begin the process of unrestrained growth that is defined as cancer, there must be changes in DNA that reprogram the cell from normal to abnormal. Cancer is the consequence of DNA coding errors that arise either directly from mutagenic events or indirectly from cell proliferation especially if sustained. Chemicals that act via direct interaction with DNA can induce cancer because they cause mutations which can be carried forward in dividing cells. Chemicals that act via non-genotoxic mechanisms must be dosed to maintain a proliferative environment so that the steps toward neoplasia have time to occur. Chemicals that induce increased cellular proliferation can be divided into two categories: those which act by a cellular receptor to induce cellular proliferation, and those which act via non-specific mechanisms such as cytotoxicity.

This undermines the 1970s concept that chemicals are either "carcinogens" or "non-carcinogens". The capacity to induce cancer should not be classified in an inflexible binary manner as present (carcinogen) or absent (non-carcinogen). The long-term rodent bioassay is neither an appropriate nor efficient to evaluate carcinogenic potential for humans and to inform risk management decisions. It is of questionable predictiveness, expensive, time consuming, and uses hundreds of animals. Although it has been embedded in practice for over 50 years, it has only been used to evaluate less than 5% of chemicals that are in use. Furthermore, it is not reproducible because of the probabilistic nature of the process it is evaluating combined with dose limiting toxicity, dose selection, and study design. The modes of action that lead to the induction of tumors are already considered under other hazardous property categories in classification (Mutagenicity/Genotoxicity and Target Organ Toxicity); a separate category for Carcinogenicity is not required and provides no additional public health protection.

We now recommend a transition from the bioassay to a decision-tree matrix that can be applied to a broader range of chemicals, with better predictivity, based on the premise that cancer is the consequence of DNA coding errors that arise either directly from mutagenic events or indirectly from sustained cell proliferation. The first step is in silico and in vitro assessment for mutagenic (DNA reactive) activity. If mutagenic, it is assumed to be carcinogenic unless evidence indicates otherwise. If the chemical does not show mutagenic potential, the next step is assessment of potential human exposure compared to the threshold for toxicological concern (TTC). If potential human exposure exceeds the TTC, then testing is done to look for effects associated with the key characteristics that are precursors to the carcinogenic process, such as increased cell proliferation, immunosuppression, or significant estrogenic activity. Protection of human health is achieved by limiting exposures to below NOELs for these precursor effects. The decision tree matrix is animal-sparing, cost effective, and in step with our growing knowledge of the process of cancer formation."

3. The published papers are attached at Annex A.

4. Members are asked to consider the papers and provide comments, particularly on aspects to address in the rolling updates and revisions to the COC guidance statement series.

Secretariat
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References

Cohen SM, Boobis AR, Dellarco VL, Doe JE, Fenner-Crisp PA, Moretto A, Pastoor TP, Schoeny RS, Seed JG, Wolf DC (2019) Chemical carcinogenicity revisited 3: Risk assessment of carcinogenic potential based on the current state of knowledge of carcinogenesis in humans. Regulatory Toxicology and Pharmacology 103, 100-105.

Doe JE, Boobis AR, Dellarco V, Fenner-Crisp PA, Moretto A, Pastoor TP, Schoeny RS, Seed JG, Wolf DC (2019) Chemical carcinogenicity revisited 2: Current knowledge of carcinogenesis shows that categorization as a carcinogen or non-carcinogen is not scientifically credible. Regulatory Toxicology and Pharmacology 103, 124-129.

Wolf DC, Cohen SM, Boobis AR, Dellarco VL, Fenner-Crisp PA, Moretto A, Pastoor TP, Schoeny RS, Seed JG, Doe JE (2019) Chemical carcinogenicity revisited 1: A unified theory of carcinogenicity based on contemporary knowledge. Regulatory Toxicology and Pharmacology 103, 86-92.

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