Threshold Doses in Chemical Carcinogenesis

Introductory Remarks

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The objective of the World Health Organization, according to its constitution, is “the attainment by all people of the highest possible level of health”. In the pursuit of this objective, WHO has carried out a number of activities related to the evaluation of health hazards of food additives, pesticides, food contaminants etc., mainly through its Expert Committees on Food Additives and Pesticide Residues. The results of the evaluation are expressed as acceptable daily intakes for man where sufficient data exist. These acceptable daily intake figures are used by many national authorities in the formulation of standards and regulations, either directly or indirectly. In the latter case it is done through the inter-governmental body, the Joint FAO/WHO Codex Alimentarius Commission. The Commission has a membership of 114 countries and is engaged in the elaboration of international food standards mainly for the protection of the health of the consumer.

In evaluating the toxicities of these chemicals, various problems have been encountered. One of these concerns the significance of exposure to very low levels of substances that have been shown to be carcinogenic at high dose levels. Some of these substances can be eliminated from the food. Others, however, cannot be readily eliminated, while still others can be readily eliminated but their elimination might involve an unrealistic economic burden to society or other types of health hazards. A realistic assessment must therefore be made of the health hazards, if any, that are associated with the exposure to such low levels of chemical carcinogens.

A Scientific Group was convened by WHO in 1973 to discuss this topic and to make recommendations. It concluded that among other things, the existence of a threshold of carcinogen may be envisaged and there are certain instances of cancer induction that may be secondary to an initial non-carcinogenic effect of a chemical. The Group recognized, however, the deficiency in our knowledge which at present precludes the determination of threshold doses of carcinogens for a human population, and recommended a number of areas in which research should be conducted.

There remains a strong need to establish procedures for the determination of threshold doses for chemical carcinogens. Vinyl chloride is a glaring example. It is unquestionably carcinogenic, even to man. Yet polyvinyl chloride has not been banned as packaging material for food and beverages although it emits vinyl chloride into the food and beverages thereby exposing the consumer.
WHO is therefore going to convene another Scientific Group on this subject this year. In preparation for this Scientific Group, I have sent a circular letter to all members of the “WHO Expert Advisory Panel on Food Additives and Contaminants” and a number of other scientists recommended to me by Panel Members. I have pleasure in stating that the responses to my letter are in general very informative and constructive, and I wish to thank all the respondents. However, it gives me even greater pleasure to state that my letter had apparently touched upon an area of great interest to the German scientific community, so that it decided to organize this international symposium. On behalf of WHO I would like to thank the sponsors and organizers. I see some in the audience who have responded to my letters; on the other hand many have not received my letter. Perhaps you will be interested in the questions I raised and the general responses received. The four questions are the following:

Do you agree with the 1973 Scientific Group that there are threshold doses for chemical carcinogens? If not, what are the reasons?

If you do agree with the concept, do you believe that there are chemical carcinogens for which sufficient data already exist for the estimation of their threshold doses?

If you feel that there are insufficient data available for this purpose for any chemical carcinogens studies so far, what are the types of data that should be generated?

Can you give other examples of “secondary carcinogens”? The 1973 Scientific Group gave as an example “the cancers of the urinary bladder observed in rats treated with Myrj 45 (polyoxyethylene monostearate) are thought to have been caused by the presence of bladder calculi, induced by the chemical rather than by its direct action”.

To the first question most respondents replied in the affirmative. Only a few said no and a few said yes but added a qualifier such as “only in the context of a dose-time-effect relationship”, “probably but not certainly”, “only in rare cases”, etc.

With respect to the second question many said that there were enough data in some cases to establish threshold doses in animals but not in man. However one expert said there were enough data on arsenic and tellurium to do so in man.

Many areas of research were recommended. These included the use of single cell in vitro studies to determine the mode of action, determination of variation of susceptibility such as the ability of the organism to activate or detoxify the chemical and to repair or eliminate the damage, dose-response relationship at lower dosage range and with larger numbers of animals, epidemiology, precise pathological examination, etc.

A large number of secondary carcinogenic chemicals were given in the replies. It is of interest that none has questioned the validity of assuming the existence of threshold doses with this type of carcinogens.

Finally, I would like to take this opportunity to again thank our German colleagues in sponsoring and organizing this symposium and I look forward to a successful meeting.