The Relative Susceptibility of Animals and Humans to the Carcinogenic Hazard Posed by Exposure to 2,3,7,8-TCDD: An Analysis of Standard and Alternative Dosimetric Measures

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Introduction

Over the past 15 years, a significant number of animal studies and human epidemiological evaluations have been conducted on 2,3,7,8-TCDD. Due to its high carcinogenic potency in many animal studies and some epidemiological data suggesting an increase in the overall rate of tumors, it has been considered a possible carcinogen in humans.

As early as 1980, it was assumed that humans might be equally, or more, susceptible to the carcinogenic hazard posed by TCDD and no reliable data were available to resolve whether this was true. However, recent epidemiology studies of people occupationally exposed to TCDD include dose measures that now may make it possible to quantitatively evaluate whether humans or test animals are more susceptible to the cancer hazard.

In 1994, the USEPA completed their reassessment of the health hazards posed by TCDD.[1] In that document (the "reassessment"), the EPA concluded that "Given the assumption that TEQ values

represent a valid comparison with TCDD exposure, some of these adverse impacts may be occurring at or within one order of magnitude of average background TEQ intake or body burden levels...." (page 9-81). The basis for this conclusion was fairly well described in chapter 9 of the draft reassessment and is presented in tables 9-3, 9-4, and 9-5. The agency relied almost exclusively on their estimates of body burden (peak or otherwise) in animals or humans to conclude that the cancer risk at a given dose was similar (within a factor of 10). They did not indicate whether humans were more or less susceptible than the most sensitive species for a given endpoint. Based on an assumption of species similarity, the linearized multistage model (LMS) and another extrapolation model were used to estimate the cancer risks to humans.

Objective

To quantitatively evaluate the relative susceptibility of animals and humans to the cancer hazard posed by 2,3,7,8-TCDD.

Methods

To investigate the comparative susceptibility to the cancer hazard, the following dosimetrics were evaluated: the lifetime average daily dose (LADD), lifetime average daily body burden and total area under the body burden vs. time curve (AUC).

In this paper, we examined the bioassay data of Kociba et al.[2] and the pathological reevaluation of the same study by Maronpot et al.[3] to understand the cancer risks to laboratory animals. The epidemiological studies of Fingerhut et al.[4] and Bertazzi et al.[5] were used to understand the possible human cancer hazard.

Because the available data seem to support the claim that the biological response to TCDD, including cancer, is related in some manner to binding with the Ah receptor, it has been suggested by numerous scientists that the area-under-the-curve (AUC) method was appropriate to describe the lifetime average daily dose.[6,7] These results were compared with the mg/kg-day measure of dose for both the animal and human studies. A physiologically-based pharmacokinetic model was also used in the analysis.[8,9]

Results and Conclusions

The results suggest that the use of body burden (average or peak) may not be the best dosimetric to describe the likelihood that animals and humans have an equal susceptibility to the carcinogenic hazard posed by 2,3,7,8 TCDD or other PCDD/PCDFs. This is particularly true when animals exposed to acute or subchronic doses are extrapolated to lifetime doses. Because of known differences in tissue concentrations between some animals and humans, the use of body burden (which in humans is predominantly in adipose tissue) as an accurate predictor of target organ concentration

or the cancer hazard is probably not optimal.[10] Direct comparison of effect and no effect levels for specific endpoints (including cancer) using lifetime average tissue levels, blood levels and AUC suggest that there are greater differences in susceptibility between animals and humans than suggested in the recent EPA reassessment.

Our results indicate that the current epidemiology data show that humans are no more, and probably less, susceptible to the carcinogenic risk of 2,3,7,8-TCDD than rodents. The bioassay and epidemiology data, plus consideration of the dose-response data on promotional effects offers additional support for a conclusion that exposure (in humans or animals) below a certain critical level is not likely to result in an increased cancer risk.

References

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