Mode of action and human relevance of dioxin (TCDD) carcinogenesis

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Dioxin is carcinogenic in experimental animals, producing tumours primarily of the liver and lung in rats and mice, but also of the oral mucosa. Dioxin is also able to promote tumours induced by DNA-reactive carcinogens, such as nitrosamines, in tissues such as the skin, liver and lung. The analysis presented here is for the hepatocarcinogenic effects of dioxin, although there is evidence that the Ah receptor plays a key role in all of the carcinogenic effects of this compound.

The postulated mode of action involves interaction of dioxin with the aryl hydrocarbon receptor (AhR), followed by inhibition of apoptosis in cells initiated either spontaneously or by prior exposure to a DNA-reactive compound, clonal expansion of transformed cells to form foci and the development of tumours. Dioxin is also cytotoxic, but the role this plays in its mode of action has yet to be determined.

Evidence for a role of AhR in the carcinogenic effects of dioxin comes from a number of sources: the carcinogenic potency of a series of structural analogues of dioxin correlates with their binding affinity for the AhR; transgenic mice expressing a constitutively active Ah receptor (CA-AhR) exhibit enhanced tumour promotion; dioxin is much less potent in a rat strain in which the AhR has a deficient transactivating domain; mouse strains genetically deficient in the AhR are less sensitive to the promoting effects of dioxin. Although AhR null mice have been used to study the carcinogenic effects of polycyclic aromatic hydrocarbons, to date no such studies have been undertaken with dioxin.

Dioxin is a potent inhibitor of apoptosis both in vivo and in vitro in cells initiated with DNA-reactive compounds, or other DNA damaging stimuli such as UV radiation. Inhibition of apoptosis is an early event relative to the onset of carcinogenesis and occurs at the same or lower doses than those causing cancer.

Dioxin results in the appearance of hepatic foci prior to the development of tumours, at doses that are the same or lower than those that are carcinogenic. Foci are GST-P positive and are pre-neoplastic in nature. The appearance of altered hepatic foci is preceded by the inhibition of apoptosis.

With respect to alternative modes of action, the overwhelming balance of evidence is that dioxin is not DNA reactive and that it is not carcinogenic through a genotoxic mechanism.

The key events proposed for the carcinogenicity of dioxin are consistent and biologically plausible with the postulated mode of action, for which the evidence is considered high.

Humans express a functionally active Ah receptor, which is responsive to dioxin, as demonstrated in vitro and observations in accidently exposed populations are consistent with this. CYP1A1 induction is often used as a surrogate for activation of

the Ah receptor. Human derived HepG2 cells exhibit effects consistent with the inhibition of apoptosis following exposure of genotoxicant-treated cells to dioxin.

There is no information on whether dioxin induces altered hepatic foci in humans, particularly in those exposed to genotoxicants. However, on the basis of what is known of the effects of genotoxicants, such as aflatoxin B1, on human liver, there is no reason to believe that dioxin could not cause clonal expansion of initiated cells in this tissue. Hence, there is no basis on qualitative grounds to exclude the relevance to humans of the mode of action for dioxin-induced tumours in experimental animals.

The key events have been characterised for their dose-response characteristics. Each shows a threshold for the effect, and this is below that for the carcinogenic response, providing strong support that the dose-response relationship for dioxin carcinogenicity is non-linear and exhibits a biological threshold. There are few data on quantitative comparison of the key events between animals and humans, other than on the relative sensitivity of the Ah receptor. Studies in vitro and with mice humanized for the AhR have shown that the human receptor is less responsive than the receptor in rodents. Hence, although it is not possible to dismiss human relevance on quantitative grounds, it may be possible to develop a chemical specific adjustment factor, reflecting the reduced affinity of the human receptor. Any such adjustment would also have to take account of the marked species differences that exist in the toxicokinetics of dioxin.