The Natural History of the Dioxin Equivalents

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Introduction. Extensive research has shown that all of the biological effects of dioxin, e.g., induction of cytochromes P4501A1 and 1A2 at low doses and a characteristic pattern of toxic effects at higher doses, are mediated via a single biochemical target, the aromatic hydrocarbon receptor (*AhR*). It has also shown that a number of other substances are qualitatively dioxin-like in eliciting the same patterns of *AhR*-mediated effects, and to an extent proportional to the administered dioxin toxic equivalents (TEQs). Such dioxin-like compounds include both chlorinated species, such as the polychlorinated dibenzodioxins and dibenzofurans (PCDD/Fs) and coplanar PCBs (cPCBs), and also non-chlorinated ones, such as the polycyclic aromatic hydrocarbons (PAHs), the cabbage-derived indolocarbazol (ICZ) (1,2), and the CYP1A-inducing constituents of fried meat, which are thought to be heterocyclic aromatic amines (HAAs) (3). Some of them, notably the PAHs and HAAs, have additional genotoxic and tumor-initiating activities that are unrelated to their dioxin-like activities. Others, notably the ICZ sources, have been found to have anticarcinogenic activities that are believed to be *AhR*-mediated.

Risk Assessment Issues. Some of the TEQ sources, notably the PCDD/Fs, have produced observable responses in sensitive animal species even at doses only slightly greater than those presented to man by current levels of environmental exposure. Although there is no unambiguous clinical or epidemiological evidence that such low level exposures have actually produced adverse effects in human populations, it is recognized that the lack of such evidence cannot exclude the possibility that adverse effects that are too subtle or too infrequent to be reliably observable may indeed be occurring. Judgments as to the existence of clinically unobservable effects are made on other grounds instead.

Currently, the TEQs derived from traditional dietary sources, such as cruciferous vegetables, are considered harmless or even beneficial to human health, whereas the TEQs derived from PCDD/Fs have been claimed to be on the verge of producing adverse effects even at the very low body burdens resulting from environmental (mainly dietary) exposures.

Underlying this apparent inconsistency may be the widely held concept that the new chemical substances produced by modern technology are unnatural, or foreign to living organisms ("xenobiotic"), and hence intrinsically more dangerous, especially to human health, than those that have been present in the environment long enough to permit adaptation.

Any use of this concept to justify a distinction between the assessed risks of PCDD/F-based TEQs and ICZ-based TEQs rests upon three scientifically testable hypotheses. These are first, that the PCDD/Fs have only recently appeared in the general environment; second, that they have significantly increased the total human TEQ burden; and third, that the human is so sensitive to TEQ that any increase will present a health risk. In order to test these hypotheses, we examine here recent findings relating to the natural history of the dioxin equivalents.

New and Old Sources of PCDD/Fs. At least three independent mass balance studies have shown terrestrial PCDD/F-based TEQ deposition rates to be 3-20 times as great as the identifiable anthropogenic emissions (4,5), indicating the likelihood of major natural sources. It is well known that trace levels of PCDD/Fs can be formed whenever carbonaceous materials containing chlorine in any form are burned. However, the PCDD/F emission rates vary widely with the conditions of combustion, making it difficult to calculate the exact contributions of forest fires, slash-and-burn agriculture, and domestic wood fires to the total global emissions. More recently it has been found that PCDD/Fs can also be formed by the action of aerobic microbial peroxides and chloroperoxidases on chlorophenols or even the humic acid of topsoil (4,6). Available data suggest that the observed PCDD/F levels in ancient environmental samples vary widely with specimen type. Century-old freshwater sediment core sections have been repeatedly observed to contain little or no PCDD/F. However, it is now known that the lack of PCDD/Fs in such media could result from their anaerobic microbial dechlorination (7). Archived British 1891-1900 herbage samples were found to contain 14% the PCDD/F of their modern counterparts, and in a congener distribution pattern similar to modern incinerator emissions (8). 1846-1889 topsoil samples from the same area showed a somewhat different congener pattern, and levels 33-67% of the modern values. Japanese marine sediment core sections dating from the fourth to the early twentieth century showed no PCDFs or PCBs, but the same PCDD levels as at present, although levels had been higher 20-30 years ago during the peak of chlorophenol use. Some PCDDs were seen even in an 8,120-year old section (9).

The simplest interpretation of the available data would be that although pyrogenic formation of PCDD/Fs (along with PAHs and cPCBs) increased with the use of coal and the now-restricted use of chlorophenols up to the 1970s (4), some natural pyrogenic formation in forest fires and microbial production in soils must have always been occurring. In short, PCDD/Fs are not solely anthropogenic or xenobiotic, and have always been present in the environment.

Relative Contributions of PCDD/Fs to Total Human TEQ. Non-chlorinated TEQ sources are widespread. The PAHs, along with other as yet unidentified *AhR* agonists, are found at much greater levels than PCDD/Fs in smoke, soot, tars, and charbroiled foods. The HAAs are formed whenever meat is cooked at high temperatures (3). The dioxin-like, but cancer-suppressing, ICZ is formed in the stomach from brassicin, which is present at 30-1000 ppm levels in cruciferous vegetables such as cabbage, cauliflower, broccoli, and Brussels sprouts (1,2). Other known dietary sources include a few plant flavonoids and spices. Lastly, it is widely suspected that there must exist some as yet unidentified endogenous hormone that serves as the natural ligand for the *AhR*.

The relative contributions of the chlorinated vs. the non-chlorinated TEQ sources to total human TEQ may be assessed via determinations of their relative contributions to CYP1A2 induction. This can be measured non-invasively via the caffeine breath test. Application of this test to yucheng patients carrying various levels of serum PCDF has defined a dose-response relationship (10) which indicates that current USA background levels of PCDD/F-based TEQ are contributing only 1-2% to the mean CYP1A2 induction. By contrast, the mean CYP1A2 activity level was found to be increased 50% by a week's dinners of pan-fried meat (3), 94% by a week's meals that contained servings of cabbage and Brussels sprouts (11), and 68% by smoking (12). In short, it would appear that PCDD/Fs from the general environment have not been making a significant contribution to total human TEQ body burdens.

TEQs and Human Evolution. It is known from archeological data that *Homo erectus* discovered fire, meat roasting, and the practice of living with fire in chimneyless shelters about 1.5 million years ago. This technological development must have produced sharply increased human exposures to PAHs, HAAs, and PCDD/Fs. As a result, our own species, *Homo sapiens*, has been under unique selective pressure to adapt to elevated TEQ levels over the entire course of its evolution. Evidence that such adaptation has occurred is presented by the facts that neither heavy smoking nor cabbage-consumption have ever been reported to produce chloracne in man, and that the modest increases in internal TEQ levels provided by non-genotoxic TEQ sources such as the cruciferous vegetables appear to be actually beneficial to human health (1,2). Even more striking, the production of characteristic dioxin-like responses, such as CYP1A induction, deformed fingernails and ocular discharges, requires lipid PCB accumulations of >600 mg/kg in man (13) but only 8 mg/kg in monkeys (14).

In summary, none of the three identified criteria for presuming that PCDD/F-derived TEQ poses different health risks -- or benefits -- than ICZ-derived TEQ appears consistent with the available data. Accordingly, we must conclude that whatever be the optimal level of human exposure for one must also be optimal for the other.

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