HEALTH EFFECTS OF DIOXINS: PEOPLE ARE ANIMALS, AND VICE-VERSA!

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2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD; dioxin) is often referred to as the most potent man-made toxicant. The prototype for a family of structurally related compounds with a common mechanism of action and spectrum of biological responses, TCDD induces a plethora of effects in multiple vertebrate species[1]. Binding of dioxin and related compounds to the Ah receptor induces a cascade of molecular and cellular responses which are life stage, tissue, and often species specific. The Ah receptor, a member of the PAS family of nuclear regulatory basic helix-loop-helix proteins, has been detected in nearly all vertebrates species examined[2]. It is highly conserved, and homologous proteins have been found in invertebrates, although these proteins do not bind dioxin. Effects of dioxins have been demonstrated in all classes of vertebrates, including recent observations in amphibians and reptiles. Environmental contamination with dioxin and related compounds has been reported to have caused failure of reproduction in Lake Trout and mink around the Great Lakes, birth defects in birds, and immune suppression leading to a die-off of seals in the Baltic. Poisoning episodes have led to loss of domestic birds, horses, and cattle. Laboratory studies have shown adverse effects, as well as a host of biochemical changes, in multiple species of fish, birds, and mammals, and in limited studies in frogs and turtles. Effects range from lethality through alterations in cell growth and differentiation. Dioxin can alter the activity of multiple enzymes, cytokines, and growth factors. Receptors for many hormones, growth factors, and cytokines are either up-or down-regulated in response to dioxins, in a tissue specific manner. The circulating levels of multiple hormones, both peptide and steroid, are affected by dioxins, by alterations either in synthesis, degradation, transport, or a combination of all of these processes. Changes in enzymes cytokines, growth factors, and hormones lead to alterations in metabolism, growth, and homeostasis. Dioxin can induce proliferation in certain tissues, and differentiation in others. Both processes can occur at the same time in certain conditions such as chloracne, often called the hallmark of dioxin toxicity. Under certain conditions, dioxin has been shown to induce apoptosis; under other circumstances, programmed cell death is inhibited. Thus, dioxin and related compounds are able to alter the basic programming of cells in a multitude of species[3].

What about people? The Ah receptor, and its cognate machinery, such as its heterodimeric partner ARNT, are present in human beings, as in other mammals. Induction of enzymes such as CYP1A1, 1A2, and 1B1 have been demonstrated not only in human cells and organs cultured *in vitro,* but in cells and organs from people who were exposed *in vivo.* Transcriptional control of the synthesis of the CYP1A family has been documented in non-human primates as well. Induction of cytokines such as IL-1β and TNFα have been shown in human tissues, as well as changes in growth factor and receptors such as those for EGF, retinoic acid, glucocorticoids, and estrogen. Dioxin can cause proliferation of epithelial cells in the medial epithelium of mouse, rat, and human palate in organ culture, in which dioxin can also block

programmed cell death of the peridermal epithelium, and inhibit epithelial to mesenchymal transformation. Dioxin can suppress the primary antibody response in lymphocytes from mouse and human, and can promote the growth of both rodent and human endometrial tissue when implanted in a murine host. Dioxin can alter calcium signalling in both human and mouse cells, as well as altering oncogene expression. Recent studies have indicated that dioxin can affect molecular processes involving *src, rel,* and *Rb* in both human and rodent cells.

What about the *in vivo* effects of dioxin? While there is no clear evidence of dioxin-like chemicals causing lethality in adult humans, there is a great deal of species variability in the sensitivity to this response. Severe wasting has recently been documented in poisoning episodes. Chloracne, which is also an effect requiring high levels of exposure, has been repeatedly observed in highly exposed human populations, as well as poisoned cattle and monkeys, and in rabbits and hairless mice in the laboratory. Dioxin is a complete carcinogen in the four laboratory species in which it has been tested - rats, mice, hamsters, and fish. Based on this clear evidence from laboratory data, suggestive epidemiological data from highly-exposed humans, and mechanistic understanding, is also considered a known human carcinogen. Dioxin has been associated with cardiac problems in fish and birds, and recent human data suggests an increase in cardiovascular disease in highly exposed people. Exposure to TCDD has been shown to be associated with a decrease in circulating testosterone levels in people and rodents. Endometriosis has been shown to occur with greater incidence and severity in monkeys exposed to dioxin. Similarly, surgically induced endometriosis has likewise is promoted by TCDD and related compounds in monkeys, rats, and mice. Epidemiological studies have suggested a similar association. Recent experiments have increased the biological plausibility of the epidemiological observations of an association between exposure to dioxin and Type II diabetes. Dioxin suppresses the glucose transporter. Mice with a defective glucose transporter develop type II diabetes. The glucose transporter is also under the control of the Hypoxia response factor, which involves ARNT. Is it possible that competition for ARNT, which is also involved in neuronal differentiation and and vascularization, among other partnering, may play a role in the toxic effects of dioxins?

The developing organism seems to be at special risk of the adverse effects of dioxin. Prenatal exposure leads to fetal toxicity in all vertebrate species examined in the laboratory, in wildlife and domestic animals, and in people. High levels of prenatal exposure have been recently shown to cause a reversal of the sex ratio, resulting in a deficit of male offspring[4]. To date, there are only limited experimental data which suggest a similar effect. However, growth retardation and effects on teeth, skin, and nails have been observed both in highly exposed human infants, non-human primates, wildlife, and laboratory species. Suppression of the immune system, clearly seen in monkeys and rodents, has been suggested in humans by an increase in respiratory and ear infections. Effects on the developing nervous system, resulting in alterations in neurobehavior and cognition, have been in highly exposed children and monkeys following prenatal exposure. There are also delayed effects which become evident at puberty in the male offspring, similar to that seen in prenatally exposed rodents. For children whose mothers are at the upper end of exposure in the general population, effects have been reported on the dental, immune, nervous, and hormonal systems.

Dioxin and related compounds cause effects in both sexes of multiple species at various

life stages and in multiple tissues. The Ah receptor and its accompanying machinery have been shown to be present and functioning in humans as well as animals. Isolated cells, tissues, and organs of people have been shown to respond similarly to those of experimental species. Multiple effects have been reported in highly exposed people. Several populations have been shown to exhibit subtle effects at the high end of background. There is a great deal of homology of response to dioxins between wildlife, laboratory animals, and human beings. *Homo sapiens sapiens* are in the genus *Homo*, family *Homidiae*, order *Primates*, class *Mammalia*, sub-phylum *Vertebrata*. Every response seen in every animal species may not occur in people, but the weight of evidence demonstrates that humans are a sensitive species to many of the biological effects of this ubiquitous environmental contaminant and related compounds.

(This abstract does not reflect EPA policy.)

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4. Mocarelli,P., Gerthoux,P.M., Ferrari, E. et al. Lancet 355:1858-63, 2000.