Interaction between TCDD and other teratogens in developmental toxicity: Implications to public health

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1. Developmental toxicity of dioxins: what we know

Developmental toxicity is a characteristic biological response of dioxins, with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) showing the most serious toxic effects. Until recently, it was thought that frank TCDD-induced teratogenic effects were not detected in any species other than mice except at doses that were overtly toxic to the dam.[1,2] However, although other species are more resistant than mice to the developmental toxicity of dioxins,[3] in a critical review in which the various TCDD-induced responses in different species were discussed, it was shown that decreased fetal growth and prenatal mortality are also observed in rats, guinea pigs, hamsters, rabbits and monkeys at doses that are toxic for the dam.[4] Although in recent years a number of investigators have examined various aspects of the reproductive and developmental toxicity of dioxins, according to the best of our knowledge the groups of Dr. L.S. Birnbaum (HERL, US EPA) and Dr. R. Peterson (University of Wisconsin, Madison, WI) in the USA, and that of Dr. J. Tuomisto from Finland (National Public Health Institute, Kuopio) have been the most active groups in this field.

It is now well established that in mice TCDD specifically targets the developing secondary palate and urinary tract in embryonic tissues inducing cleft palate and hydronephrosis,[5] whereas changes on the developing immune system, leading to altered differentiation of lymphocytes have also been observed.[6] Developmental effects were also reported in rats, guinea pigs and hamsters at similar maternal doses than those given to mice.[7] It has been shown that although there are species and tissue specific responses associated with the embryotoxicity and teratogenicity of TCDD, the toxic potency of that chemical is similar (within 10-fold) during prenatal development in those species.[7]

Developmental toxicity of dioxins in human infants has been produced following accidental exposure to complex mixtures including other susbtances. Exposed human infants were affected by developmental and/or psychomotor delays.[8] Some recent studies have corroborated the potentially negative effects of dioxins and dioxin-related compounds on human growth and development.[9-12]

2. Interactions of TCDD and other chemicals in developmental toxicology

From a public health perspective, the potential reproductive and developmental risk of environmental dioxins should probably be assessed taken into account that exposure to dioxins may occur concurrently with other chemicals that also have a notorious potential teratogenicity. Even in the case that some of those chemicals may not be toxic at environmental doses, it is now well known that exposure to combination or mixtures of chemicals may result in highly exaggerated toxicity.[13-15]

Toxic interaction refers to the qualitative and/or quantitative modification of the toxicity of one chemical by another, the process principally occurring within the organism after the exposure phase.[15] Interactions can either result in additive, greater-than-additive (potentiation or synergism), or less-than-additive (antagonism) toxic response. Over a thousand studies published to date report the occurrence of supra- or infra-additive toxicity from combined exposure to two chemicals.[15] The possibility of environmental chemical exposures causing adverse reproductive and developmental effects is a major public health concern. However, despite the fact that human exposure to chemicals rarely is limited to only a single compound, an overwhelming large portion of the toxicology studies to date deals with single chemicals.[14]

With regard to the developmental toxicity studies of TCDD in which pregnant animals were exposed to TCDD alone or in combination with other chemicals, some of the most striking results of those studies are summarized in Table 1. Notwithstanding, informations about the developmental effects caused by interactions with other environmental chemicals -which can also be teratogens- on the TCDD-induced developmental toxicity were not found.[16] Among those environmental chemicals, metals such as arsenic, cadmium, lead and mercury, some pesticides, or various hydrocarbons would be of especial concern.[17] In a recent review on chemical interactions in developmental toxicity, it has been shown that of approximately 160 studies of concurrent exposures reviewed, about one third reported no interactive effects (including additive effects), another one third reported antagonistic effects, and the final third reported potentiative or synergistic effects.[18] Undoubtedly, potentiative and synergistic effects should be especially worrying.

3. Effects of maternal stress on chemical-induced developmental toxicity

In relation to the above, another issue that should be also taken into account is the influence of maternal stress during gestation on the potential embryo/fetal toxicity of TCDD (or other dioxins and dioxin-related compounds). Maternal stress can be induced by a number of very diverse causes and can range from physical to psychological, from mild to severe, and from obvious to unrecognized.[19] Maternal stress during gestation can produce significant fetal and/or postnatal effects and can enhance the developmental toxicity of a number of teratogens. In recent years, experimental studies showed that maternal stress significantly enhanced the embryo/fetal toxicity of metals (arsenic, lithium, mercury),[20-23] ethanol,[24] or all-*trans*-retinoic acid[25] among other well known teratogens. However, data on the potential effects of maternal stress on TCDD-induced teratogenicity have not been reported.

4. Conclusions

It is now well established that TCDD is a developmental toxin which induces cleft palate and hydronephrosis in the mouse embryo, as well as other fetal anomalies in that and other species of mammals. Recently, notorious advances toward understanding the mechanism of TCDD-induced developmental toxicity were done.[1-5] However, the knowledge of the embryo/fetal toxic effects of dioxins shows still some important gaps that should be investigated. Because of the general population -including pregnant women- is exposed to dioxins mainly through the food, the implication of other significant environmental toxins, drugs, or even maternal stress on the potential TCCD-induced teratogenicity would be of great concern to public health.

5. References

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Table 1. A summary of results from a number of interaction studies between TCDD and other chemicals

Chemicals	Species	Dosing period (gestational days)	Route	Comments	Reference
TCDD + HCB-1 or HCB-2	Mice	10-13	po	HCB-2 had no effect on the incidence of TCDD-induced cleft palate. HCB-1 in combination with TCDD resulted in a 10-fold increase in the incidence of cleft palate	Birnbaum et al.[26]
TCDD + HC	Mice	10-13	TCDD, po HC, sc	Synergistic effect evidenced by a 100% incidence of cleft palate, decreased litter size and fetal weight, and an increase in fetal mortality related to the HC dose	Birnbaum et al.[27]
TCDD + retinoic acid	Mice	10 or 12	po	Incidence of cleft palate dramatically enhanced by coadministration of both chemicals. The pattern consisting in growth factors required for normal palatogenesis, acting in concert at the appropiate levels, is disrupted by TCDD inducing cleft palate	Birnbaum et al.[28] Abbot & Birnbaum[29] Abbot & Birnbaum[30]
TCDD + HCB-3	Mice	9, HCB-3 10, TCDD	po	Cotreatment with TCDD and HCB-3 resulted in a significant decrease in the number of litters and fetuses with cleft palate compared to that observed with TCDD alone	Biegel et al.[31]
TCDD + HCB-3	Mice	9, HCB-3 10, TCDD	po	HCB-3 antagonized TCDD-induced malformations (cleft palate and hydronephrosis) over a narrow range of doses	Morrissey et al.[52]
TCDD + HC	Mice	10-13	HC, sc TCDD, po	A cross-regulation of the Ah-receptor and the glucocorticoid receptor was observed. It could be important in the synergistic interaction between TCDD and HC for the induction of cleft palate	Abbott et al.[33] Abbott[34]

Abbreviations. HCB-1: 2,3,4,5,3′,4′-hexachlorobiphenyl; HCB-2: 2,4,5,2′,4′,5′-hexachlorobiphenyl; HC: hydrocortisone; HCB-3: 2,2′,4,4′,5,5′-hexachlorobiphenyl.

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