Teratogenic Risk by chlorinated dioxins: is it likely in man?

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An increased incidence of palatal cleft and of some other congenital malformations secondary to a low exposure to chlorinated dioxins in the environment was recently claimed by some physicians in Austria and has since caused much public concern in this country. We therefore make a attempt here to review the evidence for dioxin related malformations in the fetus on the basis of epidemiologic data, of studies in laboratory animals and of in vitro studies with cultured palatal shelves of embryonic origin.

I) Epidemiologic data:
The largest study on the frequency of birth defects was conducted in the area around Seveso, Italy, which was contaminated by TCDD in July 1976. From January 1st, 1977 to December 31, 1992 a total of 15291 newborns (still and alive) were examined for malformations [1]. The evaluation was performed separately in three areas, the first immediately surrounding the factory with an average TCDD concentration of 192.8 $\mu g/m^2$, the second further from the factory in the direction in which the wind was blowing at the time of the accident with an average TCDD-concentration of 3 $\mu g/m^2$ and the third zone with an average concentration of 0.9 $\mu g/m^2$ of TCDD. In the most highly contaminated area 26 births were observed, none of this infants had any major structural defect. The frequencies of major defects detected in the remaining areas were 29.9/1000 and 22.1/1000 respectively. A frequency of 27.7/1000 was registered in the control area. H. Rehder[2] et al investigated 30 interrupted pregnancies and 4 spontaneous abortions embryologically and histomorphologically and did not find indications of mutagenic teratogenic or fetotoxic effects of TCDD here. Several reports on reproductive effects of an exposure against TCDD contaminated Phenoxyherbicids in Vietnam likewise failed to give a statistically significant increase of congenital malformations [3,4,5]. Statistically significant odds ratios for hydadiform moles after exposure [6] is noticeable, moles however are not related to congenital defects. 410 births were identified during the period of January 1, 1972 through December 31, 1982 in 9 TCDD contaminated areas of Eastern Missouri, when several horse areas and

dirty roads were sprayed there for dust control with a mixture that contained waste oil and dioxin. This group of births was compared with a matched set of 820 unexposed births and the results did not provide evidence that TCDD exposure had a substantial impact on several reproductive parameters including several subcategories of birth defects [11].

II. Studies with laboratory animals:
TCDD induced a characteristic pattern of developmental malformations in mice, which is highly reproducible and includes hydronephrosis, cleft palate and thymic hypoplasia [7]. It is very interesting, however, that this is confined to mice. In all other laboratory animals tested TCCD causes maternal and embryo/feto toxicity but does not induce a significant increase in the incidence of structural abnormalities even at toxic dose levels. Strains of mice being AH nonresponsive do not show the typical TCDD induced malformations either [8].

III. In vitro studies with palatal shelves:
Embryonic palatal shelves of various origin (mouse, rat, human) were studied in organ culture in the presence of a various concentrations of TCDD. Interestingly the mouse cells exhibited the highest sensitivity ($5x10^{-11}$M TCDD inhibited cell differentiation and 10^{-10} M TCDD was cytotoxic) palatal shelves of rat or human origin were up to two orders of magnitude less sensitive [9,10].

Conclusions: The available epidemiologic data as well as animal studies and in vitro investigations make it unlikely, that TCDD causes malformations of human fetuses at least below the dose level which would result in maternal and embryonic toxicity including fetal lethality. Epidemiologic data which were obtained after a more than a hundred fold higher exposition as compared to the level in the area of Amstetten/Austria did not statistically increase the malformation rate. Although these data do not rule out completely a teratogenic effect of TCDD, it appears to be highly unlikely that such an effect could be claimed on the basis of casuistic observations in small populations.

References:
1 Mastroiacovo P, Spagnolo A, Marni E, Meazza L, Bertollini R, Segni G, Borgna-Pignatti C. Birth defects in the Seveso area after TCDD contamination. [published erratum appears in JAMA 1988 Aug 12; 260 (6): 792] JAMA 1988; 259:1668-72.
2 Rehder H, Sanchioni L, Cefis F, Gropp A. Pathologisch-embryologische Untersuchungen

an Abortusfaellen im Zusammenhang mit dem Seveso-Unglueck. (Pathological and embryological studies on abortion cases related to the Seveso accident). Schweizerische Medizinische Wochenschrift. Journal Suisse de Medecine 1978, 108: 1617-25
3 Hatch MC, Stein ZA. Agent Orange and risks to reproduction: the limits of epidemiology. Teratogenesis Carc 1986, 185-202
4 Pearn JH. Herbicides and congenital malformations: a review for the paediatrician. Australian Paediatric Journal 1985, 21: 237-42
5 Friedman JM. Does Agent Orange cause birth defects? Teratology 1984, 29: 193-221
6 Sterling TD, Arundel AV. Health effects of phenoxy herbicides - a review. Scand J Work Environ Health 1986, 12: 161-173
7 Couture LA, Abbott BD, Birnbaum LS. A critical review of the developmental toxicity and teratogenicity of 2,3,7,8-tetrachlorodibenzo-para-dioxin - recent advances toward understanding the mechanism. Teratology 1990, 42: 619-627.
8 Hassoun E, D'Argy R, Dencker L, Lundin LG, Borwell P. Teratogenicity of 2,3,7,8-tetrachlorodibenzofuran in BXD recombinant inbred strains. Toxicology Letters 1984, 23: 37-42.
9 Abbott BD, Birnbaum LS. TCDD exposure of human embryonic palatal shelves in organ culture alters the differentiation of medial epithelial cells. Teratology 1991, 43: 119-32.
10 Abbott BD, Birnbaum LS. Rat embryonic palatal shelves respond to TCDD in organ culture. Toxicology And Applied Pharmacology 1990, 103: 441-51.
11 Stockbauer JW, Hoffman RE, Schramm WF, Edmonds LD. Reproductive outcomes of mothers with potential exposure to 2,3,7,8-tetrachlorodiebenzo-p-dioxin. American Journal Of Epidemiology 1988, 128: 410-9