Summary and Biography of Dioxin Toxicity

Prepared by N. Chalfin and M. Lappé
Center for Ethics and Toxics
Gualala, CA 95445
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Summary of Toxicological Effects:

Dioxins interfere with the production and activity of enzymes, hormones, other growth factors, thereby adversely affecting reproduction, growth, and development through a variety of mechanisms. They are also capable of producing cancer in exposed animals, including but not limited to thyroid cancer and lymphopoietic neoplasms, and are known to the State of California to cause cancer more generally.

General Discussion:

Dioxins, among the better known and studied endocrine disruptors, are a family of related compounds differing in the number and position of chlorine atoms on the basic underlying structure. The toxicity of each member of the family varies considerably and is usually described relative to the most toxic. Together, they demonstrate several different mechanisms of hormone-disrupting action and have diverse biological effects.

Dioxins result from heating mixtures of chlorine and organic compounds in industrial processes, such as the bleaching of paper pulp, production of some pesticides or preservatives, especially pentachlorophenol, or during incineration of chlorine-containing materials. Because many consumer products contain chlorinated organic compounds (e.g. polyvinyl chloride), municipal, medical, and hazardous waste incinerators are leading dioxin sources. It is not easily broken down in the environment, accumulating in soils and sediments and biomagnifying as it passes up the food chain. Dioxins bioaccumulate in fat tissue with as estimated half-life in humans of approximately seven years.

There may be significant regional variations depending on local industrial activity, but dioxin is widely spread around the globe. Beef, pork, fish, shellfish, and animal and human milk are the major sources of human exposure to dioxins. Because breast milk has a high fat content, nursing infants are actually exposed to higher daily amounts of dietary dioxin than most adults and may receive more than 10 percent of their anticipated lifetime exposure during this particularly vulnerable period of mental and physical development.[1] Although there is some variation with geographical location and diet, many people have dioxin levels at or near those known to cause harmful effects in animal studies.[2]

In animal studies, dioxin has a wide range of health effects, which differ among the fetus, newborn, and adult. Some are apparent only with large doses, but cancer, immune system toxicity, and reproductive and developmental effects occur at low levels

of exposure. Dioxin causes the liver to produce metabolic enzymes at exposures of 1-10 picograms per kilogram daily, a level similar to average daily adult human exposures. (A picogram is one-trillionth of a gram.) These enzymes alter the metabolism of hormones and other endogenous or exogenous chemicals. Enzyme induction occurs at levels that also cause immune system toxicity in mice and reproductive effects in rats.[3]

In rats, thyroid tumors occur at doses as low as 1,400 pg/kg/day.[4] There is considerable variability in the toxicity of dioxin among adults of different animal species but much less among fetuses and infants, particularly with respect to the sensitivity of offspring to developmental effects. For example, adult hamsters are several thousand times more resistant to dioxin toxicity than adult guinea pigs.[5] But the hamster fetus is only ten times more resistant to dioxin that the guinea pig fetus. Similarly, early life stages of fish and birds are more sensitive to dioxin toxicity than adults.[6,7]

From these data, one might suspect that dioxin toxicity in human fetuses would be similar to that in fetuses of other species, even if human adults were relatively resistant. Sufficient exposure to dioxin during pregnancy causes prenatal mortality in the monkey, guinea pig, rabbit, rat, hamster, and mouse. The response is dose related, and there is a species difference. Monkeys and guinea pigs are the most sensitive, followed by rabbits, rats, hamsters, and mice, which are the most resistant. In these species, the maternal dose necessary to cause prenatal mortality ranges from 1 to 500 µg/kg (cumulative dose). The timing of maternal exposure is just as important as the magnitude of the dose, often demonstrating a window of vulnerability. In the guinea pig, for example, prenatal death is caused by a single dose of 1.5 µg/kg on day 14 of pregnancy, whereas later in pregnancy, larger amounts are needed.[8]

Similarly, a single low maternal dose of dioxin at a critical time in pregnancy may cause permanent developmental effects in male offspring, including altered sexual differentiation of the brain.[9] On day 15 of a typical twenty-one-day pregnancy in rats, most organs are formed, but the hypothalamic-pituitary-gonadal (HPG) axis is just beginning to function. The critical period of sexual differentiation of the brain extends from late fetal life through the first week of postnatal life. A single low maternal dose of dioxin (0.16 µg/kg) on that day of pregnancy reduces male testosterone levels, delays descent of the testicles, decreases anogenital distance (making it more female-like), and reduces prostate weight and sperm production in offspring.[10] It also demasculinizes their sexual behavior in the months that follow. A single maternal dose of just 0.064 µg/kg on day 15 of pregnancy causes a 43 percent reduction in sperm production in male offspring.

Dioxin does not attach to the estrogen receptor, yet is causes both estrogenic and antiestrogenic activity in different tissues of the body. Both dioxin and PCB's attach to another intracellular receptor, called the Ah-receptor, whose function is not otherwise fully understood. (Unlike dioxins, some forms of PCBs also attach to the estrogen receptor.) The occupied Ah-receptor is transported into the nucleus of a cell, where it attaches to DNA, influencing the activity of genes, which regulate chemical production. By this mechanism, dioxin indirectly influences estrogen activity. Its antiestrogenic effects, which seem to predominate, may result from causing the cells to produce an

enzyme that metabolizes the body's normal estrogen or decreasing the number of estrogen receptors available for normally occurring estrogen.[11,12]

Epidemiological Studies: In the Ranch Hands study, reproductive histories of men who sprayed Agent Orange in Vietnam from 1962 to 1971 were examined beginning in 1978 in an attempt to see if exposure to dioxin might have had adverse effects in their children.[13]

Agent Orange is a mixture of two herbicides, almost always contaminated with dioxin. Dioxin in the blood of participants was measured years after exposure, and an attempt was made to estimate earlier levels from those results. An increase in all nervous system defects in offspring was found. However, increases in spina bifida and cleft palates were too few to allow formal statistical analysis. One finding that is difficult to explain was an increased risk for spontaneous abortion, all birth defects, and specific developmental delays in the low – but not the high – dioxin exposure group.

Another study of Vietnam veterans found that opportunity for Agent Orange exposure was associated with an increased risk of spinal cord abnormalities (spina bifida) and cleft palates in offspring.[14] The National Academy of Sciences has concluded that there is limited but suggestive evidence of a relationship between paternal Agent Orange exposure and spina bifida in offspring.

In a study of 248 chemical production workers in New Jersey and Missouri, investigators found that workers with higher dioxin levels had higher amounts of luteinizing hormone and follicle-stimulating hormone and lower amounts of testosterone than a control group from the neighborhood.[15] These results must be interpreted with caution since it was a cross-sectional study (all measurements of dioxin, testosterone, and gonadotropins were done on the same blood specimen, making it difficult to determine cause-and-effect relationships), but the results are consistent with the effects of dioxin in animal studies.

In 1977, an industrial accident in Seveso, Italy, released large amounts of dioxin, contaminating the environment and exposing local residents. From 1977 to 1984, there was a marked increase in the female-to-male birth sex ratio among those most heavily exposed.[16] Almost twice as many girls as boys were born during those years. Over the next ten years, the ratio began to return to normal. The mechanism by which dioxin may have this effect on sex determination is unclear. In this same population, there was no increase in the rate of birth defects, as determined from a birth defects registry, when compared to an unexposed population.[17] However, in this study, the number of children of mothers with the highest likelihood of exposure was too small to assess specific categories of birth defects. Other limitations include possible exposure misclassification and unrecognized spontaneous abortions that may have resulted from fetal malformations. Children of exposed women have not been examined for subtle structural of functional developmental deficits.[18]

In Times Beach, Missouri, an area contaminated with dioxin-containing oil that had been spread on roads for dust control, there was no apparent increased risk of fetal deaths or low-birth-weight babies.[19] There was, however, a two-to-three-fold increase in risk of nervous system defects and undescended testicles, though this was not statistically significant. Because of the small sample size, a six-fold increase in risk would have been necessary in order to achieve statistical significance.

Investigators in the Netherlands found that higher dioxin levels in breast milk correlate with lower thyroid hormone levels in breast-feeding infants.[20] This finding is particularly important since the correlation appears at current levels of ambient dioxin exposure. Moreover, in pre-term and low-birth-weight babies, decreased thyroid hormone in the first weeks of life is associated with increased risk of neurological disorders, including the need for special education by age nine.[21] Although the thyroid hormone levels in the Netherlands study were still in the normal range, it is possible that the observed changes will influence infant development, a subject that will require further research.

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[1] Smith AH. Infant exposure assessment for breast milk dioxins and furans derived from waste incineration emissions. *Risk Analysis*. 7(3):347-353, 1987.

[2] Birnbaum LS. The mechanisms of dioxin toxicity: relationship to risk assessment. *Environmental Health Perspectives*. 102(Suppl 9):157-167, 1994.

[33] Aldercreutz H, Hockerstedt K, Bannwart C, et al. Effect of dietary componenets, including lignans and phytoestrogens, on enterohepatic circulation and liver metabolism of estrogens and on sex hormone binding globulin (SHBG). *Journal of Steroids & Biochemistry* 27(4-6):1135-1144, 1987.

[4] Huff J. Dioxins and mammalian carcinogenesis. In Schecter A (ed). *Dioxins and Health*. New York: Plenum Press, 1994.

[5] Olson JR, Holscher MA, Neal RA. Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the Golden Syrian hamster. *Toxicology and Applied Pharmacology*. 55:67-78, 1980.

[6] Gilbertson M. Effects on fish and wildlife populations. In: Kimbrough RD, Jensen AA (eds). *Halogenated Biphenyls, Tertphenyls, Napthalenes, Dibenzodioxins, and Related Products*. 2nd ed. Amsterdam: Elsevier Science Publishers, 1989.

[7] Walker MK, Peterson RE. Potencies of polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyl congeners for producing early life stage mortality in rainbow trout. *Aquatic Toxicology*. 21:219-238, 1991.

[8] Couture LA, Abbott BD, Birnbaum LS. A critical review of the developmental toxicity and teratogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin: recent advances toward understanding the mechanism. *Teratology*. 42:619-627, 1990.

[9] Mably TA, Moore RW, Goy RW, et al. In utero and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-p-dioxin. 2. Effects on sexual behavior and the regulation of LH secretion in adulthood. *Toxicology & Applied Pharmacology*. 114:108-117, 1992.

[10] Mably TA, Moore RW, Peterson RE. In utero and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-p-dioxin: 1. Effects on androgenic status. *Toxicology & Applied Pharmacology* 114:97-107, 1992.

[11] McKinney JD, Waller CL. PCBs as hormonally active structural analogues. *Environmental Health Perspectives* 102(3):290-97, 1994.

[12] Birnbaum LS. The mechanism of dioxin toxicity: Relationship to risk assessment. *Environmental Health Perspectives* 102(Suppl 9):157-167, 1994.

[13] Wolfe WH, Michalek JE, Miner JC, et al. Paternal serum dioxin and reproductive outcomes among veterans of Operation Ranch Hand. *Epidemiology*. 6(1):17-22, 1995.

[14] Erickson JD, Mulinare J, McClain PW, et al. Vietnam veterans' risks for fathering babies with birth defects. *JAMA*. 252:903-912, 1984.

[15] Egeland GM, Sweeney MH, Fingerhut MA, et al. Total serum testosterone and gonadotropins in workers exposed to dioxin. *American Journal of Epidemiology*. 139(3):272-281, 1994.

[16] Mocarelli P, Brambilla P, Gerthoux PM, et al. Change in sex ratio with exposure to dioxin. *Lancet*. 348:409, 1996.

[17] Mastroiacovo P, Spagnolo A, Marni E, et al. Birth defects in the Seveso area after TCDD contamination. *JAMA*. 259:1668-1672, 1988.

[18] Birnbaum LSI. Endocrine effects of prenatal exposure to PCBs, dioxins, and other xenobiotics: implications for policy and future research. *Environmental Health Perspectives*. 102:676-679, 1994.

[19] Stockbauer JW, Hoffman RE, Schramm WF, et al. Reproductive outcomes of mothers with potential exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *American Journal of Epidemiology*. 128:410-419, 1988.

[20] Koopman-Esseboom C, Morse D, Weisglas-Kuperus N, et al. Effects of dioxins and polychlorinated biphenyls on thyroid hormone status of pregnant women and their infants. *Pediatric Research* 36:468-473, 1994.

[21] den Ouden AL, Kok JH, Verkerk PH, et al. The relation between neonatal thyroxine levels and neurodevelopmental outcome at age 5 and 9 years in a national cohort of very preterm and/or very low birth weight infants. *Pediatric Research*. 39:142-145, 1996.