TERATOLOGY 36:399–400 (1987)

Letters

"Teratogen": A Case Against Redefinition: Response to Johnson's Editorial Comment Re:"Teratogen"

To the Editor:

Johnson ('86) recently discussed definitional differences between teratogenesis and carcinogenesis and implications of false positives and false negatives. Discussing the concern that concepts and terminology from carcinogenesis research may become inappropriately associated with teratogenesis, he indicated that lay people tend to think of birth defects in the same frame of reference as cancer. Most people are perhaps unaware that, unlike carcinogenesis, teratogenesis is a threshold phenomenon. That is, they associate the ability of an agent to produce birth defects as an "all or none" response without regard for the dosage required to produce defects taken into consideration. A significant concern expressed by Johnson was that information from animal studies in which even extremely high dosages of the test agent are administered is ultimately summarized with a label of "teratogen" or "nonteratogen" for regulatory purposes. In this context, Johnson stated, "A false positive from a test for developmental toxicology in laboratory mammals is one wherein the substance is labeled as 'teratogenic' even though maternally toxic dosage was needed to produce the effect." He then encouraged restricting use of the term "teratogen" to substances that either "(1) adversely affect development at dosage levels below the adult-toxic exposure level or (2) if generally equally toxic to adults and embryos, are experienced at maternally toxic levels."

Although I agree with many of the concerns raised by Johnson, I do not agree with restricting usage of the term as he has proposed. Johnson's proposal is to amend the very concept of teratogenesis. It is clear, from the early work of Warkany, through the classic period of Wilson, Fraser, and Kalter and right up to the present (see Schardein, '85), that the term teratogenesis has been defined and used to refer to adverse effects on the structure and function of the conceptus. Consider Wilson's ('73, p. 4) oft-quoted definition of teratology: "Teratology is the science dealing with the causes, mechanisms, and manifestations of developmental deviations of either a structural or functional nature." It is clear that a similar definition was intended in 1954 when Wilson and Warkany sent out the first letter regarding formation of a teratology society (see Wilson and Warkany, '85). And most recently, Schardein ('85, p. 1) defined a teratogen as "an agent that induces structural malformations, metabolic or physiological dysfunction, or psychological or behavioral alterations or deficits in the offspring, either at birth or in a defined postnatal period." Additionally, the major medical dictionaries and *Webster's Third International Dictionary* also define it in terms of adverse effects of structure and function on the conceptus, *with no further qualifications*. Why, then, should the term be redefined so as to apply only in relation to maternal toxicity as Johnson is proposing? Although this novel definition recognizes an important aspect of teratogenesis, viz. its possible relationship to maternal toxicity, it does so at the expense of restricting the term to an unacceptable degree. Although I am not advocating that they should be, other restrictions might also be applied to the definition. For example, a restriction could be based upon biotransformation (e.g., if a metabolite is the proximate teratogen, then the metabolite would be defined as "teratogenic" but the parent compound would not be so defined). Or perhaps "teratogen" should be limited to cases in which the toxic agent crosses the placenta. Or should test species be considered?

Such restrictions would be scientifically constricting. In addition to inappropriate selectivity based upon only one aspect of concern, restriction based upon maternal toxicity has other undesirable implications. First, "maternal toxicity" must be defined. The definition might be based, initially, upon statistically significant decreases in maternal weight gain and feed consumption. But should these phenomena be ascertained daily, weekly, or otherwise? If these are normal, but other observations on maternal animals are not (e.g., respiratory rate, pelage appearance, blood enzymes, liver and kidney weights), should the additional factors be considered as indicating maternal toxicity? It is evident that the concept of maternal toxicity is complex, and achieving a universally acceptable definition would likely be difficult, if not impossible.

A second problem is that restricting use of the term teratogen based upon maternal toxicity implies that maternal toxicity or illness produces malformations. There are certainly examples in which this may be true, but there are also many examples in which it is not. Such an implication could ultimately create more problems than would be solved by changing the definition (i.e., if "maternal illness produces malformations," then women may elect abortions after *any* illness).

I infer that Johnson's second point would define a teratogen as a compound that is approximately equally toxic to adult and developing organisms, and exposures could occur at these levels. Not directly stated, then, is the potential for maternal toxicity being possibly used as a monitor or predictor of developmental toxicity. Based on this, a final potential problem is concerned with defining "adult to embryo toxicity" for various classes of chemicals and with limiting exposures based upon maternal toxicity. For therapeutic agents, adult toxicity may be fairly well defined, although developmental toxicity may often not be as well characterized. Regardless, drugs are often administered at toxic doses (think of the last patient you saw on cancer chemotherapy). Even more alarming, however, are the numerous agents to which people may be exposed environmentally or occupationally, an area of increasing concern. For the vast majority of these, information on adult toxicity, to say nothing of developmental or reproductive toxicity, is limited or lacking. Where adult toxicity is known, most of the data were generated from studies with laboratory animals, and exposures are often not as well monitored, or controlled, in humans as they would be in experimental studies. Therefore, using maternal toxicity as the basis on which to predict or limit potential developmental toxicity of either therapeutic or industrial agents may frequently be impractical.

Thus, whereas I agree that the issue of maternal toxicity is an important consideration in developmental toxicology, it should not be the determinant in defining a teratogen. It would help alleviate confusion if authors were to provide a careful description of the signs of maternal as well as embryo/fetal toxicity for which observations were made and which were and were not affected. If more steps need be taken, and I am not implying that they should be, a far better approach than to redefine the entire concept of teratogenesis would be to develop a new term for the regulatory issues Johnson has in mind. Perhaps we should consider something like "terasant" [*teras* producing *At Non* (maternally) (toxic doses)]. While we all agree that misinterpretation of the term "teratogen" can be a problem, it is doubtful that redefining the central concept of teratology represents the solution.

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