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PERSPECTIVE

Origins of Behavioral Teratology and Distinctions Between Research on Pharmaceutical Agents and Environmental/Industrial Chemicals[1]

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NELSON, B. K. *Origins of behavioral teratology and distinctions between research on pharmaceutical agents and environmental/industrial chemicals*. NEUROTOXICOL TERATOL **12**(4) 301–305, 1990.—Most behavioral teratology studies have focused on pharmaceutical agents. Investigations of developmental toxicity are lacking for the majority of the nearly 100,000 industrial chemicals currently in use. Only some three dozen chemicals have been examined for behavioral/neurochemical deviations in offspring following maternal exposures. Examination of industrial agents for developmental toxicity, therefore, remains a major public health need. Most developmental research addresses the effects of pharmaceutical agents, but these studies frequently do not address environmental/industrial concerns due to fundamental differences in experimental methodology. The route, duration, and timing of exposure, usefulness of fostering of offspring, and potential concomitant exposure of both parents are all variables which should be treated differently in research on industrial chemicals as opposed to pharmaceutical agents. After briefly tracking the history of behavioral teratology, the present paper discusses differences in application of behavioral teratological principles to industrial versus pharmaceutical agents, and points to the largely untested number of industrial chemicals needing investigation.

Industrial chemicals Drugs Solvents Teratology Behavioral teratology Developmental disorders

BEHAVIORAL teratology is a research specialty which investigates the functional effects of developmental exposure to exogenous agents on the nervous system. Functional effects are typically measured using behavioral, neurochemical, or neuropathological end points. This paper summarizes the historical development of behavioral teratology and discusses how behavioral teratological evaluations of industrial agents have differed from those of pharmaceutical agents. Its intent is to stimulate thought and discussion comparing these related fields of study and to encourage developmental toxicology assessment of a wider variety of industrial agents.

ORIGINS OF BEHAVIORAL TERATOLOGY

Behavioral teratology had its roots in the fields of psychology, anatomy, and pharmacology (11,51). Some of the earliest experimental results related to behavioral teratology came from laboratories investigating the effects of early experience or malnutrition on later behavior, the administration of sex hormones to juveniles, and the enduring effects of x-irradiation (11). From these beginnings, the field has branched to encompass much broader areas of concern, in fact outgrowing the limited scope implied in the title of "behavioral teratology."

The early research focus was on behavior and its assessment, with limited concern about strict control of other, potentially confounding, experimental variables (e.g., litter size, postnatal contributions to observed effects, statistical issues). Much of this early research was critically reviewed by Joffe (24), who called attention to the apparent lack of concern over methodological issues such as the confounding of pre- and postnatal variables. Kimeldorf and Hunt (26) summarized many of the general phenomena observed with irradiation [see also the excellent review by Hicks and D'Amato (21)]. Although much of the early work focused on behavioral end points, strong interest was also shown in histopathological changes following prenatal exposure to various agents, as summarized in a 1972 conference (49).

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Examining this early research in behavioral teratology, one notes an almost exclusive investigation of therapeutic agents. Undoubtedly, an important reason for this focus on therapeutic agents was the impetus given the entire field now known as teratology by the thalidomide tragedy of the early 1960's. Some 10,000 malformed infants were born, primarily in Europe, as a result of maternal ingestion of the sedative-hypnotic and antinausea medication, thalidomide, during pregnancy (42). Although this drug had not been approved for use in the United States, the Food and Drug Administration (FDA) reacted strongly by establishing guidelines which required testing of new drugs for their ability to produce birth defects in experimental animals. Clearly, research interest was concentrated on drugs, both in morphological teratology and in the fledgling field of behavioral teratology [e.g., (18, 29, 49, 57)]. Werboff and Gottlieb (56) coined the term "behavioral teratology" to refer to the study of the development and behavior of offspring following "prenatal administration of *pharmacological agents* to pregnant animals" (emphasis added).

Whereas the thalidomide tragedy may be considered the major stimulus for research in teratology, ethanol can be considered the primary stimulus for research in behavioral teratology. Since Jones and Smith published their paper describing the Fetal Alcohol Syndrome (25), an extensive literature has accumulated on the behavioral teratogenic effects of ethanol, both in humans and experimental animals [e.g., (1–3)]. The key elements of this syndrome, which is seen frequently in the children of alcoholic mothers, include pre- and postnatal growth retardation, abnormal facies and other malformations. The hallmark of this syndrome, however, is behavioral and intellectual dysfunction characterized by hyperactivity, delayed motor development, and mental retardation. In fact, it has been suggested that ethanol represents the single greatest cause of preventable mental retardation in humans (12).

Fully one-half of all research in behavioral teratology has investigated ethanol as the independent variable. Research to develop an animal model and characterize this syndrome, aimed at preventing its occurrence, has been well received by both private and public funding agencies. It is evident that long-term exposure to high levels of ethanol is required to produce the Fetal Alcohol Syndrome; in experimental animals, blood levels above 200 mg% appear to be required to produce behavioral teratogenic effects (1–3). However, consumption of lower levels of ethanol has been implicated in producing lesser degrees of mental subnormality (45).

DEVELOPMENT OF INTEREST IN INDUSTRIAL CHEMICALS

While the 1960's and early 1970's emphasized the potential teratogenicity of drugs, the later 1970's and the 1980's emphasized the teratogenicity of environmental/industrial chemicals. Popular books such as Rachel Carson's *Silent Spring* and environmental catastrophes, including those at Love Canal and Times Beach, helped to dramatize the adverse health effects of environmental agents, including reproductive problems. Concurrently, with increasing numbers of women entering the work force, the ability of industrial agents to produce malformations and/or less obvious deviations in offspring following occupational exposures became a matter of concern (48). At least five conferences and numerous addresses in the late 1970's focused on the adverse reproductive effects of occupational exposures (4, 5, 10, 23, 31). Few of these addresses discussed potential behavioral effects, although an earlier paper by Weiss and Spyker (54) speculated on some effects of environmental pollutants on CNS function over the lifetime of exposed individuals. [Conference proceedings addressing behavioral effects include one paper on Minamata disease in (10); a paper on methodological concerns in (23); and two papers in (31).]

Apparently the first reference to occupationally induced behavioral teratology was made by Spyker (44) at the 1973 Behavioral Toxicology Workshop for Early Detection of Occupational Hazards. She reviewed some of the early research on methylmercury, and discussed some methodological issues unique to behavioral teratology. At present, behavioral teratology is recognized to be of sufficient importance that the World Health Organization guidelines for assessing the effects of occupational health hazards on reproductive functions (14) include a section on postnatal evaluations. The emphasis in the field, however, remains where funding is the strongest—the behavioral teratology of drugs [e.g., (22,40)].

Attention was directed to environmental/industrial agents because of several outbreaks of congenital methylmercury poisoning resulting from environmental exposure. In Japan, human poisonings resulted from dumping the effluent from an acetaldehyde plant into Minamata Bay (32). In 1955, some 1600 cases of severe neurological disease were found in the Minamata area of Kyushu, Japan (19). In 1958, Kitamura [as discussed in (19)] speculated that environmental exposures may have been responsible for the large number of infants born with symptoms similar to those produced by cerebral palsy. In 1959, the Japanese study group looking into the *adult* form of methylmercury poisoning, which came to be known as Minamata disease, concluded that the symptoms were due to exposure to methylmercury; this conclusion was based on body burden measures and related data. Methylmercury entered the food chain through fish in Minamata Bay which were ultimately consumed by local villagers, some of whom were pregnant. Several years later, investigators concluded that methylmercury was also responsible for similar symptoms developed by 26 infants born to the exposed mothers (19). An identical event occurred ten years later in Niigata, Japan, thus confirming the neurological and behavioral toxicity of methylmercury. By 1985, a total of 40 cases of infants affected by transplacental methylmercury intoxication had been identified in Japan (46).

Earlier Swedish cases of cerebral palsy with mental deficiency were suspected to have been caused by congenital poisoning following maternal consumption of seed grain treated with mercury (15,19). An independent incident in Iraq added evidence to the hypothesis that the Swedish cases were caused by mercury exposure. In Iraq, seed grain treated with methylmercury was accidentally used to make bread which was consumed by a large number of people [(7,19); see also (17)]. Thousands were hospitalized, and approximately 500 people died. Among those who survived in the affected area were a small number of pregnant women. At least 6 of 15 infants exposed congenitally to methylmercury showed gross impairment of motor and mental development, with cerebral palsy, microcephaly, deafness, and blindness. It is noteworthy that in approximately one-half of these cases, no clinical symptoms were noted in the mothers of the affected infants. Five-year follow-up evaluations of 32 prenatally exposed children (including the original 15) revealed dose-dependent toxicity ranging from cerebral palsy in the most severely affected cases to developmental delays for those exposed to low levels of methylmercury. Further, cases which had been pronounced normal at birth developed symptoms over this 5-year period (8).

The relationship between methylmercury exposure and adverse pregnancy outcome was summarized by Koos and Longo [(28); see also (42)], who clearly demonstrated that methylmercury can produce teratogenic and behavioral teratogenic effects in humans. This demonstration of behavioral teratogenic effects in humans, occurring about the same time as the reports on Fetal Alcohol Syndrome, may have contributed to the wide and rapid acceptance of the behavioral teratogenicity of ethanol (25). In addition, numerous studies in experimental animals have demonstrated the teratogenic and behavioral teratogenic effects of methylmercury in experimental animals (39).

TABLE 1

DIFFERENCES BETWEEN STUDIES OF DRUGS AND THOSE ON INDUSTRIAL CHEMICALS

Pharmaceutical Agents	Industrial Chemicals
1) Pharmacological properties known	Pharmacological properties rarely known
2) Body burden characterized	Body burden information lacking
3) Developmental/reproductive toxicology information relatively complete	Developmental/reproductive toxicology information lacking
4) Routine routes of exposure (oral or IP)	Frequently inhalation or percutaneous exposure
5) Mechanism of action important	Mechanism of action not key issue
6) Exposure limited to sensitive periods	Exposure must cover entire developmental period
7) Fostering/cross-fostering issues relevant	Fostering/cross-fostering issues less important
8) Maternal exposure usually of primary interest	Both maternal and paternal exposures of importance
9) Negative results only moderately useful	Negative and positive results equally useful

In spite of the early research on methylmercury, and subsequently on other metals, behavioral teratology research still maintains a focus on drugs. Relatively few studies have been published on environmental or industrial agents. For example, the *Handbook of Behavioral Teratology* (40) has 12 chapters on alcohol and drugs, but only 4 chapters discuss occupationally relevant chemicals (a chapter each on lead, cadmium, insecticides, and industrial solvents). A cursory review for the years 1986 and 1987 of the primary journal which publishes research in this area (*Neurotoxicology and Teratology*) substantiates this imbalance. About 15 papers can be found on the prenatal effects of ethanol, and one or two papers each on carbon monoxide, drugs of abuse, tobacco, caffeine, methylmercury, trimethyl tin, diazepam, and a few other pharmaceutical agents. Studies involving occupational agents are notably in the minority.

From an estimated 5 million total chemicals (33), approximately 30 of over 100,000 industrial chemicals in use (43) have been investigated for behavioral teratogenicity; about half of these chemicals are heavy metals and pesticides that were studied for effects found outside the occupational environment (35,36). Providing a reliable estimate of the behavioral teratogenicity of these chemicals is a difficult task. One approach is to generalize from those chemicals that have been investigated to date. Nelson (36) noted that about one-half of all solvents investigated for behavioral teratogenicity have shown positive effects in experimental animals. If that figure could be generalized validly to all industrial chemicals, or even to industrial solvents, an extremely large number would be expected to be behavioral teratogens. What is needed are many more evaluations of the behavioral teratogenicity of industrial chemicals.

A second approach to defining the magnitude of the problem of behavioral teratology could be to draw parallels between the number of behavioral teratogenic drugs and the number of drugs that are teratogenic. An overview of the literature would suggest that more than 10% of the drugs reported to be teratogenic in experimental animals also produce behavioral teratogenicity in experimental animals. The problem with basing such an estimate for industrial chemicals on reports on drugs is that too few industrial compounds have been evaluated for teratogenic effects, and fewer still have been evaluated for behavioral teratogenic effects.

Rather than attempting to estimate the percent of chemicals that are likely to be teratogenic, another approach to predicting the behavioral teratogenicity in industrial chemicals would be to evaluate individual chemical structures, and predict which structures are most likely to be behavioral teratogens. Although we did not observe strong structure-activity relationships in the developmental toxicology of a series of industrial alcohols (37), other chemical classes have shown more positive structure-activity relationships [e.g., the glycol ethers (20)]. Further, clues may be available from structural similarities between industrial chemicals and drugs that are behavioral teratogens, or from structures that resemble putative neurotransmitters. This approach is largely theoretical, and much work would be required before its utility would be demonstrated.

METHODOLOGY AS A MAJOR THEME IN BEHAVIORAL TERATOLOGY

In addition to studies on ethanol and other drugs, a second dominant theme in behavioral teratology has been concern with methodological issues [e.g., (6, 16, 27, 30, 34, 41, 44, 50, 55)]. Particularly since Japan (47) and Great Britain (9) have included behavioral teratology testing as part of their premarketing requirements for new drugs, there has been a great deal of speculation and concern that the United States would also adopt such requirements [e.g., (13, 38, 53)]. Many teratologists and behavioral teratologists believe that it would be premature to implement such requirements because current knowledge provides an inadequate base for selecting a comprehensive screening battery. Nonetheless, the concern has prompted several leading U.S. manufacturers to establish testing programs for behavioral teratology (38).

DIFFERENCES BETWEEN STUDIES ON DRUGS AND THOSE ON INDUSTRIAL CHEMICALS

Despite the attention paid to methodological issues in behav-

ioral teratology, the planning, design and implementation of research on therapeutic agents may differ from those used for environmental or industrial chemicals (see Table 1). Because the vast majority of research in behavioral teratology has been conducted on therapeutic agents, there is a tendency to judge screening studies of industrial agents using the same criteria used for these more definitive studies. This section of the paper will evaluate these criteria and address differences between studies of therapeutic agents and screening studies of industrial chemicals.

Many of these differences occur because much more information is typically available on drugs than industrial chemicals. Although not always true, information on pharmacological properties (e.g., absorption, biotransformation, half-life, excretion) is frequently available for drugs under test. Methods for blood level determinations are often standardized and frequently available within most clinical laboratories. In many cases, standard teratology examinations have been completed for several dosages of the drug in question, and sufficient information usually is available to select appropriate effective doses for behavioral teratology examinations. Frequently, several routes of exposure also have been studied. Typically, these studies continue well beyond initial screening, with mechanisms of action becoming the paramount concern. Consequently, our knowledge of the timing and duration of effective exposures becomes delimited, providing important and useful information on the most susceptible stage for production of the malformations or deviations. Occasionally, behavioral teratology investigations have been completed for the drug of interest, so particular tests or behaviors are known to be affected; further testing can then focus on those behaviors. A common practice is to foster or cross-foster the offspring to delineate the contributions of maternal toxicity to any effects observed in the offspring. In short, because of information obtained during drug testing, experimental conditions in later studies can often maximize effects.

In contrast, behavioral teratology screening studies of industrial agents must be undertaken with minimal information. Although basic toxicological information (e.g., the LD_{50}) may be available, it is likely that little is known about the pharmacological properties of the test agent compared to what is known about pharmaceutical agents. Often, methods for determining body burden (e.g., blood) levels of the agent have not been developed. Frequently, there is no published literature on the developmental or reproductive toxicology of the agent in question, so the study must be designed to obtain this information. The effective dose of the chemical must be estimated from scanty information which generally is based on reports of acute toxicity following exposure via a single route in adult animals. Although the route of exposure may not be paramount in drug studies, it is critically important for those who must use limited hazard information on industrial chemicals. If inhalation exposures are the method of choice, a complicated technology comes into play. Facilities may further limit the experimental design since points on the exposure-effect curve may most conveniently be generated at different times. Even the largest laboratories can generate but a few concentrations of the test agent simultaneously. As an example of this problem, the test system used at NIOSH requires nearly six months to complete a behavioral teratology investigation involving a single concentration of one chemical. Because confounding variables (e.g., effects of seasonal changes, different technicians working with or testing the animals) may intervene with the passage of time, our inability to conduct simultaneous trials makes it difficult to compare the results of multiple concentrations.

Additional considerations where screening studies of industrial agents differ from those of more definitive studies include the following: exposure durations must be sufficient to detect effects throughout development. Since the detection of hazard is critical in industrial work, fostering or cross-fostering of animals is less important in initial studies than in studies addressing the mechanism of action. Initially, it is not critical to know if the maternal animals contribute to the effects observed in the offspring. Teratology evaluations of pharmaceutical agents concentrate on exposure of the female, but screening studies of industrial chemicals must take into account the fact that paternal exposure may accompany maternal exposure to the agent in question. Knowledge of the mechanism of action is not important to initial identification of a hazard, but identification of mechanisms for classes of chemicals would reduce the testing effort now required for individual chemicals, and mechanisms would be relevant to risk assessment.

NEED FOR FURTHER BEHAVIORAL TERATOLOGY TESTING

In addition to ethanol, a number of other drugs have been investigated for behavioral teratogenicity, particularly other drugs of abuse, various anticonvulsants, and antimitotic agents (40). This research has provided a sufficient data base to propose principles by which some drugs are behavioral teratogens and others are not (52). However, these principles are not well established except for the drug classes for which the majority of research has been completed (e.g., anticonvulsants).

Efforts to detect behavioral teratogenicity in human populations may be of limited utility because of the small sample of data available for industrial agents. However, surveillance programs focusing on the behavioral teratology of specific agents may be of some value. Since experimental testing for behavioral teratogenicity in humans is impossible, it is imperative that additional research be undertaken using appropriate animal models to determine the potential risk of behavioral teratogenicity in human populations. Principles developed from drug research can serve as the basis for prioritizing additional research on industrial agents. In testing high priority chemicals, the validity of using principles derived from research on pharmaceutical agents will be assessed, and general principles may then be proposed for the behavioral teratogenicity of industrial chemicals. The lack of information on the behavioral teratogenicity of most industrial chemicals makes both positive and negative findings useful in risk assessment.

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