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Fundamentals and possibilities of classification of occupational substances as developmental toxicants

Abstract It is now widely accepted that describing and labeling of chemicals as developmental toxicants on a purely qualitative basis does not make sense. Agents possessing the potential to induce reproductive or developmental toxicity present a risk of human harm only under certain conditions. This critical fact cannot be properly communicated with a simple designation as “positive” or “negative”. Rather, a number of parameters that deal with dose or concentration, frequency, duration and route of exposure must also be conveyed. Unsubstantiated blacklisting is equally counterproductive for preventive medicine as downplaying of the toxicity of chemicals. Gender-based restrictions on exposure at workplaces of women of childbearing age are neither socially acceptable nor scientifically justifiable. Therefore, the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area published in 1983 a quantitatively based classification concept, which became effective in 1985 and was modified in the following years. The present contribution summarizes what is required for an integrated judgment on the relevance of laboratory and epidemiological data for predicting the potential risk associated with exposure at workplaces to occupational chemicals. Methyl mercury, carbon disulfide, dimethylformamide, ethanol, toluene, N,N-dimethyl acetamide, nitrous oxide, methanol, ethyl benzene, and phosphorus pentoxide will be described as examples of classified substances.

Key words Developmental toxicants · Classification scheme

Introduction

Several thousand developmental toxicants have been identified in laboratory animals, whereas only about 50 have demonstrated this proclivity in the human species (Schardein and Keller 1989). This tremendous difference is certainly not sufficiently explained by differences in species susceptibility. Rather it is due to either absence of exposure or exposure to lower concentrations. Difficulties in demonstrating associations or proving causation in the human because of confounders and low power are additional reasons for these differences (Schardein et al. 1985). Developmental toxicity data reported in the literature are often unevaluated, incomplete, and inconclusive. This is perhaps one of several reasons why regulatory agencies worldwide have so far not proposed a quantification scheme. For example, a current Directive of the European Union that became effective in 1993 provides a classification of reproductive toxicants into three categories (EEC 1993 a):

1. Substances known to cause developmental toxicity in humans
2. Substances which should be regarded as if they cause developmental toxicity to humans
3. Substances which cause concern for humans owing to possible developmental toxic effects.

Substances which do not meet the criteria specified in detail for the three categories must not be classified, as, for example, is the case when adequate evidence exists to show that the metabolite or mode of action responsible for induction of developmental toxicity is not produced in or is not relevant to man.

Although this regulation is science-based because it requests state of the art investigations as a prerequisite for classification and because it calls for consideration of the dose-response effects, it remains qualitative rather than quantitative. Similarly, the guidelines for developmental toxicity risk assessment of the U.S. EPA (1991) are not yet quantitatively based but the agency has committed itself to development of an additional approach for more quantitative dose-response evaluation (Vandenberg 1994). Therefore, the need for a quantitatively based classification concept is evident.
Definition and detection of developmental toxicants

Karrh et al. (1981) defined an embryo-fetotoxin, now generally called a developmental toxicant, as a chemical which manifests an effect upon the conceptus during any of the stages of gestation, from fertilization to birth. It may induce death, structural malformations, metabolic or physiological dysfunction, growth retardation, or psychological and behavioral alterations which may be manifest at birth or during the postnatal period. The definition of the German MAK Commission, as well as many other definitions, is very similar and includes any alteration from the physiological norm in the development of the organism which leads to pre- or postnatal death or to permanent morphological or functional damage of the offspring.

The question of how to classify developmental toxicants is closely associated with the methods by which they are detected.

Recognition of developmental toxicants is possible through experimental animal studies, epidemiological observations, or specific identification of malformation syndromes. All have a number of pitfalls and drawbacks that need to be addressed but cannot be dealt with at length in this review.

Animal studies

No animal studies have led directly to identification of a human developmental toxicant (Shepard 1982). However, when data for many of the agents recognized as human developmental toxicants have been compared to the experimental animal data, in almost all cases the agents have been found to produce developmental toxicity in animals, too. In at least one species tested the types of effects were similar to those in humans (Nisbeth and Karch 1983; Kimmel et al. 1990; Slikker 1994). Therefore it is widely accepted that there is ample evidence that effects produced in animal models are predictive of human outcome for basically all kinds of agents. As to the degree of certainty of predicting that an effect seen in animals could occur in humans, there are a number of confounding differences between mammalian species. These differences in both structure and physiology account for the fact that concordance between animal and human data bases is limited. In particular, concordance is not sufficiently high that the effects observed in animals would serve as guidance for clinicians and epidemiologists to focus only on certain types of adverse outcomes of pregnancy (Schwetz 1994). This lack of concordance must not be lamented, because for the detection and classification of developmental toxicants it is not the type of damage but any damage that matters. Therefore, the U.S. EPA (1991) concluded that a biologically significant increase in any of the four manifestations of developmental toxicity (death, structural abnormalities, growth alterations, and functional deficits) may be considered indicative of an agent’s potential for disrupting development and producing a developmental hazard. Similarly, Moore et al. (1995), discussing cross-species extrapolation, consider it to be one of several default assumptions “that any manifestation of reproductive or developmental toxicity is relevant to humans unless the mechanism by which it occurs is impossible in humans.”

The importance of the type of damage notwithstanding, the great value of animal studies with respect to developmental toxicity is that they provide the only means of establishing dose-response relationships which are central to the understanding of developmental toxicity and without which quantitative evaluation is not possible (O’Flaherty and Clarke 1994).

Well-defined regulatory test guidelines for developmental toxicity are available, the most recent being the ICH harmonized tripartite guideline on “detection of toxicity to reproduction for medicinal products” (ICH 1994), which is also applicable to chemicals. A fairly recent survey on and description of available testing procedures, including a test for determining the priority of substances for further investigation, was provided by ECETOC (1992). The studies defined in the guidelines should be considered the default protocols that are used when there is no other protocol that is known to be more appropriate for the chemical under evaluation (Schwetz 1994). It needs to be emphasized, however, that despite their proven utility, animal data can be fallible, thereby necessitating that the review and interpretation be performed by scientists with appropriate training and experience (Moore et al. 1995).

Human studies

Literature addressing such studies is numerous. With regard to the present question as to the utility as well as the limitations of human studies for detecting developmental toxicants, reference will be made only to review articles.

According to a 1985 OTA Report (U.S. Congress 1985), epidemiological studies can be divided into three broad classes: descriptive, analytical, and experimental.

For ethical reasons, experimental studies are difficult to undertake in industrial settings because subjects must be assigned to exposed groups. Therefore, such studies are practically nonexistent and only descriptive and analytical studies are utilized for studying reproductive impairment.

Case reports and large-scale surveillance programs are the two types of descriptive studies. Case reports have been more successful so far than surveillance programs. For example, DBCP infertility and rubella as a causative agent of birth defects were detected in case reports.

Analytical studies are subdivided into cross-sectional, case control, and cohort studies. The significance of these studies for risk assessment in prenatal toxicity has recently been discussed by the U.S. EPA (1991), Goujard (1992), ECETOC (1992), EEC (1993b), and Moore et al. (1995), and, somewhat earlier, by Levin (1983).

A cross-sectional study, in which a group of people is surveyed for risk factors (exposure) and disease, does not