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CHEMICALS WHICH CAUSE BIRTH DEFECTS — TERATOGENS: A SPECIAL CONCERN OF RESEARCH CHEMISTS

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ABSTRACT

Women who are research chemists suffer an unusually high risk of being exposed to teratogenic chemicals (chemicals which cause birth defects) for the principal reason that they spend a good share of their lives in the laboratory in contact with wide variety of chemicals including new chemicals which may be unsuspected teratogens.

Women research chemists therefore need to be able (a) to recognize known teratogens and (b) to predict teratogenicity of a compound that has not been tested. This article discusses these two points with an emphasis on the following topics: how to obtain information on teratogenicity of chemicals; how to interpret teratogenicity data from the literature; and how to make an educated guess about the teratogenicity of chemical compounds.

INTRODUCTION

Teratology* is the scientific study of biological monstrosities and malformations. A teratogen is an agent which acts during pregnancy to produce physical or functional defects in the embryo, fetus, or offspring [1]. The latter defects may be caused also by agents other than teratogens, such as agents which damage sperm. Since the latter agents act prior to pregnancy, technically they are not considered teratogens but are referred to as "birth-defect-via-sperm-damage" agents or sometimes broadly as mutagens that cause damage to sperm [2]. This article deals mainly with teratogens, but some aspects of birth-defect-via-sperm-damage agents will also be discussed.

Teratogenic agents may be chemicals, e.g. drugs, agricultural chemicals, common solvents and reagents, or physical factors, such as X-rays, or viruses. In this article only chemicals will be discussed.

The identification of human teratogens poses a major problem. In most

* Greek: teratos = monster; logia = science.

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cases not enough statistically-valid data are available. The use of a powerful scientific tool — experiment — is obviously precluded in humans. Even in rare unfortunate cases of the widespread use of a very potent human teratogen such as thalidomide, it may take a rather long time to discover their teratogenicity [3]. In several cases a drug has been classified as teratogenic based on only few observations of severe malformations in children exposed to drugs in utero [4]; the teratogenic effect of such drugs was not statistically proven beyond doubt. Existing statistics are complicated by the fact that information about the use of drugs in pregnancy obtained from mothers of teratogenic children is sometimes not very reliable. Thus, many of the mothers who took thalidomide during pregnancy have had strong feelings of guilt and this has, on occasion, led them, consciously or subconsciously, to deny that they had taken any drug [4].

Another serious problem in identifying human teratogens is that the prediction of teratogenicity of chemicals in humans based on studies on animals is often very poor. This is illustrated in Table 1 which shows comparison of doses required for teratogenic effects of thalidomide in various mammalian species. The data from Table 1 show that some animal species are much more sensitive to thalidomide than others, and that the human species happens to be among the most sensitive of mammals. The extrapolation of animal data on humans is very difficult also because the most commonly used laboratory animals — mice and rabbits — have a very primitive placenta compared to humans [6a].

Another difficulty in identifying teratogens is the possibility that teratogenic effects may not be noticeable in the newborn, but may show up years later. For example, rats exposed to phenobarbital in utero suffered from delayed onset of puberty, disorders in the estrous cycle, and infertility [7]. In another example, a single dose of ethylnitrosourea, a potent carcinogen, given to pregnant rats was found to produce in the offspring not only teratogenic but also carcinogenic effects, the latter being observed much later than the former [8]. An example of a well-studied "delayed"

TABLE 1

COMPARISON OF DOSES REQUIRED FOR TERATOGENIC EFFECTS OF THALIDOMIDE IN VARIOUS MAMMALIAN SPECIES [5a]

Species	Lowest dose (mg/kg) for detectable effects
Human	0.5—1.0
Cat	0.5
Rabbit	2.5
Monkey	10
Rat	10
Mouse	31
Armadillo	100
Dog	100
Hamster	350

TABLE 2
DATA ON HUMAN "DES-DAUGHTERS" AS COMPARED TO CONTROL GROUP [9a]

	Placebo-exposed controls	DES-exposed
Number examined	319	346
Irregular menses	10%	15%
Married	48%	54%
History of pregnancy	31%	21%
Live births	22%	13%
Vaginal adenosis	1.3%	63%
Ridges of vagina and cervix	0%	38%

teratogen in humans is that of DES (diethylstilbestrol), an artificial estrogen given in the past as a drug to many pregnant women. DES causes abnormalities such as vaginal adenosis, ridges of the vagina, and other defects in the daughters of the mothers who took this drug during pregnancy [9a]. This is illustrated in Table 2.

In the males exposed to DES in utero (Table 3), various functional abnormalities such as testicular hypoplasia and abnormal semen were observed. Also, the average sperm density was somewhat decreased as compared to the placebo-exposed control [9a].

The identification of teratogens is further impeded by the occurrence of the spontaneous abortions of the teratogenic embryo/fetus. If a spontaneous abortion occurs before a woman knows that she is pregnant, it is left unnoticed and the teratogenic effect is reflected as a decreased fertility. In cases when a woman knew that she was pregnant, the teratogenic effect would be observed as an increase in the miscarriage rate. Well known examples of such teratogens are anesthetic gases [9b, 10] and lead [9c]. Teratogenic effects in the latter two examples may occur also when only males are

TABLE 3
DATA ON HUMAN "DES-SONS" AS COMPARED TO CONTROL GROUP [9a]

	Eliasson scores* of semen analysis	
	Placebo-exposed controls	DES-exposed
Average Eliasson score	2.5	4.9
Eliasson score ≥ 5 (pathological semen)	16%	32%
Eliasson score > 10 (severely pathological semen)	8%	18%

* Combines the sperm count, the sperm mobility, the mobility grade, and the sperm morphology into one quantitative number.

TABLE 4
EFFECTS OF LEAD ON HUMAN REPRODUCTION [9c]

	Effect
a	Decrease the fertility of a male by causing teratospermia, hypospermia, and asthenospermia (abnormal, deficient, and weak sperm, respectively).
b	Lead to miscarriage, stillbirth, and increased perinatal mortality if female is exposed.
c	Cause high abortion rate amongst the wives of lead workers (cf. a).
d	Cause birth defects (convulsions, macrocephally) if female is exposed during pregnancy.

directly exposed to these teratogens. Table 4 illustrates multiple damaging effects of lead on human reproduction [9c]. Lead is thus an example of a teratogen which is also a "birth-defect-via-sperm-damage" agent.

Difficulties in identifying human teratogens outlined above prevent scientists in many cases from labeling teratogens as "proven" human teratogens. This, coupled with the difficulties encountered in attempts to determine safe levels of exposure of embryo/fetus to teratogens, leaves the door open for many legal disputes concerning the use of teratogens. Examples of such disputes are the Bendectine Case about the use of the suspected teratogenic drug, bendectine, [11, 12] and cases related to the exposure to teratogenic chemicals in the work place (e.g. the lead pigments case) [13] or in the environment (e.g. the case of the pesticide 2,4,5-T) [14]. Confrontations over issues of female as well as male reproductive hazards in the work place and related court cases are described in details in reference 13 which also examines how government, chemical companies, and unions are approaching the problem of protection of workers and their unborn children from injury at the work place.

Teratogens represent a potential danger to almost any woman in modern society, since teratogens such as drugs, agricultural chemicals, and environmental pollutants may be difficult to avoid. Women who are exposed to teratogens in their work place, such as nurses exposed to anesthetic gases, workers in the chemical industries, etc., have an additional risk. However, women who are research chemists suffer an unusually high risk of being exposed to teratogens, for the principal reason that they are very often exposed to new chemicals which may be unsuspected teratogens. Since women research chemists spend a good share of their lives in the laboratory in contact with wide variety of chemicals, they need to be able to do the following: (a) recognize known teratogens; (b) predict teratogenicity of a compound that has not been tested; and (c) protect themselves from proven or suspected teratogens. The objective of this article is to briefly discuss the points (a) and (b).

How to obtain information on teratogenicity of chemicals

Probably the most concise source of data on teratogens is a reference book by T. H. Shepard [1]. This book provides information about teratogenicity of chemicals and other teratogenic agents. The type of malformations and malfunctions observed as the effect of particular teratogens is also given, as well as the pharmacological procedures and animal species used in the teratogenicity tests. The 1980 edition of this book has over one thousand entries.

Women working in the medicinal chemistry field will appreciate comprehensive treatment of teratogenic drugs given by Nishimura and Tanimura [15] and by Schardein [16].

However, the most comprehensive source of data on known or suspected teratogenic chemicals is the "Registry of Toxic Effects of Chemical Substances" (RTECS) [17]. RTECS is a compendium of toxicity data abstracted from the scientific literature and published by the National Institute of Occupational Safety and Health (NIOSH). For example, the 1978 edition of RTECS includes toxicity data, such as type of toxicity, toxic dose levels, route of exposure or administration, as well as species exposed, for nearly 34,000 different substances. Out of these only about 500 are teratogens (ca. 1.4%). An average of about 1500 new toxic compounds are added to RTECS every quarter, about 30 of which are teratogens. A list of 527 teratogenic substances obtained by computer search of RTECS has been published [18]. The subfile of the RTECS "Tumorigenic, Teratogenic, and Mutagenic Citations" is available in a microfiche form [19].

Information about teratogens may be also obtained from The Environmental Teratology Information Center (ETIC), which was established in 1975 at Oak Ridge National Laboratory with the objective to collect, organize, and disseminate information on the evaluation of chemical, biological, and physical agents for teratogenic activity.

Interpretation of teratogenicity data from the literature

In general, the interpretation of data on teratogenicity of chemicals is very difficult for numerous reasons which were discussed in the Introduction. A chemist who attempts to interpret teratogenicity data from RTECS may experience special difficulties, namely, the evidence for teratogenicity of substances listed in RTECS is unevaluated. In addition, many of the compounds on the teratogen list have been so identified on the basis of animal data. As pointed out in the Introduction, the prediction of teratogenicity of chemicals in humans which is based only on animal studies is often very poor. Data in RTECS are of uneven quality: in some instances a teratogen has been so identified on the basis of a single study performed on just one animal species, in some other cases teratogenicity might have been based on the epidemiological studies in humans. Therefore, a teratogen list per se is not sufficient. One should study the original research reports and attempt to evaluate them. Chemists may find the following three references helpful in accomplishing the latter task, since these references represent critical

TABLE 5
INDUSTRIAL CHEMICALS WHOSE REPRODUCTIVE HAZARDS ARE REVIEWED BY BARLOW AND SULLIVAN [20]

Chemical	Chemical
Acrylonitrile	Formamides
Aniline	Lead (organic)
Arsenic and its compounds	Manganese and its compounds
Benzene	Mercury and its compounds (inorganic)
Benzo[*a*]pyrene	Methyl *n*-butyl ketone (MBK)
Beryllium	Methyl chloroform
Boric acid (boron)	Methyl ethyl ketone (MEK)
Cadmium and its compounds	Nitrogen dioxide
Carbon monoxide	Ozone
Carbon tetrachloride	Platinum and its compounds
Chlordecone (Kepone)	Polybrominated biphenyls (PBB)
Chloroform	Polychlorinated biphenyls (PCB)
Chloroprene	Selenium and its compounds
Dibromochloropropane (DBCP)	Styrene
Dichlorobenzene	Tellurium and its compounds
1,1-Dichloroethane	Tetrachloroethylene
Dichloromethane	Thallium and its compounds
Dioxane	Toluene
Epichlorohydrin	Toluene-2,4-diisocyanate (TDI)
Ethylene dibromide	*o*-Toluidine
Ethylene dichloride	Trichloroethylene
Ethylene oxide	Vinyl chloride
Fluorocarbons	Vinylidine chloride
Formaldehyde	Xylene

evaluation of numerous animal and human data on teratogens. First is the book by Barlow and Sullivan titled "Reproductive Hazards of Industrial Chemicals. An Evaluation of Animal and Human Data" [20]. This book reviews the world-wide medical and scientific literature on reproductive hazards in animals and man of about 50 of the most commonly used industrial chemicals. These compounds are listed in Table 5. Where no adequate human data is available, an attempt is made to evaluate the animal data to predict human hazard. In addition to teratogenicity, a wide variety of other effects is considered, such as sex differences in toxicity, placental transfer, effects on hormone secretion, sperm counts and morphology, estrous cycles, menstrual cycles, and postnatal development.

The second reference is a review article by Strobino, et al., titled "Chemical and Physical Exposure of Parents: Effects on Human Reproduction and Offspring" [21]. The authors present a critical evaluation of the reports published up to 1976 of detrimental effects of various drugs and other chemicals on reproduction or offspring of exposed parents. The effects resulting from maternal exposure before conception, maternal exposure during pregnancy, and paternal exposure are evaluated separately. Teratogenic

chemicals, other than drugs whose effects are reviewed by Strobino et al. [21], are: anesthetic gases, vinyl chloride, mercury, lead, polychlorinated biphenyls (PCB), dioxin, and alcohol. The third reference is the book by Nisbet and Karch titled "Chemical Hazards to Human Reproduction" [5]. This book is a critical evaluation and documentation of the current evidence of the reproductive hazards of various drugs and chemicals. Examples of teratogenic chemicals, other than drugs whose effects are reviewed in the reference 5 are: lead, selenium, cadmium, anesthetic gases, carbon monoxide, phthalate esters, formaldehyde, carbon disulfide, and laboratory solvents.

The number of chemicals whose teratogenicity is critically evaluated in the reference 5, 20 and 21 is roughly one tenth of the number of chemicals listed as teratogenic in RTECS.

When a compound is identified as a teratogen, its dose effects need to be considered. Unfortunately, very little has been published on dose—response relationships for human teratogens, and there is no systematic compilation of dose—response relationships for animal teratogens [5b]. The available animal data show that usually the dose—response relationships rise steeply after the dose required to produce the first effect is exceeded [5b]. This empirical observation has been used as a basis for the claim that threshold (safe) doses usually exist for teratogens in animals [5b, 20a]. However, it is not clear that the assumption of thresholds can be extrapolated to humans [5b]. More research is needed to establish the characteristics of dose—response relationships in humans, and to establish under what circumstances thresholds can be assumed to exist [5b].

More than half of the 527 teratogens listed as such in RTECS show biological activity, most often as drugs for human or animal use or as agricultural chemicals [22] (Table 6). Comprehensive reviews of the teratogenicity hazard to humans from drugs are provided in references 15a and 16. Reference 15b also evaluates teratogenicity of pesticides.

How to make an "educated guess" about the teratogenicity of chemical compounds

From the previous section it is clear that finding the information about the teratogenicity of chemical compounds and interpreting it is often a difficult and time-consuming task with the results which are, more often than not, unsatisfactory.

An even more difficult task is posed when one wishes to predict the teratogenicity of a compound which has not been tested for teratogenicity. Research chemists need to make such predictions since they typically work with a variety of new chemicals or previously reported chemicals which have not been tested for teratogenicity. Many of the research chemicals are only of the "academic interest" and there is a very little hope that they will be routinely tested for teratogenicity in the near future.

Ideally, a scientist should be able to make a scientifically sound prediction about the teratogenicity of a chemical just by looking at its structure. Such predictions would be based on a thorough understanding of the mechanism

of action [23] and structure—activity relationships of teratogens [6b, c]. In reality, however, this is not possible, because at this time we have only a limited knowledge of these [23, 6b, c]. Well known teratologists Shepard, Miller, and Marois wrote in 1975 [6d]:

"Ideally, at some time in the future (1990?), it should be possible to predict teratogenic activity based on chemical structure of a compound and how it is metabolized".

At this time it seems that the 1990 time mark is overly optimistic. What scientists can do at the present time, however, is to make an "educated guess" about the teratogenicity of a new compound based on the chemical structures and the biological activities displayed most often by the known teratogens [22]. This "educated guess" method is described in details in the reference 22. We shall summarize here only its main features.

Careful investigation of chemical structures and biological activities of 527

TABLE 6
CLASSIFICATION OF TERATOGENS BY BIOLOGICAL ACTIVITY [22]

Classification	Compound
Anticoagulants	e.g. Coumarins
Anticonvulsants	Barbiturates, hydantoins, oxazolidines, and succinimides
Antineoplastics	e.g. Nitrogen mustards and others alkylating agents, antimetabolites such as purine, pyrimidine, and folic acid antagonists, antibiotics such as actinomycin D, mitomycin C, alkaloids such as colchicine and vincristine
Cardiovascular agents	e.g. Vasoconstrictors and vasodilators
Carcinogenics	Azo dyes, nitrosamines, polynuclear hydrocarbons, chlorinated hydrocarbons
Chelating agents	d-Penicillamine, EDTA, BAL
Chemotherapeutic agents	e.g. Antibiotics, sulfonamides, quinine, and related substances
CNS affecting agents	Some anaesthetics, hypnotics, narcotics, sedatives, tranquilizers, analgesics
Diuretics	Xanthines, thiadiazoles
Hormones and antihormones	Corticosteroids, androgens, progestogens, estrogens, antithyroid drugs, ACTH, epinephrine, insulin and oral hypoglycemics such as sulfonylureas
Neuropharmacological agents	e.g. Organophosphorus anticholinesterases like parathion; amphetamines, atropines, ganglion-blocking agents such as tetraethylammonium chloride
Pesticides	Herbicides like 2,4-D and 2,4,5-T; insecticides like carbamates, chlorinated hydrocarbons, thiophosphates; fungicides
Psychotomimetics	LSD and mescaline
Vitamins	Vitamins A and D in high dossage

teratogens revealed that most teratogens display the chemical structures presented in Table 7 and the biological activities shown in Table 6 [22]. The contents of these tables demonstrate that terratogens display a great variety of chemical structures and biological activities in which no simple pattern is obvious.

The "educated guess" procedure suggests that if the compound has or is expected to have the type of biological activity displayed in Table 6, one should assume that it is teratogenic, despite the fact that we may not understand the mechanism of its teratogenic action, even to the point that we do not know if the compound is a structurally specific or a nonspecific teratogen. For example, medicinal chemists working on the development of antineoplastic agents for cancer chemotherapy, or alkaloid chemists working with derivatives of vincristine, which happens to be an antineoplastic, should assume that such compounds are teratogenic. This procedure is likely to produce false positives, since not all estrogen derivatives are estrogenic, for example, or not all diuretics, for example, will be teratogenic.

If the compound in question is a derivative of a known teratogen (consult RTECS [17] or the teratogen list in the references 18, 19 or 22), or it has a structure displayed by known teratogens (Table 7), the "educated guess" would be that such compound is teratogenic. Thus, if a compound is an imide, one should assume that it is teratogenic, since many imides, including thalidomide, are teratogens. This guess is likely to produce false positives, probably more in structurally specific than in nonspecific teratogens.

If the compound in question has both the chemical structure shown in Table 7 and the biological activity displayed in Table 6, one should be even more suspicious that the compound is a teratogen.

TABLE 7
CLASSIFICATION OF TERATOGENS BY CHEMICAL STRUCTURES [22]

Teratogen	Teratogen
Acrylates	Phenethylamines
Alkaloids	Phenothiazines
Amides	Phthalimides
Amines and ammonium salts	Piperazines
Azo compounds	Polynuclear hydrocarbons
Barbituric acid derivatives	Purines
Benzodiazepines	Pyrimidines
Carbamates	Salicylates
Chlorinated hydrocarbons	Steroids
Folic acid derivatives	Sulfonamides
Glutamic acid derivatives	Tetracyclines
Hydrazines	Thiadiazoles
Hydantoins	Thiocarbamates
Imides	Thiophosphates
Indandiones	Triazenes
Metals (Pb, Hg, Cd, As, etc.)	Triazines
Nitroso compounds	Ureas

Examples of the predictive power of this method are given in the reference 22.

The contents of Table 6 and 7 are analyzed in much detail in the reference 2 which also gives some easy-to-understand explanations of the fact that some particular chemical structures are often found in teratogens.

In summary of this section, it is possible to make an "educated guess" about the teratogenicity of the chemicals which have not been tested. This procedure is not very exact and it may produce false positives. However, at the present time we do not have a better way to predict teratogenicity.

A note on teratogenic chemicals common in the research laboratories

Many commonly used laboratory solvents such as CCl_4, $CHCl_3$, CH_2Cl_2, $CHCl_2CH_3$, dioxane, xylene, MEK, etc. represent reproductive hazards [20]. Central nervous system defects were observed in children born to mothers exposed to organic solvents during pregnancy [24]. It is possible that some of the malformations observed in infants of women who worked in the university laboratories [25] or other laboratories [26, 27] are also due to the organic solvents. Extra caution should be taken when working with the organic solvents, otherwise the exposure to these solvents may be quite significant since they are volatile and typically used often and in large quantities.

Chemists working with any of the chemicals presented in Table 5, all of which are commonly found in the research laboratories, should consult reference 20 which contains detailed information about exposure levels and routes, pharmacological effects, and various other useful data.

CONCLUSIONS

Teratogenic chemicals are a special concern of women research chemists. In this paper various aspects of teratogenicity of chemicals are presented which we believe will be useful to women research chemists. Various sources of information on teratogenicity of chemicals are discussed. Due to the numerous difficulties in identifying and studying human teratogens, the teratogenicity data reported in the literature are often unevaluated, incomplete, and inconclusive. Therefore, a caution must be excercised in interpreting the teratogenicity data. Classification of teratogens by biological activity and by chemical structures is discussed as a useful tool in predicting teratogenicity of the compounds which have not been tested.

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