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Teratogenicity and the Threshold of Toxicological Concern concept

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Abstract

The Threshold of Toxicological Concern (TTC) is a principle that refers to the possibility of establishing a human exposure threshold value for all chemicals below which there is no significant risk to human health. The database study documented here was prompted by the question on whether such thresholds would cover irreversible structural developmental (teratogenic) effects, or whether these effects would need an extra safety factor. From the database of 38 compounds compiled here, only 8 compounds showed teratogenicity at lower doses than general embryotoxicity. All these compounds would be excluded from the TTC concept because of their genotoxic properties. This database therefore does not justify an extra safety factor for teratogenic compounds within the TTC concept.

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Samenvatting

Het principe van de Threshold of Toxicological Concern (TTC) verwijst naar de mogelijkheid om voor alle chemische stoffen een humane blootstellinggrens te bepalen, waaronder geen noemenswaardig risico optreedt voor de gezondheid van de mens. Deze grenswaarde is in de eerste plaats gebaseerd op carcinogenese gegevens. Voor andere gevoelige effecten, zoals neurotoxiciteit en ontwikkelingseffecten gelden hogere grenswaarden. Daarbij is met name de chemische structuur bepalend voor de hoogte van de TTC. De vraag is of grenswaarden afgeleid op basis van algemene toxiciteit ook van toepassing kunnen worden beschouwd voor teratogene effecten, danwel of voor deze effecten een extra veiligheidsfactor in rekening gebracht moet worden. Dit zou het geval kunnen zijn indien teratogene effecten bij lagere doseringen gevonden worden dan meer algemene effecten op de ontwikkeling, zoals groeivertraging en foetale sterfte.

In dit rapport wordt een database gepresenteerd, waarmee het mogelijk is de NOELs voor teratogeniteit met de NOELs van andere ontwikkelingseffecten en de NOELs van maternale toxiciteit van dezelfde stof te vergelijken. Om bruikbare studies naar ontwikkelingstoxiciteit te vinden van stoffen met teratogene effecten zijn meerdere bronnen geraadpleegd, en zijn de originele wetenschappelijke artikelen geanalyseerd. Alleen stoffen met onomstreden teratogene effecten werden in de database vermeld. Het idee was dat als een teratogeen effect bij een lagere dosering optreedt dan een ander toxisch ontwikkelingseffect, er een extra veiligheidsfactor 10 overwogen zou moeten worden. Om dit te bepalen is voor iedere stof de ratio bepaald van de NOEL voor ontwikkelingseffecten en de NOEL voor teratogene effecten. Stoffen waarvan de ratio groter is dan 1, zouden een extra factor 10 nodig hebben.

Uit de hier samengestelde database van 38 chemische stoffen blijkt dat slechts 8 stoffen een ratio opleveren die groter is dan 1. Voor al deze stoffen geldt dat ze vanwege hun genotoxiciteit al in een vroege fase buiten het TTC concept gehouden worden. Deze database geeft daarmee geen aanleiding voor een extra veiligheidsfactor in het TTC concept voor stoffen met een teratogeen effect. De database in dit rapport is echter nog maar een voorlopige inventarisatie en laat geen definitieve conclusies toe. De database dient als basis voor verder onderzoek door de ILSI Europe Threshold of Toxicological Concern Task Force.

Summary

The Threshold of Toxicological Concern (TTC) is a principle that refers to the possibility of establishing a human exposure threshold value for all chemicals below which there is no significant risk to human health. The threshold value is primarily based on carcinogenesis data. For other potentially sensitive endpoints, such as neurotoxicity and developmental toxicity, higher TTC values are applicable, based largely on their chemical structure. The database study documented here was prompted by the question on whether such thresholds would cover irreversible structural developmental (teratogenic) effects, or whether these effects would need an extra safety factor. This would be relevant when teratogenicity occurs at lower doses than general developmental toxicity such as growth retardation and fetal death.The database presented is intended to compare the NOELs of teratogenicity with the NOELs of general developmental toxicity and the NOELs of maternal toxicity of the same compound. The studies tabulated in the database were retrieved from a variety of sources, and original scientific literature was analysed. Only those compounds producing undisputed teratogenic effects were included in the database. The additional safety factor was considered as possibly being necessary if teratogenic effects of compounds were to generally occur at lower doses than other signs of developmental toxicity. For this reason, an Embryotoxicity/Teratogenicity ratio of each compound was determined by dividing the NOEL for embryotoxicity by the NOEL for teratogenicity. Compounds with an E/T ratio greater than 1 would need an additional safety factor.

From the database of 38 compounds compiled here, only 8 compounds showed a ratio larger than 1. All these compounds would be excluded from the TTC concept because of their genotoxic properties. This database therefore does not justify an extra safety factor for teratogenic compounds within the TTC concept. The database reflects an initial incomplete inventory, and does not allow for definitive conclusions. It can, however, be used as a starting point for further work by the ILSI Europe Threshold of Toxicological Concern Task Force.

1 Introduction

The Threshold of Toxicological Concern (TTC) is a principle that refers to the possibility of establishing a human exposure threshold value for all chemicals, below which there is no significant risk to human health (Kroes et al., 2000, Barlow et al., 2001). The TTC value was based on a dietary concentration of carcinogenic chemicals which would give rise to less than one in a million (1×10^{-6}) upper-bound lifetime risk of cancer. From that dietary concentration, a human daily exposure level of 1.5 μg/person was derived. Human exposure thresholds for non-carcinogenic endpoints were also calculated, and it was concluded that these were likely to be higher than any threshold derived from carcinogenic potency data. However, the question was raised whether a threshold based on carcinogenesis data would cover some potentially sensitive endpoints, such as developmental toxicity, and if not, whether some of these endpoints would need lower thresholds. An Expert Group on TTC, established by ILSI Europe, developed and analysed a developmental toxicity database and concluded that developmental toxicity did not have lower NOELs than other non-cancer endpoints. Then the question was raised whether irreversible structural developmental (teratogenic) effects would need an additional safety factor. It was considered that this additional safety factor might be deemed necessary if teratogenic effects of compounds would generally occur at lower doses than other signs of developmental toxicity. To determine this, a database comparing No Observed Effect Levels (NOELs) of teratogenic effects with NOELs of other developmental effects of teratogenic compounds was needed. The aim of the present study is to establish a database of teratogens to provide a basis for discussion about the need for an additional safety factor for teratogenic effects. It is attempted in the database to separate teratogenicity (irreversible structural malformations) from general developmental effects (reduced growth, general retardation, death) and also indicate any maternal toxicity.

Two possible approaches can be envisaged. Firstly, if teratogenicity occurs at doses at least tenfold higher than general developmental toxicity, an extra safety factor for teratogenicity is not meaningful. Secondly, since NOAELs and their relative value are critically dependent on the choice of doses and their spacing, it can be argued that only teratogenicity occurring below doses which cause general developmental toxicity would be considered a sufficient trigger for an additional safety factor. Thus, when teratogenicity and general developmental toxicity occur at the same doses, no extra safety factor is required. In addition, we will discuss the role of maternal toxicity in this issue, as teratogenic effects occurring in the absence of

maternal toxicity may be valued differently from teratogenic effects occurring at overt maternally toxic dose levels.

2 Materials and Methods

2.1 Criteria for selecting substances with teratogenic effects

To compare the NOELs of teratogenic effects with NOELs of other developmental effects and maternal effects of the same compound, several different starting points have been used in order to obtain a database as complete and varied as possible.

References screened for compounds with teratogenic effects were:

1. Reports of the Health Council of the Netherlands, Committee 543 on Reproductive Toxicity of Substances.
2. The list of compounds that are officially categorised as reproductive toxicants by the European Commission, Category 1 + 2, R61, toxic to reproduction.
3. Database in 'Munro et al., 1996, Food and Chemical Toxicology 34, 829-967'
   - From the appendix: all the compounds that have been tested for teratogenicity ('Study Type: terat.') and with 'Endpoint Type: msk, mult, ter, ltl'.
   - From the reference list: all the compounds listed in the Integrated Risk Information System (IRIS).
4. The list of endocrine disrupters defined by the Health Council of the Netherlands, Environment Commission on Endocrine Disrupters.
5. WHO, Environmental Health Criteria documents.
6. Additional miscellaneous references were retrieved from MEDLINE, when referred to as teratogenic.

Since it was not always clear whether an effect should be categorised as teratogenic or generally developmentally toxic, only those compounds which showed undisputed teratogenic effects in the available studies were included.

2.2 Criteria for selecting toxicological studies

Multigeneration studies, and studies using pre-mating or postnatal exposure only were not taken into consideration. Thus, only the genuine developmental toxicity (teratogenicity) studies were used, which assess the effects of maternal exposure to a compound on prenatal development. Since it was often unclear what an author considered as a teratogenic / devel-

opmental effect, only the studies with clear descriptions of effects were included. Moreover, all the data listed in the database were retrieved from the primary scientific literature only. Studies for which only abstracts were available were not included. Poorly performed and/or reported studies were excluded from the database. Some compounds were not included in this database although reported as teratogenic by the authors when the effects or their relation to exposure were disputable. Studies without a NOEL for teratogenicity and for embryotoxicity were not used for the database, as were the studies which only used one dose, since no NOEL could be derived from those studies. When more than one study was available for one compound in the same animal species, with the same route of exposure and dose range, and different NOELs were identified, the study with the lowest NOEL was retained.

2.3 Parameters included in the database

Data including the NOEL, and sometimes the LOEL, concerning maternal and embryotoxicity and teratogenicity were reported. Although the terms NOEL (No Observed Effect Level) and LOEL (Lowest Observed Effect Level) are used in this paper, it should be made clear that the effects of importance here are adverse effects. Maternal toxicity was included in the table, to allow discussion on the possibility of direct versus indirect adverse effects of the compound on the embryos. Direct adverse effects are developmental/teratogenic effects in the absence of maternal toxicity at the same dose. Effects observed at doses at which maternal toxicity is also detected may be direct or indirect, and a simple conclusion is then not always possible. In some studies maternal toxicity was not (well) reported, these studies were nonetheless included in the database. Although one would like to infer that if clear maternal toxicity had been observed it would have been reported, this cannot be concluded with certainty.
The boundary between general embryotoxicity and teratogenicity is not always clear-cut. Teratogenic effects are defined as irreversible structural developmental effects, which are often life-threatening to the embryo or the pup. Retarded growth, and everything that could be a secondary consequence of growth retardation (retarded ossification, split vertebrae, wavy ribs, shortened ribs) were classified as general developmental toxicity. In some occasions however, such effects were classified as teratogenic, when clearly described by the author of the article, e.g. when a specific skeletal malformation (e.g. split vertebrae) occurred in isolation in an otherwise normally developed fetus. When hydronephrosis was the only terato-

genic effect observed, it was included in the table only when the severity was referred to as 'moderate' or more.

All routes of administration (diet, gavage, inhalation, intraperitoneal and intravenous injection) were included, even if this was not the most relevant route of exposure when compared to the human situation.

Since the effects can be species-dependent, the results were given separately for each species tested.

To compare the NOELs from the table with the TTC, all NOELs needed to be expressed in mg/kg body weight. In the literature reporting inhalation studies, the doses were expressed in parts per million (ppm). These doses were converted into mg/m^3, using existing tables in the Merck Index or the DOSE (Dictionary of Substances and their Effects; Royal Society of Chemistry) database. Then the doses expressed in mg/m^3 were translated into mg/kg body weight, using the following conversion factor:

Dose (mg/kg body weight) = Volume respired/hour x Duration of exposure x Exposure concentration (mg/m^3) / Body weight.

Fixed values were used for the parameters 'volume respired/h' and 'body weight' for each species tested. The values are given in table 1. The completed table for all inhalation studies included in the database is given in appendix 1.

Table 1: Fixed values for the volume respired/day and hour, and for the body weight of several animal species commonly used in toxicity testing.

Animal	Volume respired/day ($x\ 10^{-3}\ m^3$)	Volume respired/h ($x\ 10^{-3}\ m^3$)	Body weight (g)
rat	223	9	350
mouse	39	2	30
hamster	130	5	140
guinea pig	400	17	840
rabbit	2000	83	3800

3 Results

The database shown in table 2 (see pages 19-32) contains 49 studies with demonstrated teratogenic endpoints, including 38 different compounds. In 9 of these studies no NOELs but only LOELs have been determined for general embryotoxicity. For teratogenicity this was the case in only 2 studies. Maternal toxicity was not or poorly described in 4 studies. A teratogenic effect was found in the absence of maternal toxicity in 16 studies. Table 3 and 4 summarise the data given in table 2. The tables give an overview of the number of studies with an Embryotoxicity/Teratogenicity ratio (E/T ratio, table 3) and a Maternal toxicity/Teratogenicity ratio (M/T ratio, table 4) that are smaller, equal or greater than 1. When different studies yielded different ratios for the same compound, the highest ratio found was used for the classification in tables 3 and 4.

Table 3: Summary of the studies and compounds included in the database, classified according to their Embryotoxicity/Teratogenicity ratio.

	E/T ratio	Compounds
< 1	16 studies 10 cemicals	Chloroform; DEHP; MnDPDP; Manganese chloride; Methanol; 2-Methoxypropanol-1; Mirex; Ochratoxin A; Sodium salicylate; Trichlorfon.
= 1	24 studies 20 chemicals	Acetazolamide; Acetonitrile; Aflatoxin B1; Antiallergic Sm 875 SE; Benomyl; Boric acid; Butyl benzyl phthalate; Dichloroacetic acid; Dichloroacetonitrile; N,N-dimethylformamide; Ethylene oxide; Etretinate; Hexabromobiphenyl; Lithium carbonate; 2-Methoxyethanol; 2-Methoxypropylacetate-1; Polybrominated biphenyls; Sodium arsenite; Trichloroacetonitrile; Xylene mixture.
> 1	9 studies 8 chemicals	Bromochloroacetonitrile; ETU; 1PeBDF; 4PeBDF; Sodium selenite; TBDD; TBDF; TCDD.

Table 4: Summary of the studies and compounds included in the database, classified according to their Maternal toxicity/Teratogenicity ratio.

	M/T ratio	
< 1	12 studies 9 chemicals	Acetazolamide; Antiallergic Sm 875 SE; Butyl benzyl phthalate; Chloroform; Dichloroacetic acid; Hexabromobiphenyl; Mirex; Sodium selenite; Trichloroacetonitrile.
= 1	11 studies 8 chemicals	Acetonitrile; Dichloroacetonitrile; N,N-dimethylformamide; Lithium carbonate; Polybrominated biphenyls; Sodium salicylate; Trichlorfon; Xylene mixture.
> 1	23 studies 20 chemicals	Aflatoxin B1; Benomyl; Boric acid; Bromochloroacetonitrile; DEHP; Ethylene oxide; ETU; MnDPDP; Manganese chloride; Methanol; 2-Methoxyethanol; 2-Methoxypropanol-1; 2-Methoxypropylacetate-1; Ochratoxin A; 1PeBDF; 4PeBDF; Sodium arsenite; TBDD; TBDF; TCDD.

It is important to note that compounds with structural alerts for genotoxicity or direct evidence of genotoxicity, and 2,3,7,8-dibenzodioxins and 2,3,7,8-dibenzofurans or any of their halogenated analogues, are ruled out of the TTC concept at an earlier step of the risk assessment. Thus, in this analysis, all compounds with E/T ratio >1 are excluded from the TTC decision tree, either due to genotoxicity or because of maternal toxicity at lower doses (in the case of sodium selenite).

4 Discussion

The teratogens tabulated in the present study represent no more than an initial inventory of existing data, which is far from complete and therefore perhaps not fully representative of teratogenic compounds in general. This inventory should therefore be considered as a starting point for discussion rather than for the derivation of definitive conclusions. Most of the chemicals included in the database are retrieved from existing inventories, as explained in the chapter Materials and Methods. In addition, some chemicals were selected by searching for teratogenicity in literature search systems such as MEDLINE. Many different lists were identified which referred to this class of compounds, but it often proved difficult to find appropriate data concerning their teratogenicity in animals. Full text reports were not available of studies from industry, and their abstracts often lacked sufficient information for our purpose. For compounds that are known as human teratogens, few useful studies on animal toxicity were available. Some of the studies that did describe teratogenic effects in animals could not be included in the table for several reasons, as listed in Materials and Methods. In spite of these limitations, the database gives an impression of the relationship between maternal toxicity, embryotoxicity and teratogenicity over a range of teratogenic compounds.

The initial idea was that if compounds had an Embryotoxicity/Teratogenicity ratio (E/T ratio) greater than 0.1, there would be a need for an extra uncertainty factor of 10 for irreversible structural effects in the TTC concept. However, most of the studies are not set up to determine a dose-response curve in sufficient detail to allow determination of the threshold dose, that is the dose that represents the boundary between ‘no effect’ and ‘effect’. This raises the question about the feasibility of looking for a specific difference of at least 10, since the observed differences are critically dependent on the doses and their spacing chosen in the study. In addition, the suggestion for the necessity of an extra safety factor in case of teratogenic effects presupposes that teratogenic effects are more severe hazards than other developmentally toxic effects. This suggestion is often made and is justified on emotional grounds as well as with arguments such as quality of life aspects related to congenital anomalies. One should keep in mind however that findings recorded as general developmental toxicity also include severe effects, such as increased numbers of resorptions and embryonic death. Taken together, teratogenicity occurring at doses without general embryotoxicity is both a justifiable as well as a practical trigger for specific action under the TTC concept. Of the 49 studies in-

cluded in the table, 40 have an E/T ratio smaller than or equal to 1, and no specific action would be needed for these compounds on the basis of their teratogenicity. Nine studies (8 compounds) have an E/T ratio which is greater than 1. All these compounds except for sodium selenite are already ruled out at an earlier stage of the TTC approach because of structural alerts for carcinogenicity. Therefore, according to this limited database (and ignoring selenite for a moment, see below), there seems to be no need for an additional safety factor in the TTC concept for teratogenic effects.

The exceptional case of sodium selenite is of interest for several reasons. Selenium is an essential trace element, necessary for instance as a cofactor to glutathione peroxidase. It is not an industrial chemical in usual terms and therefore perhaps less pertinent to the TTC concept discussion. Furthermore, the study of Ferm et al. (1990), from which the E/T ratio of selenite was derived, had several features in its design which increased the likelihood of finding specific teratogenicity in the absence of general toxicity. Firstly, doses were applied on a single day only, which reduces the chances of induction of maternal toxicity and secondary general embryotoxicity. Secondly, dosing was done at gestational day 8, at which the embryo is specifically sensitive for developing neural tube defects. Thirdly, the various dose levels used were very closely spaced (0, 23, 58, 80, 90, 100, 110 μmol/kg), increasing the likelihood of finding different NOELs for different end points. Fourthly, the animal species used, the hamster, is particularly prone to encephalocele and exencephaly, which sometimes occur spontaneously in control animals. The Ferm study shows a low incidence of encephalocele (1/81, 2/61, 2/88) already in all low dose groups, with 0/71 in the vehicle control group. In the highest three dose groups, apart from increased encephalocele (8/78, 9/105, 11/48), also exencephaly was found (3/78, 2/105, 4/48). Increased resorptions and reduced fetal growth occurred at the two highest doses, and maternal mortality occurred at the four highest dose groups (1/8, 1/8, 1/10, 4/9), with a high incidence in the highest dose group. Therefore, teratogenicity, general embryotoxicity and maternal toxicity are induced at dose levels very close together in this study, and the significance in terms of human risk of the neural tube defects found here at a dose without observed general embryotoxicity is unclear. The cases of single maternal mortalities in three dose groups should also be considered treatment related in view of the close spacing of doses and of the high mortality incidence in the highest dose group. Thus, the teratogenic effects in this study are found in higher than background incidences only at dose levels where maternal mortality occurs. In such cases, there is no specific safety

concern as regards teratogenicity within the TTC concept. Other studies on sodium selenite with different designs have always found teratogenicity only in the presence of general toxicity. The Dutch Health Council, after reviewing all the available data, concluded that classification and labelling of selenite for developmental toxicity was not indicated. One message of this encounter with the Ferm study is that using single studies as the basis for the database has its disadvantages. The wider perspective should always be kept in mind, but this was not considered feasible within the scope of the present database. Furthermore, this study using six doses would be an interesting one for comparing the various toxicities using a benchmark approach which uses dose-response modelling for derivation of critical effective doses. This would certainly give more insight into the relationship between maternal effects, general developmental effects and teratogenic effects than is possible with the NOEL approach.

In the database, we have also indicated the ratio between maternal NOEL and teratogenicity NOEL (M/T ratio). All the compounds with an E/T ratio >1 also have an M/T ratio >1 (except sodium selenite), indicating that these compounds are teratogenic at doses without general toxicity to the fetus or the mother. The fact that selenite does not follow this rule illustrates again that this is a special case (see above). Two studies, with etretinate and lithium, did not mention the presence or the absence of maternal toxicity, but these compounds are known to have very little adverse effects on the mother at teratogenic dosages. There are at least eight compounds included in the table (benomyl, DEHP, ETU, etretinate, lithium, methanol, methoxyethanol and TCDD) which are known teratogens. All these compounds have an M/T ratio greater than one and they all cause teratogenicity in the absence of maternal toxicity in at least one of the animal species studied. Only two of these compounds (ETU and TCDD) also have an E/T ratio greater than one. For the application of the TTC concept, it may be pragmatic to only consider the E/T ratio of developmental toxicants that cause teratogenicity in the absence of maternal toxicity at the same dose.

This exercise shows the importance of being careful with the choice of data and the way to analyse them for the application of safety factors, as already mentioned in Kroes et al., (2000). One must be careful not to apply exaggerated empirical (rather than data-derived) safety factors, since this may lead to one endpoint dominating the safety evaluation process when the hazard relevant to the circumstances of human exposure may be different (Kroes et al., 2000). An alternative approach, as proposed by the Expert Group on TTC, would be to analyse the teratogenicity data included in the table the same way the Expert Group on TTC

analysed data about other specific endpoints, such as developmental toxicity or neurotoxicity. The teratogenicity NOELs would be divided by 100 and 1000 and compared with the calculated TTC for the three classes as determined by Cramer et al., (1978):

- Class I: Substances of simple chemical structure and efficient modes of metabolism, which would suggest a low order of oral toxicity. The calculated human exposure threshold for this class is 1800 µg/person/day. (Kroes et al., 2000)
- Class II: 'Intermediate' substances which possess structures that are less innocuous than class I substances but do not contain structural features suggestive of toxicity like those substances in class III. The calculated human exposure threshold for this class is 540 µg/person/day. (Kroes et al., 2000)
- Class III: Substances of a chemical structure that permits no strong initial presumption of safety or may even suggest significant toxicity or have reactive functional groups. The calculated human exposure threshold for this class is 88 µg/person/day. (Kroes et al., 2000)

If the resulting value (NOEL/100 or NOEL/1000) is lower than the TTC for the specific class than there is no problem. However, if the resulting values were equal to or greater than the calculated threshold value, it would mean that an extra safety factor is needed. The database collected in the present study can also be employed for this alternative approach.

In conclusion, the present database has mapped the relationship between maternal, general developmental and teratogenic adverse effects of a series of chemicals in developmental toxicity studies. The database is a first inventory with a limited number of chemical compounds. On the basis of the collected data it appears that there is no need for an additional safety factor in the TTC concept for teratogenic effects.

Table 2: Ratios of teratogenicity vs developmental toxicity and maternal toxicity in published literature.

Compound	Species	Route	Experi-mental period	Dose	Maternal toxicity	Embryotoxicity	Teratogenicity	Ratio E/T	Ratio M/T	Reference
Acetazo-lamide	Japanese White rabbit	Gavage	GD 6-18	Control 50 100 150 mg/kg	- Red. bwg Red. bwg Red. bwg LOEL: 50 mg/kg	- - Decr. bw, red. ossification Decr. bw, red. ossification NOEL: 50 mg/kg	- - Thoracic, lumbar, caudal vert. malf. missing vert. Thoracic, lumbar, caudal vert. malf. missing vert. NOEL: 50 mg/kg	1	<1	Nakatsuka et al., 1992
Acetonitrile	Golden hamster	Inhala-tion	GD 8 60 min † GD 14	Control 142 300 395 632 mg/kg	- - - Irritation, excessive salivation, respiratory difficulty Lethargy, ataxia, hy-pothermia, eye/nose irritation, gasping 4/12 NOEL: 300 mg/kg	- - - Decr. bw Decr. bw NOEL: 300 mg/kg	- - - Exencephaly, encephalo-cele, rib fusions Exencephaly, encephalo-cele, rib fusions, ectopia cordis NOEL: 300 mg/kg	1	1	Willhite CC, 1983
Acetonitrile	Golden hamster	Gavage	GD 8 Single dose † GD 15	Control 100 200 300 400 mg/kg	- - - Death 1/6 Death 4/12 NOEL: 200 mg/kg	- Decr. bw Decr. bw Decr. bw Decr. bw, resorptions LOEL: 100 mg/kg	- - - Fused ribs Fused ribs NOEL: 200 mg/kg	<1	1	Willhite CC, 1983
Aflatoxin B1	Hamster	Ip injec-tion	GD 8 Single dose † GD 11	Control 2 4 6 8 mg/kg	? ? ? Death 2/5 Lethal 3/3 (NOEL: 4 mg/kg)	- - Incr. resorptions Totally resorbed - NOEL: 2 mg/kg	- - Anencephaly - - NOEL: 2 mg/kg	1	(2)	Elis and DiPaolo, 1967

Compound	Species	Route	Experi-mental period	Dose	Maternal toxicity	Embryotoxicity	Teratogenicity	Ratio E/T	Ratio M/T	Reference
Antiallergic Sm 857 SE	Sprague-Dawley rat	Ga-vage	GD 7-17 † GD 21	Control 20 90 400 mg/kg	- - Decr. bwg Decr. bw, enlarged spleen NOEL: 20 mg/kg	- - - Incr. resorptions, red. bw, split vert. body NOEL: 90 mg/kg	- - - Microphtalmia, vert.-costal defects NOEL: 90 mg/kg	1	0.22	Nishimura et al., 1988
Benomyl	Wistar rat	Ga-vage	GD 7-16 † GD 21	Control 15.6 31.2 62.5 125 mg/kg	- - - - - -	- - - Decr. bw, red. ossifica-tion Decr. bw, red. ossifica-tion, death NOEL: 31.2 mg/kg	- - - Encephalocele, fused ribs & vert. Encephalocele, fused ribs & vert. NOEL: 31.2 mg/kg	1	> 4	Kavlock RJ, 1982
Benomyl	CD-1 mice	Ga-vage	GD 7-17 † GD 18	Control 50 100 200 mg/kg	- - - - -	- Supernum. ribs, enl. lat. ventr., enl. renal pelves Supernum. ribs, enl. lat. ventr., enl. renal pelves, decr. bw Supernum. ribs, enl. lat. ventric., enl. renal pelves, decr. bw, death LOEL: 50 mg/kg	- - Cleft palate, hydrone-phrosis, fused ribs & vert., short/kinky tail Cleft palate, hydrone-phrosis, fused ribs & vert., short/kinky tail, hydrocephaly, poly/oligodactyly NOEL: 50 mg/kg	<1	> 4	Kavlock RJ, 1982

Compound	Species	Route	Experi-mental period	Dose	Maternal toxicity	Embryotoxicity	Teratogenicity	Ratio E/T	Ratio M/T	Reference
Boric acid	Swiss albino mice	Diet	GD 0-17	Control 248 452 1003 mg/kg	- Renal damage Incr. renal tubular dilatation Incr. renal tubular dilatation, incr. rel. kidney wt LOEL: 248 mg/kg	- Pale spleen Decr. bw, pale spleen Decr. bw, pale spleen, incr. resorptions LOEL: 248 mg/kg	- - Short rib XIII Short rib XIII NOEL: 248 mg/kg	<1	<1	Heindel et al., 1992
Boric acid	Sprague-Dawley rat	Diet	GD 0-20	Control 19 36 55 76 143 mg/kg	- - - - - Incr. rel. kidney wt NOEL: 76 mg/kg	- - - - Decr. bw, wavy rib Decr. bw, wavy rib NOEL: 55 mg/kg	- - - - Short rib XIII Short rib XIII NOEL: 55 mg/kg	1	1.38	Price et al., 1996a
Boric acid	New Zealand White rabbit	Gavage	GD 6-19 Once daily	Control 62.5 125 250 mg/kg	- - - Decr. food cons., red. bwg, vaginal bleed-ing NOEL: 125 mg/kg	- - - Incr. Resorptions, complete prenatal loss NOEL: 125 mg/kg	- - - Intervent. septal defect, enl. aorta, double outlet right vent., NOEL: 125 mg/kg	1	1	Price et al., 1996b
Bromo-chloro-aceto-nitrile (BCAN) (+ tricaprilin as carrier)	Long-Evans rat	Gavage	GD 6-19 † GD 20	Control 5 25 45 65 mg/kg	- - Incr. kidney wt Incr. kidney wt Incr. kidney, spleen, liver wt, red. bwg, death NOEL: 5 mg/kg	- - Decr. bw Decr. bw, incr. resorp-tions Decr. bw, incr. resorp-tions NOEL: 5 mg/kg	- Cardiovasc. defects Cardiovasc. & renal defects Cardiovasc. & renal defects Cardiovasc. & renal defects LOEL: 5 mg/kg	>1	>1	Christ et al., 1995

Compound	Species	Route	Experi-mental period	Dose	Maternal toxicity	Embryotoxicity	Teratogenicity	Ratio E/T	Ratio M/T	Reference
Butyl benzyl phtalate (BBP)	Wistar rat	Gavage	GD 7-15 Once daily † GD 20	Control 500 750 1000 mg/kg	- Decr. food cons. Decr. food cons Decr. food cons, red. bwg LOEL: 500 mg/kg	- - Incr. resorptions and deaths, decr. bw. No live fetuses NOEL: 500 mg/kg	- - Cleft palate, fused sternebrae No live fetuses NOEL: 500 mg/kg	1	<1	Ema et al., 1992
Chloroform	Sprague-Dawley rat	Inhalation	GD 6-15 † GD 21	Control 27 89 268 mg/kg	- Red. bwg & food consumption Red. bwg & food consumption Anorexia & severe bw loss, few dams pregnant LOEL: 27 mg/kg	- Red. ossification, wavy ribs Red. ossification Red. ossification, incr. resorptions, very few fetuses alive LOEL: 27 mg/kg	- - Acaudia, short tail, imperforate anus, subcutaneous edema Subcutaneous edema NOEL: 27 mg/kg	<1	<1	Schwetz et al., 1973
Dichloro-acetic acid (DCA)	Long-Evans rat	Gavage	GD 6-15 † GD 20	Control 14 140 400 mg/kg	- - Red. bwg Red. bwg, incr. liver, spleen & kidney wt. NOEL: 14 mg/kg	- - - Decr. length & bw NOEL: 140 mg/kg	- - - Defect between ascending aorta and right vent., microphtalmia NOEL: 140 mg/kg	1	0.1	Smith et al., 1992
Dichloro-acetonitrile (DCAN) (+ tricaprilin as carrier)	Long-Evans rat	Gavage	GD 6-19 † GD 20	Control 5 15 25 45 mg/kg	- - - Incr. liver wt Red. bwg, incr. liver, kidney & spleen wt. NOEL: 15 mg/kg	- - - Postimplant. loss Postimplant. loss, decr. length & bw NOEL: 15 mg/kg	- - - Cardiovasc. & skeletal defects Cardiovasc. & skeletal defects NOEL: 15 mg/kg	1	1	Smith et al., 1989

Compound	Species	Route	Experi-mental period	Dose	Maternal toxicity	Embryotoxicity	Teratogenicity	Ratio E/T	Ratio M/T	Reference
Di (2-ethylhexyl) phthalate (DEHP)	ICR-JCL mice	Diet	GD 0-18 † GD 18	Control 70 190 410 830 2200 mg/kg	- - - - - - -	- - Incr. resorptions, red. bw Incr. resorptions, red. bw Incr. resorptions, red. bw Incr. resorptions, red. bw NOEL 70 mg/kg	- - - Neural tube defects, tail anomalies Neural tube defects, tail anomalies Neural tube defects, tail anomalies NOEL 190 mg/kg	0.37	> 11.58	Shiota and Nishimura, 1982
N,N-di-methyl-form-amide	Sprague-Dawley rat	Gavage	GD 6-15	Control 166 503 1510 mg/kg	- - Decr. bwg Decr. bwg NOEL 166 mg/kg	- - Incr. resorptions & skeletal variations Incr. resorptions & skeletal variations NOEL 166 mg/kg	- - Cleft palate, tail aplasia, anasarca Tail aplasia, anasarca NOEL 166 mg/kg	1	1	Hellwig et al., 1991
Ethylene oxide	CD-1 mice	Iv injec-tion	GD 6-8 Once daily † GD 17	Control 75 150 mg/kg	- - - -	- - Red. bw NOEL: 75 mg/kg	- - Incr. skeletal malf. NOEL: 75 mg/kg	1	> 2	LaBorde and Kimmel, 1980
Ethylene-thiourea (ETU)	Wistar rat	Gavage	GD 6-15 Once daily	Control 5 10 20 40 80 mg/kg	- - - - - Incr. mortality NOEL: 40 mg/kg	- - - - - Decr. bw NOEL: 40 mg/kg	- - Hypoplastic cerebellum Cephalic malf. Cephalic malf. Cephalic malf. NOEL: 5 mg/kg	8	8	Khera KS, 1973

Compound	Species	Route	Experi-mental period	Dose	Maternal toxicity	Embryotoxicity	Teratogenicity	Ratio E/T	Ratio M/T	Reference
Ethylene-thiourea (ETU)	Golden hamster	Gavage	GD 6-13 † GD 14	Control 90 270 810 mg/kg	- - - - -	- - - Incr. resorptions, decr. bw NOEL: 270 mg/kg	- Malf. lumbar & sacral vert. Skeletal malf. Skeletal & external malf. LOEL: 90 mg/kg	>3	> 9	Teramoto et al., 1978
Etretinate	Sprague-Dawley rat	Gavage	GD 8 Single dose † GD 20	Control 1 3 6 10 15 25 mg/kg	? ? ? ? ? ? ? ?	- - - - Incr. resorptions Incr. resorptions, decr. bw. Incr. resorptions, decr. bw. NOEL: 6 mg/kg	- - - - Exencephaly, meningo-cele, cleft palate, eye defects Exencephaly, meningo-cele, cleft palate, eye defects Exencephaly, meningo-cele, cleft palate, eye defects NOEL: 6 mg/kg	1	?	Narsingh et al., 1990
2,2',4,4',5,5'Hex-abromo-biphenyl (HBB)	B6C3F1 mice	Diet	GD 6-15 † GD 17	Control 21 63 106 159 mg/kg	- Incr. liver wt Incr. liver wt Incr. liver wt Incr. liver wt & mortality, red.bwg LOEL: 21 mg	- - Decr. bw Decr. bw Decr. bw, incr. resorp-tions NOEL: 21 mg/kg	- - Cleft palate, cystic brain deviation Cleft palate, cystic brain deviation Cleft palate, cystic brain deviation NOEL: 21 mg/kg	1	< 1	Welsh and Morgan, 1985

Compound	Species	Route	Experimental period	Dose	Maternal toxicity	Embryotoxicity	Teratogenicity	Ratio E/T	Ratio M/T	Reference
Lithium carbonate	Wistar rat	Gavage	GD 6-15 † GD 20	Control 50 100 mg/kg	? ? ? ? ?	- - Incr. resorptions, red bw NOEL: 50 mg/kg	- - Skeletal malf., shortening of limbs NOEL: 50 mg/kg	1	?	Marathe and Thomas, 1986
Lithium carbonate	HaM/ICR mice	Gavage	GD 6-15 † GD 18	Control 200 465 mg/kg	- - Incr. death NOEL: 200 mg	- - Incr. resorptions NOEL: 200 mg/kg	- - Cleft palate NOEL: 200 mg/kg	1	1	Szabo KT, 1970
Mangafo-dipir trisodium (MnDPDP)	Sprague-Dawley rat	Iv-injection	GD 6-17 † GD 20	Control 10 20 40 µmol/kg	- - - - -	- Wavy ribs Wavy ribs Wavy ribs, incr. post-implantation loss, decr. bw LOEL: 10 µmol/kg	- - Distorted long bones Distorted long bones NOEL: 10 µmol/kg	<1	>4	Grant et al., 1997
Manganese Chloride	Sprague-Dawley rat	Iv-injection	GD 6-17 † GD 20	Control 0.63 2.52 5.03 mg/kg	- - - - -	- Wavy ribs Decr. bw, wavy ribs Incr. postimplantation loss, decr. bw, wavy ribs LOEL: 5 µmol/kg	- - Distorted long bones Distorted long bones NOEL: 5 µmol/kg	<1	>8	Treinen et al., 1995
Methanol	CD-1 mice	Inhalation	GD 6-15 † GD 17	Control 493 986 2465 3697 4929 7394 mg/kg	- - - - - - - -	- - Cervical rib CR CR, incr. resorptions & mortality CR, incr. resorptions & mortality, red. bw CR, incr. resorptions & mortality, red. bw NOEL: 493 mg/kg	- - - Cleft palate, exencephaly Cleft palate, exencephaly Cleft palate, exencephaly Cleft palate, exencephaly NOEL: 986 mg/kg	0.5	>7.5	Rogers et al., 1993

Compound	Species	Route	Experi-mental period	Dose	Maternal toxicity	Embryotoxicity	Teratogenicity	Ratio E/T	Ratio M/T	Reference
2-Methoxy-ethanol	Sprague-Dawley rat	Iv injection	GD 13 Single dose † GD 20	Control 100 250 350 500 mg/kg	- - - - - -	- Red. bw Red. bw Red. bw Red. bw LOEL: 100 mg/kg	- - Ectrodactyly Ectrodactyly Ectrodactyly NOEL: 100 mg/kg	<1	>5	Sleet et al., 1996
2-Methoxy-ethanol	Sprague-Dawley rat	Liquid diet	GD 7-18 † GD 20	Control 16 31 73 140 198 290 620 mg/kg	- - - - Decr. bwg Decr. bwg Decr. bwg, malaise Decr. bwg, diarrhea, resp. diff., hair loss, malaise NOEL: 73 mg/kg	- Red. bw Red. bw Incr. resorptions Totally resorbed Totally resorbed Totally resorbed Totally resorbed LOEL: 16 mg/kg	- - Double and/or misplaced aortic arches Double and/or misplaced aortic arches, esophogal & tracheal stenosis - - - - NOEL: 16 mg/kg	<1	4.56	Nelson et al., 1989
2-Methoxy-ethanol	New Zealand White rabbit	Inhalation	GD 6-18 † GD 29	Control 1 4 21 mg/kg NOEL: 4 mg/kg	- - - Decr. bwg NOEL: 4 mg/kg	- - - Incr. resorptions & minor variations, red. bw NOEL: 4 mg/kg	- - - Incr. external, soft tissue & skeletal malformations NOEL: 4 mg/kg	1	1	Hanley et al., 1984

Compound	Species	Route	Experi-mental period	Dose	Maternal toxicity	Embryotoxicity	Teratogenicity	Ratio E/T	Ratio M/T	Reference
2-Methoxy-propanol-1	Hima-layan rabbit	Inhala-tion	GD 6-18	Control 72 111 173 269 mg/kg	- - - Decr. bwg Decr. bwg, fecal blood NOEL: 111 mg/kg	- Skeletal variations Skeletal & soft tissue variations Skeletal & soft tissue variations Skeletal, external & soft tissue variations LOEL: 72 mg/kg	- - Skeletal malf. Skeletal malf. Skeletal, external & soft tissue malf. NOEL: 72 mg/kg	<1	1.54	Hellwig et al., 1994
2-Methoxy-propyl-ace-tate-1	Wistar rat	Inhala-tion	GD 6-15 † GD 20	Control 96 478 2373 mg/kg	- - Decr. bw, slight seda-tion, pulsative respira-tion Decr. bw , slight seda-tion, pulsative respira-tion NOEL: 96 mg/kg	- - - Red. bw, incr. resorp-tions NOEL: 478 mg/kg	- - - Incr. number of split vertebrae NOEL: 478 mg/kg	1	0.2	Merkle J, 1987
2-Methoxy-propyl-ace-tate-1	Hima-layan rabbit	Inhala-tion	GD 8-18	Control 26 105 395 mg/kg	- - - - -	- - - Red. bw NOEL: 105 mg/kg	- - - Anomalies of the digits and sternum, septal and ventricular defect NOEL: 105 mg/kg	1	>3.76	Merkle J, 1987
Mirex	Wistar rat	Gavage	GD 6-15 † GD 22	Control 1.5 3.0 6.0 12.5 mg/kg	- - Red. incidence of pregnancy Red. incid. of pregn., incr. death Red. incid. of pregn., incr. death NOEL: 1.5 mg/kg	- - Incr. resorptions Incr. resorptions, red. bw Incr. resorptions, red. bw NOEL: 1.5 mg/kg	- - - Subcut. edema, scoliosis, cleft palate, short tail Subcut. edema, scoliosis, cleft palate, short tail NOEL: 3.0 mg/kg	0.5	0.2	Khera et al., 1976

Compound	Species	Route	Experimental period	Dose	Maternal toxicity	Embryotoxicity	Teratogenicity	Ratio E/T	Ratio M/T	Reference
Ochratoxin A	Sprague-Dawley rat	Gavage	GD 6-15 † GD 20	Control 0.25 0.5 0.75 1 2 4 8 mg/kg	- - - - Decr. bwg Decr. bwg Dehydrated, bw loss Bw loss, diarrhea, polydipsia, polyuria NOEL: 0.75 mg/kg	- Wavy ribs, asymmetrical stern. Red. ossif., wavy ribs, asymmetrical stern. Red. bw & ossif., incr. resorptions Incr. resorptions, red. bw & ossification Total resorption Total resorption Total resorption LOEL: 0.25 mg/kg	- - Subcut. edema Subcut. edema, short snout Subcut. edema, short snout, open eyes - - - NOEL: 0.25 mg/kg	<0.5	3	Brown et al., 1976
1,2,3,7,8-Pentabromodibenzofuran (1PeBDF)	C57BL/6N mice	Gavage	GD 10 Single dose † GD 18	Control 0.25 0.50 1.0 2.0 3.0 4.0 mg/kg	- - - - - - - -	- - - - - - - -	- - - - - Cleft palate Hydronephrosis, cleft palate NOEL: 2.0 mg/kg	>2	>2	Birnbaum et al., 1991
2,3,4,7,8-Pentabromodibenzofuran (4PeBDF)	C57BL/6N mice	Gavage	GD 10 Single dose † GD 18	Control 0.2 0.4 0.8 1.6 2.4 4.0 mg/kg -	- - - - - - - -	- - - - - - - -	- - - - Hydronephrosis Hydronephrosis, cleft palate Hydronephrosis, cleft palate NOEL: 0.8 mg/kg	>5	>5	Birnbaum et al., 1991

Compound	Species	Route	Experimental period	Dose	Maternal toxicity	Embryotoxicity	Teratogenicity	Ratio E/T	Ratio M/T	Reference
Polybrominated biphenyls	Wistar rat	Gavage	GD 13 Single dose † GD 20	Control 40 200 400 800 mg/kg	- - - Decr. bwg Decr. bw NOEL: 200 mg/kg	- - - Red. bw Red. bw NOEL: 200 mg/kg	- - - Cleft palate Cleft palate, diaphragmatic hernia NOEL: 200 mg/kg	1	1	Beaudoin AR, 1977
Sodium arsenite	Golden hamster	Iv injection	GD 8 Single dose † GD 15	Control 2 5 10 mg/kg	- - - - - NOEL: 2 mg/kg	- - Incr. resorptions Incr. resorptions NOEL: 2 mg/kg	- - Cranioschisis Cranioschisis NOEL: 2 mg/kg	1	>5	Willhite CC, 1981
Sodium salicylate	Sprague-Dawley rat	Gavage	GD 6-15 Once daily	Control 30 90 180 mg/kg	- - - Red. food cons. NOEL: 90 mg/kg	- - Delayed ossification Delayed ossification, red. bw, incr. resorptions NOEL: 30 mg/kg	- - - Cranioschisis NOEL: 90 mg/kg	0.33	1	Fritz and Giese, 1990
Sodium selenite	Syrian hamster	Gavage	GD 8 Single dose † GD 13	Control 3.98 10.0 13.84 15.57 17.30 19.0 mg/kg	- - - Incr. lethality Incr. lethality Decr. bwg, incr. lethality Decr. bwg, incr. lethality NOEL: 17.3 mg/kg	- - - - - Red. bw & length Red. bw & length NOEL: 15.57 mg/kg	- - - - Encephalocele, exencephaly Encephalocele, exencephaly Encephalocele, exencephaly NOEL: 13.84 mg/kg	1.125	0.72	Ferm et al., 1990

Compound	Species	Route	Experi-mental period	Dose	Maternal toxicity	Embryotoxicity	Teratogenicity	Ratio E/T	Ratio M/T	Reference
2,3,7,8-Tetrabromo-dibenzo-p-dioxin (TBDD)	C57BL/6 N mice	Gavage	GD 10 Single dose † GD 18	Control 0.003 0.006 0.012 0.024 0.048 0.096 0.192 mg/kg	- - - - - - - - -	- - - - - - - - -	- - - Hydronephrosis Hydronephrosis Hydro-nephrosis, cleft palate Hydronephrosis, cleft palate Hydronephrosis, cleft palate NOEL: 0.006 mg/kg	> 32	> 32	Birnbaum et al., 1991
2,3,7,8-Tetrabromo-dibenzofuran (TBDF)	C57BL/6 N mice	Gavage	GD 10 Single dose † GD 18	Control 0.025 0.05 0.1 0.2 0.25 0.5 1.0 mg/kg	- - - - - - - - -	- - - - - - Incr. mortality Incr. mortality NOEL: 0.25 mg/kg	- - - Hydronephrosis Hydronephrosis, cleft palate Hydronephrosis, cleft palate Hydronephrosis, cleft palate Hydronephrosis, cleft palate NOEL: 0.05 mg/kg	5	> 20	Birnbaum et al., 1991
2,3,7,8-Tetrachloro-dibenzo-p-dioxin (TCDD)	CF-1 mice	Gavage	GD 6-15	Control 0.001 0.01 0.1 1.0 3.0 µg/kg	- - - - - - - -	- - - - - - - -	- - - Cleft palate Cleft palate, dilated renal pelvis NOEL: 0.1 µg/kg	>30	> 30	Smith et al., 1976

Compound	Species	Route	Experi-mental period	Dose	Maternal toxicity	Embryotoxicity	Teratogenicity	Ratio E/T	Ratio M/T	Reference
Trichlorfon (dipterex)	CD-1 mice	Gavage	GD 7-16 † GD 17	Control 200 300 400 mg/kg	- Decr. bwg Incr. lethality, decr. bwg Incr. lethality, decr. bwg, vasodilatation LOEL: 200 mg/kg	- Delayed ossification Delayed ossification Delayed ossification, incr. resorptions LOEL: 200 mg/kg	- - Defects in the urinary system Defects in the urinary system NOEL: 200 mg/kg	<1	<1	Courtney et al., 1986
Trichlorfon (dipterex)	CD rat	Diet	GD 6-15 † GD 21	Control 76 145 375 432 519 mg/kg	- - - - Red. food intake, decr. bwg Red. food intake, decr. bwg NOEL: 375 mg/kg	- - - Doubled vert. centra, wavy ribs Doubled vert. centra, wavy ribs, red. bw, incr. resorptions Doubled vert. centra, wavy ribs, red. bw, incr. resorptions NOEL: 145 mg/kg	- - - - Central nervous system, skull & limb defects Central nervous system, skull & limb defects NOEL: 375 mg/kg	0.39	1	Staples et al., 1976
Trichloro-acetonitrile (TCAN)	Long-Evans rat	Gavage	GD 6-18 † GD 20	Control 15 35 55 75 mg/kg	- - Incr. liver wt, decr. bwg Incr. liver, spleen & kidney wt, decr. bwg Death, non-pregnant NOEL: 15 mg/kg	- - - Incr. resorptions, red. bw & length Incr. resorptions NOEL: 35 mg/kg	- - - Levocardia, microphtal-mia, anophtalmia - NOEL: 35 mg/kg	1	0.43	Christ SA, 1996

Compound	Species	Route	Experi-mental period	Dose	Maternal toxicity	Embryotoxicity	Teratogenicity	Ratio E/T	Ratio M/T	Reference
Xylene mixture	Wistar rat	Inhalation	GD 1-21 † GD 21	Control 2 8 80 mg/kg ?	? ? ? ? ?	- - Incr. postimplantation loss, red. bw & ossifi-cation Incr. postimplantation loss, red. bw & ossifi-cation NOEL: 2 mg/kg	- - Hemorrhages Hemorrhages, hydro-cephalus, microphtalmia NOEL: 2 mg/kg	1	?	Mirkova et al., 1983
Xylene mixture	CD-1 mice	Gavage	GD 6-15 † GD 18	Control 0.52 1.03 2.06 2.58 3.10 4.13 mg/kg	- - - Incr. liver wt Incr. liver wt Death 12/38, decr. bwg, incr. liver wt Lethal NOEL: 1.03 mg/kg	- - - Red. bw Red. bw, wavy ribs Red. bw, wavy ribs, incr. resorptions - NOEL: 1.03 mg/kg	- - - Cleft palate Cleft palate Cleft palate - NOEL: 1.03 mg/kg	1	1	Marks and Ledoux, 1982

Abbreviations used in the database:

'**-**' = no, or no relevant effects
'**?**' = effects not mentioned
bw = body weight
bwg = body weight gain
cardiovasc. = cardiovascular
CR = cervical rib
decr. = decreased
enl. = enlarged
incr. = increased
intervent. = interventricular
Ip = intraperitoneal
Iv = intravenous
lat. vent. = lateral ventricles
malf. = malformations/malformed
red. = reduced
stern. = sternebrae
subcut. = subcutaneous
supernum. = supernumerary
vert. = vertebrae/ vertebral
wt = weight

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Appendix 1 Dose recalculation for the inhalation studies

	Animal	Volume respired/h (x 10^{-3} m^3)	Duration of exposure (h)	Exposure concentra-tion (x 10^3 ppm)	Exposure Concentra-tion (g/m3)	Total Body dose (mg)	Body weight (kg)	Dose (mg/kg bw)	Reference
Acetonitrile	hamster	5	1	1.8	3.2	17	0.12	142	Willhite CC,
		5	1	3.8	6.7	36	0.12	300	1983
		5	1	5,0	8.8	47	0.12	395	
		5	1	8,0	14.0	76	0.12	632	
Chloroform	rat	9	7	0,03	0.14	9,4	0.35	27	Schwetz et al.,
		9	7	0,10	0.48	31	0.35	89	1973
		9	7	0,30	1.44	94	0.35	268	
Methanol	mouse	2	7	1,0	1.30	15	0.03	493	Rogers et al.,
		2	7	2,0	2.60	30	0.03	986	1993
		2	7	5,0	6.50	74	0.03	2465	
		2	7	7,5	9.75	111	0.03	3697	
		2	7	10	13.0	148	0.03	4929	
		2	7	15	19.5	222	0.03	7394	
2-Methoxy-	rabbit	83	6	0.003	0.010	4,8	3.8	1	Hanley et al.,
ethanol		83	6	0.010	0.032	16	3.8	4	1984
		83	6	0.050	0.16	80	3.8	21	

	Animal	Volume respired /h (x 10^{-3} m^3)	Duration of exposure (h)	Exposure concentra-tion (x 10^3 ppm)	Exposure Concentra-tion (mg/m3)	Total Body dose (mg)	Body weight (kg)	Dose (mg/kg bw)	Reference
2-Methoxy-	rabbit	83	6	0.15	0.54	272	3.8	72	Hellwig et al.,
propanol-1		83	6	0.23	0.84	422	3.8	111	1994
		83	6	0.35	1.31	656	3.8	173	
		83	6	0.55	0.20	1022	3.8	269	
2-Methoxy-	rat	9	6		0.60	33	0.35	96	Merkle J,
propyl-		9	6		3.0	167	0.35	478	1987
acetate-1		9	6		14.9	830	0.35	2373	
2-Methoxy-	rabbit	83	6		0.2	100	3.8	26	Merkle J,
propyl-		83	6		0.8	400	3.8	105	1987
acetate-1		83	6		3.0	1500	3.8	395	
Xylene	rat	9	6		0.01	0.56	0.35	2	Mirkova et al.,
mixture		9	6		0.05	2.79	0.35	8	1983
		9	6		0.5	28	0.35	80	

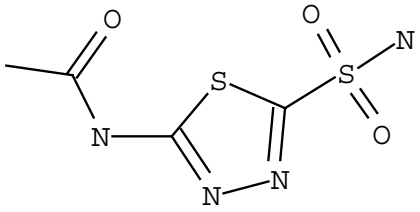
Appendix 2 Compounds excluded from the table

The compounds listed below were carefully looked at and indicated teratogenic effects. However, they were not added to the database for several reasons, such as: uncertainty about the teratogenicity found (the results were scattered); deficiencies in study design or reporting; only abstracts or human studies were available; only one dose was used which was teratogenic (the NOEL could thus not be determined); the compound caused only postnatal teratogenic effects.

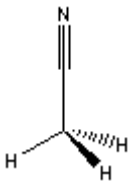
Acetylsalicylic acid
Aluminum
Aluminum nitrate
Arsenate
Arsenic
Arsenite
2-Bromoacetic acid
Cadmium
Hexavalent chromium
Cyclophosphamide
di-n-butyphthalate (DBP)
2,4-dichlorophenyl-p-nitrophenyl ether
Diuron
Dimethoate
Dipterex
2-Ethoxyethanol
Ferbam
Glycol ethers
Imidan
Linuron
Methanol
Methotrexate
Methylmercury
Nickel carbonyl
N-nitrosoethylenethiourea
Reserpine
Selenite
Thalidomide
Thiram
Vitamine D2

Appendix 3 Structures of the tabulated compounds

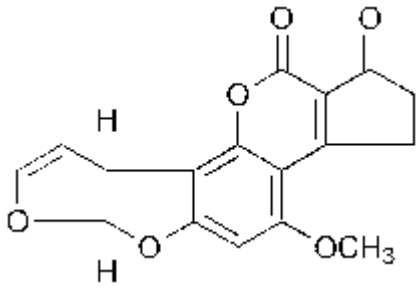
Acetazolamide
$C_4H_6N_4O_3S_2$



Acetonitrile
CH_3CN



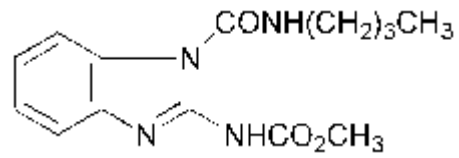
Aflatoxin B1



Antiallergic Sm 857 SE
11-Oxo-11H-pyrido(2,1-b)quinazoline-2-carboxylic acid

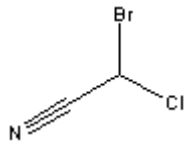
Benomyl

$C_{14}H_{18}N_4O_3$

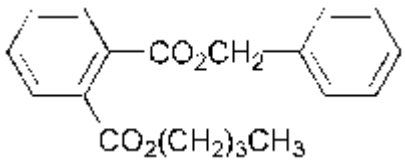


Boric acid
BH_3O_3

Bromochloroacetonitrile
BrCHCl(CN)

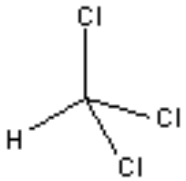


Butyl benzyl phthalate

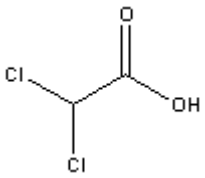


Chloroform

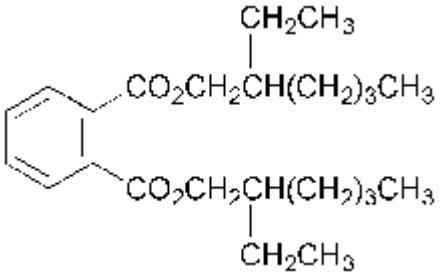
$CHCl_3$



Dichloroacetic acid
Cl_2CHCO_2H

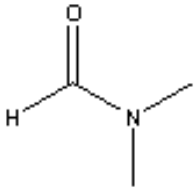


Di(2-ethylhexyl) phthalate (DEHP)

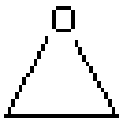


N,N-dimethylformamide

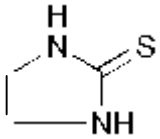
C_3H_7NO



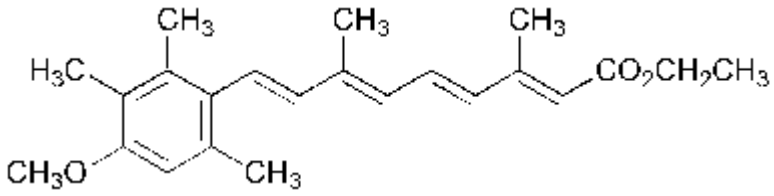
Ethylene oxide
C_2H_4O



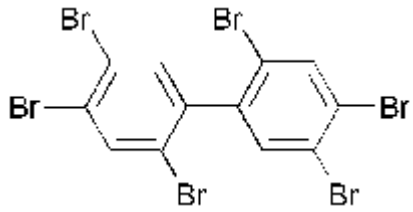
Ethylenethiourea



Etretinate

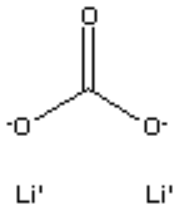


2,2',4,4',5,5'-hexabromobiphenyl

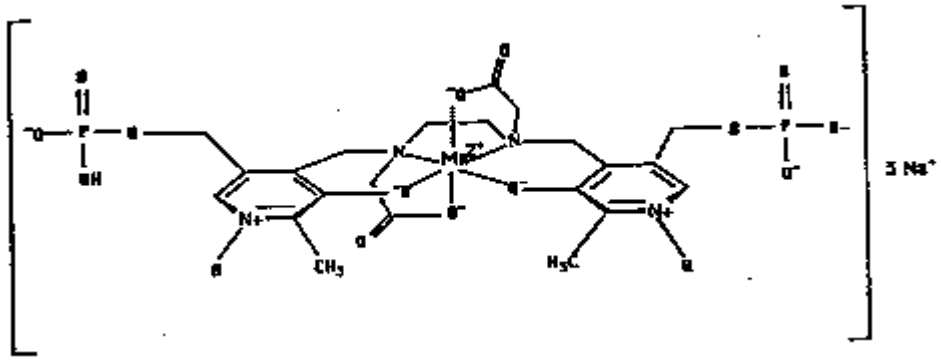


Lithium carbonate

CLi_2O_3



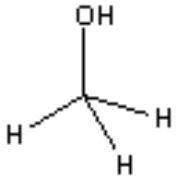
Mangafodipir trisodium



Manganese Chloride

$MnCl_2$

Methanol
CH_3OH

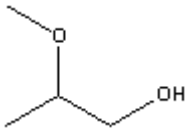


2-Methoxyethanol (Ethylene glycol monomethyl ether)

$HOCH_2CH_2OCH_3$

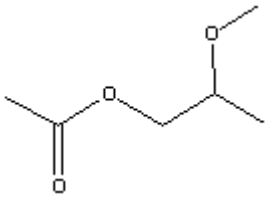
2-Methoxypropanol-1

$CH_3CH(OH/CH_3)CH_2(OH/CH_3)$



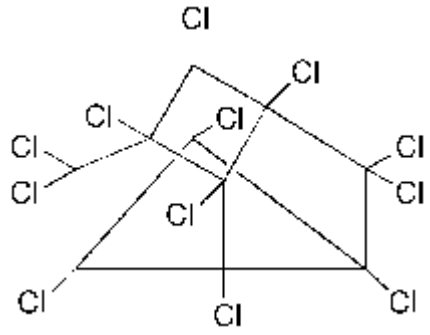
2-Methoxypropylacetate-1

$CH_3CH(OCH_3)CH_2OC(O)CH_3$

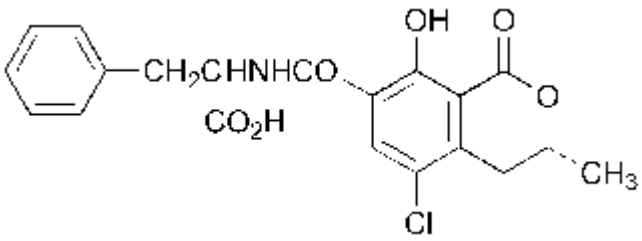


Mirex

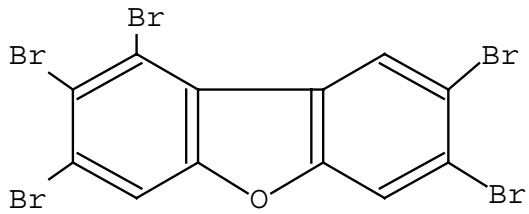
1,1a,2,2,3,3a,4,5,5,5a,5b,6-dodecachlorooctahydro-1,3,4-metheno-1H-cyclobuta[cd]pentalene



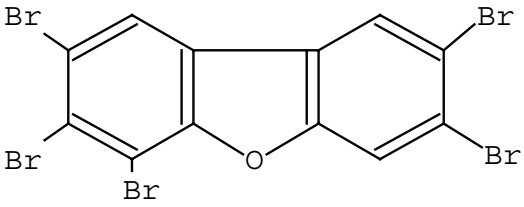
Ochratoxin A



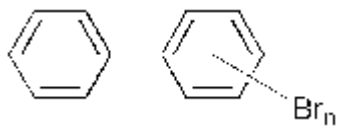
1,2,3,7,8-Pentabromodibenzofuran
(1PeBDF)



2,3,4,7,8- Pentabromodibenzofuran
(4PeBDF)

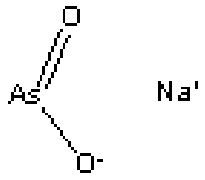


Polybrominated biphenyls

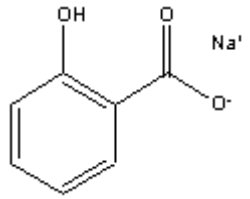


Sodium arsenite

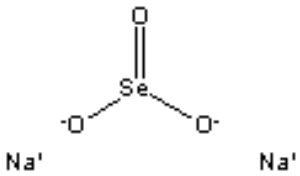
$NaAsO_2$



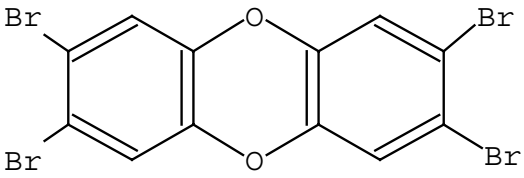
Sodium salicylate
$C_7H_5NaO_3$



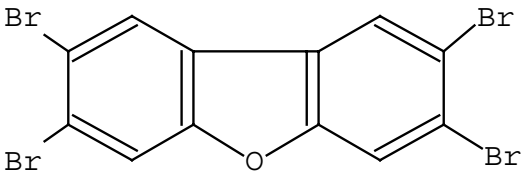
Sodium selenite
Na_2O_3Se



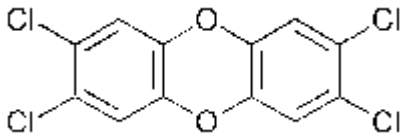
2,3,7,8-Tetrabromodibenzo-p-dioxin (TBDD)



2,3,7,8-Tetrabromodibenzofuran (TBDF)

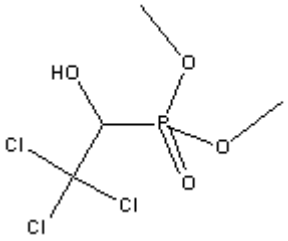


2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)

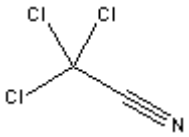


Trichlorfon

$C_4H_8Cl_3O_4P$



Trichloroacetonitrile
C_2C_3N



Xylenes
C_8H_{10}