COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Assessment of the adequacy of the 10-fold uncertainty factor to allow for interspecies variation in developmental toxicity

Identification of the list of human developmental toxicants

Secretariat
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Identification of human developmental toxicants

A list of human developmental toxicants was compiled. The intention was that this list should be broad and not limited to pharmaceuticals if possible, but also be limited to substances with positive developmental toxicity data in humans. The list was compiled from a combination of reviews of human developmental toxicity (Schardein and Keller, 1989; Nau, 1986; Newman et al., 1993), guidance to medical professionals on pharmaceuticals (The Merck Manual Online), and the EU Regulation on the classification, labelling and packaging of substances (Regulation (EC) No. 1272/2008). Some possible additional pharmaceuticals which are human developmental toxicants were indicated by general internet searching. These were confirmed by consulting the British National Formulary (BNF) where possible.

The substances identified from the Merck Manual Online were those listed as known or suspected human teratogens. The substances identified from Regulation (EC) No. 1272/2008 were category 1A reproductive toxicants (known human reproductive toxicants) under the new Globally Harmonised System of classification and labelling of substances, which also had one of the following hazard statement codes assigned: H360D ("May damage the unborn child"), H360FD ("May damage fertility. May damage the unborn child") or H360Df ("May damage the unborn child. Suspected of damaging fertility").

The initial list was as follows, with the reference sources indicated by the following key:

MER – Merck Manual. Accessed at http://www.merckmanuals.com/professional/index.html
SCH – Schardein and Keller (1989)
NAU – Nau (1986)
NEW – Newman et al. (1993)
CLP – Regulation (EC) No. 1272/2008
BNF – British National Formulary No. 62, September 2011
OTH – Other, non-validated, sources listing known human teratogens

1,2-diethoxyethane	CLP
ACE inhibitors	MER
Aminopterin	SCH, MER
Androgens	MER
Aspirin	SCH
Azauridine	SCH
Busulfan	SCH
Caffeine	SCH
Carbamazepine	MER
Chlorambucil	SCH
Cyclophosphamide	SCH
Cytarabine	SCH
Danazol	MER
Diethylstilboestrol	SCH, MER
Ethanol	SCH
Ethisterone	OTH

Etretin	NAU
Etretinate	NAU, MER
Fluorouracil	SCH
Hexachlorobenzene	SCH
Isotretinoin	SCH, NAU, NEW, MER
Lead	CLP
Lithium	SCH, MER
Mechloroethamine	SCH
Methimazole	MER
Methotrexate	SCH, NEW, MER
Methylmercury	SCH
Nicotine	OTH
Norethisterone	BNF
Norprogesterones	MER
Oxadiargyl	CLP
PCBs	SCH
Penicillamine	SCH, MER
Phenytoin	SCH, MER
Propranolol	SCH
Streptomycin	SCH, MER
Tetracycline	MER
Testosterone	BNF
Thalidomide	SCH, NEW, MER
Trimethadione	MER
Valproic acid	SCH, NAU, NEW, MER
Warfarin	SCH, CLP

Ethylene oxide, carbon disulphide and toluene (SCH), and carbon monoxide (CLP), were also identified but excluded as it was clear that human developmental toxicity data would relate to exposure by inhalation rather than oral. The relevant entries in Regulation (EC) No. 1272/2008 are also listed in the appendix.

Since the pharmaceutical groups “androgens” and “ACE inhibitors” were identified as developmental toxicants, it was necessary to identify lists of substances in these classes, and the following specific substance names were identified from the BNF:

ACE inhibitors

Captopril
Cilazapril
Enalapril maleate
Fosinopril sodium
Imidapril hydrochloride
Lisinopril
Moexipril hydrochloride
Perindopril erbumine
Perindopril arginine
Quinapril
Ramipril
Trandolapril

Androgens

Testosterone and esters
Mesterolone

Additional developmental toxicants identified

Subsequent to the initial list being produced, the following additional substances were identified from Schardein and Macina (2007):

Vitamin A
Methyltestosterone (an androgen but not previously identified)
Paramethadione
Primidone
Fluconazole
Ergotamine
Propylthiouracil
Medroxyprogesterone
Phenobarbital
Valsartan
Iodine

Some additional substances in the Schardein and Macina (2007) review were not included because it was clear from the review that the developmental toxicity resulted from non-oral routes of exposure, there was a lack of convincing evidence that they are human developmental toxicants, or a lack of comparative data in rats or rabbits.

References

Schardein JL, Keller KA (1989). Potential human developmental toxicants and the role of animal testing in their identification and characterization. *Crit Rev Toxicol* 19: 251-339

Schardein JM, Macina OT (2007). Human developmental toxicants: aspects of toxicology and chemistry. CRC Taylor and Francis.

Nau H (1986). Species differences in pharmacokinetics and drug teratogenesis. *Environ Health Perspect* 70: 113-129

Newman LM, Johnson EM, Staples RE (1993). Assessment of the effectiveness of animal developmental toxicity testing for human safety. *Reprod Toxicol* 7: 359-390

Appendix

Chemicals identified from Table 3.1 of Annex VI of the CLP regulation, classified as Repr. 1A AND containing the hazard statement codes H360D (“May damage the unborn child”), H360FD (“May damage fertility. May damage the unborn child”) or H360Df (“May damage the unborn child. Suspected of damaging fertility”).

carbon monoxide

slimes and sludges, copper electrolyte refining, decopperised

warfarin (ISO); [1]
(*S*)-4-hydroxy-3-(3-oxo-1-phenylbutyl)-2-benzopyrone; [2]
(*R*)-4-hydroxy-3-(3-oxo-1-phenylbutyl)-2-benzopyrone [3]

oxadiargyl (ISO);
3-[2,4-dichloro-5-(2-propynyloxy)phenyl]-5-(1,1-dimethylethyl)-1,3,4-oxadiazol-2(3*H*)-one;
5-*tert*-butyl-3-[2,4-dichloro-5-(prop-2-ynyloxy)phenyl]-1,3,4-oxadiazol-2(3*H*)-one

lead hexafluorosilicate

silicic acid, lead nickel salt

lead compounds with the exception of those specified elsewhere in this Annex

lead alkyls

lead diazide;
lead azide

lead diazide;
lead azide [≥ 20 % phlegmatiser]

lead chromate

lead di(acetate)

trilead bis(orthophosphate)

lead acetate, basic

lead(II) methanesulphonate

lead sulfochromate yellow;
C.I. Pigment Yellow 34;
[This substance is identified in the Colour Index by Colour Index Constitution Number, C.I. 77603.]

lead chromate molybdate sulfate red;
C.I. Pigment Red 104;
[This substance is identified in the Colour Index by Colour Index Constitution Number, C.I. 77605.]

lead hydrogen arsenate

1,2-diethoxyethane

lead 2,4,6-trinitro-*m*-phenylene dioxide;
lead 2,4,6-trinitroresorcinoxide;
lead styphnate

lead 2,4,6-trinitro-m-phenylene dioxide;
lead 2,4,6-trinitroresorcinoxide;
lead styphnate (≥ 20 % phlegmatiser)