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

Table comparing LOAELs for developmental toxicity in humans, rats, rabbits and non-human primates for human developmental toxicants

Secretariat
October 2013

Chemical	**Chemical / pharmaceutical group**	**LOAEL in humans (mg/kg bw)***	**Basis**	**Reference**	**LOAEL in rats (mg/kg bw)**	**Basis**	**Reference**	**LOAEL in rabbits (mg/kg bw)**	**Basis**	**Reference**	**LOAEL in non-human primates (mg/kg bw)**	**Basis**	**Reference**
5-Fluorouracil	Antineoplastic antimetabolite	EXCLUDE – NO ORAL HUMAN DATA *7 (i.v.)*	*Skeletal abnormalities (bilateral radial aplasia, absent thumbs and some fingers absent)*	*Stephens et al. (1980)*	*12 (i.p.)*	*Malformations*	*Murphy (1962)*	*83 i.m. or i.p.?*	*Intrauterine growth retardation*	*Schardein and Keller (1989)*	*20*	*Resorption and low birth weight in monkeys*	*Wilson (1971)*
6-Azauridine EXCLUDE – NON ORAL EXPOSURE	*Antineoplastic antimetabolite*	*125 (single i.v. dose)*	*Micromolar degeneration of trophoblast*	*Vojta and Jirasek (1966)*	*12 (i.p.)*	*Malformations (5.8% of fetuses)- encephalocele and gastroschisis)*	*Gutova et al. (1971)*	*500 (route of exposure unclear – likely to not be oral)*	*Facial deformity*	*Morris (1970)*	*NO DATA*	--	--
Aminopterin	Antifolate	0.03	Malformations. Apparently similar doses caused fetal death in many other cases.	Thiersch and Wash (1952)	0.0125	Growth retardation	Schardein and Keller (1989)	15 (i.v. single dose on GD12)	Malformations and embryolethali-ty	Goeringer and DeSesso (1990)	0.1-0.2	Abortions in macaque monkeys	Wilson and Gavan (1967), Wilson and Fradkin (1969), Wilson (1972)
Aspirin	NSAID	20-67[a]	Reduced birth weight, increased perinatal mortality	Corby (1978); Schardein and Keller (1989)	100	Supernumerary ribs	Wickramaratn e (1988)	200	Reduced litter size	Schardein et al. (1969)	≈300[b]	Spontaneous abortion	Wilson (1971)
Busulfan	Alkylating agent	0.008-0.07 (varied dose taken during term)	Low birth weight	Bishop and Wassom (1986)	18 (single i.p. dose on GD 12)	Growth retardation and various abnormalities	Murphy et al. (1958)	NO DATA	--	--	NO DATA	--	--
Caffeine	Constituent of foods and drinks	3.3	Decrease in birth weight	COT (2008)[c]	6	Minimal delay in ossification of sternum	Collins et al. (1981)	100	Malformations	Schardein and Keller (1989), citing Bertrand et al. (1970)	10-15	Spontaneous abortion and miscarriage in cynomolgus monkeys	Gilbert et al. (1988)
Captopril	ACE inhibitor	1.67[a]	Oligohydramn-ios and associated congenital abnormalities such as fetal limb contractures, skull calvarial hypoplasia, cranio-facial deformation and hypoplastic lung development	Martin (2008)	10	Reduced implantation, increased resorptions, fetal growth retardation, decreased skeletal ossification	Al-Shabanah et al. (1991)	~13 (3.3 mg/rabbit[d])	Increased stillbirth	Pipkin Broughton et al. (1980)	NO DATA	--	--
Carbamazepine	Anticonvulsant drug	20[e]	Increased	Jentink et al.	200	Reduced fetal	Vorhees et al.	NO DATA	--	--	NO DATA	--	--

			odds ratio for spina bifida	(2010)		weight	(1990)						
Chlorambucil	Alkylating agent	0.07	Agenesis of kidney and ureter	Ostensen (1992, 1994)	3 (i.p)	Decreased kidney weight, early embryo loss	Kavlock et al. (1996); Giavini et al. (1984)	NO DATA	--	--	NO DATA	--	--
Cilazapril	ACE inhibitor	EXCLUDE. NO HUMAN DATA	--	--	*NO DATA*	--	--	*NO DATA*	--	--	*NO DATA*	--	--
Cyclophosphamide	Alkylating agent	3.3[f]	Multiple congenital abnormalities	Zemlickis et al. (1993)	6.2	Decreased fetal weight	Ujhazy et al. (1993)	2 (i.v. data only)	Malformations	Schardein and Keller (1989), citing Gerlinger and Clavert (1964)	5 (i.m. data only)	Growth retardation and cleft lip in rhesus monkeys	McClure et al. (1979)
Cytarabine	Antineoplastic antimetabolite	EXCLUDED. Human cases identified all involved i.v. administration *2 (but also administered other chemotherapeutic agents)*	*Distal limb defects*	*Schafer (1981)*	*20 (i.p.)*	*Malformations and fetal death*	*Chaube et al. (1968)*	*NO DATA*	--	--	*NO DATA*	--	--
Danazol	Androgen	3.3	Virilisation of females fetus	Brunskill (1992)	>250	No effects in a developmental toxicity study according to drug label	US National Library of Medicine[g], Schardein and Macina (2007)	60	"Inhibition of fetal development"	US National Library of Medicine[g], Schardein and Macina (2007)	NO DATA	--	--
Diethylstilboestrol	Oestrogen	0.08 increasing in graduated fashion to 2.5	Miscarriage, preterm birth, low birth weight; and the following in offspring: adenosis of vagina and/or cervix, psychiatric disorders in females, primary infertility of females, testicular abnormality[h]	Bamigboye and Morris (2003)	≥0.045	BMD5 for frequency of total resorptions	Piersma et al. (2002)	>1.75 (s.c.)	No teratogenic effects	Morris (1970)	0.11-0.26	Irregular menstruation, vaginal ridging and/or cervical hooding, vaginal adenosis in female rhesus monkeys. Abnormalities of external genitalia including testicular hypoplasia, preputial adhesions or undescended tested in male rhesus monkeys	Hendrickx et al. (1979), Thompson et al. (1981)
Enalapril	ACE inhibitor	0.67[a]	Oligohydram-	Tabacova	3	Decreased fetal	Al-Harbi et al.	3	Increased fetal	Minsker et	NO DATA	--	--

			nios and associated congenital abnormalities such as fetal limb contractures, skull calvarial hypoplasia, cranio-facial deformation and hypoplastic lung development	(2005)		weight, hydroureter.	(1992)	(statistically significant difference only at 30)	death	al. (1990)			
Ergotamine	Mycotoxin	0.025	Mean daily dose taken in case-control surveillance associated with low birthweight and preterm birth	Banhidy et al. (2007); EFSA (2012)	10	Increased fetal loss, decreased fetal weight, delayed skeletal ossification	EFSA (2012); Grauwiler and Schon (1973)	1	Increased post-implantation loss and possible treatment-related post-implantation loss (limited dose-response)	Grauwiler and Schon (1973)	NO DATA	--	--
Ethanol	Recreational drug	<19-114[l]	Developmental neurotoxicity	Lewis et al. (2012)	1200	Developmental neurotoxicity	Qiang et al. (2002)	>2400	No effects	Schwetz et al. (1978)	260 given as a single weekly dose of 1.8 g/kg bw)	Reduce cognitive and motor performance and distractibility in offspring of pig-tailed macaques	Schneider et al. (2011)
Ethisterone (pregneninolone, 17α-ethynyltestosterone)	Progestogen; has androgenic action	0.5	Masculinisation of female fetus	Wilkins et al. (1958)	40 (based on 10 mg/rat)[j]	Kawashima et al. (1977)	---	<4 mg/kg, based on a dose of "<1 mg", assumed to be the dose per animal[d]	Virilisation of female fetus	Courrier and Jost (1942), as cited by Schardein and Macina (2007)	NO DATA	--	--
Etretin (acitretin)	Retinoid	1[f]	Limb defects and craniofacial malformations	De Die-Smulders et al. (1995)	15	Malformed humeri.	Kistler and Hummler (1985)	0.6	Slight increase in malformations	Kistler and Hummler (1985)	NO DATA	--	--
Etretinate	Retinoid	0.75	Malformations	Schardein and Macina (2007)	4	Exencephaly, craniofacial defects, cleft palate, skeletal defects	Aikawa et al. (1982), as cited by Shepard and Lemire (2004)	NO DATA	--	--	NO DATA	--	--
Fluconazole	Fungicide	6.7	Multiple malformations	Pursley et al. (1996); Lopez-Rangel and Van Allen (2005); Lee et al. (1992)	25	Developmental variations, according to drug label insert	Schardein and Macina (2007)	75	Abortion, according to drug label insert	Schardein and Macina (2007)	NO DATA	--	--
Fosinopril sodium	ACE inhibitor	EXCLUDE. NO	--	--	*NO DATA*	--	--	*NO DATA*	--	--	*NO DATA*	--	--

		HUMAN DATA											
Hexachlorobenzene	Former pesticide and environmental contaminant	*0.8- but effects appear likely to be due to lactational exposure*	*Cutaneous lesions, fever, diarrhoea, vomiting, weakness, convulsions, enlarged livers and progressive wasting in infants of mothers who consumed contaminated bread. Possibly related to lactational exposure.*	*WHO (1997)*	*2*	*Effects in neurobehavioural tests indicative of hyperactivity in offspring of female rats given 4 daily doses 2 weeks prior to breeding.*	*Goldey and Taylor (1992), WHO (1997)*	*NO DATA*	--	--	*NO DATA*	--	--
Imidapril hydrochloride	ACE inhibitor	EXCLUDE. NO HUMAN DATA	--	--	*NO DATA*	--	--	*NO DATA*	--	--	*NO DATA*	--	--
Iodine	Essential trace element	2.2	Neonatal hypothyroidism	WHO (2009)	250 (2500 mg/kg in diet and assumed diet consumption of 0.1 kg/kg bw)	Increased death of neonates (<10% surviving for 3 days), increase in parturition time	Arrington et al. (1965)	7.5 (250 mg/kg in diet and assumed diet consumption of 0.03 kg/kg bw)	Decreased survival of pups (70% died within 3 days, most within first few hours)	Arrington et al. (1965)	NO DATA	--	--
Isotretinoin	Retinoid	0.17	Case report of stillbirth with multiple malformations characteristic of isotretinoin teratogenicity	Ayme et al. (1988)	30	Post implantation loss and various malformations	Henck et al. (1987)	3	Malformations. Borderline increase in resorptions	Tzimas et al. (1994)	2	Embryolethality (fetal death or abortion) in cynomolgus monkeys	Hummler et al. (1990)
Lead	Environmental contaminant – EXCLUDED. NOT POSSIBLE TO DISTINUGISH EFFECTS OF PRENATAL EXPOSURE FROM POSTNATAL IN HUMAN STUDIES		*Associated with 1 IQ point deficit in children. Fetus assumed to be similarly susceptible.*		*120 (estimated from 0.1% in drinking water)*	*Female offspring: delayed vaginal opening, irregular periods of dioestrous accompanied by absence of corpora lutea. Male offspring: decreased sperm count, enlarged prostate, decreased volume of the sexually dimorphic nucleus of the preoptic area of the hypothalamus*	*IARC (2006)*				*NOT SOUGHT*		
Lisinopril	ACE inhibitor	EXCLUDE.	--	--	*NO DATA*	--	--	*NO DATA*	--	--	*NO DATA*	--	--

		NO HUMAN DATA											
Lithium	Mood stabiliser	Dose-response unknown. Therapeutic dose range 1-26	Congenital heart defects (possibly circa 1%), including some cases of Ebstein's anomaly.	Shepard et al. (2002); Schardein and Keller (1989)	100	Skeletal abnormalities, decreased implantations, decreased pup weight	Marathe and Thomas (1986)	>40	No effects.	Gralla and McIlhenny (1972)	>25	No effects	Gralla and McIlhenny (1972)
Mechlorethamine	Alkylating agent	EXCLUDE. Only IV Data *0.067 (i.v.)*	*Case of renal malformation*	*Mennuti et al. (1975)*	*0.5 (s.c.)*	*Fetal death or resorption, syndactyly or absent digits, cleft palate*	*Haskin (1948)*	*0.1 (i.v.)*	*Malformations*	*Gottschewski (1964)*	*NO DATA*	--	--
Medroxyprogesterone	Progestogen	0.04	Virilisation of female fetus and hypospadias in males	Schardein and Macina (2007)	4 (based on 1 mg/rat)[j]	Virilisation of female fetus	Kawashima et al. (1977)	1 (s.c.)	Cleft palate	Andrew and Staples (2002)	300 (i.m.)	Cynologus monkeys: Masculised external genitalia in female fetus and hypospadias, micropenis and hypoplastic testes in males; hypoplastic adrenal, thymus and thyroid glands	Prahalada and Hendrickx (1982)
Mesterolone	Androgen	EXCLUDE. NO HUMAN DATA	--	--	*NO DATA*	--	--	*NO DATA*	--	--	*NO DATA*	--	----
Methimazole	Antithyroid drug	Normal maintenance dose range is 0.08-0.25	A congential cutaneous malformation (aplasia cutis congenita)	Mancini (2004)	1.5	Subtle developmental neurotoxicity secondary to hypothyroidism	Albee et al. (1989)	NO DATA	--	--	NO DATA	--	--
Methotrexate	Antifolate	0.04	Hypertelorism, oxycephaly due to fusion of the coronal sutures and digital defects	Shepard 1979	0.2	Fetal death and malformation	Schardein and Keller (1989), citing Wilson and Fradkin (1967)	0.3 (single i.v. dose on GD10)	Increased incidence of malformations	Jordan et al. (1977)	3	Abortion or resorption in rhesus monkeys	Wilson (1973)
Methylmercury	Environmental contaminant	≥0.0018 (BMD5)	Developmental neurotoxicity. Boston naming test. Chronic intake corresponding to maternal hair level at BMD5.	Budtz-Jorgensen et al. (1999). Cited by National Academy of Sciences/National Research Council (2000).	0.268	Developmental neurotoxicity study – deficit in motor coordination in rotorod test and learning deficit in the passive avoidance response test, and focal	Sakamoto et al. (2002), maternal dose calculated by Hassauer et al. (2012)	NO DATA	--	--	0.05	Impaired visual recognition memory	Gunderson et al. (1988)

						cerebellar dysplasia							
Methyltestosterone	Androgen	0.17	Virilisation of female fetus	Grumbach and Ducharme (1960)	~2 (based on 0.5 mg/rat[j]	Virilisation of female fetus	Kawashima et al. (1977)	NO DATA	--	--	NO DATA	--	--
Misoprostol	Synthetic prostaglandin E analogue	0.0067	Multiple malformations, including limb reduction defects, brain abnormalities, gastroschisis and Mobius syndrome	Schardein and Macina (2007)	1.6	No effects in rats dosed at 1.6 mg/kg bw/day on GDs 7-17 or 10 mg/kg bw/day on GDs 6-15. Number of resorptions was decreased at 1.6 mg/kg bw/day in a fertility study	Therapeutic Goods Administration (2012)	1	Increased number of resorptions	Therapeutic Goods Administra-tion (2012)	NO DATA	--	--
Moexipril hydrochloride	ACE inhibitor	EXCLUDE. NO HUMAN DATA	--	--	*NO DATA*	--	--	*NO DATA*	--	--	*NO DATA*	--	--
Nicotine	Recreational drug	EXCLUDED. NON-ORAL EXPOSURE	--	--	*NOT SOUGHT*	--	--	*NOT SOUGHT*	--	--	*NOT SOUGHT*	--	--
Norethisterone (norethindrone)	Progestogen	0.17	Virilised female offspring	Schardein and Macina (2007)	~20 (based on 5 mg per rat)[j]	Virilisation of female offspring	Kawashima et al. (1977)	~1 (0.25 mg/rabbit[d])	Fetal resorption	Allen and Wu (1959)	3.6 (based on 125 g/monkey/ week)	Masculinisation of female offspring of rhesus monkeys	Wilson and Fradkin (1969)
Norprogesterone	Progestogen	NO DATA	--	--	NO DATA	--	--	NO DATA	--	--	NO DATA but >0.7 (progesterone) based on 250 mg/monkey/ wk	No effects	Wilson and Gavan (1967)
Oxadiargyl	Herbicide	EXCLUDED. No human data	--	--	*320*	*Fetal growth retardation*	*EC (2002)*	*NOT SOUGHT*	--	--	*NO DATA*	--	--
Paramethadione	Anticonvulsant	25[k]	Multiple abnormailities - 'fetal trimethadione syndrome'	German et al. (1970)	264	Effect on fetal survival, litter size and weight.	Buttar et al. (1976)	NO DATA	--	--	170 (based on 600 mg and bw of about 3.5 kg)	Spontaneous resorption of embryo	Poswillo (1972)
PCBs	Environmental contaminant	EXCLUDE -*Dietary intake levels could not be determined from human studies*	*Associated with developmental neurotoxicity, decreased birth weight and growth in the first 6 years of age and possible developmental immunotoxicity in various epidemiologica*	*WHO (2003)*	*3*	*Developmental neurotoxicity: alterations in three activity-dependent behavioural tests*	*Lilienthal and Winneke (1991), WHO (2003)*	*NO DATA*	--	--	*0.005*	*Increased fetal and neonatal mortality*	*Arnold et al. (1995), WHO (2003)*

			l studies										
Penicillamine	Chelating agent and immunosuppressant	17	Congenital diffuse cutis laxa, severe micrognathia, contractures of all limbs and CNS abnormalities including agenesis of the corpus callosum.	Pinter et al. (2004)	540	Malformations	Keen et al. (1983)	NO DATA	--	--	NO DATA	--	--
Perindopril arginine	ACE inhibitor	EXCLUDE. NO HUMAN DATA	--	--	*NO DATA*	--	--	*NO DATA*	--	--	*NO DATA*	--	--
Perindopril erbumine	ACE inhibitor	EXCLUDE. NO HUMAN DATA	--	--	*NO DATA*	--	--	*NO DATA*	--	--	*NO DATA*	--	--
Phenobarbital	Anticonvulsant	1.5[l]	Malformation and mental retardation	Thakker et al. (1991)	80	Decreased litter size, increased offspring mortality, vertebral and sternal malformations	McColl et al. (1966)	50	Defects of sternum and skull, increased fetal resorption	McColl et al. (1966)	NO DATA	--	--
Phenytoin	Anticonvulsant	1.67	A malformation syndrome known as fetal hydantoin syndrome	Adams et al. (1990), Hanson and Smith (1975)	100	Developmental neurotoxicity	Mowery et al., 2008, Elmazar et al. (1981)	75	Malformations	McClain and Langhoff (1980)	10	Renal ectopia and retrocaval ureter in rhesus monkeys	Wilson (1973)
Primidone	Barbiturate-type anticonvulsant	2.1	Cases of embryopathy at therapeutic dose levels of drug, 125-1500 mg/day	Schardein and Macina (2007)	120	Embryolethality, developmental neurotoxicity	Pizzi et al. (1998)	NO DATA	--	--	NO DATA	--	--
Propranolol	Beta blocker	0.5	Fetal growth retardation	Pruyn et al. (1979)	50	Decreased neonatal pup weight	Schoenfeld et al. (1978)	NO DATA	--	--	NO DATA	--	--
Propylthiouracil	Antithyroid drug	2.5	Neonatal hypothyroidism	Schardein and Macina (2007)	Unknown (original papers in French and unobtainable)	Thyroid lesions, including enlargement	Schardein and Macina (2007)	22	Decreased fetal weight, increased relative thyroid weight	Krementz et al. (1957)	NO DATA	--	--
Quinapril	ACE inhibitor	EXCLUDE. NO HUMAN DATA	--	--	*>100*	*No developmental effects*	*Dostal et al. (1991)*	*NO DATA*	--	--	*NO DATA*	--	--
Ramipril	ACE inhibitor	EXCLUDE. NO HUMAN DATA	--	--	*NO DATA*	--	--	*NO DATA*	--	--	*NO DATA*	--	--
Streptomycin	Antibiotic	EXCLUDE	--	--	*ONLY*	--	--	*NO DATA*	--	--	*NO DATA*	--	--

		D. Human cases reports were non-oral exposure			*REFERENCE NOT IN ENGLISH AND RELATES TO I.P ADMINISTRATION*								
Testosterone	Androgen	*Not known. Other drugs such as methyltest-osterone also administer-ed in the reported cases* EXCLUDE	*Cliteromegaly and fusion of the labioscrotal folds*	*Grumbach and Ducharme (1960)*	*20 (based on 5 mg/rat)*	*Virilisation of female fetus*	*Kawashima et al. (1977)*	*NO DATA*	--	--	*5 (based on 25 g/monkey/ week)*	*Masculinisation of female offspring of rhesus monkeys*	*Wilson and Fradkin (1969)*
Tetracycline	Antibiotic	17	Discolouration of teeth	Cohlan (1977)	540	Reduced skeletal ossification	WHO (1996)	>10 i.v.	No effect.	Tubaro (1964)	NO DATA	--	--
Thalidomide	Sedative drug	0.42	Specific teratogenic effects	Lenz and Knapp (1962), Newman et al. (1993)	50	Increased percentage of litter with skeletal variations	Schumacher et al. (2000)	25	Malformations in Dutch belted rabbit (≈30% of live offspring) and New Zealand rabbit (3.8% of fetuses but 40% of litters affected)	Staples and Holtkamp (1963), Schumach-er et al. (2000)	0.625	Malformations of offspring of rhesus monkeys	Wilson (1971)
Trandolapril	ACE inhibitor	EXCLUDE. NO HUMAN DATA	--	--	*NO DATA*	--	--	*NO DATA*	--	--	*NO DATA*	--	--
Trimethadione	Anticonvulsant	15-40[m]	Fetal trimethadione syndrome: epicanthal folds, V-shaped eye brows, los-set ears, irregular teeth, microcephaly, mental retardation and orofacial clefting. Affects up to 70% of pregnancies.	Malone and Dalton (1997)	200	Cardiac abnormalities	Veuthey et al. (1990)	NO DATA			60	Colonic atresia, short tail, 2/6 spontaneous abortions in rhesus monkeys	Wilson (1973)
Valproic acid	Anticonvulsant	≈13-17	Increased risk of various malformations including neural tube defects and hypospadias.	Tomson and Battino (2009)	100	Dose-related increase in lumbar ribs	Narotsky et al. (1994)	150	Increased incidence of supernumer-ary ribs	Petrere et al. (1986)	20	Mild craniofacial defects in 1/3 rhesus monkey offspring	Mast et al. (1986)

			Decreased IQ.										
Valsartan	Angiotensin II receptor antagonist	1.1	Oligohydram-nios and pulmonary hypoplasia	Briggs and Nageotte (2001)	600	Decreased fetal weight, decreased pup weight, decreased pup survival, slight delays in developmental milestones	US National Library of Medicine[n]	5	Resorptions, litter loss, abortion, decreased fetal weight	US National Library of Medicine[n]	NO DATA	--	--
Vitamin A (3.33 IU = 1 ug RE)	Vitamin	>0.05 (retinol equivalents, RE)	Cranial-neural crest defects	Rothman et al. (1995)	7.5 (RE)	Delayed incisor eruption	Kutz et al. (1989)	2.5 RE	Reported lowest teratogenic dose	EVM (2003)	6 (RE)	Abortions and malformations in cynomolgus monkey (Macaca fascicularis)	Hendrickx et al. (1997, 2000)
Warfarin	Anticoagulant	0.04-0.08 (varied dose)	Fetal warfarin syndrome	Hall et al. (1980)	0.16	Embyonic loss, structural malformations	ECHA (2012)[o]	≈1 (i.m.). (1-3 mg/kg bw given every second or third day)	Stillborn fetuses with widespread subcutaneous haemorrhage.	Hirsh et al. (1970)	NO DATA	--	--

*Where the LOAEL in humans is on a per person basis this has been converted to a per kg bodyweight basis assuming a body weight of 60 kg unless another value appeared more appropriate.
[a]Dose not known. Normal daily therapeutic dose range entered.
[b]The dose level is inconsistently reported. Wilson (1972) indicated that the LOAEL was 200 mg/kg bw/day, but Wilson (1971), reporting details of the same study, indicates that six doses of 200 mg/kg bw were administered over four days, i.e. approximately equivalent to an average of 300 mg/kg bw/day over the four days. A value of 300 mg/kg bw/day has been entered as the LOAEL.
[c]The 2008 COT statement on the reproductive effects of caffeine has been used to identify the LOAEL.
[d]Dose per rabbit. Body weight or strain of rabbit not available. A body weight of 4 kg has been assumed.
[e]Dose not known. The highest normal maintenance dose in treating epilepsy of 1200 mg has been assumed.
[f]Dose taken in a case report.
[g]Source is US National Library of Medicine "DailyMed". FDA Label Insert for danazol capsule (AvKARE, inc.). Accessed at http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=d30a0bb0-d8e4-e17a-0f8b-6696a2712e98 4 June 2013
[h]Data source is a randomised double-blind placebo controlled trial cited and evaluated by Bamigboye and Morris (2003). Effects listed are those with statistically significantly increased risk ratios only (e.g. there was also a raised risk ratio for cancers of the genital tract in female offspring, which was not statistically significant in this study).
[i]Based on a prospective study which identified an association between four variants in alcohol dehydrogenase genes and IQ at 8 years of age in the children of mothers who consumed small-moderate amounts of alcohol during pregnancy (<1-6 UK units/week) but not in the children of mothers who abstained from alcohol during pregnancy. This may, therefore, reflect effects in sensitive individuals.
[j]Doses were stated per rat. Rats were Wistar rats of more than 13 weeks of age. A body weight of 250 g has been assumed.
[k]Doses taken mostly not reported, and other drugs also taken in many cases, though normal infants were born in some later pregnancies in which diones were removed.
[l]Phenobarbital exposure during pregnancy has been associated with a syndrome of minor malformations, retarded growth and functional impairment. However, the critical doses are unclear. The usual oral dose range is 0.5-10 mg/kg bw/day. The lowest dose identified in a case report involving phenobarbital monotherapy has been entered.
[m]Literature indicates that all dose levels are teratogenic; therefore the lower end of the normal therapeutic range has been entered.
[n]Source is US National Library of Medicine "DailyMed". FDA Label Insert for valsartan capsule (Novartis Pharmaceuticals Corporation). Accessed at http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=0dd5fd1c-ab03-4860-87d6-4a95df6e7b7a 24 June 2013
[o]Secondary citation and evaluation of "Mirkova E, Antov G (1983). Experimental evaluation of the risk of prenatal pathology under effect of warfarin – coumarin rodenticide. Hig. Zdrav. 25, 476-482" in ECHA (2012). Doses tested ranged 0.04-0.32 mg/kg bw/day by gavage. It was not possible to evaluate embryotoxic/teratogenic effects below doses of 0.16 mg/kg bw/day as the data were not reported.

Notes

The effects listed are those occurring at the lowest LOAELs that have been listed. Additional effects often occurred at higher doses.

In some cases the references given are reviews or other papers which cited the results from papers published in languages other than English.

Data in italics are for substances which have been excluded from consideration.

References

Aikawa M, Sato M, Noda A, Udaka K (1982). Toxicity study of etretinate. III. Reproductive segment 2 study in rats. *Yokuri Chiryo* 9: 5095-5108, 5117-5143

Allen WM, Wu DH (1959). Effects of 17alpha-ethyinyl-19-nortestosterone on pregnancy in rabbits. *Fertil Steril* 10: 424-438

al-Shabanah OA, al-Harbi MM, alGharabli NM, Islam MW (1991). The effect of maternal administration of captopril on fetal development in the rat. *Res Commun Chem Pathol Pharmacol* 73: 221-230

Andrew FD, Staples RE (1977). Prenatal toxicity of medroxyprogesterone acetate in rabbits, rats and mice. *Teratology* 15: 25-32

Arrington LR, Taylor RN, Ammerman CB, Shirley RL (1965). Effects of excess dietary iodine upon rabbits, hamsters, rats and swine. *J Nutr* 87: 394-398

Banhidy F, Acs N, Puho E, Czeizel AE (2007). Ergotamine treatment during pregnancy and a higher rate of low birthweight and preterm birth. *Br J Clin Pharmacol* 64: 510-516

Bamigboye AA, Morris J (2003). Oestrogen supplementation, mainly diethylstilbestrol, for preventing miscarriages and other adverse pregnancy outcomes. Cochrane Database of Systematic Reviews 2003, Issue 3. Art. No.: CD004353. DOI: 10.1002/14651858.CD004353

Bertrand M, Girod J, Rigaud MF (1970). Ectrodactylie provoquee par la caffeine chez les rongeurs. Role de facteurs specifiques et genetiques. *C R Soc Biol* 164: 1488-1489

Briggs GG, Nageotte MP (2001). Fatal fetal outcome with the combined use of valsartan and atenolol. *Ann Pharmacother* 35: 859-861

Broughton Pipkin F, Turner SR, Symonds EM (1980). Possible risk with captopril in pregnancy. *Lancet* 1: 1256

Brunskill PJ (1992). The effects of fetal exposure to danazol. *Br J Obstet Gynaecol* 99: 212-215

Budtz-Jorgensen E, Keiding N, Grandjean P (1999). Benchmark modeling of the Faroese methylmercury data. Research Report 99/5. Prepared at the University of Copenhagen, Denmark for the US Environmental Protection Agency.

Buttar HS, Dupuis I, Khera KS (1976). Fetotoxicity of trimethadione and paramethadione in rats. *Toxicol Appl Pharmacol* 37: 126

Chaube S, Kreis W, Uchida K, Murphy ML (1968). The teratogenic effect of 1-β-D-arabinofuranosylcytosine in the rat. Protection by deoxycytidine. *Biochem Pharmacol* 17: 1213-1216

Courrier R, Jost A (1942). Fetal intersexuality provoked by pregneninolone administered during pregnancy. *C R Soc Biol (Paris)* 136: 395-396

Dostal LA, Kim SN, Schardein JL, Anderson JA (1991). Fertility and perinatal/postnatal studies in rats with the angiotensin-converting enzyme inhibitor, quinapril. *Toxicol Sci* 17: 684-695

EC (2002). Review report for the active substance oxadiargyl. Finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on 3 December 2002 in view of inclusion of oxadiargyl in Annex I of Directive 91/414/EEC. European Commission, SANCO/3053/99-final, 28 November 2002

ECHA (2012). Proposal for Harmonized Classification and Labelling Based on the CLP Regulation (EC) No 1272/2008, Annex VI, Part 2. Substance Name: Warfarin. Submitted by Ireland. Version 2, November 2012. European Chemicals Agency. Accessed online 30 May 2013 at http://echa.europa.eu/documents/10162/13626/clh_proposal_warfarin_cz016705-16_en.pdf

EFSA (2012). Scientific Opinion on ergot alkaloids in food and feed. EFSA Panel on Contaminants in the Food Chain (CONTAM). European Food Safety Authority. EFSA Journal 10:2798 (158 pp). Available at: http://www.efsa.europa.eu/en/efsajournal/doc/2798.pdf

Elmazar MMA, Sullivan FM (1981). Effect of prenatal phenytoin administration on the postnatal development of the rat: a behavioural teratology study. *Teratology* 24: 115-124

EVM (2003). Safe upper levels for vitamins and minerals. Expert Group on Vitamins and Minerals. May 2003. Available at: http://cot.food.gov.uk/pdfs/vitmin2003.pdf

Gerlinger P, Clavert J (1964). Action du cyclophosphamide injecte a des lapines gestantes sur les gonads embryonnaires. *C R Acad Sci Ser D* 258: 2899-2901

German J, Kowal A, Ehlers KH (1970). Trimethadione and human teratogenesis. *Teratology* 3: 349-361

Gilbert SG, Rice DC, Reuhl KR, Stavric (1988). Adverse pregnancy outcome in the monkey (Macaca fascicularis) after chronic caffeine exposure. *J Pharmacol Exp Ther* 245: 1048-1053

Goeringer GC, DeSesso JM (1990). Developmental toxicity in rabbits of the antifolate aminopterin and its amelioration by leucovorin. *Teratology* 41: 560-561

Goldey E, Taylor DH (1992). Developmental neurotoxicity following prenatal maternal exposure to hexachlorobenzene in rats. *Neurotoxicol Teratol* 14: 15-21

Gottschewski GHM (1964). Mammalian blastopathies due to drugs. *Nature* 201: 1232-1233

Grauwiler J, Schon H (1973). Teratological experiments with ergotamine in mice, rats, and rabbits. *Teratology* 7: 227-236

Grumbach MM, Ducharme JR (1960). The effects of androgens on fetal development. *Fertil Steril* 11: 157-180

Gunderson VM, Grant-Webster KS (1988). Visual recognition memory deficits in methylmercury-exposed Macaca fascicularis infants. *Neurotoxicol Teratol* 10: 373-379

Haskin D (1948). Some effects of nitrogen mustard on the development of external body form in the fetal rat. *Anat Rec* 102: 493-511

Hassauer M, Kaiser E, Schneider K, Schuhmacher-Wolz (2012). Collate the literature on toxicity data on mercury in experimental animals and humans, part 1 – data on organic mercury. Supporting Publications 2012, EN-297, European Food Safety Authority. Available at: http://www.efsa.europa.eu/en/supporting/doc/297e.pdf

Hendrickx AG, Hummler H, Oneda S (1997). Vitamin A teratogenicity and risk assessment in the cynomolgus monkey. *Teratology* 55:68

Hendrickx AG, Peterson P, Hartmann D, Hummler H (2000). Vitamin A teratogenicity and risk assessment in the macaque retinoid model. *Reprod Toxicol* 14: 311-323

Kawashima K, Nakaura S, Nagao S, Tanaka S, Kuwamura T, Omiri Y (1977). Virilizing activities of various steroids in female rat fetuses. *Endocrinol Jpn* 24: 77-81

Kistler A, Hummler H (1985). Teratogenesis and reproductive safety evaluation of the retinoid etretin (Ro 10-1670). *Arch Toxicol* 58: 50-56

Krementz ET, Hooper RG, Kempson RL (1957). The effect on the rabbit fetus of the maternal administration of propylthiouracil. *Surgery* 41: 619-631

Kutz SA et al (1989). Vitamin A acetate: a behavioral teratology study in rats. *Drug Chem Toxicol* 12: 259-275

Lee BE, Feinberg M, Abraham JJ, Murthy AR (1992). Congenital malformations in an infant born to a woman treated with fluconazole. *Pediatr Infect Dis* 11: 1062-1064

Lewis SJ, Zuccola L, Smith GD, Macleod J, Rodriguez S, Draper ES, Barrow M, Alati R, Sayal K, Ring S, Golding J, Gray R (2012). Fetal alcohol exposure and IQ at age 8: evidence from a population-based birth-cohort study. PLOS One 7: e49407

Lopez-Rangel E, Van Allen MI (2005). Prenatal exposure to fluconazole: an identifiable dysmorphic phenotype. *Birth Defects Res A Clin Mol Teratol* 73: 919-923

McColl JD (1966). Teratogenicity studies. *Appl Ther* 8: 48-52

McClure HM, Wilk AL, Horigan EA, Pratt RM (1979). Induction of craniofacial malformations in rhesus monkeys (Macaca mulatta) with cyclophosphamide. *Cleft Palate J* 16: 248-256

National Academy of Sciences/National Research Council (2000). Toxicological effects of methylmercury. National Academy Press, Washington, DC

Pizzi WJ, Newman AS, Shansky A (1998). Primidon-induced embryolethality and DRL deficits in surviving offspring. *Neurotoxicol Teratol* 20: 3-7

Poswillo DE (1972). Tridione and paradione as suspected teratogens. An investigation in subhuman primates. *Ann Roy Coll Surg Engl* 50: 367-370

Prahalada S, Hendrickx AG (1982). Teratogenicity of medroxyprogesterone acetate (MPA) in cynomolgus monkeys. *Teratology* 25: 67A-68A

Pursley TJ, Blomquist IK, Abraham J, Anderson HF, Bartley JA (1996). Fluconazole-induced congenital anomalies in three infants. *Clin Infect Dis* 22: 336-340

Rothman KJ, Moore LL, Singer MR, Nguyen U-SDT, Mannino S, Milunsky A (1995). Teratogenicity of high vitamin A intake. *N Engl J Med* 333: 1369-1373

Sakamoto M, Kakita A, Wakabayashi K, Takahashi H, Nakano A and Akagi H (2002). Evaluation of changes in methylmercury accumulation in the developing rat brain and its effects: a study with consecutive and moderate dose exposure throughout gestation and lactation periods. *Brain Res* 949: 51-59

Sarkar K, Kinson GA, Rowsell HC (1986). Embryo resorption following administration of steroidal compounds to rats in mid pregnancy. *Can J Vet Res* 50: 433-437

Schafer AI (1981). Teratogenic effects of antileukemic chemotherapy. *Arch Intern Med* 141: 514-515

Schardein JL, Blatz AT, Woosley ET, Kaump DH (1969). Reproduction studies on sodium meclofenamate in comparison to aspirin and phenylbutazone. *Toxicol Appl Pharm* 15: 46-55

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

Shepard TH (1974). Teratogenicity from drugs – an increasing problem. *Dis Mon* June: 1-32

Shepard TH, Lemire RJ (2004). Catalog of teratogenic agents. 11th ed. The John Hopkins University Press, Baltimore, Maryland

Stephens JD, Golbus MS, Miller TR, Wilber RR, Epstein CJ (1980). Multiple congenital anomalies in a fetus exposed to 5-fluorouracil during the first trimester. *Am J Obstet Gynecol* 137: 747-749

Therapeutic Goods Administration (2012). Australian Public Assessment Report for misoprostol. Proprietary product name: GyMiso. Department of Health and Ageing, Australian Government. October 2012. Accessed at http://www.tga.gov.au/pdf/auspar/auspar-misoprostol-121002.pdf

Vorhees CV, Acuff KD, Weisenburger WP, Minck DR (1990). Teratogenicity of carbamazepine in rats. *Teratology* 41: 311-317

Wilson JG (1971). Use of rhesus monkeys in teratologic studies. *Fed Proc* 30: 104-109

Wilson JG (1972). Abnormalities of intrauterine development in non-human primates. *Acta Endocrinol* 71: 261-292

Wilson GH, Fradkin R (1967). Interrelations of mortality and malformations in rats. *Abstr 7th Annu Meet Teratol Soc*, p57-58

WHO (1996). Tetracycline. In: *Toxicological evaluation of certain veterinary drug residues in food*. WHO Food Additives Series, No. 36. World Health Organization, Geneva

WHO (2003). Polychlorinated biphenyls: human health aspects. Concise International Chemical Assessment Document, No. 55. World Health Organization, Geneva

WHO (2009). Iodine and inorganic iodides: human health aspects. Concise International Chemical Assessmentr Document, No. 72. World Health Organization, Geneva