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

Introduction

1. The COT first considered this topic at the December 2013 meeting. The approach taken in TOX/2013/42 was to generate a list of human developmental toxicants and to identify LOAELs for these substances in humans, rats and rabbits, and also for comparison, non-human primates. Human LOAELs were taken to be the lowest doses associated with cases of developmental toxicity in case reports, or were identified from epidemiological studies, or for some pharmaceuticals were based on the normal therapeutic dose range where there was evidence of an association between taking the pharmaceutical and adverse developmental outcomes but no dose-response data.

2. At the December 2013 meeting, the Committee concluded that there were strong indications that the 10-fold uncertainty factor for interspecies variation in developmental toxicity, applied to the most sensitive of either rats or rabbits, was not always adequate. The Committee made several requests. These were:

- Separating the data for substances for which the human LOAELs were estimated from case reports and from epidemiological studies
- Indicating whether developmental effects observed were related to the intended pharmacology of pharmaceuticals
- Taking into account the possible developmental effects of the medical conditions being treated with pharmaceuticals themselves
- Contacting the UK Teratology Information Service (UKTIS) to see if they would be able to share any unpublished information on cases of developmental toxicity.
- Exploring the availability of data for non-developmental outcomes.

3. This paper presents the additional information the Committee requested.

Comparison of NOAELs, including updated data and relationship of developmental effect to intended pharmacology

4. Table 1 is a modified version of Table 2 from paper TOX/2013/42, with additional columns to indicate whether the human LOAEL was estimated from case reports or from epidemiological studies and whether the developmental effects are related to the intended pharmacological action for pharmaceuticals. Revised human LOAELs for etretin and misoprostol are indicated in bold. Where the human LOAEL is indicated to be based on case reports, this does not necessarily mean that epidemiological studies were not available, but often for the pharmaceuticals, epidemiological studies compared taking the pharmaceutical to not taking it and did not assess dose response, so data from case reports were then used to identify the LOAEL. In some cases, where the LOAEL is indicated to have been based on an epidemiological study, there is a footnote to indicate that the epidemiological study did not assess the dose-response relationship and so the LOAEL was taken to be the normal therapeutic dose level or range.

5. The human LOAEL for etretin (also known as acitretin) has been reduced based on information from the UK Teratology Information Service (UKTIS) of a case of multiple malformations following the taking of 25 mg/day etretin for the first four weeks of gestation and 50 µg/day thyroxine at an unknown stage of pregnancy (Toxbase, 2014). The outcome was ventricular septal defect, transposition of the great arteries, micrognathia and bilateral dysplastic external ears. The malformations are consistent with retinoic embryopathy. Assuming a body weight of 60 kg, the LOAEL has been taken to be 0.42 mg/kg bw/day.

6. The LOAEL for misoprostol has been reduced as subsequent to the last meeting a report of six cases of misoprostol teratogenicity in the Philippines was identified (Chiong et al., 2009). Two of the cases followed the taking of single 0.2 mg oral doses of misoprostol. The paper states that there was no use of misoprostol intravaginally in these cases and no other abortifacients were taken. Multiple malformations were described, including Mobius syndrome, consistent with other cases of embryopathy resulting from misoprostol exposure. Therefore the LOAEL from human case reports is now taken to be 0.0033 mg/kg bw (assuming 60 kg bodyweight).

Table 1: Summary table of the comparison on LOAELs for developmental toxicity in humans, rats, rabbits and non-human primates

Chemical	**Chemical / pharmaceutical group**	**LOAEL in humans (mg/kg bw/day)**	**LOAEL in rats (mg/kg bw/day)**	**LOAEL in rabbits (mg/kg bw/day)**	**LOAEL in non-human primates (mg/kg bw/day)**	**Human data type from which the LOAEL was derived**	**Developmental toxicity related to intended pharmacology?**
Aminopterin	Antifolate	0.03	0.0125	*15 (i.v.)*	0.1-0.2[a]	Case reports	No, but malformations may be related to effects on cell division
Aspirin	NSAID	20-67	100	200	300	Epidemiology[b] – prospective study	Yes
Busulfan	Alkylating antineoplastic	0.008-0.07	*18 (i.p.)*	N/A	N/A	Case reports	Yes
Caffeine	Natural food constituent	3.3	6	100	10-15	Epidemiology – prospective study	No
Captopril	ACE inhibiter	1.67	10	13	N/A	Epidemiology – for ACE inhibiters in general, which included captopril[b] – cross sectional.	Yes –believed to result from hypoperfusion of the fetal kidneys during development
Carbamazepine	Anticonvulsant	20	200	N/A	N/A	Epidemiology[b] – case-control	No
Chlorambucil	Alkylating antineoplastic	0.07	*3 (i.p.)*	N/A	N/A	Case reports	No, but malformations may be related to effects on cell division
Cyclophosphamide	Alkylating antineoplastic	3.3	6.2	*2 (i.v.)*	*5 (i.m.)*	Case reports	No, but malformations may be related to effects on cell division
Danazol	Androgen	3.3	>250	60	N/A	Case reports	Yes

Diethylstilboestrol	Oestrogen	0.08-2.5	≥0.045	*1.75 (s.c.)*	0.11-0.26	Epidemiology – prospective, clinical trial	Yes
Enalapril	ACE inhibiter	0.67	3	3	N/A	Case reports – doses unclear, normal therapeutic dose assumed	Yes –believed to result from hypoperfusion of the fetal kidneys during development
Ergotamine	Mycotoxin and used medicinally for the treatment of migraine	0.025	10	1	N/A	Epidemiology – case-control	No, but -decreased birth weight may be related to placental vasoconstriction
Ethanol	Recreational drug	<19-114	1200	>2400	260	Epidemiology – prospective study	No
Ethisterone	Progestogen	0.5	40	<4	N/A	Case reports	No (the developmental effect was an androgenic effect)
Etretin	Retinoid	~~1~~ **0.42**	25	0.6	N/A	Case reports	No
Etretinate	Retinoid	0.75	4	N/A	N/A	Case reports	No
Fluconazole	Fungicide drug	6.7	25	75	N/A	Case reports	No
Iodine	Essential trace element	2.2	250	7.5	N/A	Case reports	Yes – neonatal hypothyroidism related to general toxicity of excess iodine to the thyroid
Isotretinoin	Retinoid	0.17	30	3	2	Case reports	No
Lithium	Mood stabiliser	1-26	100	>40	>25	Epidemiology[b] – overall review of epidemiology, strongest evidence from	No

						case-control studies	
Medroxyprogesterone	Progestin	0.04	4	*1 (s.c.)*	*300 (i.m.)*	Case reports	No (the developmental effect was an androgenic effect)
Methimazole	Antithyroid	0.08-0.25	1.5	N/A	N/A	Case reports	No
Methotrexate	Antifolate	0.04	0.2	*0.3 (i.v.)*	3	Case reports	No, but malformations and intrauterine growth restriction likely due to effects on cell division
Methylmercury	Environmental contaminant	≥0.0018	0.268	N/A	0.05	Epidemiology – prospective studies	No, not a drug. Related to neurotoxicity of methylmercury but developing nervous system more susceptible
Methyltestosterone	Androgen	0.17	2	N/A	N/A	Case reports	Yes
Misoprostol	Prostaglandin E1 analogue	~~0.0067~~ **0.0033**	1	1.6	N/A	Case reports	No (except for the deliberate use to stimulate uterine contraction to induce abortion)
Norethisterone	Progestogen	0.17	20	1	3.6	Case reports	No (the developmental effect was an androgenic effect)
Paramethadione	Anticonvulsant	25	264	N/A	170	Case reports	No
Penicillamine	Chelating agent and immunosuppressant	17	540	N/A	N/A	Case reports	No
Phenobarbital	Anticonvulsant	1.5	80	50	N/A	Case reports	No
Phenytoin	Anticonvulsant	1.67	100	75	10	Case reports	No
Propranolol	Beta-blocker	0.5	50	N/A	N/A	Case reports	No

Propylthiouracil	Antithyroid drug	2.5	N/A	22	N/A	Case reports	Yes – neonatal hypothyroidism
Primidone	Barbiturate-type anticonvulsant	2.1	120	N/A	N/A	Case reports	No
Tetracycline	Antibiotic	17	540	*>10 (i.v.)*	N/A	Case reports	No
Thalidomide	Sedative drug	0.42	50	25	0.625	Case reports	No
Trimethadione	Anticonvulsant	15-40	200	N/A	60	Case reports (based on reports of a high incidence of cases of a specific malformation syndrome), and therapeutic dose range	No
Valproic acid	Anticonvulsant	13-17	100	150	20	Epidemiology – overall review of epidemiology including prospective studies	No
Valsartan	Angiotensin II receptor antagonist	1.1	600	5	N/A	Case reports	At least in part – oligohydramnios and pulmonary hypoplasia
Vitamin A	Essential nutrient	>0.05	7.5	2.5	6	Epidemiology – prospective study	No
Warfarin	Anticoagulant	0.04-0.08	0.16	*1 (i.m.)*	N/A	Case reports	No, but likely related to effect on vitamin K

[a]Some of the LOAELs are ranges. For the human data, this was due to limitations meaning that it was not possible to identify more precisely a LOAEL. For the animal data (non-human primates for two substances) this was due to the dose tested being reported as a range (aminopterin) or a dose level per animal being used (diethylstilboestrol), which resulted in different intakes per kg bodyweight in the animals as their bodyweights varied.
[b]Epidemiology study/studies did not assess dose-response. Human LOAEL was taken to be the normal therapeutic dose level or dose range.

Ratios of LOAELs for substances for which the human LOAELs were estimated from case reports

7. Table 2 lists the ratios of LOAELs in rats, rabbits and non-human primates to humans, and the ratios of the LOAELs in the most sensitive of either rats or rabbit to humans, for those substances for which the human LOAELs were estimated based on data from case reports. Again, the changes for etretin and misoprostol due to the lowering of the estimated LOAELs for humans are highlighted in bold.

Table 2: Ratios of LOAELs in laboratory animals to humans, for substances for which the human LOAEL was based on data from case reports

Chemical	**Chemical / pharmaceutical group**	**Ratio of LOAEL in species to humans**			**Ratio of LOAEL in most sensitive of rats or rabbits to humans**
		Rats	**Rabbits**	**Non-human primates**	
Aminopterin	Antifolate	0.4	N/A	3.3-6.7	0.4
Busulfan	Alkylating agent	257-2250 (i.p.)	N/A	N/A	*257-2250 (i.p.)*
Chlorambucil	Alkylating antineoplastic	*43 (i.p.)*	N/A	N/A	*43*
Cyclophosphamide	Alkylating antineoplastic	1.9	*0.6 (i.v.)*	*1.5 (i.m.)*	*0.6 (i.v.)* or 1.9
Danazol	Androgen	>76	18	N/A	18
Enalapril	ACE inhibiter	4.5	4.5	N/A	4.5
Ethisterone	Progestogen	80	<8	N/A	<8
Etretin	Retinoid	~~25~~ **60**	~~0.6~~ **1.4**	N/A	~~0.6~~ **1.4**
Etretinate	Retinoid	5.3	N/A	N/A	5.3
Fluconazole	Fungicide drug	3.7	11	N/A	3.7
Iodine	Essential trace element	114	3.4	N/A	3.4
Isotretinoin	Retinoid	176	17.6	1.8	17.6
Medroxyprogesterone	Progestin	100	*25 (s.c.)*	*7500 (i.m.)*	*25 (s.c.)* or 100
Methimazole	Antithyroid	6-19	N/A	N/A	6-19
Methotrexate	Antifolate	5	*7.5 (i.v.)*	75	5
Methyltestosterone	Androgen	12	N/A	N/A	12
Misoprostol	Prostaglandin E1 analogue	~~149~~ **303**	~~239~~ **485**	N/A	~~149~~ **303**
Norethisterone	Progestogen	118	5.9	21	5.9
Paramethadione	Anticonvulsant	10.6	N/A	6.8	10.6

Penicillamine	Chelating agent and immunosuppressant	32	N/A	N/A	32
Phenobarbital	Anticonvulsant	53	33	N/A	33
Phenytoin	Anticonvulsant	60	45	6	45
Primidone	Barbiturate-type anticonvulsant	57	N/A	N/A	57
Propranolol	Beta-blocker	100	N/A	N/A	100
Propylthiouracil	Antithyroid drug	N/A	8.8	N/A	8.8
Tetracycline	Antibiotic	32	*>0.6 (i.v.)*	N/A	*>0.6 (i.v.)* or 32
Thalidomide	Sedative drug	120	60	1.5	60
Trimethadione	Anticonvulsant	5-13	N/A	1.5-4	5-13
Valsartan	Angiotensin II receptor antagonist	545	4.5	N/A	4.5
Warfarin	Anticoagulant	2-4	*12.5-25 (i.v.)*	N/A	2-4

8. The ratio of the lowest LOAEL in either rats or rabbits to humans clearly exceeds 10 for 13 out of 30 substances (43%). If only considering the data from studies using oral dosing, the ratio of the LOAEL in the most sensitive of either rats or rabbits to humans is clearly greater than 10 for 12 out of 28 substances (also 43%). If further restricting the analysis to substances tested in both rats and rabbits using oral dosing, the ratio of the LOAEL in the most sensitive of these two species to humans is greater than 10 for 6 out of 13 substances (46%). The ratio exceeds 30 for 4 out of these 13 substances (31%). The ratio exceeds 100 for 1 of these 13 substances (7.7%), misoprostol.

9. The Committee considered at its December 2013 meeting that a ratio greater than 100 would be of clear concern where the human LOAEL was estimated from case reports. For misoprostol, the estimated human LOAEL, based on data seen by the Committee in December 2013 was 149 times lower than the LOAEL in rats and 239 times lower than the LOAEL in rabbits. Taking into account newly identified study reporting on a number of cases of misoprostol teratogenicity in Filipino children, the human LOAEL has been reduced to 0.0033 mg/kg bw/day, which is 303 times lower than the LOAEL in rats and 485 times lower than the LOAEL in rabbits. Misoprostol is a prostaglandin E1 analogue which is used to prevent gastric ulcers, to induce abortion and to induce labour. It is used in some countries in self-attempts to induce abortion. The basis of the LOAELs for misoprostol is summarised in Table 3 below. The human data relate to the taking of a single dose, whereas the data in laboratory animals are from studies with repeated dosing.

Table 3: Basis of LOAELs in humans, rats and rabbits for misoprostol

Species	Estimated LOAEL (mg/kg bw/day)	Basis	Effects observed	Reference
Humans	Previous estimate: 0.0067 **New data: 0.0033**	Review of case reports **Two case reports following single oral doses of 0.2 mg/person**	Multiple malformations, including limb reduction defects, brain abnormalities, gastroschisis and Mobius syndrome **Multiple malformations including Mobius syndrome**	Schardein and Macina (2007) **Chiong et al. (2009)**
Rats	1.6	Two regulatory fertility studies in rats. Males dosed from 70-71 days premating to mating, females treated from 14-15 days premating to GD 7 or parturition. Treated males mated with treated females	Number of implantations decreased at 1.6 mg/kg bw/day and higher. Increased resorptions at 1 mg/kg bw/day in one study, but not in the other at 1.6 mg/kg bw/day, and at 10 mg/kg bw/day*	Therapeutic Goods Administration (2012)
Rabbits	1	Developmental toxicity study summarised in a regulatory review. Rabbits dosed GD 6-18 with 0, 0.1, 0.3 or 1 mg/kg bw/day	No fetotoxicity or teratogenicity, but increased number of resorptions at the top dose of 1 mg/kg bw/day	Therapeutic Goods Administration (2012)

*The effect on the number of implantations and particularly resorptions was taken to be an early developmental effect. It was also reported that in two teratology studies in rats, there was no evidence of embryotoxicity, fetotoxicity or teratogenicity with dosing up to 10 mg/kg bw/day on GDs 6-15 or up to 1.6 mg/kg bw/day on GDs 7-17.

10. The basis for the large difference between humans on the one hand and rats and rabbits on the other is unclear. No data were identified from non-human primates for comparison. In contrast to rats and rabbits, misoprostol is associated with malformations in humans. Although the data were taken from case reports, the association with malformations is supported by the results of

a systematic review and meta-analysis of case-control studies, which reported associations between the use of misoprostol and any congenital defect (OR = 3.56; 95% CI: 0.98-12.98), Mobius syndrome (OR = 25.31; 95% CI: 11.11-57.66), and terminal transverse limb defects (OR = 11.86; 95% CI: 4.86-28.90) (da Silva Dal Pizzol et al., 2006).

11. Where the dose had been indicated in case reports, this ranged from 0.2 to 16 mg/day, which appears to have been the commonly-taken dose range. The large dose range is likely related to there having been large numbers of cases of self-administration of misoprostol in attempts to induce abortion. Dividing 0.2 by 60 kg bodyweight gives the LOAEL of 0.0033 mg/kg bw/day. If an attempt was made to identify the human LOAEL using the epidemiological data, then since the epidemiological data did not assess dose-response, the human LOAEL would need to be estimated from the dose range taken. Taking this to be 0.2-1.6 mg/day, the human LOAEL would be equivalent to 37-303 times lower than the LOAEL in rats and 59-485 times lower than the LOAEL in rabbits. Thus the ratio of the lowest LOAEL in rats or rabbits to humans would be greater than 10 even if taking the upper end of the usual dose range to be the human LOAEL.

12. In addition to misoprostol, three other substances had ratios of LOAELs in the most sensitive of either rats or rabbits to humans of >30. The cut-off of 30 has been used here as an intermediate value between 10 and 100, and to identify those substances, other than misoprostol, for which it appears the most likely of all the substances that a 10-fold uncertainty factor does not adequately cover interspecies extrapolation. These include thalidomide, for which an assessment in TOX/2013/42 indicated that inter-individual variation in human susceptibility was not a significant factor in the large rations between LOAELs in rats or rabbits and humans. These substances are listed in Table 4, below, together with the bases of their LOAELs in humans, rats and rabbits.

Table 4: Substances for which the ratios of their LOAELs in the most sensitive of either rats or rabbits to humans (estimated using data from case reports) are greater than 30, other than misoprostol, and the bases of the LOAELs

Substance	Species	Estimated LOAEL (mg/kg bw/day)	Basis	Effects observed	Reference
Phenobarbital	Humans	1.5	Lowest case reports	Malformations and mental retardation	Thakker et al. (1991)
	Rats	80	Developmental toxicity study	Decreased litter size, increased offspring mortality, vertebral and sternal malformations	McColl et al. (1966)

	Rabbits	50	Developmental toxicity study	Defects of sternum and skull, increased fetal resorption	McColl et al. (1966)
Phenytoin	Humans	1.67	Lowest case reports	Specific pattern of malformations known as fetal hydantoin syndrome	Adams et al. (1990), Hanson and Smith (1975)
	Rats	100	Developmental neurotoxicity studies (2 studies)	Deficits in various neurobehavioural tests. Decreased offspring body weight and survival, and decreased brain weight, were also observed in one of the two studies	Mowery et al. (2008), Elmazar et al. (1981)
	Rabbits	75	Developmental toxicity study	Increased resorptions and various malformations NOAEL = 50 mg/kg bw/d.	McClain and Langhoff (1980)
Thalidomide	Humans	0.42	Lowest case reports for which thalidomide was known to have been taken during the sensitive period and characteristic malformations resulted	Malformations characteristic of thalidomide embryopathy.	Lenz and Knapp (1962), Newman et al. (1993)
	Rats	50	Developmental toxicity study	Increased average percentage of litter with skeletal variations	Schumacher et al. (1968)
	Rabbits	25	Developmental toxicity study	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), Schumacher et al. (1968)

Ratios of LOAELs for substances for which the human LOAELs were estimated from epidemiological data

13. Table 5 lists the ratios of LOAELs in rats, rabbits and non-human primates to humans, and the ratios of the LOAELs in the most sensitive of either rats or rabbit to humans, for those substances for which the human LOAELs were estimated based on data from case reports.

Table 5: Ratios of LOAELs in laboratory animals to humans, for substances for which the human LOAEL was based on data from epidemiological studies

Chemical	**Chemical / pharmaceutical group**	**Ratio of LOAEL in species to humans**			**Ratio of LOAEL in most sensitive of rats or rabbits to humans**
		Rats	**Rabbits**	**Non-human primates**	
Aspirin	NSAID	1.5-5	3-10	4.5-15	1.5-5
Caffeine	Natural food constituent	1.8	30	3-4.5	1.8
Captopril	ACE inhibiter	6	7.8	0.6	6
Carbamazepine	Anticonvulsant	10	N/A	N/A	10
Diethylstilboestrol	Oestrogen	0.02-0.6	*0.7-22 (s.c.)*	0.04-3.3	0.02-0.6
Ergotamine	Mycotoxin	400	40	N/A	40
Ethanol	Recreational drug	10.5->63	>21->126	2.3->14	10.5->63
Lithium	Mood stabiliser	3.8-100	>1.5->40	>0.96->25	>1.5->40
Methylmercury	Environmental contaminant	≤149	N/A	≤28	≤149
Valproic acid	Anticonvulsant	5.9-7.7	8.8-11.5	1.2-1.5	5.9-7.7
Vitamin A	Essential nutrient	<150	<50	<120	<50

14. The ratio of the lowest LOAEL in either rats or rabbits to humans clearly exceeds 10 for 2 out of 11 substances (18%). If only considering the data from studies using oral dosing, the results are the same. If only considering the data from substances tested in both rats and rabbits using oral dosing, the ratio of the LOAEL in the most sensitive of either rats or rabbits to humans is clearly greater than 10 for 2 out of 8 substances (25%). For two substances the ratios may be either below or above 10, and if excluding these, the ratio exceeds 10 for 2 out of 6 substances (33%).

15. However, one of these two substances is ethanol. As described in TOX/2013/42, the basis of the human LOAEL was 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 to moderate amounts of alcohol during pregnancy (<1 to 6 UK units per week), but not in the children of mothers who abstained from alcohol during pregnancy. This result therefore reflects an effect of small to moderate consumption of ethanol in sensitive individuals. Excluding ethanol leaves ergotamine, for which the estimate of the human LOAEL is 400 times lower than that in rats and 40 times lower than that in rabbits. The basis of these LOAELs is summarised in Table 6 below.

Table 6: Basis of LOAELs in humans, rats and rabbits for ergotamine

Species	Estimated LOAEL (mg/kg bw/day)	Basis	Effects observed	Reference
Humans	0.025	Mean[a] daily dose taken in case-control surveillance	Associated with increased incidence of low birth weight[b] and preterm birth[c]	Banhidy et al. (2007)
Rats	10	Developmental toxicity study conducted in accordance with then-current US Food and Drug Administration guidelines. Administered on days 6-15 of gestation.	Increased fetal loss, decreased fetal weight and delayed skeletal ossification at 10 mg/kg bw/day and higher. NOAEL = 3 mg/kg bw/day.	Grauwiler and Schon (1973)
Rabbits	1	Developmental toxicity study conducted in accordance with then-current US Food and Drug Administration guidelines. Administered on days 6-18 of gestation.	Increased resorptions, post-implantation loss, and possible pre-implantation loss at the lowest dose of 1 mg/kg bw/day and above, though no clear dose-response relationships.	Grauwiler and Schon (1973)

[a]The paper indicates that the mean daily dose was 1.5 mg/person, equal to 0.025 mg/kg bw/day for a 60 kg person. The recommended dose was 25 drops, two or three times daily, which corresponds to a dose range of 1.2-1.8 mg/day.
[b]Defined as a birth weight of <2500 g. Adjusted prevalence odds ratio = 2.8 (95% CI: 1.2-6.5)
[c]Defined as <37 completed weeks (<259 days). Adjusted prevalence odds ratio = 1.9 (95% CI: 1.0-4.0)

16. The epidemiology indicates an association with decreased birth weight and preterm birth. The mean gestation age was 0.7 weeks shorter and the mean body weight, 196 g lower. Adjusted prevalence odds ratios for low birth

weight and preterm birth are given in the footnotes to the table. The effect was more evident in male infants than females, and appears to have been stronger following dosing in the third trimester. The authors indicate that the effect was primarily intrauterine growth retardation: “An analysis of gestational age and specific birth weights indicated intrauterine growth retardation, though the gestational age was also shorter in the treated group.” The mean dose level of 1.5 mg/day (the apparent dose range was 1.2-1.8 mg/day) has been taken to be the human LOAEL. The authors concluded that the effect might be explained by the vasoconstriction effect of ergotamine on the placenta (Banhidy et al., 2007).

17. There was some indication of a smaller effect when pregnant women were treated with another product which provided a lower dose of ergotamine of 0.3 mg/day. Crude comparisons indicated that the mean gestation age was shorter, birth weight was smaller, the proportion of preterm births was greater and the proportion of low birthweight newborns was greater in this group compared to the unexposed group. However, the number of infants born to mothers who had received this low dose product was too low for further analysis.

18. The developmental toxicity studies in rats and rabbits were published in the early 1970s but were conducted in accordance with then-current US Food and Drug Administration guidelines. The NOAEL in rats was 3 mg/kg bw/day, and doses associated with increased fetal loss, decreased fetal weight and decreased fetal ossification also caused reduced maternal body weight compared to controls. EFSA (2012) conducted benchmark dose modelling of total fetal mortality versus number of corporea lutea in this study, with the aim of estimating a BMDL10. No models acceptably fit the data, possibly because dichotomous models had to be used rather than nested dichotomous models using litter-specific data. However, for indicative purposes, EFSA indicated that the calculated BMDL10s had ranged between 2 and 6 mg/kg bw/day. EFSA also modelled the effects on maternal body weight gain, and estimated BMDL10s ranging 2.5-3.7 mg/kg bw/day.

19. The results in rabbits were less clear. There were statistically significant increases in resorptions and post-implantation loss in all treated groups (1, 3, 10 and 30 mg/kg bw/day) compared to controls, but without dose-response relationships. Pre-implantation loss was also statistically significantly increased at 1 and 3 mg/kg bw/day, but not at 10 and 30 mg/kg bw/day. The LOAEL has been taken to be the lowest dose tested in this study (1 mg/kg bw/day). As this was the lowest dose tested it is possible that lower doses would also have caused observable effects. There was no clear effect on maternal weight gain in rabbits, in contrast to the study in rats.

Medical conditions

20. The COT indicated the need to take into account possible developmental effects of the treatment-condition itself. For example, epilepsy has been associated with a slight increase in the incidence of malformations.

The text below describes where and how this was taken into account when estimating the human LOAELs. This was limited to anticonvulsants.

21. The key data for carbamazepine were taken from an epidemiological study in which taking carbamazepine was compared to taking no anti-epileptic drug and a significant association was identified with spina bifida. As the study did not assess the dose-response relationship, the human LOAEL was taken to be the normal therapeutic dose range.

22. The LOAEL for valproic acid was based on a recent review of the epidemiology, which found that doses of valproic acid above about 800-1000 mg/day were associated with significantly higher malformation rates than either lower doses or therapy with other anti-epileptic drugs. In addition, maternal valproic acid exposure was also associated with reduced offspring IQ, but not at doses lower than 800-1000 mg/day when compared to unexposed controls or to therapy with other anti-epileptic drugs. Doses of valproic acid below 800-1000 mg/day were considered of low risk, and 800-1000 mg/day, equivalent to 13-17 mg/kg bw/day, was taken to be the LOAEL. However, there is some uncertainty about this LOAEL given that the comparison of malformation rates was to other anti-epileptic drugs. It is possible that the actual LOAEL would be lower. For example, in a prospective UK study the rate of major malformations was 9.1% at maximum daily valproic acid doses >1000 mg/day, 6.1% at doses of 600-1000 mg/day, and 4.1% at doses <600 mg/day (Morrow et al., 2006). The latter incidence rate is clearly higher than that for low doses of carbamazepine (<400 mg/day, 1.7%) and lamotigrine (<100 mg/day, 1.3%) in the same study. Based on these data the LOAEL for valproic acid should perhaps be taken to be 600 mg/day, equivalent to 10 mg/kg bw/day. This is 10 times lower than the LOAEL in rats and 15 times lower than the LOAEL in rabbits.

23. The human LOAELs for paramethadione and trimethadione were identified from case-reports. These case-reports were for a specific pattern of malformations known as the fetal trimethadione syndrome, and this is unlikely to be caused by epilepsy.

24. The human LOAEL from phenytoin was identified from case-reports. These case-reports were for a specific pattern of malformation known as the fetal hydantoin syndrome, and this is unlikely to be caused by epilepsy.

25. It is recognised that the human developmental data on phenobarbital are difficult to interpret due to the common use of multidrug therapy and because epilepsy itself may result in malformations. However, a spectrum of minor malformations, retarded growth and functional impairment has been described following phenobarbital use (Schardein and Macina, 2007). In an epidemiological study which screened pregnant women at delivery to identify three groups – infants exposed to anticonvulsant drugs, infants unexposed to anticonvulsant drugs but with a maternal history of seizures, and infants unexposed to anticonvulsant drugs and with no maternal history of seizures (to act as a control) - the total incidence of singleton infants with major malformations, microcephaly, growth retardation, midface hypoplasia and/or

hypoplasia of the fingers (one or more) was 17/64 (26.6%) for phenobarbital monotherapy compared to 6/98 (6.1%) of unexposed infants born to women with a history of seizure and 43/508 (8.5%) of unexposed infants born to women with no history of seizure (Holmes et al., 2001). Using the latter group as the controls, the adjusted odds ratio was 3.9 (95% CI, 1.4-10.9. Case reports involving monotherapy with phenobarbital were used to identify the LOAEL. The lowest dose involved a case of malformation (including dysmorphic features, absence of distal phalanges of fingers and toes and nail hypoplasia) and mental retardation following therapy with 90 mg/day phenobarbital throughout pregnancy (Thakker et al., 1991).

26. Similarly to phenobarbital, it is recognised that the human developmental toxicity data for pirimidone are difficult to interpret. Nevertheless, a syndrome of features has been described and attributed to pirimidone, including facial dysmorphism, microcephaly, poor somatic development, short stature and cardiac defects. Case reports have involved doses between 125 mg and 2000 mg per day (Schardein and Macina, 2007). The lower end of this range was taken to be the LOAEL.

Non-developmental outcomes

27. At the December 2013 meeting, the Committee requested that the availability of data for non-developmental outcomes be explored. The Committee recognised that data may be available for environmental chemicals with epidemiological data such as methylmercury, lead and fluoride, and for organophosphate pesticides, which had historically been tested in human volunteer studies in addition to laboratory animal studies. Information is provided below on methylmercury, lead, fluoride and acetylcholinesterase-inhibiting pesticides in addition to other information on assessments of the validity of the 10-fold uncertainty factor for interspecies extrapolation identified by the secretariat. Some of these were also referred to in TOX/2013/42, but are described again in this paper, in slightly more detail, to allow comparisons to be drawn to the other data that are described. These papers were identified from the secretariat's knowledge of the literature. They include some published assessments specifically of an uncertainty sub-factor of 4 for interspecies differences in toxicokinetics.

A PubMed search did not identify any additional useful papers specifically on the validation of uncertainty factors for species variation. One paper which used comparisons of LC_{50} data in various fish species to suggest values for interspecies uncertainty factors to be used in both toxicological and ecotoxicological risk assessment has not been described in this paper as it was considered to provide less useful data than the other papers described (Calabrese and Baldwin, 1994).

Methylmercury

28. The COT report on variability and uncertainty in toxicology (COT, 2007) included an investigation of what the PTWI for methylmercury would be if

based only on data from laboratory animals and compared this to the PTWI set by JECFA based on epidemiological data. The lowest appropriate NOAEL was 0.01 mg/kg bw/day, which was based on both renal toxicity in a 24-month chronic toxicity study in rats and decreased body weight in a 52-month study in monkeys. Applying the default uncertainty factor of 100, the PTWI would be 0.7 µg/kg bw/week. This was lower than the PTWI set based on epidemiological studies of neurodevelopmental toxicity of 1.6 µg/kg bw/week. It was concluded that this provided support for the default 100-fold uncertainty factor when applied to data from laboratory animals. EFSA has subsequently reduced its tolerable weekly intake (TWI) to 1.3 µg/kg bw/week, but this conclusion still applies.

Lead

29. Plunkett (1999) estimated what a chronic oral reference dose (RfD, defined similarly to a TDI) would be for lead if based on data in laboratory animals. The lowest NOAEL was identified to be 0.09 mg/kg bw/day based on effects on renal morphology in a 9-month study in rats. NOAELs for other endpoints, including neurodevelopmental toxicity in rats, were higher. Applying an uncertainty factor to the NOAEL of 0.09 mg/kg bw/day of 100 would result in an RfD of 0.9 µg/kg bw/day. Examining the original paper, there was an increase in kidney weight compared to controls in males but not females at the suggested NOAEL (mean actual weight 18% higher, $p<0.05$; mean relative weight 20% higher, not statistically significant). However, there were no histopathological changes at this dose level (Fowler et al., 1980). In comparison to this suggested RfD, EFSA (2010) estimated from epidemiological data a BMDL1 for increased systolic blood pressure equivalent to a dietary intake of 1.5 µg/kg bw/day, a BMDL10 for chronic kidney disease equivalent to 0.63 µg/kg bw/day and a BMDL1 for decreased IQ in children equivalent to 0.5 µg/kg bw/day. Consistent with the existing COT view, EFSA concluded that there was no evidence of a threshold for these endpoints in humans. As the suggested RfD based on laboratory animal data is above the BMDLs derived from epidemiological data for chronic kidney disease and decreased IQ, it appears unlikely that an RfD or TDI for lead based on data from laboratory animals and using the default uncertainty factor of 100 would be adequately protective.

Fluoride

30. The secretariat has not identified a specific comparative assessment of human and animal data for fluoride. However, data have been examined in the following reviews and opinions: the International Programme on Chemical Safety (IPCS) Environmental Health Criteria report on fluorides, which was published in 2002 (WHO, 2002), the Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profile for fluorides, hydrogen fluoride and fluorine, published in 2003 (ATSDR, 2003), and the EFSA Opinion on the tolerable upper intake level for fluoride, published in 2005 (EFSA, 2005). The most complete review of laboratory animal studies was provided by the ATSDR toxicological profile. The lowest appropriate NOAEL from animal studies appears to have been 0.15 mg/kg bw/day, based on decreased

vertebral strength and decreased bone mineralisation in a study in rats administered sodium fluoride in the drinking water for 16 or 48 weeks (ATSDR, 2003). The LOAEL in this study was 0.5 mg/kg bw/day. The LOAEL was also 0.5 mg/kg bw/day for decreased thyroxine (T4) level and increased T3-resin uptake ratio in a study in rats administered sodium fluoride in drinking water for two months and the LOAEL was 0.8 mg/kg bw/day for increased bone formation rate in a study in mice administered sodium fluoride in drinking water for 4 weeks; no NOAELs were identified from these studies (ATSDR, 2003). LOAELs were higher in other animal studies of fluorides. In comparison, the tolerable upper intake level for fluoride set by EFSA based on epidemiological data was 0.1 mg/kg bw/day in children aged 0 to 8 years, based on dental fluorosis as the critical endpoint, and 0.12 mg/kg bw/day for older age groups based on increased risk of bone fracture (EFSA, 2005). Since the overall NOAEL from the laboratory animal studies of 0.15 mg/kg bw/day is only 1.25 times higher than the UL of 0.12 mg/kg bw/day, it appears that the use of animal data and standard uncertainty factors would be adequately protective for fluoride.

Acetylcholinesterase-inhibiting pesticides

31. The Joint FAO/WHO Meeting on Pesticide Residues (JMPR) has set ADIs and ARfDs for a number of organophosphate and N-methylcarbamate pesticides based on erythrocyte acetylcholinesterase inhibition in human volunteer studies. Data are also available from studies in laboratory animals and could be compared. The EU has a policy of not using data from human volunteer studies to set reference values for pesticides and so the EU's reference values are based on data in laboratory animals, using a standard default uncertainty factor of 100 in most cases. In this author's experience, reference values set for organophosphates and N-methylcarbamates based on human data have been at or above those set based on animal data. However, this was not the case for another acetylcholinesterase-inhibiting pesticide, ethephon.

32. Ethephon is a dibasic phosphonic acid used as a plant growth regulator. The phosphonic acid dianion form can phosphorylate serine residues in the active site of cholinesterases resulting in inhibition of the enzyme activity. The JMPR has set an ARfD based on an overall NOAEL from human volunteer studies conducted in the 1970s and an uncertainty factor of 10 (WHO, 2003). The LOAEL was identified from a 28-day study in which no inhibition of erythrocyte acetylcholinesterase activity was observed but clinical signs and symptoms consistent with acetylcholinesterase inhibition were reported, including gastrointestinal disturbance and urinary urgency. The EU set an ARfD by applying an uncertainty factor of 120 to a NOAEL from a 28-day dog study based on erythrocyte acetylcholinesterase inhibition. This uncertainty factor was higher than the default factor of 100 in order to ensure that there was a margin of 10 to the human NOAEL (EFSA, 2008). A limitation in interpreting these data is the lack of observation of inhibition of erythrocyte acetylcholinesterase activity at the LOAEL in humans. This was not discussed by the JMPR, while EFSA (2008) indicated that limited information was

available on the methodology used to assess cholinesterase inhibition in the human studies. The human studies were conducted in the 1970s.

Other assessments of the adequacy of a 10-fold uncertainty factor for interspecies extrapolation

Paracetamol

33. The COT report on variability and uncertainty in toxicology also noted that the NOAEL for the hepatotoxicity of paracetamol in rats was >1000 mg/kg bw/day; in mice it was 150 mg/kg bw/day; and in humans it had been estimated to be around 200 mg/kg bw/day, though there was noted to be considerable interindividual variability related to differences in the rate of metabolic activation, the amount of glutathione available for conjugating the cytotoxic metabolite, and its rate of clearance (COT, 2007). The COT considered that these data supported the use of 10-fold uncertainty factor, applied to data from the most sensitive species, to extrapolate to humans.

The use of comparative data for several pesticides

34. Zeilmaker et al. (1995) considered the use of uncertainty factors in setting reference values / health-based guidance values for chemicals and stated that the publication of comparative toxicological data for several pesticides in human and laboratory animals by Hayes (1967) was the “only study aimed at validating the interspecies uncertainty factor”. According to Zeilmaker et al., the ratios between comparative dose descriptors for acute toxicity in rats and humans (e.g. largest dose without effect, smallest with effect, largest non-fatal dose, etc.) ranged 1.9 to 100, with a geometric mean of 11, and the ratios between comparative dose descriptors for chronic toxicity (e.g. NOAELs, doses with small effects) in rats and humans ranged 0.58-9.4, with a geometric mean of 2.9. Although these figures appear to be broadly correct, it is not clear exactly how they were calculated from the data presented by Hayes (1967), but it does appear that the largest ratio between rats and humans for acute toxicity was about 100 and the largest ratio between rats and humans for chronic toxicity was about 10.

Antineoplastic drugs

35. Price et al. (2008) compared maximum tolerated doses in humans for 64 antineoplastic drugs following subacute exposure (5 days) with similar toxicological data for up to four laboratory species: mouse, rat, monkey and/or dog.

36. The maximum tolerated dose in humans was defined as the dose level at which no more than 1 in 6 cancer patients experienced dose limiting toxicity, with two or more patients experiencing dose limiting toxicity at the next higher dose. The comparators in laboratory animals varied. In some cases, the maximum tolerated dose was used, which in laboratory animals was defined as the highest dose that suppressed body weight by no more than 10% in a 90-day chronic study. In some cases, typically for dogs and

monkeys, the comparator was the TDL (toxic dose low), which was defined as the lowest dose that produced pathological alterations in haematological, chemical, clinical or morphological endpoints. In some cases, typically for rats and mice, the comparator was the LD10, defined as the acute dose resulting in the death of 10% of the population of test animals. Where the data did not relate to a 5-day period of dosing, the data were "normalised" to a 5-day dosing regimen by summing the total dose administered and dividing by 5.

37. Further limitations were that the dosing was parenteral in both humans and the laboratory animals, and thus there might be more variability if the dosing was oral due to differences in oral absorption between species; that most of the substances were directly toxic rather than metabolically activated, and thus the results may not be applicable to substances requiring metabolic activation; and possibly that the human data were from patients with cancer, which might have affected their susceptibility.

38. In general, toxicity increased with a species' body weight. The mean ratio between rats and humans was 6.5, the median was 3.0, and an uncertainty factor of 10 would be adequate to extrapolate from rats to humans for 81% of the antineoplastic drugs. The mean ratio between mice and humans was 20, the median ratio was 7.7, and a 10-fold uncertainty factor would be adequate to extrapolate from mice to humans for 63% of substances. The mean ratio between dogs and humans was 3.5, the median was 1.0, and a 10-fold uncertainty factor would be adequate to extrapolate from dogs to humans for 97% of substances. The mean ratio between monkeys and humans was 3.6, the median was 2.5, and a 10-fold uncertainty factor would be adequate to extrapolate from monkeys to humans for 95% of substances.

39. The data indicated that testing in multiple species, and using the data for the most sensitive species, would tend to increase the adequacy of the 10-fold uncertainty factor for extrapolating to humans. For example, while the 10-fold uncertainty factor using data for mice alone was indicated to be adequate for 63% of substances, and using data for rats alone was indicated to be adequate for 81% of substances, this increased to 85% of substances when considering the data for both rats and mice and using the most sensitive of these species for each substance.

Comparing EPA RfDs based on human data to those derived from animal data

40. Dourson et al. (2001) examined chronic oral reference doses (RfDs) set for 18 chemicals by the United States Environmental Protection Agency (US EPA) based on human data, and compared these to the RfDs that would have been set if based on data in laboratory animals. For seven out of the 18 substances (39%), the RfDs set using human data were lower than they would have been if based on animal data. This indicates that the use of animal data would have been adequately protective for 61% of substances. RfDs set using human data were more than 3-fold lower than they would have been using animal data for four substances (22%).

41. The reasons for the large differences were the critical effect in humans not being identified in laboratory animals or humans being more than 10-fold more sensitive to the same effect. For example, the RfD for silver was based on a human NOAEL of 0.014 mg/kg bw/day for argyria, whereas the critical LOAEL (a NOAEL was not identified) used to propose an animal data-derived RfD was 89 mg/kg bw/day for ventricular hypertrophy in a 218-day study in rats. Argyria is a blue-grey colouration of the skin caused by the accumulation of silver sulphide and silver selenite. This results from the accumulation of thiol- or protein-bound silver in skin, followed by UV light-induced photo-reduction to zero-valent silver then transformation into silver sulphide and further into silver selenite by exchange reactions. Thus, it is perhaps not surprising that it would not be observed in standard toxicology studies in laboratory animals. The barium human NOAEL was 0.21 mg/kg bw/day based on increased blood pressure, whereas the critical NOAEL identified from laboratory animals was 45 mg/kg bw/day based on increased kidney weight in rats. Cataract formation was observed in humans dosed with 2 mg/kg bw/day 2,4-dinitrophenol as a clinical therapy for weight loss, but the NOAEL for this endpoint in 6-month studies in rats was 130 mg/kg bw/day.

Assessments of the adequacy of a sub-factor of 4 for interspecies variation in toxicokinetics

42. Although there has been only limited assessment specifically of the adequacy of the 10-fold uncertainty factor for interspecies variation, there has been some work assessing the adequacy of a sub-factor of 4 for interspecies variation in toxicokinetics. Members will recall that the 10-fold uncertainty factor has been divided into sub-factors of 4 for interspecies differences in toxicokinetics and 2.5 for interspecies differences in toxicodynamics for the purposes of allowing part of the composite uncertainty factor to be replaced with chemical-specific data where available. This unequal subdivision of the 10-fold uncertainty factor for interspecies variation was based on the observation that there was an approximately 4-fold difference between rats (the most commonly used test species) and humans in basic physiological processes that are major determinants of clearance and elimination of chemicals, such as cardiac output and liver and renal blood flows.

43. Walton et al. (2001a) assessed differences in “internal dose” (taken as being the inverse of clearance) for the same administered dose per kg of bodyweight for human CYP1A2 substrates (caffeine, theobromine, theophylline and paraxanthine) in humans, rats, rabbits, dogs and mice. The magnitudes of the mean ratios between humans and mice (10.6) and humans and rats (5.4) exceeded the uncertainty factor of 4, whereas the mean ratios between humans and rabbits (2.6) and humans and dogs (1.6) were below 4. The paper focused on mean differences, presumably due to the limited dataset. However, the rate of clearance of caffeine following oral dosing (adjusted for body weight), for example, was 10-fold higher in rats compared to humans, 10.2-fold higher in mice compared to humans, and 4.9-fold higher in rabbits compared to humans.

44. Walton et al. (2001b) assessed differences in clearance between humans, rats, rabbits, dogs and mice for substances for which glucuronidation was the major pathway of metabolism in either humans or the test species. The mean ratios of clearance in the test species and humans, considering only the data for oral dosing (data were also available for i.v. dosing), were 4.5 for mice, 9.1 for rats, 8.7 for rabbits and 9.7 for dogs. All these ratios exceed a factor of 4. Considering only substances metabolised primarily by glucuronidation in both humans and the test species (and limited to oral dosing), the ratios were 5.5 for mice, 21 for rats, 0.95 for rabbits and 8.6 for dogs. All these ratios except the ratio for rabbits to humans exceed a factor of 4. There was also observed to be wide variation between substances. For example, the rate of clearance of oxazepam was 38-fold higher in rats than humans following oral dosing, but that for zomepirac was 4.8-fold lower.

45. Walton et al. (2004) assessed differences in internal exposure (taken as being the inverse of clearance) for the same dose per kg of bodyweight for substances eliminated renally, unmetabolised in humans, rats, rabbits, dogs and mice. The mean ratios between humans and the test species were 13 for mice, 5.2 for rats, 3.3 for rabbits and 1.6 for dogs. Thus, the ratios for rats and mice exceeded the uncertainty factor of 4, while the mean ratios for rabbits and dogs were below 4. Again, there was variability from chemical to chemical. For example, the rate of clearance of aciclovir in rats was 1.8 times higher than in humans, but the rate of clearance of cefotetan was 19 times higher.

46. Schneider et al. (2004) compared toxicokinetic data for a number of pharmaceuticals from six species including humans, LD_{50}s from eight animal species, NOAELs for pesticide in rats, mice and dogs, and toxicity for antineoplastics in humans and multiple animal species, and concluded that allometric scaling allowed reasonably for interspecies differences on average for all datasets except the LD_{50}s. The data on antineoplastic drugs are not described here since they were also analysed by Price et al. (2008), as described above. The median species ratios for total clearance (adjusted for bodyweight) for the pharmaceuticals compared to expectations based on caloric demand were as follows: the ratio for mouse:human was 7.1 compared to 7.2 expected, the ratio for rat:human was 4.8 compared to 4.1 expected, the ratio for rabbit:human was 3.2 compared to 2.2 expected, the ratio for monkey:human was 1.5 compared to 2.0 expected, and the ratio for dog:human was 2.0 compared to 1.5 expected. The raw data are not presented in the paper. However, the authors fit a log-normal distribution to the data for all the animal species combined compared to human data after adjusting for caloric demand and published a 95^{th} percentile of this distribution of 6.49. By multiplying this figure by the adjustment factors for caloric demand used in the paper, the following 95^{th} percentile figures for extrapolation to humans can be estimated: mouse = 46.7, rat = 26.6, rabbit = 14.3, monkey = 13.0, dog = 9.7. These figures are substantially above the uncertainty sub-factor of 4 for interspecies variation in toxicokinetics.

Summary and discussion

47. The data have been separated in this paper for substances for which the human LOAEL was based on case reports and substances for which the human LOAEL was based on epidemiological data.

48. The COT indicated at the December 2013 meeting that where the human LOAELs were based on case reports it might be necessary to compare the ratios of LOAELs to the full default 100-fold uncertainty factor since the human LOAEL may additionally reflect inter-individual variation. The ratio of the lowest LOAEL in rats or rabbits to humans exceeds 100 for one substance, misoprostol, at 303. For three other substances, the ratios of the lowest LOAELs in rats or rabbits to humans are greater than 30. The basis of the LOAELs for these substances in humans, rats and rabbits are described in Tables 3 and 4 for the Committee's consideration.

49. Of the substances for which the human LOAELs are based on data from epidemiological studies (or the normal human dose range where epidemiological substances have not examined dose-response but have identified an association between exposure and no exposure), the ratios of the lowest LOAELs in rats or rabbits to humans exceeds 10 for two substances. One of these is ethanol, for which the data relate to an association in people with certain variants in alcohol dehydrogenase genes, and thus the human data reflect effects in sensitive individuals. The other substance is ergotamine. The basis of the LOAEL for ergotamine in humans, rats and rabbits is described in Table 6.

50. The Committee had noted at the December 2013 meeting that it would be useful to consider the indications for which the pharmaceuticals were taken, as some medical conditions may predispose directly to adverse developmental outcomes. This was taken into account so far as possible when estimating the human LOAELs for anticonvulsants taken by people with epilepsy, as described in paragraphs 20-26 of this paper.

51. The Committee had requested that the availability of data for non-developmental endpoints be explored further. This paper describes assessments that have been made of the adequacy of applying a 100-fold uncertainty factor to data from laboratory animals, assessments specifically of the adequacy of a 10-fold uncertainty factor for interspecies variation, and assessments specifically of the adequacy of a sub-factor of 4 for interspecies variation in toxicokinetics. It appears that applying an uncertainty factor of 10 to extrapolate from laboratory animals to humans, or 100 to a NOAEL in laboratory animals to set a TDI or similar reference value, is adequate for most but not all substances. A sub-factor of 4 appears to often not be adequate to allow for toxicokinetic variation in extrapolating from laboratory animals to humans. The Committee may wish to consider what conclusions it can draw from these data and whether the results are similar to, or different from, those for developmental toxicity.

Questions on which the views of the Committee are sought

52. Members are invited to consider and comments on the data presented in this paper, and in particular to consider the following questions:

i). At the December 2013 meeting the Committee concluded that there were strong indications that the 10-fold uncertainty factor for interspecies variation in developmental toxicity was not always adequate. Is this still the Committee's conclusion? Are there any further conclusions that can be drawn?

ii). Can any conclusions be drawn from the data on non-developmental endpoints? Do these data suggest any differences between developmental and non-developmental endpoints in terms of the adequacy of the 10-fold uncertainty factor for interspecies variation?

iii). How would the Committee wish this topic to be taken forward further?

Secretariat
April 2014

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