ACP 9/5 (338/2009)
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ADVISORY COMMITTEE ON PESTICIDES

MEETING DATE: 30TH JUNE 2009

COMPARISION OF AOEL, ADI, AND ARfD VALUES

Following the High Court judgment on the recent judicial review, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) held an initial discussion on the risk assessment of bystander and resident exposure to plant protection products in April 2009.

It was observed that a theme in the judgment was the security of the toxicology on which the AOEL (Acceptable Operator Exposure Level) was based and an implication of uncertainty about the toxicological effects of pesticides. Both the duration of exposure in the studies used to support the AOEL and of exposure of residents were issues that it was suggested should be considered further. It was also noted that acute bystander exposure could be considered. To facilitate further discussion the COT requested a tabulation of information on AOELs and ADIs for a range of active substances. The Committee asked for this to include information on the critical toxic effect and the type of study.

This paper is a first draft of CRD's response to the COT request. Table 1 gives the AOEL, oral absorption, ADI, and where appropriate the ARfD, values for substances included in Annex I of Directive 91/414/EEC. CRD have in addition included the information on ARfDs as this is relevant when considering the need for an acute risk assessment. The fifth column of Table 1 shows the ratio of the AOEL to the ADI, corrected for oral absorption. This ratio shows, based on the available data, how much lower a lifetime daily (chronic) exposure would have to be compared to an exposure at the AOEL, for a similar level of risk. The distribution of the ratios of AOEL:ADI is shown in Figure 1.

The sixth column of Table 1 shows the ratio of the ARfD, corrected for oral absorption, to the AOEL. This ratio shows for those cases where acute toxicity is a concern, how much higher than the AOEL an acute exposure could be for there to be a similar level of risk, based on the available information. The distribution of the ratios of ARfD:AOEL is shown in Figure 2.

The details of the toxicology have so far been collated for twenty examples where the data sources were readily available. The information is shown in Table 2.

Table 1 Directive 91/414/EEC Annex I Reference doses and oral absorption values, with a comparisons of AOEL:ADI and ARfD:AOEL, both corrected for oral absorption.

Important: some of the information in this table has been automatically transcribed from a CRD database, and some transcription errors have been identified and corrected. However, until Table 2 has been completed the values in Table 1 must be regarded as a draft.

Active substance	AOEL*	Oral absorption	ADI *	ARfD*	AOEL / (ADI x Oral Abs %)	(ARfD x Oral Abs %) / AOEL
Alpha cypermethrin	0.01	45%	0.015	0.04	1.5	1.8
Amidosulfuron	1.4	100%	0.2	not needed	7.0	not applicable
Benthiavalicarb	0.1	100%	0.1	not needed	1	not applicable
Bifenthrin	0.0075	50%	0.015	0.03	1.0	2.0
Benfluralin	0.05	33%	0.005	not needed	30	not applicable
Bromoxynil	0.01	100%	0.01	0.04	1.0	4.0
Bromuconazole	0.025	100%	0.01	0.1	2.5	4.0
Chlormequat	0.04	100%	0.04	0.09	1.0	2.3
Chlorothalonil	0.009	30%	0.015	0.6	2.0	20
Chlorpyrifos	0.01	100%	0.01	0.1	1.0	10
Chlorsulfuron	0.43	73%	0.2	not needed	2.9	not applicable
Clodinafop-propargyl	0.026	75%	0.003	0.05	12	1.4
Clofentazine	0.01	50%	0.02	not needed	1.0	not applicable
Cymoxanil	0.01	75%	0.013	0.08	1.0	6.0
Cyprodinil	0.03	100%	0.03	not needed	1.0	not applicable
Dichlorprop-p	0.35	100%	0.06	0.5	5.8	1.4
Diflubenzuron	0.0066	33%	0.012	0.4	1.7	20
Diflufenican	0.11	58%	0.2	not needed	0.9	not applicable
Diphenylamine	0.1	100%	0.075	not needed	1.3	not applicable
Ioxynil	0.01	100%	0.005	0.04	2.0	4.0
2,4-D	0.15	100%	0.05	not needed	3.0	not applicable
2,4-DB	0.08	100%	0.02	not needed	4.0	not applicable
ABAMECTIN	0.0025	100%	0.0025	0.005	1.0	2.0
ACETAMIPRID	0.12	100%	0.07	0.1	1.7	0.8
AZIMSULFURON	0.2	100%	0.1	not needed	2.0	not applicable
AZOXYSTROBIN	0.1	100%	0.1	not needed	1.0	not applicable
BENFLURALIN	0.05	33%	0.005	not needed	30	not applicable
BENTAZONE	0.13	100%	0.1	0.25	1.3	1.9
BENZOTHIADIAZOLE	0.1	100%	0.1	not needed	1.0	not applicable
CAPTAN	0.1	100%	0.1	0.1	1.0	1.0
CARBENDAZIM	0.02	100%	0.02	0.02	1.0	1.0
CARFENTRAZONE-ETHYL	0.6	100%	0.03	not needed	20	not applicable

Active substance	AOEL*	Oral absorption	ADI *	ARfD*	AOEL / (ADI x Oral Abs %)	(ARfD x Oral Abs %) / AOEL
CHLOROTOLURON	0.215	100%	0.04	not needed	5.4	not applicable
CHLORPROPHAM	0.05	100%	0.05	0.5	1.0	10
CHLORPYRIFOS-METHYL	0.01	100%	0.01	0.1	1.0	10
CINIDON-ETHYL	0.02	35%	0.01	not needed	5.7	not applicable
CLOPYRALID	1	100%	0.15	not needed	6.7	not applicable
CYAZOFAMID	0.3	100%	0.17	not needed	1.8	not applicable
CYCLANILIDE	0.0045	60%	0.0075	0.015	1.0	2.0
CYHALOFOP BUTYL	0.03	100%	0.003	not needed	10	not applicable
CYPERMETHRIN	0.06	50%	0.05	0.2	2.4	1.7
DAMINOZIDE	0.16	35%	0.45	not needed	1.0	not applicable
DELTAMETHRIN	0.0075	75%	0.01	0.01	1.0	1.0
DIMETHENAMID-P	0.04	100%	0.02	0.25	2.0	6.3
DIMETHOATE	0.001	100%	0.001	0.01	1.0	10
DIMETHOMORPH	0.15	100%	0.05	0.6	3.0	4.0
DIMOXYSTROBIN	0.02	100%	0.004	0.004	5.0	0.2
DINOCAP	0.003	70%	0.004	0.004	1.1	0.9
DIQUAT	0.001	10%	0.002	not needed	5.0	not applicable
EPOXICONAZOLE	0.008	50%	0.008	0.023	2.0	1.4
ETHOFUMESATE	2.5	100%	0.07	not needed	36	not applicable
ETHOPROPHOS	0.001	100%	0.0004	0.01	2.5	10
ETHOXYSULFURON	0.06	100%	0.04	not needed	1.5	not applicable
ETOXAZOLE	0.03	60%	0.04	not needed	1.3	not applicable
FAMOXADONE	0.0048	40%	0.012	0.2	1.0	17
FENAMIDONE	0.3	100%	0.03	not needed	10	not applicable
FENAMIPHOS	0.0008	100%	0.0008	0.0025	1.0	3.1
FENHEXAMID	0.3	100%	0.2	not needed	1.5	not applicable
FIPRONIL	0.0035	100%	0.0002	0.009	18	2.6
FLAZASULFURON	0.02	100%	0.013	not needed	1.5	not applicable
FLORASULAM	0.05	100%	0.05	not needed	1.0	not applicable
FLUAZINAM	0.004	35%	0.01	0.07	1.1	6.1
FLUDIOXONIL	0.59	100%	0.37	not needed	1.6	not applicable
FLUMIOXAZINE	0.018	83%	0.009	0.05	2.4	2.3
FLUOROXYPYR	0.8	100%	0.8	not needed	1.0	not applicable
FLUPYRSULFURON-METHYL	0.08	60%	0.035	not needed	3.8	not applicable
FLURTAMONE	0.02	38%	0.03	not needed	1.8	not applicable
FLUSILAZOLE	0.005	100%	0.002	0.005	2.5	1.0

Active substance	AOEL*	Oral absorption	ADI *	ARfD*	AOEL / (ADI x Oral Abs %)	(ARfD x Oral Abs %) / AOEL
FLUTHIAMIDE	0.017	100%	0.005	0.017	3.4	1.0
FOLPET	0.1	100%	0.1	0.1	1.0	1.0
FORAMSULFURON	0.1	20%	0.5	not needed	1.0	not applicable
FORMETHANATE	0.004	100%	0.004	0.005	1.0	1.3
FOSTHIAZATE	0.005	100%	0.004	0.005	1.3	1.0
GLYPHOSATE	0.2	30%	0.3	not needed	2.2	not applicable
IMAZALIL	0.05	100%	0.025	not needed	2.0	not applicable
IMAZAMOX	14	100%	9	not needed	1.6	not applicable
IMIDACLOPRID	0.08	100%	0.06	0.08	1.3	1.0
INDOXACARB	0.004	60%	0.006	0.125	1.1	19
IODOSULFURON METHYL SODIUM	0.05	70%	0.03	not needed	2.4	not applicable
IPRODIONE	0.3	100%	0.06	not needed	5.0	not applicable
IPROVALICARB	0.015	100%	0.015	not needed	1.0	not applicable
ISOXAFLUTOLE	0.02	60%	0.02	not needed	1.7	not applicable
KRESOXIM-METHYL	0.9	63%	0.4	not needed	3.6	not applicable
LAMBDA-CYHALOTHRIN	0.0025	50%	0.005	0.0075	1.0	1.5
LINURON	0.009	100%	0.003	0.03	3.0	3.3
MALEIC HYDRAZIDE	0.25	100%	0.25	not needed	1.0	not applicable
MANCOZEB	0.035	50%	0.05	0.6	1.4	8.6
MCPA	0.04	100%	0.05	0.15	0.8	3.8
MCPB	0.06	100%	0.01	0.05	6.0	0.8
MECOPROP	0.04	100%	0.01	not needed	4.0	not applicable
MECOPROP-P	0.04	100%	0.01	not needed	4.0	not applicable
MEPANIPYRIM	0.07	100%	0.02	0.3	3.5	4.3
MESOSULFURON-METHYL	0.2	3%	1	not needed	6.7	not applicable
MESOTRIONE	0.015	70%	0.01	0.02	2.1	0.9
METALAXYL-M	0.08	100%	0.08	not needed	1.0	not applicable
METCONAZOLE	0.01	100%	0.01	0.01	1.0	1.0
METHIOCARB	0.013	100%	0.013	0.013	1.0	1.0
METHOXYFENOZIDE	0.1	60%	0.1	0.2	1.7	1.2
METIRAM	0.016	60%	0.03	not needed	0.9	not applicable
NICOBIFEN	0.1	44%	0.04	not needed	5.7	not applicable
OXADIARGYL	0.006	59%	0.008	not needed	1.3	not applicable
OXAMYL	0.001	100%	0.001	0.001	1.0	1.0
OXASULFURON	0.013	100%	0.013	not needed	1.0	not applicable

Active substance	AOEL*	Oral absorption	ADI *	ARfD*	AOEL / (ADI x Oral Abs %)	(ARfD x Oral Abs %) / AOEL
PENDIMETHALIN	0.234	100%	0.125	not needed	1.9	not applicable
PHENMEDIPHAM	0.13	100%	0.03	not needed	4.3	not applicable
PICALINOFEN	0.03	60%	0.014	0.05	3.6	1.0
PICOLINAFEN	0.03	60%	0.014	0.05	3.6	1.0
PICOXYSTROBIN	0.043	100%	0.043	not needed	1.0	not applicable
PIRIMICARB	0.035	100%	0.035	0.1	1.0	2.9
PROCYMIDONE	0.035	100%	0.025	0.035	1.4	1.0
PROHEXADIONE CALCIUM	0.35	100%	0.2	not needed	1.8	not applicable
PROPAMOCARB HYDROCHLORIDE	0.29	100%	0.29	1	1.0	3.4
PROPOXYCARBAZONE-SODIUM	0.3	25%	0.4	not needed	3.0	not applicable
PROPYZAMIDE	0.08	100%	0.02	not needed	4.0	not applicable
PROSULFURON	0.06	100%	0.02	not needed	3.0	not applicable
PYMETROZINE	0.03	100%	0.03	0.1	1.0	3.3
PYRACLOSTROBIN	0.015	50%	0.03	0.03	1.0	1.0
PYRAFLUFEN-ETHYL	0.112	56%	0.2	0.2	1.0	1.0
PYRIDATE	0.036	100%	0.036	not needed	1.0	not applicable
PYRIMETHANIL	0.12	72%	0.17	not needed	1.0	not applicable
QUINOXYFEN	0.14	70%	0.2	not needed	1.0	not applicable
RIMSULFURON	0.07	70%	0.1	not needed	1.0	not applicable
SILTHIOFAM	0.1	100%	0.064	not needed	1.6	not applicable
SPINOSAD	0.012	50%	0.024	not needed	1.0	not applicable
SPIROXAMINE	0.024	70%	0.025	not needed	1.4	not applicable
SULFOSULFURON	1	100%	0.24	not needed	4.2	not applicable
TEBUCONAZOLE	0.03	100%	0.03	0.03	1.0	1.0
TEPRALOXYDIM	0.06	100%	0.025	0.4	2.4	6.7
THIACLOPRID	0.02	100%	0.01	0.03	2.0	1.5
THIAMETHOXAM	0.08	100%	0.026	0.5	3.1	6.3
THIFENSULFURON-METHYL	0.07	100%	0.01	not needed	7.0	not applicable
THIOPHANATE-METHYL	0.08	100%	0.08	0.2	1.0	2.5
TOLCLOFOS-METHYL	0.2	100%	0.064	not needed	3.1	not applicable
TOLYLFLUANID	0.3	100%	0.1	0.25	3.0	0.8
TRIADIMENOL	0.05	100%	0.05	0.05	1.0	1.0
TRIBENURON-METHYL	0.07	100%	0.01	0.2	7.0	2.9
TRICLOPYR	0.05	100%	0.03	0.3	1.7	6.0
TRIFLOXYSTROBIN	0.06	60%	0.1	not needed	1.0	not applicable

Active substance	AOEL*	Oral absorption	ADI *	ARfD*	AOEL / (ADI x Oral Abs %)	(ARfD x Oral Abs %) / AOEL
TRINEXAPAC	0.34	100%	0.32	not needed	1.1	not applicable
TRITICONAZOLE	0.025	100%	0.025	0.05	1.0	2.0
ZIRAM	0.015	50%	0.006	0.08	5.0	2.7
ZOXAMIDE	0.3	60%	0.5	not needed	1.0	not applicable

* Units for all AOELs, ADIs, and ARfDs are mg/kg bw/day
More details are provided for the first twenty substances (shown in lower case) in Table 2.

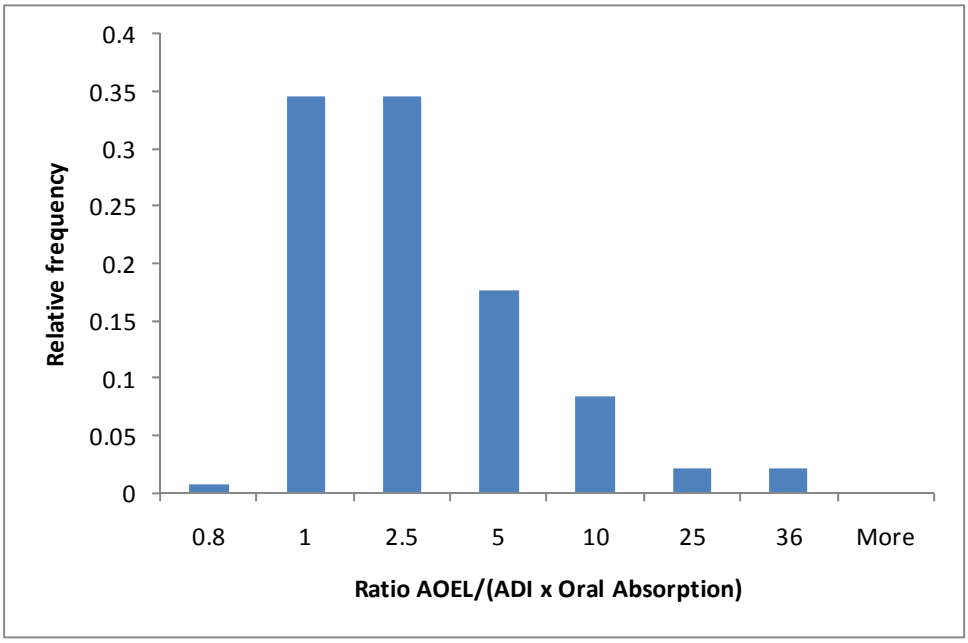

Figure 1 Distribution of ratios of AOEL:ADI, corrected for oral absorption, for 142 active substances included in Directive 91/414/EEC Annex 1

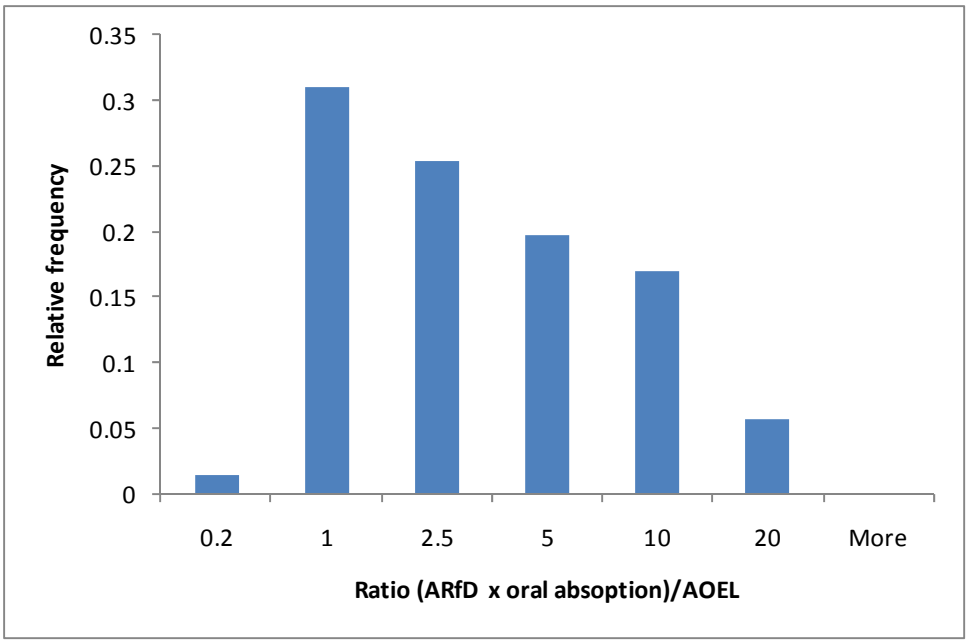

Figure 2 Distribution of ratios of ARfD:AOEL, corrected for oral absorption, for 71 actives substances where an ARfD was set when included in Directive 91/414/EEC Annex 1.

Table 2 Directive 91/414/EEC Annex I Reference doses and oral absorption values, with a comparisons of AOEL:ADI and ARfD:AOEL, both corrected for oral absorption and further toxicological details for the first twenty substances in Table 1. (note this information is available as a spreadsheet file – see below)

Active substance	AOEL*	NOAEL*	Oral absorption	SF	AOEL LOAEL*	AOEL study	AOEL effects	ADI *	NOAEL*	SF	ADI LOAEL*	ADI study	ADI effects	ARfD*	NOAEL*	SF	ARfD LOAEL*	ARfD study	ARfD effects	AOEL / (ADI x Oral Abs %)	(ARfD x Oral Abs %) / AOEL
Alpha cypermethrin	**0.01**	2.3	45%	100	6.75	90 day dog	clinical signs (irritation senconday to systemic toxicity)	**0.015**	1.5	100	3	1 year dog	clinical signs (irritation senconday to systemic toxicity)	**0.04**	4	100	20	rat acute neurotoxicity study	death and severe clinical and neurobehavioural changes	1.5	1.8
Amidosulfuron	**1.4**	144.1	100%	100	261	3month and one year dog studies	clin chem (increased potassium, glucose and magnesium levels) urinalysis (lower specific gravity)	**0.2**	22.5	100	153	2 generation rat study	reduced body weight and changes in organ weights (brain, seminal vesicles)	**not needed**						7.0	not applicable
Benthiavalicarb	**0.1**	10	100%	100	100	rat teratology study	increased adrenal and liver weights	**0.1**	9.9	100	249.6 (dose spacing 0, 50, 200 (NOAEL), 5000 (LOAEL) and 10000)	2 year rat study	based on decreased MCV and MCH, increased Plt, increased γGT, increased liver/kidney weight, increased liver and kidney cell alterations	**not needed**						1	not applicable
Bifenthrin	**0.0075**	1.5	50%	100	3	1 year dog	Neurotoxic effect: tremors; reduction in tail latency; staggered gait and exaggerated hindlimb flexion	**0.015**	1.5	100	3 (dog) 2 (rat)	1 year dog + developmental studies (rat)	Neurotoxic effect: tremors; reduction in tail latency; staggered gait and exaggerated hindlimb flexion (maternal toxiticity; reduced bodyweight gain and tremours)	**0.03**	35	100	11.8	90 day neurotoxicity study	tremours	1.0	2.0
Benfluralin	**0.05**	17	33%	100	74	90 day rat study	liver weight increase, liver/spleen pigmentation (haemosiderosis?), RBC effects	**0.005**	0.5	100	5.4	2 year rat study	liver cell pigmentation, hyalin droplets, liver and thyroid tumours	**not needed**						30	not applicable
Bromoxynil	**0.01**	1 (dog)	100%	100	7.14 (rat) 11.1 (dog)	90 day rat/dog	reduction in bodyweight gains and effects on the liver (increased weights hyperplasia)	**0.01**	1.3 (18 month mouse)	100	4	18 month mouse supported by 1 year dog	reduction in body weight and effects on the liver; (liver tumours mouse)	**0.04**	4	100	12.5	rat developemental	malformations (pronounced narrowing of the aortic arch - possibly treatment related, increased incidence of 14th thoracic ribs	1.0	4.0
Bromuconazole	**0.025**	2.5	100%	100	25	3 month and one year dog studies	liver weight increase, increased alkaline phosphatase and transaminase activity, adrenal cortical vacuolation	**0.01**	0.88-1.09	100	6.48	2 year rat study	based on increased incidence of periacinar hepatocyte vacuolation, and clear cell foci	**0.1**	10	100	70	rat developemental	based on increased incidence of 7th cervical ribs, and increased placental weights	2.5	4.0
Chlormequat	**0.04**	4	100%	100	10	1 year dog study	neurological effects (increased salivation and diarrhea)	**0.04**	4	100	10	1 year dog study	neurological effects (increased salivation and diarrhea)	**0.09**	9	100	13	4-week dog studies	neurological effects (increased salivation) manifested from the first week of treatment	1.0	2.3
Chlorothalonil	**0.009**	1.5	30%	100	10.6	2 year rat study	pre-neoplastic and neoplastic lesions in the kidney and the forestomach	**0.015**	1.5	100	3	90 day rat	histopathological changes in the stomach and the kidneys as well as an increase of the organ weight for kidneys	**0.6**	60 (single dose rat)	100	175	several studies; single dose, 28 day and mechanistic all in the rat	changes in kidney histopathology, and in renal cell proliferation (as measured by BrdU incorporation	2.0	20

Active substance	AOEL*	NOAEL*	Oral absorption	SF	AOEL LOAEL*	AOEL study	AOEL effects	ADI *	NOAEL*	SF	ADI LOAEL*	ADI study	ADI effects	ARfD*	NOAEL*	SF	ARfD LOAEL*	ARfD study	ARfD effects	AOEL / (ADI x Oral Abs %)	(ARfD x Oral Abs %) / AOEL
Chlorpyrifos	**0.01**	1	100%	100	5	90-day rats, mice and dogs	Nervous system / Inhibition of Acetyl-cholinesterase	**0.01**	1	100	3	2-years rats, mice and dogs	Nervous system / Inhibition of Acetyl-cholinesterase	**0.1**	10	100	50	Acute and delayed neurotoxicity studies in rats	FOB Changes	1.0	10
Chlorsulfuron	**0.43**	60.6	73%	100	254.6	1 year dog study	reduced body weight gain in females, and increased testicular weight in males	**0.2**	20	100	104	2 year rat study	decreased body weight and body weight gain	**not needed**						2.9	not applicable
Clodinafop-propargyl	**0.026**	3.4	75%	100	7.5	1 year dog study	Skin lesions, changes in haematological parameters (indicative of anaemia) and in biochemical parameters (liver) vacuolated cell foci in the adrenal cortex, focal atrophy of the zygomatic glands.	**0.003**	0.32	100	10.2	2 year rat study	changes in haematological parameters (indicative of anaemia) and in clinical biochemical parameters (liver), increased liver, kidney and ovary weights, decreased testes weights. Increased incidence of non-neoplastic changes in liver, ovary, lungs, kidneys, thyroid and adenohypophysis, increased incidence of neoplastic changes in liver (benign and malignant hepatocellular tumours), prostate (adenomas), and ovaries (tubular adenomas)	**0.05**	44	100	44	two-generation reproduction study in rats	decreased pup weight, pup losses, delayed physical development and macroscopic changes in the kidneys	12	1.4
Clofentazine	**0.01**	2.65	50%	100	26.5	90 day rat study	Increased liver weights and decreased haemoglobin	**0.02**	2 (rat) 1.7 (dog)	100	33 (dog) 17.3 (rat)	2 year rat, 1 year dog	rat: slight increase in the number of follicular cell tumours in the thyroid and Increased relative liver weights and liver cell hypertrophy, characterized by centrilobular hepatocyte enlargement and by vacuolisation and fat deposits. dog: increased liver weights	**not needed**						1.0	not applicable
Cymoxanil	**0.01**	1.3	75%	100	5.7	3 month and one year dog studies	reduced plasma Na and K, increased MCV and reduced MCHC	**0.013**	1.3	100	5.7	1 year dog	reduced plasma Na and K, increased MCV and reduced MCHC	**0.08**	8	100	16	rabbit developemental study	reduced maternal bodyweight gain	1.0	6.0

Active substance	AOEL*	NOAEL*	Oral absorption	SF	AOEL LOAEL*	AOEL study	AOEL effects	ADI *	NOAEL*	SF	ADI LOAEL*	ADI study	ADI effects	ARfD*	NOAEL*	SF	ARfD LOAEL*	ARfD study	ARfD effects	AOEL / (ADI x Oral Abs %)	(ARfD x Oral Abs %) / AOEL
Cyprodinil	**0.03**	3.14	100%	100	18.95	90 day rat	Body weight reduction .Minor liver changes (hepatocellular hyperthrophy and necrosis in the rat) and increased weight of thyroids and hyperthrophy of follicular epithelium in the rat	**0.03**	2.7	100	35.6	2 year rat study	Increased relative liver and kidney weight in the rat. Degenerative changes in the liver	**not needed**						1.0	not applicable
Dichlorprop-p	**0.35**	35	100%	100	114	90 day rat	Reduced bodyweight and bodyweight gain, increase liver weights, eosinophillic cytoplasm, decreased RBC parameters.	**0.06**	6	100	59	18 month mouse study	Increased incidence and severity of chronic nephropathy in the kidneys (mouse).	**0.5**	50	100	100	rabbit developemental study	Reduced maternal bodyweight and bodyweight gain	5.8	1.4
Diflubenzuron	**0.0066**	2	33%	100	10	1 year dog study	Increase in MetHb	**0.012**	1.2	100	6.4	91 week mouse stduy	Increased methaemoglobin and sulfhaemoglobin.	**0.4**	80 (LOAEL)	200	not applicable	28 day rat study	Increased methaemoglobin	1.7	20
Diflufenican	**0.11**	19.47	58%	100	196.6 (10 fold dose spacing)	90 day rat study	Reduced bodyweight gain, liver (hepatocyte hypertrophy)	**0.2**	23.27	100	119.6	2 year rat study	reduced bodyweight gain	**not needed**						0.9	not applicable
Diphenylamine	**0.1**	9.6 (rat) 10 (dog)	100%	100	25 (dog)	90 day rat, 90 day and one year dog	RBC; Splenic congestion and haemosiderosis; extramedullary haematopoiesis; clinical chemistry	**0.075**	7.5	100	24.9	2 year rat	Red blood cell, splenic congestion with haemosiderosis, and related histopathological changes in the spleen, kidney and liver	**not needed**						1.3	not applicable
Ioxynil	**0.01**	1	100%	100	7.2 (rat) 3 (dog)	90 day rat/dog	liver (hypertrophy and enzyme induction) and thyroid effects (hyperactivity).	**0.005**	0.5	100	1.5	2 year rat study	reduced bodyweight gain, liver (hypertrophy and enzyme induction) and thyroid (hyperactivity)	**0.04**	4	100	12	rat developemental	fetal effects (reduced weight and length)	2.0	4.0

It is recognised that the legibility of this table is poor. A file containing the spreadsheet use to form this Table is embedded below; for those not reading an electronic version of this paper it is available from CRD.

Microsoft Excel Worksheet