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Comparison of Acute NOAELs and Benchmark Doses for Female Brain Cholinesterase Inhibition

In cumulative risk assessment, it is important to characterize both the time frame for exposure (e.g., What is the exposure duration?) and for the toxic effect (e.g., What are the time to peak effects and the time to recovery?). In the Preliminary Cumulative Risk Assessment of the Organophoshate Pesticides (OPs) relative potency factors (RPFs) for 29 chemicals and points of departure (PODs) and the index chemical were determined based on whole brain cholinesterase (ChE) data from toxicity studies of 21 days and longer. The Office of Pesticide Programs has argued that the use of steady state data for relative potency determination generates relative potency factors (RPFs) that are reproducible and reflect less variability than RPFs derived from single-dose or short-term studies where the extent of inhibition changes rapidly immediately following dosing.

OPP has posed a question to the FIFRA SAP for the February 5-8, 2002 review concerning how best to evaluate risk, taking into account the temporal characteristics of the hazard endpoint (i.e., cholinesterase inhibition) and the temporal characteristics of the exposure patterns for the food, drinking water, and residential/nonoccupational pathways. In order to facilitate the panel discussion, a table listing the available single dose toxicity studies performed with OPs has been made. Most of the studies are acute neurotoxicity (ACN) studies (OPPT Guideline 870.6200, OPP Guideline 81-8) administered by gavage. Acute lethality studies were not included. Dose levels, no-observed-adverse-effect levels (NOAELs), and no-observed-adverse-effect levels (LOAELs) for female brain ChE are also listed in the table. The NOAELs and LOAELs were extracted from study reviews called Data Evaluation Records prepared by toxicologists of OPP. Benchmark doses (BMD) from the Preliminary Cumulative Risk Assessment for OPs calculated from 21 days and longer are included for comparison.

- *Single dose oral toxicity studies with female whole brain ChE data* are not available for 19 OPs in the Preliminary Cumulative Risk Assessment (acephate, chlorethoxyphos, chlorpyrifos, chlorpyrifos-methyl, diazinon, dichlorvos, dimethoate, disulfoton, ethoprop, fosthiazate, malathion, methidathion, methyl-parathion, mevinphos, naled, pirimiphos-methyl, profenofos, tetrachlorvinphos, and tribufos);

- *Single dose oral toxicity studies with whole brain ChE data* are available for 13 OPs in the Preliminary Cumulative Risk Assessment (azinphos-methyl, bensulide, dicrotophos, fenthion, fenamiphos, methamidophos, ODM, phorate, phosalone, phosmet, phostebupirim, terbufos, and trichlorfon);

- As of 1/22/2001, calculation of the BMD_{10} for whole brain ChE measured from female rats from oral studies of 21 days and longer was on-going for chlorethoxyphos, profenofos, and phostebupirim;

- For the remaining 12 OPs, acute NOAELs are available for female whole brain ChE:

  - Acute NOAELs and the BMD_{10} from the >21 day studies for are *within approximately 3-fold* for 7 OPs (azinphos-methyl, bensulide, methamidophos phorate, phosmet, terbufos, and trichlorfon);

  - Acute NOAELs and the BMD_{10} from the >21 day studies for are *within 4-7-fold* for 2 OPs (fenthion and phosalone);

  - Acute NOAELs were not established for 3 OPs (dicrotophos, fenamiphos, and ODM) making comparisons to the BMD_{10} from the >21 day studies difficult.

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CHEMICAL	STUDY	MRID no.	Female Dose Levels (mg/kg)	Time of ChE measurement	Acute NOAEL Female Brain ChE (% decrease in ChE)	Acute LOAEL Female Brain ChE (% decrease in ChE)	FEMALE BMD_{10} [a]	FEMALE BMDL [b]
Acephate	ACN [c]	44203302	0, 0.5, 2.5, 5, 25, 125, 500	2.5 hours post dose	0.5 (Brain sections NOT whole brain)	2.5 (78-87%)	0.63	0.57
	ACN	44203303	0, 10, 100, 500	2.5 hours, 7 and 14 days post dose	< 10 (Brain sections NOT whole brain)	10 (39-44%)		
Azinphos-methyl	**ACN**	**43360301**	**0, 1, 3, 6**	**1.5 hours post dose**	**1 (5%)**	**3 (51%)**	**0.9**	**0.8**
Bensulide	**ACN**	**43195901**	**0, 15, 50, 150**	**6.75 hours and 15 days post dose**	**50 (0%)**	**150 (18-27%)**	**32.85**	**24.32**
Chlorethoxyphos	ACN	42559210	0, 0.32, 0.76, 0.746,	ChE not measured			N/A*	N/A*
Chlorpyrifos	ACN	42669101 42495401	0, 10, 50, 100	ChE not measured			0.83	0.57
Chlorpyrifos-methyl	ACN study not available						7.51	5.23
Diazinon	ACN	431302203	0, 2.5, 150, 300, 600	3, 9, and 24 hours post dose	2.5 (10%-0%) (Brain sections NOT whole brain)	150 (26- 73%)	3.43	1.03
	ACN	43132204 43132201	0, 2.5, 150, 300, 600	Brain ChE only measured 15 days post-dose				
Dichlorvos	ACN	42655301	0, 0.5, 35, 70	ChE not measured			2.25	1.39
Dicrotophos	ACN	43759801	0, 0.5, 5, 10	3 hours post dose	<0.5	0.5 (21%)	0.04	0.03

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Dimethoate	ACN	42865102	0, 2, 20, 200	ChE not measured			0.25	0.21
Disulfoton	ACN	42755801	0, 0.24, 0.76, 1.5, 5.2	Brain ChE not measured			0.07	0.05
Ethoprop	ACN	43197701	0, 5, 25, 50	Brain ChE only measured 15 days post-dose			1.7	0.87
	ACN	43442402	0,15.7, 33	1, 3, 8, 15 days post dose	<15.7 (Brain sections NOT whole brain)	15.7 (50 - 72%)		
Fenthion	**ACN**	**44326401**	**0, 1, 75, 225**	**5.5 hours post dose**	**<1**	**1 (9%)**	**0.24**	**0.2**
Fenamiphos	ACN	44041501	0, 0.37, 1.52, 2.31	50 min post dose	> 2.31 (1%)	> 2.31	2.11	1.12
Fosthiazate	Brain sections NOT whole brain (Study review on-going)						0.50	0.28
Malathion	ACN	43146701	0, 500, 1000, 2000	15 minutes, days 7 and 14 post dose	2000 (Brain sections NOT whole brain)	>2000	326.37	269.66
Methamidophos	ACN	42770301	0, 0.9, 3, 9	2 hours post dose	< 0.9	0.9 (24-39%)	**0.08**	**0.07**
	ACN	**43025001, 43445801**	**0, 0.3, 0.7**	**2 hours post dose**	**0.3**	**0.7 (15-27%)**		
Methidathion	ACN	43145903	Brain sections NOT whole brain (Study review on-going)				0.22	0.19
	ACN	43145901	ChE not measured (Study review on-going)					

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Methyl parathion	ACN	443254401	0, 0.025, 7.5, 15	1.5 hours, 7 and 14 days post dose	0.025 (Brain sections NOT whole brain)	7.5 (76-85%)	1.41	1.05
Mevinphos	ACN	42985402, 42985401	0, 0.025, 0.1, 2.0, 3.5	45 minutes, 7 and 15 days post dose	0.1 (Brain sections NOT whole brain)	2 (25%)	0.06	0.05
Naled	ACN	42861301	ChE not measured (Study review on-going)				1	0.81
	ACN	43189601	ChE not measured (Study review on-going)					
ODM	ACN	43929901	0, 2.5, 10, 50	1.5 hours, 7 and 15 days post dose	< 2.5	2.5 (39%)	0.09	0.08
Phorate	**ACN**	**44719901**	**0, 0.25, 0.50, 1.0**	**4-5 hours and day 15 post dose**	**0.5**	**1 (65.2%)**	**0.21**	**0.19**
Phosalone	**ACN**	**44852503**	**0, 10, 25, 60**	**6 hours, days 8 and 15 post dose**	**25 (8%)**	**60 (22%)**	**3.38**	**2.6**
Phosmet	**ACN**	**44673301 44706501**	**0, 3, 4.5, 22.5**	**3 hours, 7 and 14 days post dose**	**4.5**	**22.5 (70%)**	**4.13**	**2.67**
Phostebupirim	ACN	43819801	0, 0.25, 0.5, 1	1 hour post dose	0.5	1.0 (53%)	N/A	NA
Pirimiphos-methyl	ACN	43594101	0, 15, 150, 1500	24 hours and 15 days post dose	15 (brain sections NOT whole brain)	150 (13-28%)	2.88	2.21
Profenofos	ACN	42939801 42939802	0, 95, 190, 380	Brain ChE only measured 14 days post dose			N/A	N/A
Terbufos	**ACN**	**44672003**	**0, 0.15, 0.30, 0.90**	**6 hours and day 15 post dose**	**0.30**	**0.90 (51%)**	**0.1**	**0.07**

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Tetrachlorvinphos	ACN	42912501	0, 65, 325, 650	ChE not measured			101.92	66.64
Tribufos	ACN	45194401		Brain ChE only measured 3 days post dose			1.81	1.54
Trichlorfon	**ACN**	**44578001**	**0, 10, 50, 200**	**1.5 hours post dose**	**10**	**50 (30%)**	**6.03**	**2.74**

*BMD_{10} and BMDL calculation for chlorethoxyfos, profenofos, and phostebupirim not yet complete as of 1/22/2002
a BMD_{10} = Benchmark dose resulting in 10% decrease in cholinesterase activity. Calculated from toxicity studies of 21 days and longer
b BMDL = Lower confidence interval on the BMD_{10}
c ACN = Acute neurotoxicity study