Annex I to the CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2

International Chemical Identification: Pirimiphos-methyl (ISO); O-[2-(diethylamino)-6-methylpyrimidin-4-yl] O,O-dimethyl phosphorothioate

EC Number: **249-528-5**

CAS Number: **29232-93-7**

Index Number: **015-134-00-5**

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Chemicals Regulation Division
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CONTENTS

1 HEALTH HAZARDS

1.1 Carcinogenicity

1.1.1 Animal data

1.1.1.1 Two-year combined chronic toxicity/carcinogenicity study in rats – Historical control data

Study reference:
[Anon., et al, 1974]
Detailed study summary and results:
Test type
Study pre-dated OECD and GLP guidelines
Test substance

- *Pirimiphos-methyl (86.8% pure)*

Test animals

- *Rat (Alpk:APfsd Wistar BABU)*
- *48/sex/dose*

Administration/exposure

- *Oral*
- *40/sex/dose – 104 weeks, 8/sex/dose 108 – 112 weeks*
- *0, 10, 50 & 300 ppm, equivalent to: 0, 0.4, 2.1 and 12.6 mg/kg bw/day (mean value across both sexes)*
- *Daily*
- *Historical control data – provided below*
- *Satellite groups 24/dose/sex sacrificed at 12, 26 amd 52 weeks to provide interim data on cholinesterase and clotting function.*

Study findings:

Table A1. Neoplastic findings in male and female rats treated with pirimiphos-methyl for 104 weeks.

	Males				Females			
Dose (ppm)	0	10	50	300	0	10	50	300
Total number of animals	48	48	48	48	48	48	48	48
Animals investigated*	42	43	45	42	43	45	46	47
Pancreas, islet cell adenoma	0	0	0	4 (9.5 %)	1	0	0	0
Pancreas, islet cell carcinoma	0	0	0	1 (2.4 %)	0	0	0	0

Brain, meningioma (B)	1 (2.4 %)	1 (2.3 %)	2 (4.4 %)	2 (4.8 %)	0	0	1 (2.2 %)	0
Brain, ependymoma (B/M)	0	0	0	0	0	0	0	1 (2.1 %)
Brain, ganglioneuroma (B)	0	0	0	0	0	0	0	1 (2.1 %)

Historical Control Data

Syngenta were requested to provide historical control data for the neoplastic findings in the brain and pancreas of treated rats. The historical control data was originally collated in 2004 in response to the request for additional data from PSD. The data was not considered by EFSA at the time of the original application for pesticide approval and is therefore being submitted as new data to provide context to the conclusion that the tumours recorded are spontaneous and unrelated to treatment. The tables below show the full incidences tumours found in control animals in a number of studies carried out between 1984 – 2004.

Ganglionneuromas

There was a single incidence of ganglioneuroma in one female of the top dose group as seen in table A1. There were no reported cases in previously submitted historical control data submitted to the RMS in 2000. Following submission of more recent historical control data from the applicants lab using the same strain of rat Alpk:APfsd Wistar BABU. This data confirms that the overall incidence of ganglioneuroma remained unchanged over a 20 to 25 year period and that this tumour type occurs sporadically at a low incidence in control animals. Table A2 below shows the historical control data for benign and malignant ganglioneuroma (CTL: 1984 – 2004).

Given this data, it is considered that an incidence of greater than one would be required for a positive correlation to be determined between pirimiphos-methyl administration and this tumour type. In the absence of greater numbers, the single incidence of this tumour type is considered spontaneous and incidental to treatment. Further to this, there is little precedent in the literature for chemical carcinogenesis of this tumour type.

Table A2. Historical control data for benign and Malignant Ganglioneuroma (CTL: 1984 – 2004)

Study	Start Date	ADRENAL GLAND								BRAIN				THYROID GLAND			
		Benign Ganglioneuroma				Malignant Ganglioneuroma				Benign Ganglioneuroma				Benign Ganglioneuroma			
		incidence				incidence				incidence		incidence		Incidence		Incidence	
		Females		Males		Females		Males		Females		Males		Females		Males	
A	1984/02	0/104	(0.0)	0/104	(0.0)	0/104	(0.0)	0/104	(0.0)	0/104	(0.0)	0/104	(0.0)	0/104	(0.0)	0/104	(0.0)
B	1984/10	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)
C	1985/02	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)
D	1985/08	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)
E	1986/10	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)
F	1987/02	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)
G	1987/11	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)
H	1988/06	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)
I	1989/09	0/56	(0.0)	0/56	(0.0)	0/56	(0.0)	0/56	(0.0)	0/56	(0.0)	0/56	(0.0)	0/56	(0.0)	0/56	(0.0)
J	1990/04	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)
K	1990/07	0/52	(0.0)	**1/52**	**(1.9)**	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)
L	1992/04	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)
M	1992/05	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)
N	1992/11	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)
O	1994/05	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	**1/52**	**(1.9)**	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)
P	1994/11	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)
Q	1995/01	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)
R	1995/02	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)
S	1996/04	0/51	(0.0)	0/49	(0.0)	0/51	(0.0)	0/49	(0.0)	0/51	(0.0)	0/49	(0.0)	0/51	(0.0)	0/49	(0.0)
T	1996/05	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)
U	1998/02	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)
V	1998/04	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)	0/52	(0.0)
W	2000/06	0/104	(0.0)	0/104	(0.0)	0/104	(0.0)	0/104	(0.0)	0/104	(0.0)	0/104	(0.0)	0/104	(0.0)	**1/104**	**(1.0)**

Ependymoma

The results presented in A1 shown one case of ependymal cell tumour in a top-dose group female. One case of ependymoma out of a total of 19 control males (5.3 %) has previously been reported. In the most recent historical control data submitted from the applicants lab, with the same strain of rat, the overall incidence of ependymoma was confirmed as unchanged for a 20 - 25 year period. The results from this historical data for malignant ependymoma can be seen in table A3 below.

Table A3. Historical Control Data for: Malignant Ependymoma (CTL:1984-2004)

Study Reference	Start Date	Incidence Males	Incidence Females
A	1984/02	0 /104 (0.0 %)	0 /104 (0.0 %)
B	1984/10	0 /52 (0.0 %)	0 /52 (0.0 %)
C	1985/02	0 /52 (0.0 %)	0 /52 (0.0 %)
D	1985/08	0 /52 (0.0 %)	0 /52 (0.0 %)
E	1986/10	1 /52 (1.9 %)	0 /52 (0.0 %)
F	1987/02	0 /52 (0.0 %)	0 /52 (0.0 %)
G	1987/11	0 /52 (0.0 %)	0 /52 (0.0 %)
H	1988/06	0 /52 (0.0 %)	0 /52 (0.0 %)
I	1989/09	0 /56 (0.0 %)	0 /56 (0.0 %)
J	1990/04	0 /52 (0.0 %)	0 /52 (0.0 %)
K	1990/07	0 /52 (0.0 %)	0 /52 (0.0 %)
L	1992/04	0 /52 (0.0 %)	0 /52 (0.0 %)
M	1992/05	0 /52 (0.0 %)	0 /52 (0.0 %)
N	1992/11	0 /52 (0.0 %)	0 /52 (0.0 %)
O	1994/05	0 /52 (0.0 %)	0 /52 (0.0 %)
P	1994/11	0 /52 (0.0 %)	1 /52 (1.9 %)
Q	1995/01	1 /52 (1.9 %)	0 /52 (0.0 %)
R	1995/02	0 /52 (0.0 %)	0 /52 (0.0 %)
S	1996/04	0 /49 (0.0 %)	0 /51 (0.0 %)
T	1996/05	0 /52 (0.0 %)	0 /52 (0.0 %)
U	1998/02	0 /52 (0.0 %)	0 /52 (0.0 %)
V	1998/04	0 /52 (0.0 %)	0 /52 (0.0 %)
W	2000/06	0 /104 (0.0 %)	0 /104 (0.0 %)

To conclude, for ependymoma, an incidence of greater than 1 would be required to form a positive correlation between the incidence of ependymoma and the administration of pirimiphos-methyl, therefore , in the absence of greater numbers, the single incidences of this tumour type is considered spontaneous and incidental to treatment. As with ganglioneuroma, there is little in the literature to indicate chemical carcinogenesis of this tumour type.

Tumour of the meninges

In recent historical data submitted by the applicant using the same strain of rat, it was confirmed that the overall incidence of meningioma remained unchanged over a 20 to 25 year period. This confirms that this tumour occurs sporadically at a low incidence in control animals. It is however not a rare tumour. The results of this historical control data can be seen in Table A4 below.

Table A4. Historical Control Data for: Meningioma (CTL:1984 – 2004)

Study Reference	Start Date	Incidence Males	Incidence Females
A	1984/02	1 /104 (1.0 %)	1 /104 (1.0 %)
B	1984/10	1 /52 (1.9 %)	1 /52 (1.9 %)
C	1985/02	0 /52 (0.0 %)	0 /52 (0.0 %)
D	1985/08	0 /52 (0.0 %)	1 /52 (1.9 %)
E	1986/10	1 /52 (1.9 %)	0 /52 (0.0 %)
F	1987/02	0 /52 (0.0 %)	0 /52 (0.0 %)
G	1987/11	2 /52 (3.8 %)	0 /52 (0.0 %)
H	1988/06	1 /52 (1.9 %)	0 /52 (0.0 %)
Study Reference	Start Date	Incidence Males	Incidence Females
I	1989/09	0 /56 (0.0 %)	0 /56 (0.0 %)
J	1990/04	1 /52 (1.9 %)	1 /52 (1.9 %)
K	1990/07	0 /52 (0.0 %)	0 /52 (0.0 %)
L	1992/04	0 /52 (0.0 %)	0 /52 (0.0 %)
M	1992/05	0 /52 (0.0 %)	0 /52 (0.0 %)
N	1992/11	0 /52 (0.0 %)	0 /52 (0.0 %)
O	1994/05	0 /52 (0.0 %)	0 /52 (0.0 %)
P	1994/11	0 /52 (0.0 %)	0 /52 (0.0 %)
Q	1995/01	0 /52 (0.0 %)	1 /52 (1.9 %)
R	1995/02	0 /52 (0.0 %)	0 /52 (0.0 %)
S	1996/04	0 /49 (0.0 %)	0 /51 (0.0 %)
T	1996/05	1 /52 (1.9 %)	0 /52 (0.0 %)
U	1998/02	1 /52 (1.9 %)	1 /52 (1.9 %)
V	1998/04	0 /52 (0.0 %)	0 /52 (0.0 %)
W	2000/06	0 /104 (0.0 %)	0 /104 (0.0 %)

The incidence of meningioma seen in the 2-year rat study with pirimiphos methyl is similar to that observed in control animals from contemporary and more recent studies conducted by the applicant, and are therefore considered spontaneous and incidental to treatment. There was no evidence of benign meningioma in the pirimiphos-methyl 78-week mouse study conducted in 1996.

Pancreatic islet cell tumours in rats

The incidence of islet cell tumours was questioned in top-group males upon review of the 2-year pirimiphos-methyl feeding study.

Historical control data from more recent studies using the same strain of rat, confirm that the overall incidence of islet cell tumours has remained unchanged over the last 20 - 25 years, confirming that this tumour occurs sporadically in control animals and at a similar incidence to the study in question. The results of this data can be seen in Tables A5 and A6 below.

Table A5. Historical Control Data for Islet Cell Adenoma (CTL: 1984-2004)

Study Reference	Start Date	Male	Female
A	1984/02	2 /103 (1.9 %)	3 /103 (2.9 %)
B	1984/10	1 /52 (1.9 %)	2 /52 (3.8 %)
C	1985/02	2 /52 (3.8 %)	0 /52 (0.0 %)
D	1985/08	0 /52 (0.0 %)	0 /52 (0.0 %)
E	1986/10	2 /52 (3.8 %)	1 /52 (1.9 %)
F	1987/02	0 /52 (0.0 %)	0 /52 (0.0 %)
G	1987/11	2 /52 (3.8 %)	1 /51 (2.0 %)
H	1988/06	0 /52 (0.0 %)	0 /52 (0.0 %)
I	1989/09	0 /56 (0.0 %)	2 /56 (3.6 %)
J	1990/04	0 /52 (0.0 %)	0 /52 (0.0 %)
K	1990/07	1 /52 (1.9 %)	1 /52 (1.9 %)
L	1992/04	5 /52 (9.6 %)	0 /51 (0.0 %)
M	1992/05	0 /52 (0.0 %)	0 /52 (0.0 %)
N	1992/11	2 /52 (3.8 %)	0 /52 (0.0 %)
O	1994/05	2 /52 (3.8 %)	1 /52 (1.9 %)
P	1994/11	0 /52 (0.0 %)	0 /52 (0.0 %)
Q	1995/01	0 /52 (0.0 %)	0 /52 (0.0 %)
R	1995/02	1 /52 (1.9 %)	0 /52 (0.0 %)
S	1996/04	3 /51 (5.9 %)	1 /52 (1.9 %)
T	1996/05	1 /51 (2.0 %)	1 /52 (1.9 %)
U	1998/02	1 /52 (1.9 %)	0 /52 (0.0 %)
V	1998/04	1 /52 (1.9 %)	0 /51 (0.0 %)
W	2000/06	4 /103 (3.9 %)	0 /103 (0.0 %)

Table A6. Historical Control Data for : Islet Cell Adenocarcinoma (CTL:1984-2004)

Study Reference	Start Date	Male	Female
A	1984/02	0 /103 (0.0 %)	0 /103 (0.0 %)
B	1984/10	0 /52 (0.0 %)	1 /52 (1.9 %)
C	1985/02	0 /52 (0.0 %)	0 /52 (0.0 %)
D	1985/08	1 /52 (1.9 %)	0 /52 (0.0 %)
E	1986/10	0 /52 (0.0 %)	0 /52 (0.0 %)
F	1987/02	2 /52 (3.8 %)	0 /52 (0.0 %)
G	1987/11	0 /52 (0.0 %)	0 /51 (0.0 %)
H	1988/06	0 /52 (0.0 %)	0 /52 (0.0 %)
I	1989/09	0 /56 (0.0 %)	0 /56 (0.0 %)
J	1990/04	0 /52 (0.0 %)	0 /52 (0.0 %)
K	1990/07	1 /52 (1.9 %)	0 /52 (0.0 %)
L	1992/04	0 /52 (0.0 %)	0 /51 (0.0 %)
M	1992/05	0 /52 (0.0 %)	0 /52 (0.0 %)
N	1992/11	0 /52 (0.0 %)	0 /52 (0.0 %)
O	1994/05	0 /52 (0.0 %)	0 /52 (0.0 %)
P	1994/11	1 /52 (1.9 %)	0 /52 (0.0 %)
Q	1995/01	0 /52 (0.0 %)	0 /52 (0.0 %)
R	1995/02	1 /52 (1.9 %)	0 /52 (0.0 %)
S	1996/04	0 /51 (0.0 %)	0 /52 (0.0 %)
T	1996/05	0 /51 (0.0 %)	0 /52 (0.0 %)
U	1998/02	0 /52 (0.0 %)	0 /52 (0.0 %)
V	1998/04	0 /52 (0.0 %)	0 /51 (0.0 %)
W	2000/06	0 /103 (0.0 %)	0 /103 (0.0 %)

Therefore, the incidence of islet cell tumours recorded in the 2-year pirimiphos-methyl feeding study can be considered incidental to treatment.