

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 :

Perfluoroheptanoic acid (PFHpA)

EC Number : 206-798-9
CAS Number : 375-85-9
Index Number : not available

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1 PHYSICAL HAZARDS

Not evaluated in this CLH dossier.

2 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Not evaluated in this CLH dossier.

3 HEALTH HAZARDS

3.1 Acute toxicity - oral route

Not evaluated in this dossier.

3.2 Acute toxicity - dermal route

Not evaluated in this dossier.

3.3 Acute toxicity - inhalation route

Not evaluated in this dossier.

3.4 Skin corrosion/irritation

Not evaluated in this dossier.

3.5 Serious eye damage/eye irritation

Not evaluated in this dossier.

3.6 Respiratory sensitisation

Not evaluated in this dossier.

3.7 Skin sensitisation

Not evaluated in this dossier.

3.8 Germ cell mutagenicity

Not evaluated in this dossier.

3.9 Carcinogenicity

Not evaluated in this dossier.

3.10 Reproductive toxicity

3.10.1 Animal data

3.10.1.1 Combined 90-day repeated dose toxicity study with reproduction/developmental toxicity screening (anonymous, 2017)

Study reference:

Anonymous (2017)

Detailed study summary and results:

Test type

OECD TG 408 and 422

Test substance

- Sodium perfluoroheptanoate
- *Degree of purity* : >99.3%

Test animals

- *Species/strain/sex* : sexually mature male and virgin female crl:CD1(ICR) mice
- *No. of animals per sex per dose* :
 - F0 generation : Main study phase : 20/sex/dose (except for females of the control and the highest dose : 25)
Clinical pathology phase : 15/sex/dose
 - F1 generation : 16-20/sex/group
- *Age and weight at the study initiation* : approx. 6w old

Administration/exposure

- *Route of administration* : gavage
- *duration and frequency of test/exposure period* : daily
 - F0 : males : 90d prior to mating, throughout mating and until necropsy : total of 113d, approximatively
Females : 90d prior to pairing, throughout gestation and until lactation d21 : total of 142d, approximatively; except for 5 extra females in control and highest dose groups which were not used for mating (used for gender comparison) : total of 109d (euthanised at the same time point as males)
For clinical pathology : necropsy after d75
 - F1 : PND 22 to 42 (necropsy PND43)
- *doses/concentration levels* : 0, 0.5, 10 and 50 mg/kg bw/d
- *vehicle*: deionized water

Description of test design:

- 20 F0 animals/sex/group paired to produce F1 litters. Moreover, 5 females in control and highest dose groups were not paired but continued to receive the test substance (for gender comparison).

- Clinical pathology evaluation (hematology, coagulation and serum chemistry) on 15 F0 animals/sex/group and the 5 non-mated females in control and highest dose groups at the scheduled necropsy (week 15)
- F0 males and non-mated females were euthanized at the end of mating period. F0 females were euthanized on lactation d21 for females that delivered or postmating d23 for females that failed to deliver.
- F1 pups randomly selected for the F1 generation (1/sex/litter/group). Remaining pups were necropsied on PND21.

Results and discussion

Clinical pathology phase :

- *time of death during the study and whether animals survived to termination* : no treatment-related effects
- *body weight data* : no effects

Table 1 : Mean body weight data (in g)

	Males				Females			
Dose level (in mg/kg bw/d)	0	0.5	10	50	0	0.5	10	50
D0	28.4	28.5	28.4	28.5	22.7	22.3	22.5	22.3
D35	33.9	35.2	36.1	33.8	25.8	24.9	25.1	25.2
D75	37.0	38.7	39.3	36.7	28.2	27.4	28.2	26.9

- *food consumption* : no effects
- *Hematology and coagulation* : no treatment-related effects (no significant effect observed)
- *Clinical biochemistry findings (at D75)* :
 - higher AST value in males exposed to the highest dose level and in females at all dose levels (63/112, 67/215, 79/258 and 86/228 U/L in males/females respectively at 0, 0.5, 10 and 50 mg/kg bw/d)
 - higher ALT value in both sexes at the mid and high dose levels (47/36, 39/47, 109/70 and 122/98 U/L in males/females respectively at 0, 0.5, 10 and 50 mg/kg bw/d)
 - higher ALP value in both sexes at the highest dose (122/101, 78/115, 68/95 and 227/166 U/L in males/females respectively at 0, 0.5, 10 and 50 mg/kg bw/d)
- *necropsy findings* : no effects
- *organ weight* : not evaluated in this phase
- *histopathological findings*: not evaluated in this phase

Main study phase :

F0 generation (per dose):

- *clinical observations*: no treatment-related effects

- *time of death during the study and whether animals survived to termination* : no treatment-related effects
- *body weight data* : no treatment related effects

Table 2 : Body weight data (in g)

Dose level (in mg/kg bw/d)	0	0.5	10	50
Males				
D0	28.2 (n=20)	28.1 (n=20)	28.2 (n=20)	27.8 (n=20)
D56	35.9 (n=20)	35.4 (n=20)	37.4 (n=19)	35.4 (n=20)
D109	37.1 (n=20)	36.6 (n=19)	38.2 (n=19)	36.8 (n=20)
Females				
D0	22.6 (n=25)	22.7 (n=20)	22.4 (n=20)	22.3 (n=24)
D56	26.2 (n=25)	26.6 (n=20)	27.1 (n=20)	26.5 (n=24)
D96	28.3 (n=7) ^{AB}	28.6 (n=1)	31.0 (n=1)	28.4 (n=6) ^{AB}
D109	27.8 (n=5) ^A	/	/	30.2 (n=5) ^A
GD0	26.6	27.4	27.6	27.2
GD18	50.0	49.9	53.5	52.0
LD1	33.4	34.0	35.5	34.5
LD21	25.6	36.0	37.5	36.7

A : 5 extra females in control and high dose levels not paired (gender comparison) ; B : females paired but not yet mated

- *ophthalmic findings* : no ophthalmic lesions observed
- *haematological findings* : no effects
- *clinical biochemistry findings* : effects were observed

Table 3 : Clinical biochemistry findings

Dose level (in mg/kg bw/d)	0	0.5	10	50
Males				
ALP (U/L)	77	74	74	227**
ALT (U/L)	51	86	41	165*
AST (U/L)	88	143	108	167
TG (mg/dL)	82	118	101	153*
Non-mated females				
ALP (U/L)	52	NA	NA	152*
ALT (U/L)	36	NA	NA	41
AST (U/L)	102	NA	NA	93
TG (mg/dL)	64	NA	NA	161**
Females lactation d21				
ALP (U/L)	129	95	87	99
ALT (U/L)	71	49	42*	56
AST (U/L)	142	124	101	147
TG (mg/dL)	88	120	89	137

* : $p < 0.05$; ** : $p < 0.01$

- *Thyroid hormone analysis* : Significantly lower T4 values were noted in males of the mid and high dose levels. (Not evaluated in females)
- *Functional observational battery* : no effects

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- *toxic response data by sex and dose including indices of mating, fertility, gestation, birth, viability and lactation; indicate the numbers used in calculating the indices* : reproductive parameters were unaffected

Table 4 : Reproductive parameters

Dose level (in mg/kg bw/d)		0	0.5	10	50	HCD
Mating index (%)	Male	100.0	100.0	100.0	100.0	88.8 – 100.0
	Female	100.0	100.0	100.0	100.0	95.0 – 100.0
Fertility index (%)	Male	90.0	100.0	94.7	85.0	84.0 – 100.0
	Female	90.0	100.0	95.0	85.0	88.0 – 100.0
Male copulation index (%)		90.0	100.0	94.7	85.0	86.7 – 100.0
Female conception index (%)		90.0	100.0	95.0	85.0	88.0 – 100.0

- *toxic or other effects on reproduction, offspring, postnatal growth*
- *number of P and F1 females cycling normally and cycle length* : the estrous cycle length was unaffected by the test substance (4.5, 5.0, 4.9 and 4.5d respectively at 0, 0.5, 10 and 50 mg/kg bw/d) (HCD : 4.4 – 7.0)
- *precoital interval (number of days until mating and number of estrous periods until mating)* : slight increase (2.2, 2.9, 2.7 and 2.9d respectively at 0, 0.5, 10 and 50 mg/kg bw/d) (HCD : 2.0 – 3.3)
- *number of implantations, corpora lutea, litter size* :
 - *mean number of implantation sites* : 11.9, 11.3, 12.8 and 11.8 respectively at 0, 0.5, 10 and 50 mg/kg bw/d
- *number of pre- and post-implantation loss*
- *number of dams with abortions, early deliveries, stillbirths, resorptions and/or dead fetuses*
- *duration of gestation (calculated from day 0 of pregnancy)* : similar in all groups (19.0, 19.0, 18.9 and 18.9d respectively at 0, 0.5, 10 and 50 mg/kg bw/d)
- *number of live births*
- *data on functional observations* : unaffected
- *necropsy findings* : unaffected
- *organ weight changes* : significantly higher liver weight was observed in both sexes

Table 5 : Organ weight values in males

Dose level (in mg/kg bw/d)		0	0.5	10	50
FBW (g)		36.9	36.2	38.2	37.2
Liver (g)	Abs.	1.8253	1.8342	2.1788**	3.1472**
	Rel.	4.948	5.062	5.689**	8.460**
Epididymides (g)	Abs.	0.1004	0.0964	0.1049	0.0972
	Rel.	0.272	0.267	0.276	0.262

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Testes (g)	Abs.	0.2448	0.2449	0.2501	0.2373
	Rel.	0.667	0.676	0.657	0.637
Thyroid/parathyroid (g)	Abs.	0.0042	0.0044	0.0041	0.0043
	Rel.	0.011	0.0012	0.011	0.012

** : p<0.01

Table 6 : Organ weight values in females

Dose level (in mg/kg bw/d)	Non-mated females				Females lactation d21				
	0	0.5	10	50	0	0.5	10	50	
FBW (g)	27.8	NA	NA	29.1	35.6	36.0	37.5	36.7	
Liver (g)	Abs.	1.4018	NA	NA	1.8879**	2.0740	2.2033	2.4908**	3.0901**
	Rel.	5.036	NA	NA	6.489**	5.799	6.113	6.639**	8.415**
Ovaries/oviducts (g)	Abs.	0.0251	NA	NA	0.0281	0.0327	0.0347	0.0303	0.0287
	Rel.	0.090	NA	NA	0.096	0.092	0.097	0.081	0.078
Thyroid/parathyroid (g)	Abs.	0.0038	NA	NA	0.0038	0.0051	0.0042*	0.0055	0.0049
	Rel.	0.013	NA	NA	0.013	0.014	0.012*	0.015	0.014
Uterus (g)	Abs.	0.2131	NA	NA	0.1576	0.2390	0.3073	0.2347	0.2051
	Rel.	0.769	NA	NA	0.544	0.674	0.853	0.628	0.562

NA : not applicable

- *histopathological findings: nature and severity :*
 - *liver :*

Table 7 : Histopathological changes seen in liver in males

Dose level (in mg/kg bw/d)		0	0.5	10	50
Total number animals examined		20	19	19	20
Number of animals without findings		16	2	2	0
Centrilobular hypertrophy of hepatocytes	Minimal	0	8	2	0
	Mild	0	7	2	9
	Moderate	0	2	13	11
Infiltrate, mononuclear cell	Minimal	4	7	2	2
Hepatocellular necrosis	Minimal	0	1	2	19
	Mild	0	0	0	1

Table 8 : Histopathological changes seen in liver in females

Dose level (in mg/kg bw/d)	Non-mated females				Females lactation d21			
	0	0.5	10	50	0	0.5	10	50
Total number animals examined	5	0	0	4	17	20	19	16
Number of animals without findings	1	NA	NA	0	16	2	0	0

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Centrilobular hypertrophy of hepatocytes	Minimal	0	NA	NA	0	0	8	2	0
	Mild	0	NA	NA	4	0	8	8	6
	Moderate	0	NA	NA	0	0	1	9	10
Infiltrate, mononuclear cell	Minimal	4	NA	NA	2	1	6	6	5
Hepatocellular necrosis	Minimal	0	NA	NA	1	0	0	4	7
	Mild	0	NA	NA	0	0	1	0	1

For F1 pups/litters (per dose) :

- *number of litter* : 16, 20, 18 and 16 respectively at 0, 0.5, 10 and 50 mg/kg bw/d
- *mean number of live pups (litter size)* : *live litter size at PND 0* : 11.2, 10.4, 11.9 and 11.0 respectively at 0, 0.5, 10 and 50 mg/kg bw/d
- *sex ratio at birth* : % of males per litter : 54.1, 55.4, 47.3 and 53.8 % respectively at 0, 0.5, 10 and 50 mg/kg bw/d
- *anogenital distance* :
 - *males* : 1.85, 1.85, 1.86 and 1.86 mm respectively at 0, 0.5, 10 and 50 mg/kg bw/d
 - *females* : 1.17, 1.19, 1.18 and 1.20 mm respectively at 0, 0.5, 10 and 50 mg/kg bw/d
- *viability index (pups surviving 4 days/total births)*
- *postnatal survival from birth to PND 4 (pre-selection)* : 99.6, 95.0, 99.6 and 89.3 % respectively at 0, 0.5, 10 and 50 mg/kg bw/d
- *postnatal survival from PND 4 (post-selection) to PND 21 (% per litter)* : 99.3, 99.4, 98.7 and 87.8 % respectively at 0, 0.5, 10 and 50 mg/kg bw/d
- *mean pup weight by sex* :

Table 9 : Mean offspring weight data (in g)

Dose level (in mg/kg bw/d)	Males				Females			
	0	0.5	10	50	0	0.5	10	50
PND 1	1.66	1.68	1.68	1.54*	1.58	1.61	1.59	1.52
PND 4	2.63	2.74	2.61	2.02**	2.59	2.66	2.48	2.03**
PND 10	5.95	6.03	5.80	5.00**	5.85	5.95	5.64	5.04**
PND21	11.65	11.55	10.98	9.72**	11.25	11.09	10.28	9.58**

* : p<0.05 ; ** : p<0.01

- *thyroid hormone analysis (PND 21)* :
 - *total T4 value* : 6.29, 6.53, 6.50 and 5.61 µg/dL in males respectively at 0, 0.5, 10 and 50 mg/kg bw/d and 6.31, 6.80, 6.81 and 6.47 dL in females respectively at 0, 0.5, 10 and 50 mg/kg bw/d
- *necropsy findings* :

- Necropsies of pups found dead : cleft palate was observed in 6 (1) and 3 (2) pups (litters) respectively in the low and high dose levels (1, 8, 3 and 28 examined pups respectively at 0, 0.5, 10 and 50 mg/kg bw/d)
- Scheduled pup necropsies (PND 21) : one male pup of the highest dose exhibited an enlarged parathyroid gland (17, 19, 18 and 16 examined pups respectively at 0, 0.5, 10 and 50 mg/kg bw/d)
- Necropsies of nonselected pups (PND 21) : one male pup of the highest dose showed opacity of the left eye (46, 44, 39 and 29 examined pups respectively at 0, 0.5, 10 and 50 mg/kg bw/d)
- *organ weight at PND21* :
 - *Thyroids/parathyroids* : 0.0021, 0.0019, 0.0018 and 0.0019 g in males respectively at 0, 0.5, 10 and 50 mg/kg bw/d and 0.0021, 0.0020, 0.0018 and 0.0018 g in females respectively at 0, 0.5, 10 and 50 mg/kg bw/d
- *histopathological findings* : no test substance related effect

For F1 (per dose):

- *data on physical landmarks in pups and other postnatal developmental data*
 - *balanopreputial separation* : 30.2, 30.2, 29.5 and 31.0 PND respectively at 0, 0.5, 10 and 50 mg/kg bw/d
 - *vaginal patency* : 29.9, 29.4, 30.1 and 33.1* PND respectively at 0, 0.5, 10 and 50 mg/kg bw/d
- *body weight* :

Table 10 : Body weight data (in g)

Dose level (in mg/kg bw/d)	Males				Females			
	0	0.5	10	50	0	0.5	10	50
PND 22	12.6	12.8	12.4	11.1	12.8	12.0	11.7	10.6**
PND 28	20.8	21.6	20.4	17.5**	18.3	17.8	17.0	15.0**
PND 35	26.8	27.1	27.0	24.8*	23.2	22.5	21.9	20.5**
PND 43	29.0	29.4	29.4	27.7	24.7	23.7	23.2*	22.1**

* : p<0.05 ; ** : p<0.01

- *Thyroid hormone analysis* : not evaluated
- *necropsy findings* : no test substance related effects
- *organ weight* : thyroid weight not evaluated

Table 11 : Organ weight data (in g)

Dose level (mg/kg bw/d)		Males				Females			
		0	0.5	10	50	0	0.5	10	50
FBW		29.0	29.6	29.4	27.7	24.7	23.7	23.2*	22.1**
Adrenal glands	Abs	0.0062	0.0072	0.0073	0.0075	0.0116	0.0098*	0.0102	0.0081**

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	Rela	0.022	0.025	0.025	0.027	0.047	0.041	0.044	0.036**
Brain	Abs	0.4651	0.4752	0.4641	0.4607	0.4707	0.4610	0.4580	0.4480*
	Rela	1.618	1.608	1.590	1.675	1.912	1.951	1.987	2.036
Liver	Abs	1.8019	1.8571	2.0644*	3.1381**	1.5775	1.5133	1.5513	1.8630**
	Rela	6.213	6.292	7.013**	11.309**	6.388	6.385	6.709	8.42**
Epididymides	Abs	0.0571	0.0593	0.0606	0.0561	-	-	-	-
	Rela	0.197	0.202	0.207	0.203	-	-	-	-
Testes	Abs	0.1962	0.1994	0.1998	0.1989	-	-	-	-
	Rela	0.680	0.691	0.678	0.720	-	-	-	-
Ovaries/oviducts	Abs	-	-	-	-	0.0233	0.0202	0.0209	0.0174
	Rela	-	-	-	-	0.094	0.085	0.090	0.078
Uterus	Abs	-	-	-	-	0.1740	0.1447	0.1481	0.1368
	Rela	-	-	-	-	0.704	0.605	0.640	0.613

* : p<0.05 ; ** : p<0.01

- *histopathology findings* : (brain not evaluated)

Table 12 : Histopathological changes seen in liver

		Males				Females			
		0	0.5	10	50	0	0.5	10	50
Dose level (in mg/kg bw/d)		0	0.5	10	50	0	0.5	10	50
Total number examined		17	20	18	14	17	20	18	16
Number examined without findings		10	3	1	0	10	8	6	0
Centrilobular hypertrophy of hepatocytes	Minimal	0	8	2	1	0	6	8	5
	Mild	0	8	10	5	0	1	3	9
	Moderate	0	1	5	8	0	0	0	2
Infiltrate, mononuclear cell	Minimal	7	5	1	3	7	8	5	5
	Mild	0	0	0	0	0	0	1	0
Hepatocellular necrosis	Minimal	0	0	2	7	0	0	3	8
	Mild	0	0	0	1				
	marked	0	0	0	1				

3.10.2 Human data

No available data

3.10.3 Other data (e.g. studies on mechanism of action)

No available data

3.11 Specific target organ toxicity – single exposure

Not evaluated in this CLH dossier.

3.12 Specific target organ toxicity – repeated exposure

See chapter 3.10 above.

3.13 Aspiration hazard

Not evaluated in this CLH dossier.

4 ENVIRONMENTAL HAZARDS

Not evaluated in this CLH dossier.