Committee for Risk Assessment

RAC

Annex 1

Background document

to the Opinion proposing harmonised classification and labelling at Community level of

diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide

ECHA/RAC/CLH-O-0000001405-81-01/A1

EC number: 278-355-8
CAS number: 75980-60-8

Adopted

27 October 2010

Proposal for Harmonised Classification and Labelling of a Chemical Substance

Substance Name:	diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide [IUPAC: (diphenylphosphinyl)-(2,4,6-trimethylphenyl)methanone]
EC Number:	278-355-8
CAS Number:	75980-60-8
Submitted by:	Federal Institute for Occupational Safety and Health (BAuA)
	Friedrich-Henkel-Weg 1-25
	D-44149 Dortmund
	Germany

Proposal for harmonised Classification and Labelling

Substance name: Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide [IUPAC: (Diphenylphosphinyl)-(2,4,6-trimethylphenyl)methanone]

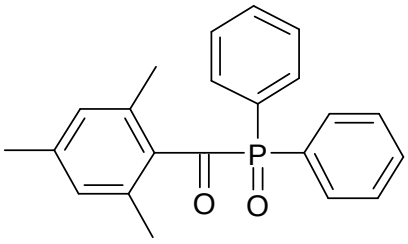
EC number: 278-355-8

CAS number: 75980-60-8

Registration number(s):

Molecular formula: $C_{22}H_{21}O_2P$

Structural formula:



Purity: 99.3 %

Impurities:

Proposed classification under Directive 67/548/EEC: Repr. Cat. 3; R62

Proposed classification under Regulation 1272/2008/EC: Repr. 2 - H361f

Proposed labelling under Directive 67/548/EEC:

Xn

R62

S(2),22, 36/37

Proposed labelling under Regulation 1272/2008/EC:

Symbol: GHS08

Signal Word: WARNING

H361f: Suspected of damaging fertility by causing atrophy of the testes.

Proposed specific concentration limits (if any): None.

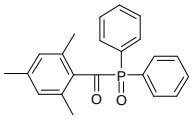
Proposed notes (if any): None.

The Risk Assessment Committee (RAC) received and reviewed the classification proposal for male fertility. A classification proposal for mutagenicity carcinogenicity, respiratory sensitisation, female fertility or developmental toxicity endpoints was not received by the RAC. The classification is based on the properties of the substance itself.

JUSTIFICATION

IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

Name: Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide
EC Number: 278-355-8
CAS Number: 75980-60-8
IUPAC Name: (Diphenylphosphinyl)-(2,4,6-trimethylphenyl)methanone
Molecular Formula: $C_{22}H_{21}O_2P$
Structural Formula:



Molecular Weight: 348.4 g/mol
Synonyms:

- Lucirin TPO
- Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide
- Chivacure TPO
- Darocur TPO
- Darocure TPO
- Genocure TPO
- Initiator 554
- Irgacure TPO
- L-TPO
- Lucirin 8893X
- Lucirin LR 8953
- Lucirin LR 8728
- Lucirin TPO solid
- Lucirin TPO-X
- Photocure TPO
- Speedcure TPO
- TPO-X

1.1 Purity/Impurities/Additives

Degree of purity: 99.3%

1.2 Physico-Chemical properties

Table 1 Summary of some physico-chemical properties

REACH ref Annex, §	Property	Value	Reference
VII, 7.1	Physical state at 20°C and 101.3 KPa	solid	
VII, 7.2	Melting / freezing point	85-92 °C	[1]
VII, 7.3	Boiling point	474.2°C (calculated)	[1]
VII, 7.5	Vapour pressure	3.045×10^{-6} Pa at 298 K	[1]
VII, 7.7	Water solubility	3.13 mg/L at 25 °C (calculated)	[2]
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.87 at 25°C (calculated)	[2]

MANUFACTURE AND USES

Not relevant for this dossier.

CLASSIFICATION AND LABELLING

The substance is not currently classified in Annex VI of Regulation (EC) No 1272/2008.

ENVIRONMENTAL FATE PROPERTIES

Not relevant for this dossier.

HUMAN HEALTH HAZARD ASSESSMENT

1.3 Toxicokinetics (absorption, metabolism, distribution and elimination)

No data available.

1.4 Acute toxicity

Not relevant for this dossier.

1.5 Irritation

Not relevant for this dossier.

1.6 Corrosivity

Not relevant for this dossier.

1.7 Sensitisation

No assessment of respiratory sensitisation has been made by the Risk Assessment Committee.

1.8 Repeated dose toxicity

1.8.1 Repeated dose toxicity: oral

1.8.1.1 Initial 28-day study

In a 28-day repeated dose study, diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide (Lucirin LR8728) (purity 99%) was administered to Sprague-Dawley rats by oral gavage once daily. The dose groups 50, 250 and 750 mg/kg bw/day consisted of five male and five female animals each; a control group of five males and five females was dosed with vehicle alone (arachis oil B.P.). Two satellite groups, each of five males and five females were treated with the high dose (750 mg/kg bw/day) or the vehicle alone throughout the twenty-eight day study period and then maintained without treatment for a further fourteen days.

Clinical signs, bodyweight, food and water consumptions were monitored during the study. Hematology, blood chemistry and urinalysis were evaluated for all main group animals during the final week of dosing. Parameters showing abnormalities were examined in satellite group animals at the end of the treatment-free period (14 days).

All animals were subjected to a gross necropsy examination with histopathological evaluation of selected tissues.

At the start of the treatment the males weighed 152 to 192g, and the females weighed 155 to 189 g, and were approximately six to seven weeks old.

Mortality: One female of the 750 mg/kg bw/day satellite group died on day 4 of treatment. One female of the control satellite group died during blood sampling on day 42 (post treatment period).

Clinical signs of toxicity: whereas no signs of toxicity were seen at 50 mg/kg bw/day, the rats of the 250 mg/kg bw/day displayed from day 4 of treatment a series of signs including salivation, red-brownish staining around the snout and the mouth as well as of the fur, which also was wet, hair loss, piloerection, hunched posture, lethargy, ptosis and diuresis. At 750 mg/kg bw/day, the same symptoms were seen and were more severe than at 250 mg/kg bw/day; additionally, diarrhea, abdominal distension and an isolated case of vocalization were reported. In the satellite 750 mg/kg bw/day group, these symptoms disappeared immediately following cessation of dosing.

Body weight development: a substantial reduction in the body weight gain of rats treated with 250 and 750 mg/kg bw/day test substance became evident during the last treatment week. Four females of the 750 mg/kg bw/day group showed weight losses during this period. Cessation of dosing resulted in a rapid recovery and normalization of the body weight gain as demonstrated in the satellite 750 mg/kg bw/day group.

Food and water consumption: whereas the food consumption was similar in all groups, a marked reduction in food efficiency during the last week of dosing was reported for the 250 and the 750 mg/kg bw/day groups, which was related to the adverse body weight effects (see above). Food efficiency turned back to normal in the 750 mg/kg bw/day satellite group following cessation of dosing. Water consumption was similar and inconspicuous in all groups.

Hematology, blood chemistry and urinalysis: a statistically significant increase in leukocyte counts, mainly related to lymphocyte fraction, was reported for the males of the 750 mg/kg bw/day group and at a lesser extent for those of the 250 mg/kg bw/day group. A slight increase in lymphocytes also was reported for the females of both the 250 and the 750 mg/kg bw/day groups. The hemoglobin levels were reduced in the males and females of the 750 mg/kg bw/day group as well as in the females of the 250 mg/kg bw/day group. The erythrocyte indices (mean corpuscular volume, mean corpuscular hemoglobin also were reduced. Platelets also were slightly reduced in the females of the 750 mg/kg bw/day group, but the clotting potential was unaffected.

In the males of the 750 mg/kg bw/day satellite group, a slight reduction in hemoglobin persisted until the end of the post exposure period but was within the normal range.

Blood chemistry: The investigated blood parameters (cholesterol, gamma glutamyl transpeptidase, alkaline phosphatase, bilirubin, triglycerides, glucose, creatinine, calcium, aspartate aminotransferase) appeared to be significantly influenced by the treatment with 250 and 750 mg/kg test substance. These changes taken together were indicative of hepatic and renal abnormalities. E.g. the increased bilirubin levels were indicative for cholestatic hepatic injury whereas the elevated creatinine levels associated to the increased blood urea levels were likely indicating renal obstruction.

The investigation of the blood parameters in the rats of the 750 mg/kg bw/day satellite group at the end of the post exposure period revealed a slight increase in cholesterol and in calcium in respectively females and males; the levels however were within the normal range and indicated reversibility.

Urinalysis: The incidence of ketones in the urine was increased in both males and females of the 750 mg/kg bw/day group, and in the males of the 250 mg/kg bw/day group. Furthermore, males and females of the 750 mg/kg bw/day group showed increased urine volume and reduced specific gravity. The urinalysis of the rats of the 750 mg/kg bw/day satellite group particularly at the end of the post exposure period demonstrated the reversibility of these findings.

Necropsy: The necropsy of the control animals, which were sacrificed on day 29 revealed no macroscopic abnormalities.

In the 50 mg/kg bw/day group, excepted for two cases (1 male and 1 female) of multiple dark foci in lungs, no abnormalities were seen.

In the 250 mg/kg bw/day group one case (male) of isolated dark foci in lungs as well as one case (female) of pale adrenals were reported.

In the 750 mg/kg bw/day group, all males showed enlarged liver, very pale adrenals and small testes. Three females displayed ventral fur loss and brown staining of the ano-genital area. One of them had a distended abdomen whereas another had liquid feces. All females had enlarged, sometimes dark liver and the adrenals were pale.

In the satellite control group, necropsy of the males revealed no abnormalities whereas two females showed lesions within the lungs such as congestion.

In the satellite 750 mg/kg bw/day group, one male showed multiple dark foci in the lungs and small testes. One female displayed general fur staining, patchy pallor of the liver and dilated blood vessels in the stomach with extensive hemorrhage and ulceration within the glandular part of the stomach and white thickening of the forestomach. The small intestine of this female also displayed dilated blood vessels and contained blood stained fluid contents. The ileum and caecum of this animal showed compacted contents and the large intestine was empty.

Organ weighing revealed a marked increase in relative liver weights for rats of both sex and of both, the 250 and 750 mg/kg bw/day groups. The relative kidney weights also were increased in males and females of the 750 mg/kg bw/day group, and in males of the 250 mg/kg bw/day group. In the satellite 750 mg/kg bw/day group, the liver still were increased in weight after two weeks without dosing; in contrast, kidney weights turned back to normal.

Histopathology revealed treatment-related changes in liver, kidney and testes. In the liver of two females of the 750 mg/kg bw/day group, periportal hepatocyte vacuolization was reported. The kidney of males and females of the 750 mg/kg groups displayed basophilia, sometimes accompanied by dilatation of distal tubules. The males of the 750 mg/kg bw/day group displayed a reduction in testicular size (mostly bilateral) that was identified microscopically as testicular atrophy (for details see Table 2 below). The testicular atrophy was also seen in males of the 750 mg/kg satellite group.

The study revealed a LOAEL of 250 mg/kg bw/day and a NOAEL of 50 mg/kg bw/day. [3]

Table 1: Body and testis weight development

Dose group/parameter	**0 mg/kg bw/day**	**50 mg/kg bw/day**	**250 mg/kg bw/day**	**750 mg/kg bw/day**	**0 mg/kg bw/day satellite**	**750 mg/kg bw/day satellite**
Body weight						
-day 0 [g]	161 ± 8	168 ± 8	170 ± 8	175 ± 9	175 ± 12	161 ± 6
-at end of study [g]	378 ± 15	372 ± 27	360 ± 30	332 ±13	468 ± 35	378 ± 15
Testis weight						
Testis weight (absolute) [g]	3.39 ± 0.27	3.92 ± 0.30	3.91 ± 0.30	3.09 ± 0.41	4.64 ± 0.56	3.61 ± 0.87
Testis weight (% body weight)	1.04 ± 0.10	1.05 ± 0.08	1.06 ± 0.07	0.91 ± 0.12	0.97 ± 0.06	0.85 ± 0.23

Table 2: Incidences and grading of testicular atrophy

Dose group/ finding	**0 mg/kg bw/day**	**50 mg/kg bw/day**	**250 mg/kg bw/day**	**750 mg/kg bw/day**	**0 mg/kg bw/day satellite**	**750 mg/kg bw/day satellite**
Number of animals	5	5	5	5	5	5
Atrophy testis 1						
Grade 1	0	4	4	1	0	0
Grade 2	0	1	1	2	0	2
Grade 3	0	0	0	1	0	0

Grade 4	0	0	0	1	0	0
Grade 5	0	0	0	0	0	1
Atrophy testis 2						
Grade 1	0	1	0	0	0	1
Grade 2	0	0	0	2	0	1
Grade 4	0	0	0	1	0	0
Grade 5	0	0	0	0	0	1

Legend: grade 1: minimal; grade 2: slight; grade 3: moderate; grade 4: marked; grade 5: severe

1.8.1.2 90-day study with emphasis on neuropathology

In a 90-day study in accordance with the EPA-TSCA guideline “functional observational battery” and “neuropathology”, Wistar rats were exposed to the test substance by oral gavage. At the beginning of the experiment, the animals were 42 days old and had a mean body weight of 191 g (males) and 156 g (females). The rats were randomly distributed into 4 test groups of 20 animals each (10 per group). The diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide (Lucirin LR8728, purity 94.8%) was administrated as a 0.5% aqueous carboxymethyl cellulose solution as 0, 100, 300 and 1000 mg/kg bw/day. During the whole experimental period, the rats were observed for mortality, clinical signs of toxicity, body weight development, and food consumption. Additionally, specific neurofunctional tests were performed at the following time points:

1. On day 3 prior to start of the experiment
2. 1, 6 and 24 hours following the first dose
3. On days 7, 14, 42, 63 and 91 of the study

These tests considered different symptoms, e.g. tremors, convulsions, lacrimation, salivation, piloerection, vocalization, paresis, paralysis and ataxia. They also considered impairments referring to, e.g., posture, locomotor activity, respiration, winking and righting reflexes, behavior, grip strength, olfaction/audition, pain perception, tail pinch and toe pinch.

Blood sampling was performed on day 33 and day 87 and served for the investigation of: (1) Hematological parameters (e.g. leucocytes and erythrocytes count, mean corpuscular volume, and hemoglobin concentration), and (2) Biochemical parameters (e.g., enzymes such as alanine aminotransferase (ALT), alkaline phosphatase (ALP) and serum gamma-glutamyltransferase (GGT), and further blood biochemical parameters such as sodium, potassium, creatinine, urea, glucose, bilirubin and cholesterol). A clotting analysis (Hepato Quick´s test) also was done.

At the end of the experimental period, the (surviving) rats were sacrificed for the purpose of necropsy.

The results of the study can be summarized as follows:

Mortality: Two females of the 1000 mg/kg bw/day group died during the experimental period.

Clinical signs of toxicity: the females of the 1000 mg/kg bw/day group showed a reduced general state of health. Lesions on the hairless skin of the extremities and reddening and scale formation on the ears were reported for both males and the females of the 1000 mg/kg bw/day group. In the males of both the 300 and the 1000 mg/kg bw/day group, the testes were reduced in size.

Body weight gain and food consumption: An increase in food consumption was reported for the females of the 1000 mg/kg bw/day, but for both, the males and the females, body weight was reduced. At 300 mg/kg bw/day, body weight reduction only concerned the males.

Hematological/biochemical parameters: In the females of the 1000 mg/kg bw/day group, erythrocytes, hemoglobin, hematocrit and thromboplastin time (Hepato Quick test) were decreased. In contrast, leucocytes, platelets, eosinophilic granulocytes and neutrophilic polymorphonuclears were increased. The ALP and γ-GGT were increased, as well as calcium, total protein, globulins and cholesterol. The triglycerides were decreased. In the males of the 1000 mg/kg bw/day group, the ALP, γ-GGT and ALT were increased, whereas the triglycerides were decreased. At 300 mg/kg bw/day, the hemoglobin and hematocrit of the females were decreased whereas the leucocytes, eosinophilic granulocytes, neutrophilic polymorphonuclears and calcium content of the blood were increased.

Neurotoxic effects: Neither functional defects nor any other signs of neurotoxicity could be observed.

Necropsy: necropsy revealed increased absolute kidney and liver weights in the females of the 1000 mg/kg bw/day group. In males, the absolute and relative testes weights were decreased (see Table 3 below) and histopathology revealed marked diffuse atrophy of the testicular parenchyma. Furthermore, the females displayed skin lesions such as scaling. At 300 mg/kg bw/day, necropsy revealed decreased absolute and relative testes weights as well as diffuse atrophy of the testicular parenchyma (see Table 4 below). The testicular findings were considered to be substance related, although a clear dose-response relationship was not visible: as can be seen in the tables below, there is no significant difference between the absolute and relative testes weights of the 300 and 1000 mg/kg bw/day dose groups. The grading of the testicular atrophy of these dose groups is also comparable.

In the 100 mg/kg bw/day dose group, one animal exhibited moderately reduced spermiogenesis. All animals of this dose group showed a minimal to moderate vacuolar degeneration of spermatogonia in some seminiferous tubules. These lesions and the focal atrophy findings were also seen in the control group up to the same grading and are not considered to be substance related. The moderately reduced spermiogenesis of one animal in the 100 mg/kg bw/day dose group with no convincing transitional steps up to a diffuse atrophy as seen in the 300 and 1000 mg/kg bw/day dose groups is interpreted as an incidental, spontaneous occurring event and not considered to be induced by the test substance.

The NOAEL established by the study was considered to be 100 mg/kg bw/day. [4]

The following tables show the individual results of the pathology report:

Table 3: Body and testes weight development; results of testes pathology

Dose group/finding	**0 mg/kg bw/day**	**100 mg/kg bw/day**	**300 mg/kg bw/day**	**1000 mg/kg bw/day**
Body weight				
day 0	190.4 ± 7.9	190.1 ± 7.4	190.9 ± 5.1	192.4 ± 5.5
day 91	498.8 ± 44	493.5 ± 29.8	451.3 ± 37	384.0 ± 27.6
Testes	10	10	10	10
absolute weights	3.563 ± 0.193 g	3.68 ± 0.353 g	1.691 ± 0.328 g	1.693 ± 0.369 g
relative weights	0.78 ± 0.062 g	0.818 ± 0.094 g	0.421 ± 0.1 g	0.477 ± 0.1 g
diffuse atrophy	--	--	10/10	10/10
edema	--	--	10/10	10/10
focal atrophy	2/10	1/10	--	--
vacuolar degeneration	7/10	10/10	--	--
reduced spermiogenesis	--	1/10	--	--

Table 4: Incidence and grading of microscopic findings

Dose group	**Grading**	**0 mg/kg bw/day**	**100 mg/kg bw/day**	**300 mg/kg bw/day**	**1000 mg/kg bw/day**
Testes		10	10	10	10
diffuse atrophy		--	--	10	10
	1 (minimal)	--	--	--	--
	2 (slight)	--	--	--	--
	3 (moderate)	--	--	1	--
	4 (marked)	--	--	9	10
	5 (severe)	--	--	--	--
edema		--	--	10	10
	1 (minimal)	--	--	--	--
	2 (slight)	--	--	3	7
	3 (moderate)	--	--	7	3
	4 (marked)	--	--	--	--
	5 (severe)	--	--	--	--
focal atrophy		2	1	--	--
	1 (minimal)	--	--	--	--
	2 (slight)	--	--	--	--
	3 (moderate)	1	--	--	--
	4 (marked)	1	1	--	--
	5 (severe)	--	--	--	--
vacuolar degeneration		7	10	--	--
	1 (minimal)	3	3	--	--
	2 (slight)	1	6	--	--
	3 (moderate)	3	1	--	--
	4 (marked)	--	--	--	--
	5 (severe)	--	--	--	--
reduced spermiogenesis	--	--	1	--	--
	1 (minimal)	--	--	--	--
	2 (slight)	--	--	--	--
	3 (moderate)	--	1	--	--
	4 (marked)	--	--	--	--
	5 (severe)	--	--	--	--

1.8.1.3 28-day study in conjunction with a 90-day study

A 28-day and a 90-day repeated dose study was carried out with 41-43 day old male Wistar rats (3 and 10 per group for the 28-day and 90-day study, respectively). This study was conducted to reproduce the above stated effects on the testes with a new batch of the test substance. The purity of the substance was determined to be 99.3%. Doses were 0 and 1000 mg/kg bw/day of the diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide in carboxymethyl cellulose (0.5% aqueous solution) which were applied to the animals once daily by oral gavage. The rats were regularly observed for

mortality and clinical signs of toxicity. At the end of the test period, the rats were sacrificed and subjected to necropsy. Weights were assessed for the whole body and particularly for the testes. Gross lesions as well as the testes were withdrawn, fixed in 4% formaldehyde, embedded in paraffin, sectioned and hematoxylin-eosin stained for histological examination.

Result of the 28-day test:

The terminal mean body weight for the treated group was 244.833 g versus 251.833 g for the control group. For the testes, the absolute mean weight was 3.193 g versus 3.14 g, whereas the relative mean weight was 1.307 g versus 1.249 g. This indicates no substance-related effects of the weight parameters. No gross or histopathologic lesions were observed [5].

Result for the 90-day test:

The terminal mean body weight for the treated group was 298.1 g versus 332.21 g for the control group. For the testes, the absolute mean weight was 2.1 g versus 3.286 g, whereas the relative mean weight was 0.718 g versus 0.996 g, which is indicative of a substance-related effect on these weight parameters. Moreover, the testes of 8/10 rats were reduced in size compared to control; they also showed a loss of turgor. The reduction in size also affected the epididymes. In one case, the thoracic region of the rat showed sparse hair. From a histopathological point of view, a slight to severe diffuse atrophy (mostly bilateral) of the seminiferous tubules of the testes was seen in all animals. In four cases, edemas as well as a minimal to slight hyperplasia of the Leydig cells were also seen. In the epididymes with reduced size, histopathology revealed oligo- to azoospermia (i.e. reduction in or absence of mature sperms). The following tables show the individual results of the ten animals that were subjected to a macroscopic and histopathological examination. Lesions were bilateral unless indicated otherwise [5]:

Table 5: Macroscopic findings

Reduction in organ size	**slight**	**moderate**
Testes	1/10	7/10
Epididymes	8/10	--

Loss of turgor	8/10

Table 6: Histopathological findings

Grading/finding	**1 (minimal**	**2 (slight)**	**3 (moderate)**	**4 (marked)**	**5 (severe)**
Epididymes: reduction/absence of mature sperm	--	--	1/10	6/10	1/10
Testes: atrophy of seminiferous tubules	--	1/10	3/10	6/10	--
Testes: Leydig cell hyperplasia	3/10*	1/10	--	--	--
Intestinal edema	2/10*	2/10	--	--	--

* one unilateral case

1.8.2 Repeated dose toxicity: inhalation

No data available.

1.8.3 Repeated dose toxicity: dermal

No data available.

1.8.4 Other relevant information

No data available.

1.8.5 Summary and discussion of repeated dose toxicity

The first 28-day subacute study revealed a number of adverse effects on body weight development, food and water consumption, blood, liver and kidney. A number of clinical signs of toxicity, macroscopic abnormalities and histopathological treatment-related changes in the liver, kidney and testes were also reported. Not only did some of these changes occur exclusively in the highest dose group (750 mg/kg bw/day), most changes were also reversible as demonstrated by a satellite group that was observed for 14 days after the cessation of treatment. A 90-day study that was intended to look for neuropathological effects of the test substance also showed that treatment with diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide leads to atrophy of the testes whereas neither neurotoxic signs nor functional defects of the animals were reported. The NOAEL determined by this study was 100 mg/kg bw/day diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide whereas the LOAEL was 300 mg/kg bw/day. The temporary unavailability of the report of the initial 28-day study prompted an investigation of these effects in a second 28-day study with a new batch of the test substance. In contrast to the first test, no adverse effects were observed on the body and testis weight of rats treated with 1000 mg/kg bw/day of diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide. Histopathology, too, did not reveal any lesions. The 90-day study that was conducted with the same dose and batch of test substance, however, did reveal a reduction in size of the testes and epididymes, which was substantiated by the histopathologic lesions found.

Based on the results of one 28-day and the 90-day studies there is clear evidence for lesions of the testes as the only indication that diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide may lead to reduced fertility of the animals. The conclusion therefore is included in Section 1.11.5 Summary and discussion of toxicity for reproduction.

1.9 Mutagenicity

No assessment of mutagenicity has been made by the Risk Assessment Committee.

1.10 Carcinogenicity

No assessment of carcinogenicity has been made by the Risk Assessment Committee.

1.11 Toxicity for reproduction

1.11.1 Effects on fertility

Multi-generation studies investigating the potential effects of diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide on fertility are not available.

Repeated dose toxicity studies reporting toxicity data to the testes are presented in Section 1.8.1 above. In the first 28-day study, male rats treated at the high dose (750 mg/kg bw/day) demonstrated reduced testes size, microscopically identified as testicular atrophy. Grading indicated increased severity of testicular atrophy at the high dose, although low-level atrophy was reported in the low- (50 mg/kg bw/day) and mid-dose (250 mg/kg bw/day) treated males. . Testicular atrophy was also observed in the satellite group (750 mg/mg bw/day) at the end of the 14 day observation period. No testicular effects were noted in a second 28-day study in rats treated with 1000 mg/kg bw/day.

In the first 90-day study, decreased absolute and relative testes weight, as well as diffuse atrophy of the testicular parenchyma and edema was observed in the mid- (300 mg/kg bw/day) and high-dose (1000 mg/kg bw/day) groups. The second 90-day study conducted at 1000 mg/kg bw/day in ten male rats, reported slight to severe diffuse atrophy (mostly bilateral) of the seminiferous tubules in the testes of all animals, edemas in four cases, as well as a minimal to slight hyperplasia of the Leydig cells. The epididymes were reduced in size and histopathology revealed oligo- to azoospermia. The weight of the available evidence supports the finding that the testes are the target organ for diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide in rat, and that the effects observed may lead to reduced male fertility.

No data is available for female fertility.

1.11.2 Developmental toxicity

No assessment of developmental toxicity has been made by the Risk Assessment Committee.

1.11.3 Human data

No data available.

1.11.4 Other relevant information

No data available.

1.11.5 Summary and discussion of toxicity for reproduction

Based on the results of one 28-day and the two 90-day studies there is clear evidence for lesions of the rat testes in response to repeated oral administration of diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide. Testicular atrophy and edema are consistently reported in three of the four repeated dose toxicity studies, with the second 90-day study indicating the reduction or absence of mature sperm in the epididymes of eight out of ten animals tested. Multi-generation studies are not available to investigate the possible impact of these findings on male fertility. However, from the

available evidence the testes are a target organ for diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide and such findings may be an indicator of reduced fertility in the male rat.

There are a number of limitations with the data set used for classification. There are no data available to show that the observed effects in the testes will lead to reduced male fertility or how severe that impact on fertility would be. Also, the effects observed in the testes in the first 28-day study are not replicated in the second 28-day study. Diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide is administered by oral gavage in all the repeated dose toxicity studies and therefore, it cannot be excluded that the effects observed may have been due to a bolus effect. To investigate the toxicokinetics of the substance by a more continuous exposure of the animals, the design of the study was changed to administration of the test substance via the feed. However, the rats avoided the diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide-treated feed for palatability reasons, which led to excessive weight loss of the animals such that they had to be sacrificed on humane grounds. An additional encapsulation to improve acceptance of diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide did not solve the palatability problem. Furthermore, the use of the limit dose (1000 mg/kg bw/day) alone in both the second 28- and 90-day studies means that no dose-response information can be obtained.

Classification:

According to the CLP classification criteria (E.C. No. 1272/2008) substances classified in Category 2 for reproductive toxicity demonstrate an adverse effect on sexual function and fertility. From the available data, the testes is a target organ for diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide in rat.. The lesions observed include testicular atrophy and edema, as well as oligo- and azoospermia demonstrated in the second 90-day study. These adverse effects occur in the absence of significant generalised toxicity. However, due to the limitations discussed above, the evidence is not sufficiently convincing to place the substance in Category 1 and classification as Repr. 2 is recommended. Also, according to the classification criteria of 67/548/EEC, classification with Cat. 2 requires demonstration of the impairment of fertility in *in vivo* studies, therefore because clear evidence for testes lesions is a valid but nevertheless only indirect indicator that diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide may lead to reduced fertility, classification with Repr. Cat. 3; R62 is appropriate.

During discussion of the dossier, the RAC considered the alternative possibility of classification as Repr 1B (under CLP). However, it was concluded that the effects observed were not severe enough to warrant this classification, taking into account the lack of a consistent effect on the testes across all four repeat dose studies.

1.12 Other effects

Not relevant for this dossier.

HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICOCHEMICAL PROPERTIES

Not relevant for this dossier.

ENVIRONMENTAL HAZARD ASSESSMENT

Not relevant for this dossier.

PBT, vPvB AND EQUIVALENT CONCERN ASSESSMENT

Not relevant for this dossier.

JUSTIFICATION FOR ACTION AT COMMUNITY LEVEL

It is proposed that the substance is classified as Repr. 2; H361f (E.C. No. 1272/2008) and Repr. Cat. 3; R62 (Directive 67/54/EEC). Harmonised classification and labelling for reprotoxicants is considered a Community-wide action under Article 114 and it is recommended that the classification proposal is considered for inclusion on Annex VI of E.C. No. 1272/2008.

OTHER INFORMATION

This substance will be registered under REACH. The producer company has been contacted during the production of this dossier and they provided the available industry reports for the substance.

References

[1] BASF AG (2004). IUCLID diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide, CAS No. 75980-60-8.

[2] BASF AG (2003). EPIWIN calculations. Department of Product Safety, unpublished data, 11 Nov 2003.

[3] BASF Japan Ltd. (1989). Lucirin LR 8728: Twenty-eight day oral (gavage) toxicity study in the rat. Safepharm Laboratories Limited, unpublished data, report No. 214/7, 7 Apr 1989.

[4] BASF AG (1991). Report on the study of the oral toxicity of Lucirin LR 8728 in conjunction with the “functional observational battery” in rats. Administration by gavage over 13 weeks. Department of toxicology, unpublished data, report No. 99S0085/86062, 10 Apr 1991.

[5] BASF AG (2001). Studie zur Hodentoxizität in Wistar-Ratten. Verabreichung per Schlundsonde bis zu 3 Monaten. Department of Toxicology, unpublished data, report No. 51C0293/99096, 19 Jan 2001.