Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

1,4-Benzenediamine, *N,N'*-mixed Ph and tolyl derivs.; Reaction mass of *N*-phenyl,*N'*-o-tolyl-phenylene diamine, *N,N'*-diphenyl-p-phenylene diamine and *N,N'*-di-o-tolyl-phenylene diamine

EC Number: 273-227-8
CAS Number: 68953-84-4

CLH-O-0000007054-80-01/F

Adopted

26 November 2021

26 November 2021

CLH-O-0000007054-80-01/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **1,4-Benzenediamine, *N,N'*-mixed Ph and tolyl derivs.; Reaction mass of *N*-phenyl,*N'*-o-tolyl-phenylene diamine, *N,N'*-diphenyl-p-phenylene diamine and *N,N'*-di-*o*-tolyl-phenylene diamine**

EC Number: **273-227-8**

CAS Number: **68953-84-4**

The proposal was submitted by **Germany** and received by RAC on **3 March 2021.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Germany has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **15 March 2021**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **14 May 2021**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Betty Hakkert**

Co-Rapporteur, appointed by RAC: **Gerlienke Schuur**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **26 November 2021** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	TBD	1,4-Benzenediamine, *N,N'*-mixed Ph and tolyl derivs.; Reaction mass of *N*-phenyl,*N'*-*o*-tolyl-phenylene diamine, *N,N'*-diphenyl-p-phenylene diamine and *N,N'*-di-*o*-tolyl-phenylene diamine	273-227-8	68953-84-4	Repr. 1B Skin Sens. 1	H360FD H317	GHS07 GHS08 Dgr	H360FD H317			
RAC opinion	TBD	1,4-Benzenediamine, *N,N'*-mixed Ph and tolyl derivs.; Reaction mass of *N*-phenyl,*N'*-*o*-tolyl-phenylene diamine, *N,N'*-diphenyl-p-phenylene diamine and *N,N'*-di-*o*-tolyl-phenylene diamine	273-227-8	68953-84-4	Repr. 1B Skin Sens. 1	H360FD H317	GHS07 GHS08 Dgr	H360FD H317			
Resulting Annex VI entry if agreed by COM	TBD	1,4-Benzenediamine, *N,N'*-mixed Ph and tolyl derivs.; Reaction mass of *N*-phenyl,*N'*-*o*-tolyl-phenylene diamine, *N,N'*-diphenyl-p-phenylene diamine and *N,N'*-di-*o*-tolyl-phenylene diamine	273-227-8	68953-84-4	Repr. 1B Skin Sens. 1	H360FD H317	GHS07 GHS08 Dgr	H360FD H317			

RAC general comment

1,4-Benzenediamine, *N,N'*-mixed phenyl and tolyl derivates (DAPD or BENPAT; the latter is used throughout) is a reaction product consisting of three main structures and some impurities. The three main constituents are:

- *N,N'*-diphenylbenzene-1,4-diamine (DPPD; CAS: 74-31-7, EC: 200-806-4)
- *N,N'*-bis(2-methylphenyl)benzene-1,4-diamine (CAS: 15017-02-4, EC: 239-102-7)
- *N*-(2-methylphenyl)-*N'*-phenylbenzene-1,4-diamine (CAS: 27173-16-6)

BENPAT is used as an anti-degradant in tires and industrial rubber products, and include widespread uses by professional workers (in formulation, re-packing, manufacturing), and the substance is used by consumers in articles (polymers). This substance is used in synthetic materials and likely released (high or low) from various long-life outdoor and indoor materials.

BENPAT does not have an existing entry in Annex VI of CLP and has not been considered for harmonised classification and labelling previously in the EU. BENPAT has been listed on the Community rolling action plan (CoRAP) in 2013. Concerns for substance evaluation were that BENPAT is suspected to be PBT/vPvB, has consumer and wide-dispersive uses, and the substance is produced/ imported in a high (aggregated) tonnage in the EU (> 1000 t/a). There are still open information requests concerning environmental fate.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

One GLP compliant guinea-pig maximisation test (GPMT; OECD TG 406) is available for BENPAT. According to this test, BENPAT is a skin sensitizer but the data does not allow for sub-categorisation.

No human studies regarding skin sensitisation are available for BENPAT. The Dossier Submitter (DS) noted that *N,N'*-diphenyl-*p*-phenylene-diamine (DPPD; CAS 74-31-7), a constituent of BENPAT (> 1 %), is a known skin sensitizer in animals and humans. DPPD has a harmonised classification for Skin Sens 1.

The DS proposed classification for effects on skin sensitization in category 1 (H317 – May cause an allergic skin reaction).

Comments received during consultation

One industry representative commented on the proposal of Skin Sens. 1 by the DS, the only comment received regarding this health hazard, and supported the proposed harmonised classification of Skin Sens. 1 without further sub-categorisation.

Assessment and comparison with the classification criteria

In the GPMT study (Klimisch score 1) animals (n = 20 per group, n = 10 in control) were induced to BENPAT by intradermal and epidermal exposure to a concentration of 5 %. RAC notes that the

purity of the test substance is not known. However, the purity of a multi-constituent substance is defined by its quantitative composition. Therefore, it is assumed that BENPAT used in this study (and also studies assessed for other toxicological endpoints) fulfils the criteria of the main identifiers, according to Chapter 4.2.2. of the REACH Guidance for identification and naming of substances under REACH and CLP[1], for multi-constituent substances. Upon re-challenge to 25 or 100 % of BENPAT on day 21 (first challenge) and day 28 (second challenge), clinical signs (oedema, blanching or desquamation) were described in 15-25 % (first challenge) and 55-75 % (second challenge) of animals 24 h or 48 h after administration of BENPAT. From these results it is concluded that BENPAT is a skin sensitizer. A high response was observed in the GPMT test upon exposure to a high concentration of BENPAT. However, there is no data available for lower concentrations of BENPAT, sub-categorisation is therefore not possible. In addition, one constituent of BENPAT, DPPD, has a harmonised classification for Skin Sens. 1 and is present in BENPAT at ≥ 1 %.

Conclusion

Based on one positive GPMT study with BENPAT, RAC considers that **classification as Skin Sens. 1 is warranted**. In addition, the presence of DPPD (≥ 1 %), which has a harmonised classification for Skin Sens. 1, supports classification of BENPAT for Skin Sens. 1.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Adverse effects on sexual function and fertility

The DS proposed classification for effects on sexual function and fertility in category 1B (H360F) based on a dose-dependent increased incidence of dystocia (obstructed labour) and increased gestational length in mid and high dose F0 female rats, and low, mid and high dose F1 female rats, observed in a GLP compliant two-generation reproduction toxicity study (OECD TG 416; RTI, 2001a). BENPAT induced dystocia and impaired oestrous cycling, and was associated with pallor, piloerection and vaginal bleeding in the high dose groups (mainly F0 dams). In addition, increased pup mortality as result of dystocia was noted. These findings were supported by similar findings in a one-generation mechanistic study (non-guideline study; RTI, 2000), where adverse effects on fertility and development upon exposure to BENPAT during pre-breeding, mating, gestation and lactation, with or without iron supplementation were observed. The DS concluded that these adverse effects on fertility were not secondary to maternal toxicity, as data on body and organ weights did not present severe maternal toxicity. Furthermore, the DS noted that observed effects in liver and kidney in dams are likely associated with dystocia and maternal infection as result of resorbing foetuses *in utero*.

Developmental effects

The DS proposed classification for effects on development in category 1B (H360D) based on a dose-dependent increase and high incidence of polycystic kidneys in rat weanlings (F1 and F2) in a GLP-compliant two-generation reproduction toxicity study (OECD TG 416). Polycystic kidneys

[1] https://echa.europa.eu/documents/10162/23036412/substance_id_en.pdf/ee696bad-49f6-4fec-b8b7-2c3706113c7d

were also observed upon treatment with BENPAT during gestation and lactation in F1 rat weanlings in a one-generation mechanistic study (non-guideline study). No polycystic kidneys were noted in rat pups in a prenatal developmental toxicity study (similar to OECD TG 414), possibly due to limitations of the chosen time window (gestation day (GD) 6-15). The DS noted that these latter studies do not allow conclusions on the effects of exposure of BENPAT on increased incidence of polycystic kidneys in weanlings upon exposure to BENPAT *in utero*, lactation and/or self-feeding. However, evidence of these renal abnormalities due to exposure to diphenylamine (DPA) and its derivates in late gestation (GD 14 onwards) in new-born rat, supported these findings (Crocker *et al.*, 1972), as DPA and its derivates are listed impurities of BENPAT. Incidence of polycystic kidneys was (mostly) not noted in dams, nor observed in two repeated dose toxicity studies (a one-year and a 28-day repeated dose toxicity study at comparable dose levels). According to the DS this demonstrated the sensitivity of embryonic kidneys to BENPAT as compared to adult kidneys.

Effects on or via lactation

Data from the one-generation mechanistic study do not allow to draw conclusion regarding increased incidence of polycystic kidneys in weanlings during lactation.

Overall conclusion of the DS

No human studies are available addressing adverse effects of BENPAT on sexual function, fertility and development. However, there is no robust data on the mode of action to conclude the observed adverse effects are not relevant to humans.

The DS proposed classification of BENPAT as presumed human reproductive toxicant in category 1B (H360FD).

The DS derived ED_{10} values of 4.3 mg/kg bw/d for polycystic kidneys in F1 female weanlings (on post-natal day (PND) 21) and 23.8 mg/kg bw/d for post-implantation loss of F0 dams with F1 litters. These values are all within the medium potency group. As a consequence, the DS did not propose a SCL.

Comments received during consultation

Adverse effects on sexual function and fertility

One Member State Competent Authority (MSCA) supported the proposal for classification on sexual function and fertility, and agreed this is warranted because of dystocia observed in the one- and two-generation studies. The MSCA noted that maternal toxicity observed in these studies, as possible cause of dystocia, should be further elaborated to assess the classification in either category 1B or 2. It was suggested that available data on hormonal levels in female rats from repeated dose toxicity studies could help to give insight in the mode of action of toxicity.

One industry representative questioned the relevance and benefits of a harmonised classification for reproductive toxicity since the exposure to the general population is extremely low and exposure control measures are applied for workers. Furthermore, it was acknowledged that dystocia observed in Sprague-Dawley rats is an established adverse effect on fertility leading to maternal and pup mortality. However, there were doubts raised about whether dystocia was observed in absence of (maternal) toxicity and the relevance of these adverse effects to humans. It was pointed out that the NOAEL (16 mg/kg bw/d) reported in a 52-week repeated dose toxicity study in F344 rats (AHF, 1996), based on changes in organ weights (liver, kidney, spleen), was at considerably lower concentrations than adverse effects noted in the two-generation reproduction toxicity study. Furthermore, this could suggest that these adverse effects could thus

be strain dependent and it cannot be presumed that observed effects (toxicity or developmental) would exist in other species or strains. Another point raised by the industry representatives was the possibly less significant effect of prostaglandins on the parturition process in humans in comparison to rats. Therefore the relevance of DPPD-induced inhibition of prostaglandin in rats to humans is not been demonstrated. The proposal did not consider known analogous effects with salicylic acid (SA) and acetyl salicylic acid (ASA). A comparison could be considered as it was demonstrated for these chemicals that prostaglandin inhibition could not be presumed to cause equal effects in rats vs. other species.

The DS acknowledged that the process of parturition differ between humans and rats but noted that the prostaglandin PGF2alpha has a relevant role in delivery in humans too. DPPD data provide supportive information, however, BENPAT is a multiconstituent and other constituents might contribute to the effects seen.

Regarding the comparison with SA and ASA, the DS noted that these chemicals present a different target profile in comparison to BENPAT (e.g. malformations (amongst which cranioschisis, and dose-related growth retardation). A different target profile is also observed in repeated dose studies.

With regard to the remarks on dystocia and maternal toxicity, the DS responded with detailed information on the high dose F0 dams with split information on earlier euthanized animals and terminal sacrificed animals. The maternal toxicity was observed not in all dams with dystocia: liver necrosis (centrilobular hepatocyte; minimal to moderate) in 7 high dose dams and kidney necrosis (cortex; minimal to marked) in 5 high dose out of 9 dams, therefore maternal toxicity may be discussed as primary cause resulting in dystocia in some dams. However, due to the fact that some dams with dystocia did not show necrotic lesions in any of these organs and the observation that the majority of necrotic lesions was only minimal to mild, it appears as not likely that these necrotic lesions are the cause of dystocia. Moreover, the necrosis could also be secondary to dystocia and haemorrhagic lesions at multiple sites. Additional information on the F1 dams resulted in the conclusion by the DS that dystocia and post-implantation loss are not secondary to the mild to moderate effects observed in liver and kidney.

Developmental effects

One MSCA noted that offspring generations (F1 and F2) are more likely to develop polycystic kidneys as compared to their parental generation. Furthermore it was commented that these effects could be considered as systemic toxicity rather than developmental toxicity in case structural disturbances of the development of the kidney have not occurred.

One industry representative acknowledged that presence of polycystic kidney was demonstrated in Sprague-Dawley rats upon exposure to BENPAT in the available reproductive toxicity studies. However, doubts were raised whether 1) these kidney effects were a developmental effect, but rather a result of direct exposure and 2) sufficient evidence was provided to expect similar effects would occur in humans. Renal effects were acknowledged but could be due to direct toxic effects and due to the low water solubility of the substance, according the industry representative. It was noted by industry representatives that there was evidence of reversibility (especially renal tubular regeneration) of renal effects, suggesting a toxicity-related effect and not a developmental effect. The tubular regeneration observed indicates that renal effects are likely reversible. As the kidneys develop, the ability to clear toxic effects induced by BENPAT increases. Hence, the incidence of polycystic kidneys decreased in F1 adults and the renal effects are thus not permanent, according to industries.

It was also noted that these kidney effects could be strain-dependent as they were not observed in repeated dose toxicity studies in F344 rats. This statement could not be verified because BENPAT has not been studied in other reproductive studies using other strain or species. The representative therefore concluded it cannot be presumed that observed effects (toxicity or developmental) would exist in other species and humans. Another point raised was regarding literature data for DPA and its derivatives causing polycystic kidneys in new-born pups as supporting evidence by the DS. The industry representative noted that no harmonised classification for reproductive toxicity is currently in place for DPA and therefore raised doubts regarding the legal basis for using literature data for DPA as supportive evidence in this proposal for BENPAT.

The DS responded that the terminology used for polycystic kidney in the two-generation study was to distinguish from spontaneous renal cysts (cortical or medullary). In addition, formation of cysts is not associated with a primary hydronephrotic mechanism according to study author. The DS concluded that the developing kidneys are more sensitive than the adult kidneys and therefore assessed the effect as foetal toxicity.

Assessment and comparison with the classification criteria

Adverse effects on sexual function and fertility

There are two reliable and relevant studies available for assessing the effects on sexual function and fertility upon exposure to BENPAT; a two-generation reproduction toxicity study and a one-generation mechanistic (supportive) study. The findings are described below per study.

In a two-generation reproduction toxicity study (OECD TG 416; Klimisch score 1; RTI, 2001a) exposure to BENPAT (0, 120, 400, 1500 ppm or 0, 7.5, 25, 100 mg/kg bw/d) via feed (in corn oil) was studied in Sprague-Dawley rats (n = 30/sex/dose group) during pre-breeding (F0-1; 10 weeks), mating (F0-2; 2 weeks), gestation (F0-2; 3 weeks) and lactation (F0-2; 3 weeks). Mortality in pregnant F0 dams was observed in the mid dose (3/24 (12.5 %)) and the high dose group (8[1]/25 (32.0 %)), occurring mostly during lactation (Table 11 CLH dossier). Increased mortality was associated with extended parturition, dystocia and highly associated with the delivery of litters with all-dead pups. No mortality was observed in F0 males. Maternal mortality in F1 animals was relatively low (25/100 mg/kg bw/d: 1/22 (4.5 %) and 1/24 (4.2 %), respectively) and only observed in F1 dams during the postnatal period. Clinical signs such as pallor, piloerection and vaginal bleeding were noted, and likely associated with dystocia. Body weight (Table 11, CLH dossier) and body weight gain were affected in F0 and F1 dams during pre-breeding, mating, gestation and lactation at the highest dose tested, but not at the end of lactation and was (mostly) not excessive. See also a summary of mortality and histopathological findings upon exposure to BENPAT in a two-generation study by RAC in the Supplemental information.

[1] Please note an inconsistency: Table 10 in CLH report notes 8 mortalities, DS reaction in RCOM reports 9. According to DS, correct mortalities is 8.

Table: Effects of BENPAT, general toxicity and reproductive parameters from an OECD TG 416 study

	F0 animals for F1 litters				**F1 animals for F2 litters**			
Dose (mg/kg bw/d)	**0**	**7.5**	**25**	**100**	**0**	**7.5**	**25**	**100**
Mortality no. dams (%)	1/24[a] (4.2)	0	3/24 (12.5)	8/25 (32.0)	0	0	1/22 (4.5)	1/24 (4.2)
Body weight dams (%) – pre-breeding[b]	-	-	-	-7	-	-	-	-7
Body weight dams (%) – mating[b]	-	-	-	-	-	-	-	-7
Body weight dams (%) – gestation[b]	-	-	-	**-10***	-	-	-	**-**
Body weight dams (%) – lactation (PND 0, 4, 7) [b]	-	-	-	**-11***	-	-	-	**-9***
General toxicity (scheduled necropsy)								
Organ weights								
Relative paired kidney weight (%) ↑				10.7 ♂ 12.0♀				10.1♂
Absolute liver weight (%) ↑				14.0♀				
Relative liver weight (%) ↑				19.8♀				
Absolute uterine weight (%) ↓			-20.4	-23.0				
Relative uterine weight (%) ↓			-20.7	-19.6				
Relative paired ovary weight (%) ↓							-17.61	
Effects on sexual function and fertility								
Abnormal cycles (%)	17.2	6.7	6.7	13.3	6.7	10	28.6**	43.3**
Mean cycle length (d)	4.7	4.5	4.7	4.7	5.1	4.8	5.5	7.2
No. of mating pairs	29	30	30	30	30	30	30	30
No. of ♂ sperm positive	26	30	26	27	26	26	24	26
No. of ♀ pregnant	24	27	24	25	22	23	22	24
No. of ♀ with live litters, PND 0	24	26	23	15**	22	22	20	21
No. of dams with live & dead pups, PND 0	2	4	3	6	3/22	5/23	4/22	11/24
No. of dams with no live litters, PND0	0	1/27[c]	1/24[c]	10/25[d]	0	1/23	2/22[c]	3/24
Gestational length (d)	22.2	22.4	22.8**	23.5**	22.2	22.8**	23.1**	23.2**
Dystocia[e]			3/24	9/25		1/23	3/22	3/24
No. of implantation sites/litter	16.9	15.9	15.6	14.5	16.5	16.4	15.1	15.0
Post-implantation loss /litter (%)	10.7	14.9	26.1**	52.3**	6.8	18.5	20.2	32.6**
No. of total pups/litter, PND 0	15.7	14.9	12.3**	12.1**	15.7	14.5	15.2[cf]	13.3
No. of live pups/litter, PND 0	15.6	14.1	11.9*	7.6**	15.6	13.7	13.4	10.8**
No. of dead pups/litter on PND 0	0.1	0.3	0.4	4.1**	0.1	0.7	0.4	2.5**
Live birth index (%)	99.2	98.0	97.0	57.5**	99.2	91.9	97.2	77.8**
Stillbirth index (%)	0.8	2.0	3.0	42.5**	0.8	7.6	2.8	22.2**
Sex ratio (% males)	50.4	54.1	55.2	44.1	44.4	47.1	46.2	48.6
Pup body weights (g) on PND 0	6.4	6.8**	6.9**	6.6	6.3	6.9**	7.0**	6.6*

* = $p < 0.05$ versus control group value; ** = $p < 0.01$ versus control group value

[a] One female control was euthanized on 17th day of prebreed dosing due to apparent broken hind limb

[b] Based on % compared to body weight in corresponding control group and information in CLH dossier or Annex. Information not available for all dose groups.

[c] Implantation sites only

[d] One female with implantation sites only

[e] From Table 2 and 3 in the RCOM. Dystocia resulted in 4 of the 8 or 9 mortalities reported.

[f] Figure from the CLH report. Seems to be incorrect and does not reflect sum of live and dead pups

Gestational length was statistically significantly increased at ≥ 25 mg/kg bw/d in F0 dams (25/100 mg/kg bw/d: 22.8/23.5 days, vs. 22.2 days in control) and at ≥ 7.5 mg/kg bw/d in F1 dams (7.5/25/100 mg/kg bw/d: 22.8/23.1/23.2 days, vs. 22.2 days in control). Dose-dependent and statistically significant changes in other reproductive parameters were noted in the high dose group in F0 dams, such as reduced live birth index (57.5 % vs. 99.2 % in control), and increased stillbirth index (42.5 % vs. 0.8 % in control) and number of dead pups per litter (4.1 vs. 0.1 in control). In F1 dams, similar statistically significant changes were reported at 100 mg/kg bw/d for live birth (77.8 % vs. 99.2 % in control) and stillbirth index (22.2 % vs. 0.8 % in control). No statistically significant changes in hormonal cycles were noted in any dose groups in F0 dams. However, there was an increased incidence of abnormal hormonal cycles (females in metestrus and upward trend cycle length) observed in F1 females at ≥ 25 mg/kg bw/d (25/100 mg/kg bw/d: 28.6 % (8/28; 2/30 not cycling) / 43.3 % (13/30), vs. 6.7 % (2/30)) in control. The abnormal hormonal cycling could be a result of exposure to BENPAT *in utero* and during lactation. No other treatment-related effects on mating, pregnancy rates, fertility indices or histopathological findings on reproductive organs were noted in F0 and F1 females in the two-generation reproduction toxicity study. No reproductive toxicity was observed in F0 and F1 males.

Signs of dystocia were noted in 3/24 (12.5 %) in the mid dose group and 9/25 (36 %) in the high dose group in F0 females. In F1 females signs of dystocia were noted in the low, mid and high dose groups (1/23 (4.3 %), 3/22 (13.6 %), 3/24 (12.5 %), respectively). Dystocia was accompanied with pallor, piloerection, vaginal bleeding (mainly F0 dams), haemorrhage and/or inflammation in uterus (mild) during late gestation (GD 23-24). Minimal, mild or moderate liver (centrilobular hepatocyte) necrosis (25/100 mg/kg bw/d: 1/3 and 7/9, respectively) and minimal, mild or marked kidney cortex necrosis (1/3 or 5/9) in F0 dams presenting dystocia were observed. No histopathological changes in liver and kidney were noted in F0 males. Liver lesions were less prominent in F1 dams (1/3 for both 25 and 100 mg/kg bw/d) presenting dystocia, while necrotic lesions in the kidney was not noted.

Some of the F0 dams presenting dystocia had no histopathological changes in the liver (minimal to moderate) or kidneys (minimal to marked; Table 2 in the RCOM): 1/3 (female #84) and 1/9 (female #108) at 25 and 100 mg/kg bw/d, respectively. In F0 dams, most histopathological changes in the liver and kidneys noted were in dams with signs of dystocia. Although histopathological changes in the kidneys (minimal to moderate) were observed in all F1 dams with signs of dystocia (Table 3 in the RCOM), the majority of incidence (polycystic kidney, inflammation acute/chronic, renal tubule regeneration) were noted in dams not presenting dystocia. In addition, histopathological changes in the liver (mild or moderate) were noted only in some F0 dams with signs of dystocia (1/3 at both 25 and 100 mg/kg bw/d). Indicating that necrotic lesions in the liver and/or kidneys could be secondary to dystocia and haemorrhagic lesions. The body weight in F0 dams in the high dose group that died or that were euthanised (mostly due to dystocia) were not different from those sacrificed in this dose group. Not all F0 dams with dystocia showed necrotic lesions in liver and kidney, and these effects were observed to be minimal to mild. On the other hand, incidence of clinical signs (piloerection, vaginal bleeding) was higher in F0 dams that died or that were euthanised in the high dose group. This together suggests that the dystocia is not secondary to the effects in liver or kidney. It cannot be excluded, however, that these lesions in the liver and kidney are the result of dystocia instead.

In a one-generation mechanistic study (non-guideline study; Klimisch score 2; RTI, 2000) Sprague-Dawley female rats (n = 20/group) were exposed to 0 (group 1) or 2500 ppm (157-436 mg/kg bw/d) BENPAT via feeding (in corn oil) during pre-breeding and mating (group 2), gestation and lactation (group 3), pre-breeding up to and including lactation (group 4) or pre-breeding up to and including lactation with iron (600 ppm iron gluconate in drinking water) supplementation (group 5). Mortality in euthanised dams was noted in group 3 (gestation: 1 (GD 19), lactation: 5 (PND 0, 3 or 4)) and in group 4 (1 (GD 24), 4 (PND 0, 3)). Clinical signs of

toxicity (alopecia, pallor, piloerection, chromodacryorrhea, pale eyes and tail) during gestation and lactation were noted in all treated groups. In addition, lower body weight (statistically significant) was noted in all exposed groups, during pre-breeding (group 2, 4 and 5; male/females, -4.5 to -9.8 %), gestation (group 3 and 5; -8.0 to -12.3 %) or lactation (group 3, 4 or 5; females, -8.8 to -12.8 %). Evidence of macrocytic anaemia (on PND 21) and increased (statistically significant) absolute/relative liver weight (not specified) and relative kidney weight (not specified) were observed in group 4 and 5.

Increased gestational length (statistically significant) associated with dystocia was observed in groups 3-5 compared to control and group 2. Other statistically significant effects on reproductive parameters included: decreased number of live pups and increased number of dead pups per litters, were observed in groups 3-5 compared to control. In group 3 and 4, gestational index and live birth index were decreased and post-implantation loss was increased (both statistically significant). In addition, number of implantation sites per litter was decreased and foetal body weight per litter was increased (14.1 % at PND 0) in group 5 (both statistically significant). This study demonstrated BENPAT-induced effects on reproductive parameters during gestation and lactation, but this was not associated to an iron-deficiency.

Table: *Effects of BENPAT on reproductive parameters from the one-generation mechanistic study (copied from the CLH dossier)*

Dose groups and effects	**Group 1**	**Group 2**	**Group 3**	**Group 4**	**Group 5**
Pre-breeding and mating, BENPAT (mg/kg bw/d)	0	250	0	250	250[a]
Gestation and lactation, BENPAT (mg/kg bw/d)	0	0	250	250	250[a]
No. of animals started	20	20	20	20	20
Mating index (%)	95.0	95.0	100	95.0	85.0
Fertility index (%)	78.9	73.7	90.0	78.9	70.6
Gestational index (%) = no. females with live litters/no. females pregnant	100	92.9	**64.7[b]**	**71.4[c]**	100
Gestational length (d), (No. animals)	22.2 ± 0.1 (13)	22.3 ± 0.1 (13)	**23.6 ± 0.2 (14)[d]**	**23.8 ± 0.2 (13)[d]**	**23.5 ± 0.2 (11)[d]**
No. of live litters, PND 0	15	13	11	10	11
No. of implantation sites/ litter	14.7 ± 0.8	13.9 ± 0.6	11.6 ± 1.2	13.5 ± 0.8	**10.6 ± 1.4[e]**
Post-implantation loss/litter (%)	12.2 ± 2.8	16.9 ± 6.8	**57.5 ± 10.4[d]**	**55.8 ± 10.6[d]**	18.0 ± 5.9
No. of live pups/litter, PND 0	12.6 ± 0.6	12.8 ± 0.6	**5.8 ± 1.5 [f]**	**6.8 ± 1.6[f]**	**8.2 ± 1.0[f]**
No. of dead pups/litter, PND 0	0.4 ± 0.2	0.2 ± 0.2	**4.1 ± 1.3[g]**	**5.3 ± 1.4[f]**	**1.3 ± 0.7**
Live birth index (%)	96.9 ± 1.3	98.9 ± 1.1	**54.6 ± 12.0[g]**	**54.0 ± 12.0 [f]**	90.0 ± 5.2
Sex ratio (% males) (PND 0)	57.0 ± 4.3	47.6 ± 3.5	64.9 ± 6.3	44.9 ± 9.4	39.4 ± 4.6

[a] Iron supplementation
[b] $p < 0.01$, Fisher's Exact Test
[c] $p < 0.05$, Fisher's Exact Test
[d] $p < 0.01$, Dunnett's Test
[e] $p < 0.05$, Dunnett's Test
[f] $p < 0.01$, Mann-Whitney U Test
[g] $p < 0.05$, Mann-Whitney U Test

Exposure to BENPAT was associated with dystocia and increased gestational length in rat one- and two-generation studies. No marked maternal toxicity was observed in both studies. Clinical signs and histopathological changes (liver and kidney) observed were likely the result of dystocia and thus secondary to dystocia. This is supported by absence of marked toxicity in two repeated dose toxicity studies available for BENPAT; a one-year dietary repeated dose toxicity study (none-guideline; ca. 3.3, 20 and 120 mg/kg bw/d) and a 28-day oral repeated dose toxicity study (similar to OECD TG 407; ca. 7.5, 30, and 120 mg/kg bw/d) in F344 rat (AHF, 1994; AHF, 1996). Besides increased relative weights of liver and kidney in the mid and high dose groups, no substance related deaths or clinical findings and no histopathological changes in liver and kidney were reported in these repeated dose toxicity studies.

There are no human data available regarding adverse effects on sexual function or fertility upon exposure to BENPAT and there is no evidence available that adverse effects on (female) fertility observed in animal studies are not relevant to humans.

Potential mode of action

Other animal studies demonstrated similar effects on dystocia and prolonged parturition upon exposure to DPPD (a BENPAT constituent), which acts as prostaglandin inhibitor (Fujimoto *et al.*, 1984; Marois, 1998). In humans, prostaglandins have an important role in various physiological mechanisms, such as pregnancy (Bakker *et al.*, 2017; Mitchell *et al.*, 1978; Reece *et al.*, 1996; Romero *et al.*, 1994). DPPD induced dystocia and prolonged parturition in animals is supportive evidence of a possible mode of action. However, it is noted that BENPAT consists of other constituents and impurities, with unknown toxicity/modes of action. As a consequence the effects observed for BENPAT cannot be solely attributed to DPPD. There is no mechanistic information indicating that the observed effects are not relevant for humans, therefore the adverse effects on sexual function and fertility reported in rats are considered relevant for classification and these effects are considered relevant to humans.

Conclusion

BENPAT exposure resulted in a dose-dependent increase in gestational length in the available two-generation study (F0 and F1) and in the one-generation study, without marked maternal toxicity. Furthermore, in the F1 generation, an increase in abnormal cycles was noted. The studies show that BENPAT results in dystocia (prolonged parturition or obstructed labour), which in most cases resulted in dead dams and pups. The histopathological effects in liver and kidneys in the highest dose group were minimal to mild and not observed in all dams presenting dystocia. Increased gestational length was also observed in the mid dose group and low dose group in F0 and F1 dams, respectively.

RAC agrees with the DS that classification for Repr. 1B is warranted for BENPAT, based on adverse effects observed on female fertility (abnormal cycles, gestational length, dystocia, and pup mortality) which are already observed in the absence of marked toxicity and are considered relevant to humans.

Developmental effects

There are four relevant studies available for assessing the effects on development upon exposure to BENPAT; two key studies and two supportive studies. The findings are described below per study.

In a two-generation reproduction toxicity study (RTI, 2001a), a statistically significant and dose-dependent post-implantation loss in F0 dams was observed (mid and high dose: 26.1/52.3 %, vs. 10.7 % in control). A dose-dependent post-implantation loss was also noted in F1 animals

reaching statistical significance at the highest dose (6.8, 18.5, 20.2 and 32.6 % for control, low, mid and high dose, respectively).

Foetal body weight was increased in F1 (7.5/25 mg/kg bw/d: 6/7 %) and in F2 pups (7.5/25/100 mg/kg bw/d: 9/11/5 %), but showing no consistent pattern. Increased pup mortality (F1 and F2) occurred mostly on PND 0 and some on PND 1-4. Pup mortality was strongly associated with prolonged parturition/dystocia.

Patent ductus arteriosus accompanied with no air in lungs and no milk in stomach were observed in many dead F1 and F2 pups in all treated groups. However, many pups died with closed ductus and air in lungs. It should be noted that many pups had autolysed abdominal organs and data should be taken with care due to low animal numbers, so no robust conclusion is possible on basis of the available information.

A dose-dependent increased incidence of polycystic kidneys was noted in F1 and F2 weanlings from the lowest dose (7.5 mg/kg bw/day) onwards. In F1 adults, polycystic kidneys were also increased in all treated groups, although incidences were lower in F1 adults in comparison to F1 weanlings. No polycystic kidneys were noted in the controls group. In the high dose F0 females, only animals with gross lesions were examined histologically, resulting in 3/9 animals showing polycystic kidneys. Polycystic kidneys were characterised by the presence of renal tubule cysts primarily in the outer medulla and occasionally in the inner medulla (papilla) and cortex. No information is available on the severity of the polycystic kidneys in F1 and F2 weanlings or on kidney function (e.g. urine analysis).

Table: *Incidence of polycystic kidneys in animals from OECD TG 416 (copied from the CLH dossier).*

	Polycystic kidneys in male animals				**Polycystic kidneys female animals**			
[mg/kg bw/d]	0	7.5	25	100	0	7.5	25	100
F0 adults [a]	0 %	0 %	0 %	0 % 0/1	0 %	0 %	0 % 0/2	33 % 3/9
F1 weanlings [b]	0 % 0/23	4 % 1/25	40 % 8/20	91 % 10/11	0 % 0/22	19 % 5/26	39 % 7/18	100 % 11/11
F1 adults [c]	0 % 0/30	17 % 5/30	33 % 10/30	70 % 21/30	0 % 0/30	7 % 2/30	3 % 1/30	60 % 18/30
F2 weanlings [b]	0 % 0/60	5 % 3/64	32 % 6/19	94 % 15/16	0 % 0/60	8 % 5/64	42 % 8/19	100 % 15/15

[a] F0 parental animals, only kidneys with gross lesions were examined histologically in any group

[b] Kidneys of three F1 and F2 weanlings per sex per litter were examined histologically in any group

[c] F1 parental animals, all kidneys were examined histologically in any group

In a prenatal developmental toxicity study (OECD TG 414 but with deviating exposure window from the current OECD TG: GD 6-15; GLP; Klimisch score 2; RTI, 1995) Sprague-Dawley rats (n = 25/dose) were exposed to 0, 20, 70, 200 mg/kg bw/d BENPAT (in corn oil) via gavage on GD 6-15. No statistically significant changes on corrected maternal body weight gain (subtracted gravid uterine weight) were noted at any dose level. No substance-related clinical signs or effects on sexual function and fertility (pregnancy rates 92-96 % in all groups) were observed in dams. A (statistically significant) dose related decrease in foetal body weight per litter was noted at 200 mg/kg bw/d. However, no notable (statistically significant) changes on developmental variations or malformations were observed in any dose groups compared to control. In addition, no evidence of polycystic kidneys in adults or pups was found in this study. However, the short exposure window is a deviation from the current test guidelines but in alignment with the test guideline applicable in 1995. According to the current OECD TG 414, a pregnant animal is exposed to a test substance from implantation to one day prior to the day of sacrifice. As indicated

by the DS, the exposure window used is not sufficient to study embryonic development of the kidney.

In a range-finding study (RTI, 1995), conducted prior to the above-described prenatal developmental toxicity study, pregnant Sprague-Dawley rats (n = 8/group) were exposed to 0, 20, 70, 200 and 600 mg/kg bw/d BENPAT (in corn oil) via gavage (once daily) at GD 6-15. In the highest dose group (600 mg/kg bw/day) 4/8 animals died (2 were found dead and 2 animals were sacrificed due to moribund condition). No unscheduled deaths were noted in other dose groups. Vaginal bleeding (1/8 (12.5 %) at 20 and 70 mg/kg bw/d, and 3/8 (33 %) at 600 mg/kg bw/d) were noted, but not at 200 mg/kg bw/d. Pale organs and internal bleedings at 600 mg/kg bw/d were observed. Body weight (-6.5 % to -16.8 %, not corrected for gravid uterine weight) and body weight gain (corrected for gravid uterine weight) were statistically significantly changed at ≥ 200 mg/kg bw/d. Foetal body weight per litter was statistically significantly reduced at ≥ 200 mg/kg bw/d (-6.3 to -12.6), but this decrease was not statistically significant in male pups at 200 mg/kg bw/d. No statistically significant changes on reproductive parameters or external malformations were noted.

In a one-generation mechanistic study (RTI, 2000), polycystic kidneys were observed in dams of group 5 (15 % (3/20) vs. 0 % in control), but examination in other treated groups did not provide gross evidence. In weanlings, haematological changes (increased haemoglobin and mean corpuscular haemoglobin concentration) and increased (relative) organ weights (liver and heart) were noted in groups 3-5. In addition, increased incidence of polycystic kidneys was observed in group 3 (female/male: 24/25 (96 %)/ 37/38 (97 %)), 4 (29/32 (91 %)/ 38/40 (95 %)) and 5 (48/48 (100 %)/ 31/34 (91 %)). In control and group 2 no incidences of polycystic kidneys were found. There was no gross evidence of polycystic kidneys in pups that died during lactation, but histopathology was not performed. Post-implantation loss was statistically significantly increased in group 3 and 4, but not in the iron-supplemented group 5. It is noted that implantation sites/litter was (statistically significantly) decreased only in the BENPAT exposed group with iron supplementation. The study indicates that the effects observed were not (fully) associated with iron deficiency. This study does not elucidate whether the BENPAT induced increase of polycystic kidneys is due to *in utero* exposure only or is a resultant of *in utero* exposure and exposure during lactation and/or diet.

Assessment of developmental effects

In a two generation study a dose-dependent increase of post-implantation loss was observed in F0 and F1 dams. Post-implantation loss was also observed in a one-generation study upon exposure during pre-breeding up to and including lactation (group 3 and 4). The post-implantation loss in the two-generation study was observed from 25 mg/kg bw/day onwards in the F0 and was dose related increased in the F1 reaching statistical significance at the highest dose (6.8 %, 18.5 %, 20.2 %, 32.6 %; for controls, low, mid and high dose, respectively). No marked non-specific toxicity was seen in the mid and high dose groups. The mortality seen in the mid and high dose F0 females was associated with dystocia. Body weight of the high dose females during gestation was about 10 % lower compared to controls (no exact figures given in the report) and no marked differences in body weight in the mid dose group as compared to the controls were reported. Effects on liver and kidney weight were noted in the high dose group and accompanied by minimal to moderate histopathological changes. All in all no marked non-specific maternal toxicity was observed and effects on post-implantation loss were dose related and statistically significant from the mid dose onwards. Post-implantation loss was also noted in the one generation reproduction mechanistic study in the groups exposed during gestation. For classification for developmental effects, post-implantation loss is considered a relevant adverse effect.

Patent *ductus arteriosus* noted in a two-generation study could indicate an adverse developmental effect on blood vessels. However, the incidence is not clear due to many cannibalised pups or pups with autolysed abdominal organs (unable to evaluate). Closure of the *ductus arteriosus* is mediated through various factors, such as oxygen and prostaglandin concentration (Hundscheid *et al.*, 2019). Patent *ductus arteriosus* together with no milk in stomach and no air in lungs were noted in dead pups, indicating this was likely due to dystocia-mediated pup mortality rather than a development effect.

Polycystic kidneys upon exposure to BENPAT were noted in F1 and F2 weanlings, and to a lesser extent in F0 (high dose group) and F1 adults (low, mid and high dose groups) in the two-generation study. These effects were noted from the lowest dose onwards in weanlings, in absence of marked non-specific maternal toxicity. This is supported by similar findings in weanlings in group 3-5 in the one-generation study. No polycystic kidneys were reported in two repeated dose toxicity studies with BENPAT using similar dose levels (0-120 mg/kg bw/d) in F344 rat (other rat strain) or in the prenatal rat developmental toxicity. However, the exposure window in the prenatal developmental toxicity study (GD 6-15) might not cover the metanephros where the permanent and functional kidney are developed (Moritz and Wintour, 1999), and deviates from the current test guidelines (OECD, 2018).

Polycystic kidneys were thus more pronounced in weanlings as compared to the effects seen in adult rats. Polycystic kidneys in weanlings can be the result of exposure to BENPAT *in utero*, to a higher sensitivity for the formation of polycystic kidneys in weaning or, of exposure to BENPAT via lactation and self-feeding. It is not possible to rule out any of these options. No information is provided on the severity/grade of the observed polycystic kidneys in weanlings. Cysts on the kidney reflect permanent change, but is mainly considered a 'grey zone' variation (Solecki *et al.*, 2003)[1], whether this relates to kidney cysts in general or polycystic kidneys as observed in weanlings after BENPAT exposure is not clear. The fact that polycystic kidneys are also observed in F1 adults does indicate the effect is not (fully) reversible. Overall, it is not clear whether polycystic kidneys are the effect of exposure *in utero,* via lactation or via the diet (or a combination thereof) and the effects seem to be non-reversible.

For DPA and its derivatives (reported impurities of BENPAT), renal cystic disease in new-born rats were reported upon exposure to DPA (1.5-2.5 % in feeding or 20 mg via tube feeding, exposure during last 7 days of gestation) by Crocker *et al*. (1972). RAC agrees with DS that, together with evidence from BENPAT, it appears that developing embryonic kidneys are more sensitive to BENPAT in comparison to adult kidneys to develop polycystic kidneys in rat. It is unclear from the available data whether this is a developmental effect due to *in utero* exposure or a post-natal developmental effect due to post-natal exposure.

Mode of action

The DS notes studies with DPPD (one of the BENPAT constituents) that also result in dystocia and longer gestational length. Mechanistic studies with co-exposure to DPPD and prostaglandin F2α show a total cancelling of the effects of DPPD (see Annex I, CLH report). It is suggested that DPPD inhibits the prostaglandin formation. Whether this mode of action is the only cause of the effects exerted by BENPAT is not clear because mechanistic studies on this mode of action with BENPAT are lacking. There are no human data available regarding adverse effects on development upon exposure to BENPAT, its constituents or impurities.

[1] "Cyst on kidney" was assessed with an IA (Index of Agreement) (%) of -35.00, classification as Gray zone/V (Variation) and Minimal information needed S (severity grading).

Conclusion

- Pup mortality is strongly associated with dystocia and is therefore not considered solely a developmental effect.
- The post-implantation loss was noted in the reproduction toxicity studies. The effects observed in the two-generation study were dose related and consistent in the F0 and F1 generation and were noted at dose levels without marked non-specific maternal toxicity. Post-implantation loss is relevant for classification for adverse effects on development.
- Effects on blood vessel (patent *ductus arteriosus*) were observed in F1 and F2 pups. The incidence is not clear due to many cannibalised pups or pups with autolysed abdominal organs (unable to evaluate). This effect in dead pups was observed together with absence of air in lungs and no milk in stomach, suggesting pups did not breathe after parturition and thus seems likely to be associated to dystocia.
- A dose-dependent increase in polycystic kidneys was noted in rat F1 and F2 weanlings, and to a lesser extent in F1 adults in a two-generation study. These effects were also noted in a one-generation study. In F0 females polycystic kidneys were observed in a few animals of the high dose only. No polycystic kidneys were reported in the available repeated dose studies (AHF, 1994; AHF, 1996). Although weanlings appear to be more sensitive to BENPAT induced polycystic kidneys, from the information available it is unclear whether these effects are solely due to *in utero* exposure or due to exposure duration lactation and the diet. According to CLP Annex I paragraph 3.7.1.4, classification for developmental toxicity is primarily intended for effects induced during pregnancy and due to parental exposure. Therefore, it is unclear whether the increase in polycystic kidneys in weanlings can be considered a developmental effect warranting classification on its own.
- There is no mechanistic information indicating that adverse effects observed in rats upon exposure to BENPAT are not relevant for humans.

The DS considered the adverse effects on development, as seen by the high incidence of polycystic kidneys in F1 and F2 offspring, as key effects for classification. The DS noted that according to the CLP regulation: *"any effect which interferes with normal development of the conceptus either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, to the time of sexual maturation", in the widest sense, should be considered as an adverse effect on development of the offspring. "However, it is considered that classification under the heading of developmental toxicity is primarily intended to provide a hazard warning for pregnant women, and for men and women of reproductive capacity. Therefore, for pragmatic purposes of classification, developmental toxicity essentially means adverse effects induced during pregnancy or as a result of parental exposure" (CLP regulation, Annex I, section 3.7.1.4).*

The available data does not allow to conclude that polycystic kidneys in the F1 and F2 weanlings were induced after treatment of dams exclusively during gestation. However, according to the DS, data on DPA and its derivative (induction of polycystic kidneys in newborn rats after treatment of dams from gestation day 14 until term) are supportive of BENPAT-induced developmental toxicity, and on this basis the DS proposes to classify BENPAT as a presumed human reproductive toxicant, development Repr. 1B.

Although RAC concurs with the DS that BENPAT warrants classification as Repr. 1B for development, the line of reasoning is somewhat different. The consistent and dose-related post-implantation loss is key for classification for development. Polycystic kidneys in weanlings are

considered as supportive evidence for this conclusion, because the effects are considered as permanent and serious, but it is not clear whether this is due to *in utero* exposure only.

Effects on or via lactation

The available one and two generation studies do not allow a conclusion regarding the effects of BENPAT due to do exposure via lactation.

There are no human data available regarding adverse effects on lactation upon exposure to BENPAT, its constituents or impurities.

RAC concurs with the DS that **no classification is warranted for lactation**.

Overall conclusion

There is no evidence for reproductive toxicity of BENPAT in humans. Therefore category 1A is not warranted for BENPAT.

Effects on sexual function and fertility (abnormal cycles, gestational length, dystocia, and pup mortality) were observed in animals. In addition, clear evidence for adverse effects on foetal development (post-implantation loss, supported by polycystic kidneys in weanlings) in animals is available. These effects are not considered secondary to marked general toxicity and are considered relevant for humans. Therefore RAC concludes that category 1B is warranted for sexual function and fertility and on development, in agreement with the DS.

For BENPAT ED_{10} values of 4.3 mg/kg bw/d for polycystic kidneys in F1 female weanlings (on PND 21) and 23.8 mg/kg bw/d for post-implantation loss of F0 dams with F1 litters are derived by the DS. RAC agrees that these values are both within the limits of the medium potency group (4 to 400 mg/kg bw/d) for the GCL, and thus a SCL is not justified.

RAC agrees with no classification for effects on or via lactation due to inconclusive data. Together this results in a recommendation for **classification as Repr. 1B; H360FD**.

Additional references

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Solecki R., Bergmann B., Bürgin H., *et al.* Harmonization of rat fetal external and visceral terminology classification. Report of the Fourth Workshop on the Terminology in Developmental Toxicology, Berlin, 18-20 April 2002. Repr. Tox. (2003) 17: 625-637

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).