Analysis of the most appropriate risk management option (RMOA)

Substance Name:	1,2-CYCLOHEXANEDICARBOXYLIC ACID, DIISONONYL ESTER (DINCH®)
EC Number:	431-890-2
CAS Number:	166412-78-8
Authority:	FRANCE
Date:	January, 2015

Cover Note

The restriction of the use of various phthalates (DEHP, BBP, DBP, DIBP) has challenged the companies to find alternative solutions for product manufacturing. Among these potential substitutes which have emerged is the 1,2-CYCLOHEXANEDICARBOXYLIC ACID, DIISONONYL ESTER (DINCH).

In the framework on the French National Strategy on Endocrine Disruptors in 2014, the French Competent Authority requested ANSES to evaluate its toxicological profile and verify whether risk management measures should be necessary for this substance.

Comments and additional relevant information are invited on this RMOA by DD Month YYYY.

1 IDENTITY OF THE SUBSTANCE

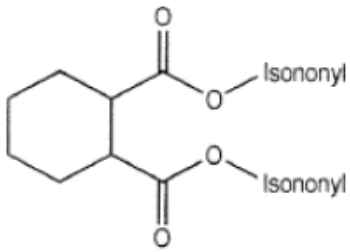
1.1 Other identifiers of the substance

Table: Substance identity

EC name:	1,2-Cyclohexanedicarboxylic acid, diisononyl ester
IUPAC name:	1,2-Cyclohexanedicarboxylic acid, diisononyl ester, reaction products of hydrogenation of di-isononylphthalates (n-butenes based)
Index number in Annex VI of the CLP Regulation	none
Molecular formula:	C_{26} H_{48} O_4
Molecular weight	424.665 g/mol
Synonyms/Trade names:	1,2-Cyclohexanedicarboxylic acid, diisononyl ester *Hexamoll* ® *DINCH*® (Trademark from BASF SE)

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



2 REGULATORY PROCESSES

2.1 Completed/ongoing regulatory processes

Table: Completed or ongoing regulatory processes

☐ Compliance check, Final decision	☐ Dangerous substances Directive Directive 67/548/EEC (NONS)
☐ Testing proposal	☐ Existing Substances Regulation - Regulation 793/93/EEC (RAR/RRS)
☐ Annex VI (CLP) (see section 3.1)	☐ Plant Protection Products Regulation - Regulation (EC) No 1107/2009
☐ Annex XV (Candidate List)	☐ Biocidal Product Regulation - Regulation (EU) 528/2012 and amendments
☐ Annex XIV (Authorisation)	☐ CoRAP and Substance Evaluation
☐ Annex XVII (Restriction)	☒ RMO Analysis
☐ (UNEP) Stockholm convention (POPs Protocol)	☐ Other (provide further details below).

2.2 Other Relevant EU legislation for the substance/group of substances

Legal instrument	EU/national	Status of DINCH
Regulation EU No. 10/2011 on substances in contact with food Based on EFSA opinion	Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) - 12th list of substances for food contact materials	In September 2006 the scientific panel on AFC from EFSA evaluated the safety of DINCH. The substance was then authorized to be used in food contact materials. A TDI of 1 mg/kg bw/day was derived.
European References	Harmonised Standards EN 71-3 (Safety of toys - Part 3: Migration of certain elements); EN 71-5 (Safety of toys - Part 5: Chemical toys (sets) other than experimental sets) and EN 71-9 (Safety of toys – requirements	According to BASF DINCH satisfies the requirements of these standards.

	concerning organic chemical compounds)	

3 HAZARD INFORMATION (INCLUDING CLASSIFICATION)

This section should include information on classification when available. In addition a short description of additional hazard information (environment and human health) relevant for the justification in section 5 could be provided.

3.1 Classification

3.1.1 Harmonised Classification in Annex VI of the CLP

There is no existing Harmonised Classification for DINCH.

3.1.2 Self classification

No self classification has been proposed.

3.1.3 CLP Notification Status

None of the notifiers proposed a classification for this substance (129 notifications for no classification).

3.1.4 Proposal for Harmonised Classification in Annex VI of the CLP

Not relevant.

3.2 Additional hazard information

3.2.1 Existing assessments

Several hazard and/or risk assessments have already been conducted :

An evaluation performed by the Australian National Industrial Chemicals Notification and Assessment Scheme, NICNAS (2012) has concluded on the risk posed by DINCH :

- Under the conditions of the occupational settings described, DINCH is not considered to pose a risk for workers, neither for public health when used in the proposed manner.
- DINCH is not considered to pose an environmental risk based on its reported use pattern.

In its opinion published in 2007, the Scientific Committee on Emerging and Newly-identified Health Risks (SCENIHR, 2008) assessed the safety of medical devices containing DEHP-plasticized PVC or other plasticizers on neonates and other groups possibly at risk. Several alternative plasticizers were analyzed, among them DINCH. Concerning the DINCH this opinion stated that it does not exert any reproductive toxicity, nor genotoxicity or carcinogenicity and that the critical endpoint is the effects observed in kidney. Nevertheless, since the effects in kidney are due to α-2-microglobulin, these effects are not considered as relevant for humans. The SCENIHR concluded that DINCH shows a different "hazard profile" than DEHP and is considered as less toxic than DEHP based on the submission dossier presented by BASF.

In a report called "Review of Exposure and Toxicity Data for Phthalates Substitutes", published in 2010 the US Consumer Product Safety Commission (CPSC) identified five chemicals as most likely alternates to dialkyl ortho-phthalates (o-DAPs) including DINCH. Dialkyl ortho-phthalates (o-DAP's) are a class comprising about 30 commercial products, which includes DEHP or DiNP. In this report, contrary to NICNAS (2012) or SCENIHR (2007), the authors stated that effects produced by DINCH on the thyroid gland in the combined chronic/carcinogenicity study (see below section 3.2) may be relevant for humans. They quoted the US EPA risk assessment forum which stated that "rodent non-cancer thyroid effects resulting from disruption of the thyroid-pituitary axis are presumed to pose a non-cancer health hazard to humans" and that "rodent cancer effects resulting from the same mechanism may pose a cancer health hazard to humans."
The conclusion of this report for DINCH was "Essentially all located information regarding the health effects of DINCH was found in the SCENIHR (2008) review of unreferenced and unpublished animal studies submitted by BASF Corporation. BASF Corporation also submitted an abstract/summary of one of these studies (the chronic toxicity/carcinogenicity study, BASF, 2005) to EPA under TSCA[1]. The available summaries of these studies are brief and generally insufficient with respect to information on experimental design and results, particularly quantitative data and dose-response relationships. While DINCH is entering the market as a component of consumer products such as children's articles, the insufficiency of these study summaries preclude independent evaluation of the results and reliable identification of adverse effect levels."
In May 2012, the TSCA Interagency Testing Committee of the US EPA added DINCH and 5 other non-phthlate plasticizers to its Priority Testing list since these substances are known to be used in children's products, including teething rings and soft plastic toys and have the potential to migrate from these products into human saliva. The rationale is the need for biomonitoring data on urine metabolites.

According to the registration dossier updated in 2012 no hazards were identified for human health or for environment. Therefore the registrant stated that according to the REACH Annex I (5.0) an exposure estimation is not necessary, nor a risk

[1] Toxic Substances Control Act

characterization and consequently all identified uses of the substance are considered as safe for both human health and environment by the registrant.

3.2.2 Hazards for human health

Most of the following information come from the registration dossier or the previous assessments described here above. A bibliographic review has also been conducted and information contained in this publications was included especially the publication by Bhat *et al*. (2014) in which a complete hazard risk assements were performed for DINCH, and the publication of the hazard profile of DINCH performed by Tox Service (2013) in the framework of GreenScreen, a method for chemicals comparative assessment.

Additionally it should be noted that BASF made available to ANSES all the study reports including the raw data.

3.2.2.1 Toxicokinetics

According to the registration dossier, rapid but incomplete absorption to all organs and tissues following an oral administration. The oral bioavailability was calculated to be around 5-6% of a high dose (1000 mg/kg bw) and around 40-49% of a low dose (20 mg/kg bw), indicating saturation of gastrointestinal absorption .

DINCH is distributed in almost all organs and tissues in 1-8 hours. No bioaccumulation has been reported. The highest levels were in GI tract, adrenal glands and liver.

In rats, after metabolisation, DINCH is partially hydrolyzed into monoisononyl cyclohexanedicarboxylate (MINCH, faeces) followed by conjugation to glucuronic acid, which is the most abundant metabolite in bile, or the hydrolysis of the remaining ester bond to yield free cyclohexane dicarboxylic acid (CHDA), the predominant urinary metabolite.

In humans the main urinary metabolite is CHDA, which accounted for a mean of 24% of the administered dose 48 h after 3 male volunteers (aged 26–38 yr) were given a single bolus dose of DINCH (Koch *et al*., 2013). The minor metabolites included the oxidized monoesters, hydroxy-MINCH (11%), oxo-MINCH (2%), and carboxy-MINCH (2%), as well as the simple monoester MINCH (<1%). Parent compound was not detected. Peak urine concentrations for the metabolites were reached within 4 h and elimination half-times ranged between 10 and 18h. Thus, 39% of the DINCH dose was excreted as identified urinary metabolites within 48 h with 36% occurring within 24 h (Bhat *et al*., 2014)

3.2.2.2 Acute toxicity

According to the registration dossier and other available studies DINCH does not exert an important acute toxicity. LD_{50} for oral route for Wistar rats is > 5000 mg/kg

bw/d and following a dermal administration the LD_{50} was > 2000 mg/kg bw/day (SCENIHR, 2008).
Based on the low vapour pressure of the substance it is unlikely that the substance poses a human health hazard on the inhalative route.

3.2.2.3 Irritation/sensitization

A moderate dermal erythema was observed after removal of the semi-occlusive patch in all New Zealand rabbits exposed to DINCH for 14 days (Registration dossier). This erythema lasts for 48h in 2 out 3 animals. A mild to moderate erythema was observed in all animals at 72h. Effects were fully reversible in 7 to 14 days (NICNAS, 2012).These results do not justify a classification for dermal irritation. DINCH is a mild dermal irritant.
Concerning eye irritation, the scores obtained in Himalayan rabbits after 48h do not warrant classification.

According to a maximization test performed in female guinea pig, no positive reactions were observed, then DINCH is not sensitizing.

3.2.2.4 Repeated-dose toxicity

In a 28-day study (following the guideline OECD 407), Wistar rats were exposed via food to DINCH at 0; 600; 3000 and 15000 ppm (equivalent to 64/66; 318/342; 1585/1670 mg/kg/d in males and females respectively) followed by a 14 days recovery period. In males, the highest dose induced a deterioration of the renal function with an increase of the degenerated epithelial cells in the urine and a significant increase of serum sodium levels at 3000 and 15000 ppm. In females the highest dose induced increased gamma-glutamyltransferase (GGT) serum levels. All these effects were reversible. A NOAEL of 3000 ppm was chosen. It has to be noted that the thyroid weight and thyroid hormone levels were not measured (NICNAS, 2012; SCENIHR, 2008).

In a **13-week study (OECD guideline 408 compliant)**, Wistar rats (20 animals per sex and dose) were exposed through food to 0; 1500; 4500 and 15000 ppm (equivalent to 107/128; 325/389; 1102/1311 mg/kg/d in males and females respectively) of DINCH. There was no effect on mortality, clinical signs or hematology.
A hyperplasia/hypertrophy of the thyroid follicles was observed in both sexes at every dose. These effects seemed to suggest a mode of action via an enzymatic induction process according . Moreover an increase of the testes relative weight was noted at all doses (with no dose-response relationship) but without histological changes in testes or reproductive tract.
A significant increase of the gamma-glutamyltransferase (GGT) serum levels and serum TSH levels were observed at the highest dose in females. In addition, blood and transitional epithelium cells were observed in urine. This increase in GGT levels could be due to enzymatic induction according to the authors. Nevertheless there is no indication of a turn over of T_3 or T_4 or a significant decrease in serum thyroid

hormones levels to support this hypothesis since only a non significant increase of T_4 was observed.
A significant increase of relative weight of liver and thyroid was reported in both sexes at the highest dose, in addition to hyperplasia/hypertrophy of the thyroid follicles. Signs of renal toxicity have been observed from 4500 ppm in males including hematuria and increase of transitional epithelium cells in the urinary tract. Furthermore, in the kidney alpha 2-microglobulin accumulation in the tubules was observed with an increase of the kidney relative weight from 15000 ppm in males and at the highest dose for females. The effect on alpha 2-microglobulin is not considered as relevant for humans, since it is present in rats only. Then NOAELs of 1500 ppm for males and 4500 ppm in females were chosen (NICNAS, 2012; SCENIHR, 2008).

In a **combined chronic toxicity/carcinogenicity study (OECD 453 compliant)** performed in Wistar rats exposed dietary to 0; 40; 200 or 1,000 mg/kg bw/day of DINCH, no treatment related mortality or increase in malignant neoplasias up were reported at any doses. Increased incidences of thyroid adenomas and increased thyroid weight were observed in both sexes at the high dose, and at mid-dose in males. Similar to the short term study transitional epithelial cells of the urinary tract were present in the urine after 3 months in high dose males. These were temporarily present and considered as adaptive as no histopathological lesions were observed in the kidneys at 12 and 24 months.
Concerning the hematology, mean corpuscular volume (MCV) was slightly but significantly reduced in all treated males and similarly mean corpuscular hemoglobin (MCH) was a little but statistically significantly decreased in both low and high dose groups after 6 months. Low and high dose male rats showed decreased MCV and MCH values after 12 months also. Slightly but statistically significant increased red blood cell counts were found in mid dose and high dose males after 12 months. Finally, high dose females exhibited higher platelet counts after 12 months .
As in previous studies, an increased alkaline phosphatase activity in the serum of high dose male rats after 12 months of DINCH exposure was detected. This was possibly indicative of mild and adaptive impairment of liver function. GGT activity was increased substantially in high dose females.
Bath et al (2014) reported changes in the absolute weight of kidney, liver, thyroid and uterus observed in this study :

		Males			**Females**		
Dose (mg/kg bw/day)		**40**	**200**	**1 000**	**40**	**200**	**1 000**
Rats exposed during 1 year							
Kidney	Absolute weight	+3.1%	**+20.3%****	**+14.2%****			
	Relative weight	-3.8%	**+8. %***	+10.4%			
Liver	Absolute weight	+5.2%	**+15.9%***	+11.1%	+6.0%	+6.0%	**+14.0%****
	Relative weight				+11.5%	**+11.7%****	**+22.2%****
Thyroid	Absolute weight				**-18.5%***	-2.2%	+2.7%
Rats exposed during 2 years							
Kidney	Absolute weight	-1.9%	**+4.5%***	**+3.1%***			
Liver	Absolute weight	+0.8%	**+6.7%***	**+68%***	-1.0%	+6.7%	**+13.8%****
	Relative weight	-2.1%	**+4.5%***	+1.3%	-2.5%	+4.9%	**+14.6%****
Thyroid	Absolute weight	-1.8%	**+68.9%****	**+52.4%****	+6.3%	+13.9%	**+70.4%****

	Relative weight	0.0%	**+71.4%***	**+42.9%****	0.0%	+11.1%	**+55.6%****
Uterus	Absolute weight				-29.2%	**-70.1%***	**-77.5%****

* p <0.05 ; ** p < 0.01

From this study, EFSA (2006) set a NOAEL of 40 mg/kg bw/day based on thyroid effects and a NOAEL of 200 mg/kg for the other adverse effects. NICNAS (2012) set the NOAEL at 40 mg/kg/d for males (LOAEL = 200 mg/kg/d) and 200 mg/kg in females (LOAEL = 1000 mg/kg/d).
However, Bhat *et al*., (2014) consider that effects on the weight of the thyroid either at interim or terminal sacrifice at every doses should be considered and consequently, that a LOAEL could be set at 40 mg/kg/day.

Summary of the effects in repeated dose studies:

Study type and doses	Effects	NOAEL	Reference
28-day Oral route (OECD 407) 5 Wistar rats/sex/dose 0, 600, 3000, 15 000 ppm	At 15 000 ppm: ↗ of the GGT activity (55%) ↘ in serum bilirubin levels (20%) Mild renal impairment (↗ number degenerated epithelial cells in urine). Reversible effects. Thyroid weight and thyroid hormones levels not assessed.	3000 ppm (318/342 mg/kg/d)	BASF (2000) Registration dossier
13-week Oral route (OECD 408) 20 Wistar rats/sex/dose 0, 1500, 4500, 15 000 ppm	From 1 500 ppm: in males: ↗ thyroid (12%), kidneys (8%) and testes (6%) In females: ↗ thyroid weight (14%) From 4 500 ppm: renal toxicity in males with ↘ in serum bilirubin and ↗ γ-glutamyltransferase. ↗ kidney (7%), testes (7%) and spleen weight (6%). In females: ↗ liver weight (6%). From 15 000 ppm: ↗ GGT in males and kidney weight (10%). ↗ thyroid (20%), liver (6%) and testes (4%) weight. In females ↗ liver (12%), and kidney (8%). ↗ TSH level with no effects on T_3 or T_4 levels. Every dose: hypertrophy of the thyroid follicles.	< 1500 ppm (107/128 mg/kg/d)	BASF (2002) Registration dossier
Combined Chronic cancerogenicity Oral route (OECD 453) 50 Wistar rats/sex/dose 0, 40, 200, 1000 mg/kg/d 2 years + 10 rats/sex/dose for interim sacrifice after 1year	40 mg/kg/d: ↘ thyroid weight (19%) in females after 1yr. 200 mg/kg/d:after 1 year in males ↗ kidney (8%), after 2-year, ↗liver (5%), thyroid (71%). In females after 1 year ↗liver (12%), drastic decrease of the uterus weight (-70.1%) after 2-year. 1000 mg/kg/d: in males, ↘ bilirubin level. ↗ thyroid weight (14%) after 1 year; ↗ thyroid (43%), liver and kidney weight after 2year. In females: ↗ γ-GT activity, ↘ bilirubin level. ↗liver (22%) after 1 year. After 2 year ↗ kidney, liver, thyroid (56%) and uterus (77%) weight.	NOAEL = 40 mg/kg/d (males) 200 mg/kg/d (females)	BASF (2005) Registration dossier

3.2.2.5 Mutagenicity

DINCH is not considered as a genotoxic substance since it gives negative results in:
- a bacterial reverse mutation test
- an *in vitro* mammalian cytogenetic test in V79 cells
- an *in vitro* mammalian cell gene mutation test in CHO cells with or without S9 mix activation
- an *in vivo* mammalian erythrocyte micronucleus test in mouse

3.2.2.6 Cancerogenicity

As described before, a **combined chronic/carcinogenicity (OECD 453-compliant)** was performed using Wistar rats, which were exposed in the diet to 0; 40; 200 or 1000 mg/kg of DINCH during 2 years.

Thyroïd

Thyroid weight was increased in both sexes with follicular cell hyperplasia and the presence of follicular adenomas. In the following table, the incidence of thyroid gland adenoma in rats exposed to DINCH during 2 years is reported (CPSC, 2010).

Dose (mg/kg bw/day)	Males	Females
0	3/50	1/50
40	5/50	3/50
200	11/50*	3/50
1 000	14/50**	9/50**

* p <0.05 ; ** p < 0.01

The registrant proposed that this occurred because of an increase of thyroid hormones (T_4 and T_3) metabolism due to liver enzyme induction by DINCH. It should however be noted that the thyroid hormones levels were not measured in this study. The SCENIHR report (2008) also considers that the effects on thyroid are due to secondary mechanisms via liver enzyme induction which is considered as not relevant for humans.

Mammary glands and uterus

After 2 years of treatment, a significant increase of fibroadenomas was observed in the mammary glands of females treated with the mid- and the highest dose while the number of females with masses in the uterus was decreased in all dose groups. According to NICNAS report (2012), the lack of dose-response relationship suggests that the uterine effects were incidental and not treatment-related.

According to the registration dossier, the mammary fibroadenomas are in the range of the historical control, the incidence of mammary fibroadenomas in the concurrent control (2%) being very low compared to historical control data (6-16.1%). The registrant also notices that there was no increased incidence of malignancies (adenocarcinomas). According to Bhat *et al.* (2014) in an independent reexamination of the mammary-gland sections performed by the Experimental Pathology Laboratories, Inc. (EPL) in 2008, mammary gland changes initially reported as hyperplasia were considered to be more characteristic of mammary-gland

fibroadenomas resulting in a numerically higher incidence of fibroadenomas for each dose group. Therefore the relevance of this finding remains unclear despite the fact that this common benign and spontaneously occurring tumor type is unique to rats. Since in the 1-year interim sacrifice group after treatment with DINCH no findings at all in the mammary gland were reported, any signs of an early induction of fibroadenoma or precursor lesions were missing. Thus, evidence indicated that these mammary fibroadenomas appeared to be only incidental, age-related lesions based on the BASF historical control ranges data, low incidence of fibroadenomas in the concurrent control group, and lack of a dose response for the occurrences of mammary adenocarcinomas, and should not be considered (Bhat *et al.*, 2014).

Liver

In females, the number of foci in the liver increased compared to controls, but there was no clear dose-response relationship, thus this finding may have been unrelated to treatment. In males, there was a slight increase in numbers of liver foci, but only in the mid- and high-dose satellite groups (12 months).

Data analysis and conclusion

Based on all the information available, the increase of fibroadenomas in mammary glands and foci in liver were not considered to be a consequence of DINCH toxicity.
On the other hand, the effects observed on the thyroid gland are more questionable.

According to the registrants, the effects observed on the thyroid gland are secondary effects only associated with liver enzyme induction and then of limited relevance to humans. Nevertheless it should be pointed out that lots of other mechanisms than induction of biotransformation liver enzymes can explain an hyperthyroidy and an increase of TSH level, which have not been examined.
More generally, the relevance to humans of thyroid effects observed in rodents is controversed due to a great difference in physiology and histology between both species. For instance, in its report the US CPSC (2010) do not agree with the statement that thyroid effects observed in rodents are not relevant for humans and quote the US EPA point of view who considers that rodent noncancer thyroid effects resulting from disruption of the thyroid-pituitary axis are presumed to pose a noncancer health hazard to humans and that rodent cancer effects resulting from this mechanism may pose a cancer health hazard to humans, and the effects on thyroid observed in this study may indeed be relevant to humans. Moreover it appears that despite the human thyroid gland is much less susceptible than the rodent one, recently more subclinical hypo- or hyperthyroidism were observed in epidemiology studies and therefore these effects on thyroid cannot completely be discarded.
Nevertheless, in the state of knowledge, the relevance for humans of carcinogenic effects in thyroid observed in rodents remains questionable. Moreover, since the effects observed following an exposure to DINCH occurred only at high doses, DINCH can reasonably not be considered as a potential thyroid carcinogen in humans.

3.2.2.7 Reprotoxicity and Developmental toxicity

A two-generation study (OECD 416 compliant) is available, in which Wistar rats were exposed by oral route (dietary) to 0; 100; 300 or 1000 mg/kg bw/day during 38 weeks. An increase of gamma glutamyltransferase (GGT), an increase of liver, kidney and thyroid gland weights in parents at the two highest dose were observed. The 1000 and 300 mg/kg bw/day F0 generation females showed also decreases in total bilirubin level.

Like in F0 generation, liver and kidney weights were affected, in fact the relative and/or absolute liver and kidney weights of the F1 parental rats were significantly increased for all dose groups. F1 generation females treated with 1000 and 300 mg/kg bw/day showed increases in serum GGT activity and decreases in total bilirubin level. Decreased total serum bilirubin concentrations were also observed in 1000 mg/kg bw/day dose F1 males. Vacuolisation of the tubular epithelia was detected in the kidneys of all high dose males and 9/25 males in the mid dose group. For this F1 generation, similar effects than in F0 were noted including thyroid weight increase with thyroid hypertrophy/hyperplasia. The absolute and relative thyroid weights for females were increased in the high dose group. Minimal to slight hypertrophy/hyperplasia of the follicular epithelia of the thyroid glands was recorded in 21/25 female rats of the high dose group and 10/25 female rats in the mid dose group. Also observed was minimal or slight (multi)focal accumulation of a flaky colloid within the lumen of the follicles of the thyroid glands in 12/25 female rats in the 1000 mg/kg bw/day high dose group and in 10/25 female rats in the 300 mg/kg bw/day mid dose group.

There were no effects on fertility and reproduction performance, and no substance-related developmental effects on the F1 and F2 generations.

At 300 mg/kg bw/day, significant elevations in relative testes weight (5–12%) F0 and F1 males were observed, which were was not dose related or associated with effects on sperm parameters (count, motility, morphology) or testes histology and was therefore considered as not relevant. At 1000 mg/kg/day, 1 male failed to produce live pups with 2 fertile females. This male had reduced testicular and epididymal weights with an apparent decrease in size and diffuse tubular atrophy of testis and azoospermia in the corresponding epididymis. Since comparable findings on the reproductive organs also occurred in a control male, the isolated infertility of this high dose male was considered incidental by the authors of the study.

Concerning the F2 generation, no substance-related differences occurred between the control and dose groups concerning the viability and mortality of F2 pups for all dose levels (NICNAS, 2012). According to this report, gross and histopathological findings did not indicate that DINCH adversely affected reproductive performance or fertility in the parental or first filial generation rats for all dose groups. There were no substance-induced signs of developmental toxicity in the progeny of F0 and F1 generation animals.

According to the authors the clinical pathology results showing the increase in GGT activity and decreased total bilirubin levels are substance-related effects and are thought to occur as a result of the induction of the hepatic microsomal enzyme system. The increased liver weights and decreased bilirubin levels are expected to be at least partly due to this induction of hepatic microsomal enzymes. Effects due to induction of the microsomal enzyme system are interpreted as an adaptive metabolic response and should thus not be considered as adverse.

Hypertrophy/hyperplasia of the follicular epithelia of the thyroid glands in the F1 generation females was considered by the registrants to be a consequence of liver enzyme induction, as described in other studies, and thus is not considered to be an adverse effect of treatment, but additional studies are missing to consider this mechanism as the mode of action of DINCH. Is should also be noted that the thyroid hormones have not been determined in this study.
A parental NOAEL of 1000 mg/kg/day for general toxicity was indicated in the registration dossier. A NOAEL of 100 mg/kg/day for general toxicity for F1 based on effects on organ weights and histopathology findings, like the vacuolisation of tubular epithelia of the kidneys in the mid and high dose F1 generation males, and the observation of flaky colloid in lumen of thyroid glands follicles in the mid and high dose F1 generation females. A NOAEL of 1000 mg/kg for F1 and F2 generations for developmental toxicity was proposed, since no adverse effects regarding development were observed. EFSA (2006) based on renal effects defined a NOAEL of 100 mg/kg for all generations.
Bhat *et al.* (2014) consider that this 2-generation study is the most relevant to define a RfD.

In a **prenatal toxicity study performed in Himalayan rabbits and Wistar rats**, animals were exposed *per os* during gestation (GD 6-19 for rats exposed to 0, 200, 600 and 1200 mg/kg bw/day; GD6-29 for rabbits exposed to 0, 100, 300 and 1000 mg/kg bw/day). No effects were reported in both species. The NOAEL were respectively 1200 mg/kg for rats and 1000 mg/kg for rabbits for parental toxicity and developmental toxicity (NICNAS, 2012; SCENIHR, 2008).

In another **developmental study** provided in the registration dossier, DINCH was administered orally to the Wistar gravid rats from day 3 post coitum to day 20 post partum at 750 and 1,000 mg/kg bw/day. Then, exposure of the offspring occurred via the mother animals during gestation and the lactation period until day 20 post partum.
The offspring (all males and 3 females) was raised to day 100-105 post partum and then evaluated. Anogenital distance (AGD) and anogenital index (AGI, AGD divided by kg bw/) were measured at day 1 after birth, and sexual maturation was also determined (testes descendance, balanopreputional separation, penis evaluation/inspection, sperm evaluation, and vaginal opening for females). The results indicated that there was no toxicity in F1 progeny with a NOAEL of 1000 mg/kg/day. The AGD ($p<0.05$) and AGI ($p<0.01$) were significantly decreased in the male high dose group (1000 mg/kg bw/day), respectively AGD 7% and AGI 8% below the control group. In female high dose group the AGI was significantly reduced by 8% ($p<0.05$) (see confidential data in Annex).
The analysis of these observations is not unanimous. According to the SCENIHR report (2008), the limited (7-8% change compared to controls) although significant alterations in the AGD and AGI are not considered of biological significance as other corresponding parameters (like testes descendance, preputial separation, vaginal opening, testes weight and histology, and sperm parameters) were not affected. Morover, in females the AGI was decreased to the same extent, contradicting the AGI to be an effect of impaired androgen-dependent development.

However, Tox Services (2013) considers that female AGD was not significantly affected by DINCH but rather, female anogenital index (AGI) was decreased. They reported that the magnitude of the AGI decrease among females was small, at only a few percent, and the apparent effect was likely exaggerated due to the slight increase in body weight among these female pups (See confidential data in Annex). Thus, the significant change in AGI would be likely driven by the very slight increase in female pup body weights combined with the very slight but not significant decrease in AGD. Moreover, according Tox Services (2013,) the reported reduction in female AGI does not reduce the validity of the male AGD findings since in 2005 Piepinbrink *et al*. reported that AGD was affected in neonatal female rats exposed *in utero* to di-ethylhexyl phthalate (DEHP).
But it is not alaways the case since in a study by Gray *et al.* (2000) the AGD was decrased by 29% in male pups compared to controls et there was no effect in females.
Nevertheless no reproductive effects were reported in the 2-generation study. Therefore despite an effect on the AGD the reproductive function seemed not to be consequently affected.

In a very recent study (Furr *et al*., 2014) it has been shown that DINCH does not exert effect on the testis testosterone production measured in fetal testis after *in utero* exposure to 750 mg/kg of DINCH from GD14 to GD18.

Consequently DINCH do not have any effect on the reproductive functions. Additionnally, DINCH might be considered to have an endocrine activity, meaning an anti-androgenic activity but more data are needed to clearly confirm or refute this hypothesis. Anyway no possible adverse related effects were identified in the two-generation study available.

3.2.2.8 Mechanistics assays

A liver enzyme induction study for 2-week was conducted in Wistar rats (5/sex) which were exposed in the diet to 15 000 ppm (equivalent to 1418 and 1568 mg/kd/day in males and females respectively) of DINCH in order to determine the potential of this substance to induce hepatic Phase I and II liver enzymes. Both male and female treated rats showed a significant increase in liver Cyt.P450 activity (2.2 fold for both sexes). Male and female rats also showed significant increases in the activities of liver EROD (2.7 and 1.6 fold, respectively), PROD (30 and 43 fold, respectively), BROD (11 and 24 fold, respectively), MUF-GT (3.3 and 2.4 fold, respectively), and HOBI-GT (7.2 and 2.7 fold, respectively). It was then concluded that DINCH is an inducer of both phase I (oxidative) and phase II (glucuronyl transferase) metabolic pathways in livers of both male and female rats.

Since liver, kidneys and thyroid seemed to be the target organs of DINCH, a cell proliferation study has been performed and provided in the REACH registration dossier. Wistar rats were exposed in the diet to 0, 40, 200 or 1000 mg/kg bw/day of DINCH during 1, 4 or 13 weeks in order to assess the effects on S-phase cell

proliferation. Highest levels of proliferation were found after 1 week of treatment, but were less pronounced after 4 weeks, and approached control levels after 13 weeks of treatment. Increased cell proliferation was observed at all dose levels. The pattern of response was both organ- and sex-dependent since cell proliferation induced by DINCH was observed in the liver and thyroid glands, and only to a lesser extent in kidneys (and in males only). Liver and thyroid cell proliferative effects were apparent in all dose groups of both sexes, but mainly after 1 and 4 weeks of treatment. However, there was evidence of thyroid follicular cell hypertrophy, mainly in the mid and high dose groups of both sexes, which progressively increased towards 13 weeks of treatment (NICNAS, 2012).

Additionally, a thyroid function study was done using the perchlorate discharge assay in order to investigate if the effects of the test substance on the thyroid gland in male Wistar rats occur via a direct effect inhibiting the iodination in the thyroid gland or by indirect mechanisms (i.e. the liver). The study was conducted in male Wistar rats which were exposed during 4 weeks to 15000 ppm of DINCH (equivalent to 1301 mg/kg bw/day) in the diet. DINCH did not cause statistically significant changes in T_3, T_4 or TSH levels. A significant increase in thyroid weight and in uptake of radiolabelled iodide into the thyroid, and a significant increase in the ratio of ^{125}iodide measured in the thyroid versus the blood were also observed. The results of this assay indicate that DINCH acts rather like Phenobarbital (the positive control used) and promotes indirectly thyroid toxicity in the rat by inducing hepatic metabolic enzyme activities. These results may be a supportive proof to the hypothesis that DINCH promotes its thyroid toxicity indirectly by inducing hepatic metabolic enzyme activities. Although the study was not totally conclusive since increase of the T_4 and T_3 levels were not significant for both Phenobarbital and DINCH. Thus, these unclear results leave the doubt remaining on the possible mechanism by which DINCH exerts its effects. Additionnally many other hypothesis on a possible mode of action have not been tested.

3.2.2.9 Critical effects and reference values

Since rodents are known to be more sensitive than humans to effects on thyroid, effects on the thyroid function observed in the 90 day study and the chronic study were not considered as relevant by several organisations which perform an assessment of DINCH hazards.

In 2006, EFSA derived a TDI of 1.0 mg/kg bw/day based on the rat subchronic toxicity study and the 2-generation rat study in which renal effects were observed in rats exposed orally to 300 mg/kg (NOAEL = 100 mg/kg bw/day).

NICNAS (2012) derived a reference value of 0.4 mg/kg bw/day based on the renal effects observed in the combined chronic/carcinogenicity study (NOAEL = 40 mg/kg bw/day).

Bhat *et al*. (2014), consider that the effects on thyroid gland (hyperplasia/ hypertrophy) may be relevant for humans, and thus derive a Reference dose (R(f)D) of 0.7 mg/kg/day based on a $BMLD_{10}$ of 21 mg/kg/day according to the effects

observed in the developmental study since the incidence of this effect was higher in this study than in the chronic study.

In the registration dossier, DNELs are available for both professionals and general population. These DNELs were based on the NOAEL of 40 mg/kg bw/day identified in the carcinogenicity study.

	DNEL – systemic effects Long-term exposure	
	Workers	**General population**
Inhalation route	35 mg/m^3	21 mg/m^3
Dermal route	41 mg/kg bw/day	25 mg/kg bw/day
Oral route	Not derived for workers	2 mg/kg bw/day

The TDI, R(f)D or DNELs especially for the general population are in the same range.

4 INFORMATION ON (AGGREGATED) TONNAGE AND USES

4.1 Tonnage and registration status

There are 2 registration dossiers and one lead registrant. The tonnage mentioned in the ECHA dissemination site it is above 10,000 tpa.
On the web, it can be found that the total tonnage reported for BASF in 2010 is about 80 000 tpa, and was increased up to 200,000 tpa in 2013 on their german production site. The other registrant Evonik manufactured up to 40 000 tpa in 2013.

From ECHA dissemination site		
☒ Full registration(s) (Art. 10)	☐ Intermediate registration(s) (Art. 17 and/or 18)	
Tonnage band (as per dissemination site)		
☐ 1 – 10 tpa	☐ 10 – 100 tpa	☐ 100 – 1000 tpa
☐ 1000 – 10,000 tpa	☐ 10,000 – 100,000 tpa	☐ 100,000 – 1,000,000 tpa
☐ 1,000,000 – 10,000,000 tpa	☐ 10,000,000 – 100,000,000 tpa	☐ > 100,000,000 tpa
☒ >+10,000 tpa		☒ Confidential

4.2 Overview of uses and exposure information

DINCH was created in 2002 by BASF in order to replace the traditional plasticizers. In the product information page by BASF, DINCH is described as the combination of an good toxicological profile and a very low migration rate that makes DINCH the plasticizer of choice for medical devices made with soft PVC products (such as respiratory tubes), the ideal additive for toys (such as modeling clay or dolls) thanks to its low migration rate, lack of odor and technical suitability. It is also used in food contact materials such as tubes or artificial wine corks, in leisure and sports products such as exercise mat or massage balls and also in wallpaper, paints and printing inks, dispersions, adhesives, cosmetics (e. g. nail polish), artificial leather, textile coatings (e. g. raincoats) and erasers.
According to INERIS (2013), DINCH is the most used alternative plasticizer in toys.

4.2.1 Uses and tonnages

According to EFSA (2006) and the Australian NICNAS (2012) public reports, in which the registrant's data is quoted, DINCH is used as a plasticizer at concentrations up to 40% and as an impact modifier in polystyrene at concentrations up to 3%. This plasticiser is used in PVC cling films for fresh meat packaging (10%), for aqueous food and fruits and vegetables (35%), artificial corks (35%), sealing gaskets for beverage containers (35%), flexible tubes for beverages, alcoholic and non-alcoholic (40%), conveyor belts for fatty foods (12%) and other foods (12%) and as polystyrene

impact modifier (3%). The conditions of contact of the food with the packaging material depend on the food and its required storage conditions (EFSA, 2006). It can also have general applications such as in wire and cable, automotive, plastisols and other similar applications.

According to a Danish report on phthalates (COWI and Danish Technological Institute, 2013), in which several surveys conducted in Netherlands, Germany, Austria and Switzerland were compiled and analysed, DINCH is the most used alternative in toys, and is present in 25% of the toy samples for NL and 48% of the samples for the other countries. This is confirmed in the report by INERIS (2013), as mentioned above.

According to a report commissioned by Anses for a specific study of the SCL (*Service Commun des Laboratoires* or Joint Laboratories Services) from the DGCCRF (French directorate for Competition Policy, consumer Affairs and Fraud Control), in order to characterize and quantify the plasticizers contained in baby articles, DINCH is present in 44% (7 out of 16) of articles made with Polyvinyl chloride (PVC) and its concentration ranges from 0.1 to 24% (DGCCRF, 2013).

Use	
Manufacture of substances	x Manufacture ☐ Formulation ☐ Uses at industrial sites ☐ Uses by professional workers ☐ Consumer Uses ☐ Article service life
Formulation of preparation and in materials for : - Plactiticizer in polymers (polymer preparations and compounds) - Phlegmatizer for peroxides - construction chemicals (concrete additive) - manufacture of coatings, inks and artist colours Manufacture of lubricants - Manufacture of sealants and adhesives	☐ Manufacture X Formulation ☐ Uses at industrial sites ☐ Uses by professional workers ☐ Consumer Uses ☐ Article service life

4.2.2 Migration rate

In the registrant dossier provided to EFSA some specific migrations rates have been included using a validated method according to EFSA. The migration rates for cling film containing 17.8 to 10% of DINCH range from 0.016 ± 0.002 to 29 ± 2 mg/dm² depending on the fat content. These results indicate that DINCH migrates quantitatively into foods with high fat content and the overall migration 10 mg/dm²

may be exceeded, contrary to fresh meat and low fat cheese for which migration of DINCH is low.
Migration of DINCH from bottle closures containing a PVC sealing layer with 37% DINCH was determined in carbonated mineral water, grape fruit juice and orange lemonade. In all cases, migration into the aqueous beverages was low, in the range of 10-30 µg/kg.
The migration into 10% ethanol, 50% ethanol and olive oil from a polystyrene sample containing 3% DINCH was determined. The migration was found to be 0.053 mg/kg for 50% ethanol after 10 days at 40°C and was below the detection limit for olive oil and 10% ethanol. EFSA has stated the substance can be used in food contact materials but it is neverthesless noted that overall migration limit into high fat content foods may be exceeded.

RIVM (2009) measures the migration of 3 different plasticizers including DINCH in saliva stimulant, which is supposed to simulate the mouthing of a toy. For DINCH a mean migration of 0.41 µg/(min x 10cm²) with a maximum migration of 0.86 µg/(min x 10cm²) was estimated.

According to the DK EPA reports on the alternatives to phthalates in medical devices (2014) DINCH has a very low migration rate (for instance 3 to 10 times lower than the DEHP in PVC) which seems to be thus suitable for sensitive uses like in tubes for internal feeding , respiratory tubes, catheters…

4.3 Additionnal information

4.3.1 Risk assessment for humans

In its report in 2009, the RIVM calculated a Margin of Safety (MoS) of 5300 for an exposure due to mouthing for a child of 8 kg who mouths a surface of 10 cm^2 of the toy during 3 hours per day, and a MoS of 5100 for an exposure due to dermal contact for a child of 15 kg who has dermal contact with a surface of 100 cm² of the toy during 3 hours a day. It is assumed in this assessment that 10 % of the total amount on the skin is taken in orally, due to hand to mouth contact. This assessment was performed based on the NOAEL of 100 mg/kg/day derived from the 2-generation study. RIVM concluded that no risk could be identified for DINCH use in children toys.

Similarly, NICNAS stated in 2008 that under the conditions of the occupational settings described, DINCH is not considered to pose unacceptable risks to workers. And that when used in the proposed manner (most significant exposure is through migration into food), DINCH is not considered to pose an unacceptable risk to public health.

Finally Bhat *et al.* (2014) concluded that for a hypothetical newborn infant exposure of 0.094 mg/kg-d to DINCH through PVC feeding tubing (Welle *et al*. 2005), the oral RfD of 0.7 mg/kg/day they derived in their assessment based on $BMLD_{10}$ of 21 mg/kg/day provides a 7.5-fold margin of safety (MoS). Yet they add that this margin is likely to be higher since the toxic moiety, while unknown, is likely a metabolite

rather than the parent compound, based on available toxicokinetic data from BASF. Hence no risk is identified for DINCH use in medical devices according to Bhat *et al.*, 2014.

The recent median (95th percentile) estimated DINCH intake of 0.14 µg/kg/day based on urinary hydroxy-MINCH concentrations in 300 individuals from the general population (Schutze *et al.,* 2014) is more than three orders of magnitude less than the RfD of 0.7 mg/kg/day derived in the assessment by Bhat *et al*. This evaluation confirm that no risk is therefore identified for the general population.

Risk assessment for humans reported above indicate that the presence of DINCH in toys does not appear to be a concern for children (RIVM, 2009). And there is no unreasonable risk for workers and consumers according to the updated NICNAS assessment (2012).

On the other hand, there may be some concern for newborns exposed through PVC feeding tubing (Bhat *et al*., 2014) since newborn and premature children are considered as populations at risk, considering that the cognitive skills are closely linked to a proper thyroid functioning. Nevertheless it should be noted that this kind of uses, meaning medical devices are not in the scope of REACH Regulation.

Concerning the effects of DINCH on the reproduction, the various studies available indicate that DINCH has only minor concerns and seems much safer than the restricted phthalates DINCH is intended to be an alternative. The effect on the AGD observed in the development study in males and females pups can be considered as weak and the effects observed for male is well below the decrease observed following an *in utero* exposure to DEHP for instance (Gray *et al*., 2000). It is nevertheless indicating an anti-androgenic activity which is however not related to any histologic changes or in testis weight, or on sperm parameters. Therefore DINCH can be considered as a safer alternative than restricted phthalates for this type of effects.

4.3.2 Environment

4.3.2.1 DINCH environmental properties

Summary of environmental fate and ecotoxicity data on DINCH (from DK EPA, 2010):

Environmental fate			Ecotoxicity				
Biodegradation	**Bio-accumulation**	**Mobility**	**Fish**	**Daphnia**	**Algae**	**Microorganisms**	**Terrestrial**
Not readily biodegradable (41% in 28 d)	BCF = 189	ND	LC_{50} (96 h) >100 mg/L	EC50 (48h) >100 mg/L NOEC (21d) ≥0.021 mg/L	EC50 (72 h) >100 mg/L NOEC (72h) ≥100 mg/L	EC_{50} >1,000 mg/L, activated sludge	LC_{50} (14 d) >1,000 mg/kg (earthworm)

DINCH cannot be classified as readily biodegradable since only 41% degradation in a CO_2 evolution test.

DINCH has a moderate bioaccumulation potential, nevertheless 90% depuration of the substance occurred within 1.6 days, and then DINCH could be considered as not likely to bioaccumulate. The log Koc = 6.59 indicates a high sorption potential.

The acute toxicity to fish was tested with zebrafish using the 96 hour static EC-test method and found to be LC_{50} >100 mg/L. Similarly, the acute EC_{50} for daphnia was found to be higher than the highest test concentration in OECD 202 of 100 mg/L. In a 21 days reproduction test (OECD 211) no effects occurred at the highest test level of 0.021 mg/L (measured) and the NOEC was therefore determined to be ≥0.021 mg/L. The rate based 72 hour EC_{50} for algae (*Scenedesmus subspicatus*) was found to be >100 mg/L and the corresponding NOEC ≥100 mg/L.

DINCH was found to be virtually non-toxic to activated sludge (EC50 >1,000 mg/L) and to earthworms in the 14 days acute artificial soil test (LC50 >1,000 mg/kg).

Based on the ecotoxicity data available, DINCH is considered to be not toxic up to the limit of water solubility.

DINCH does not fulfil the criteria for being a PBT or vPvB substance.

According to the NICNAS report (2012), half-life in air through reaction with hydroxide radicals is determined using the AOP program produced by Syracuse Corporation. The following values were generated using the EPIWIN modelling on the notified chemical:

Compartment	Half-life
Air	8.35 hours
Surface water	360 days
Soil/aerobic sediment	720 days
Anaerobic sediment	3240 days

It is anticipated that DINCH would display similar half-lives in each of the environmental compartments, and potentially be persistent in some soils and sediments due to it being not readily biodegradable.

4.3.2.2 Environmental exposure

According to the NICNAS report (2012), a release of DINCH in the environment during importation and transport is expected to be minimal, except if an accidental spillage occurs.

Concerning the PVC compounding, 2 main methods exist (dryblending and plastisol blending). Dryblending is not supposed to induce any emissions into air since they are supposed to be minimal (0.0037% claimed by registrant) and would largely be trapped by local exhaust ventilations systems. Concerning plastisol blending, which will take place in stirred vessels at ambient temperature, no any significant emission of plasticizer is expected.

About the PVC product manufacture, according to NICNAS report (2012), an estimated 0.035% per year of the imported volume of DINCH would be released into the environment due to the manufacture of PVC products. It is indicated also that extrusion equipment would periodically be cleared of off-grade polymer using a purging process. This process will account for approximately 0.4% of the waste of DINCH. The purged material would be recycled or collected and buried in an approved landfill as general waste.

Some recycling of PVC products will occur at specialised PVC recyclers. Ultimately, however, the majority of the objects containing the notified chemical will be disposed of to landfill at the end of their useful life. As the notified chemical is not bound within the PVC matrix, it will be lost from PVC articles containing it. This release may occur through blooming followed by volatilisation or leaching.

The recommended method by NICNAS of disposal of liquid wastes containing materials such as DINCH is by burning in an approved incinerator.

Majority of DINCH will be incorporated into impact modified food packaging (85%) and in general applications such as wire and cable, automotive, plastisols and other similar applications. During the lifetime of the articles, DINCH may be released from the article either through blooming (movement to the surface of the plastic) followed by evaporation or through leaching.

Wastes generated during compounding with PVC or manufacture of plastic articles will enter either landfill or the sewage system. Simple treat modelling of DINCH indicates that 26% will be released to air, 3% to water, 68% to sludge and 1% degraded resulting in 69% removal during passage through a sewage treatment plant (EU, 2001).

5. CONCLUSION : JUSTIFICATION FOR NO FURTHER ACTION

Hexamoll DINCH is a substance that has been developed to replace phthalates in various applications, especially in sensitive ones like medical devices or toys. In the framework on the French National Strategy on Endocrine Disruptors in 2014, the French Competent Authority requested ANSES to evaluate its toxicological profile and verify whether risk management measures should be necessary for this substance.

It should first be recognized that DINCH is a well studied substance for which several recent long term studies have been provided. All the requirements as described in the annexes VII, VIII, IX & X have been fulfilled. It should also be noted that two Member States (Denmark[2] and Sweden[3]) have performed comparative evaluations of alternative plasticizers such as DINCH and both concluded that DINCH is a promising alternative included for sensitive uses like medical devices.

Based on available data, exposure to DINCH lead to modifications of thyroid gland volume and therefore induced adenoma and hyperplasia in rodents. Based on the fact that, compared to humans, rodents have a specific thyroid morphology and have therefore an increased susceptibility to develop thyroid cancer and since the doses leading to effects are very high, it is very unlikely that DINCH is a carcinogenic substance for humans.

The non relevance for humans of such effect on thyroid observed in rodent has been recently questioned. Recently it has been showed that a link exists between hypothyroid and hepatic cancer in humans (Hassan et al., 2009). However, it should be noted that the relevance of effects on thyroid observed in rodents is not specific

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[2] The conclusion of Danish EPA (2014) was: "*.... data on COMGHA, DEHT, DINCH, DOA and TOTM were available with varying levels of information and type of endpoints investigated. For these, a clear and definite conclusion on a possible endocrine disrupting effect was not possible, as the underlying mechanism of endocrine disrupting effects has not been fully investigated. It is however noted that the available data for COMGHA, DEHT and DINCH do not indicate a need for further investigations.*
A discussion is on-going in relation to DINCH due to potentially relevant effects in reproductive/developmental and thyroid endpoints. It is noted that this has been argued from the producer not to be relevant effects, and further supported by authorities (NICNAS, EFSA and SCENIHR)".

[3] *The Phthalates strategy from KEMI (2014) in Sweden concluded on alternatives in medical devices "In a review of options for replacing phthalates on the candidate list in medical devices were considered the most promising options include: 1) COMGHA - glycerides, castor-oil mono-, hydrogenated, ACETATES (CAS # 736150-63-3) 2) DEHT - Di (2-ethylhexyl) terephthalate (CAS # 6422-86-2) and 3) DINCH - Diisononylcyclohexandicarboxylate (CAS No. 166412-78-8). This assessment was based on these substances are more extensive data do not indicate concern for reproductive toxicity or endocrine disruptors.*

to the DINCH itself but is a general question. This topic has to been touched upon at the European level, as asked by FR in the ECHA ED expert group in November 2014. Indeed, the publication cited above shows new highlights on the relevance of thyroid effects observed in animals (especially rodents) and therefore the choice of the species to use when new studies need to be conducted.

The levels of thyroid hormones have only been measured in the 90-d study and were not affected despite a significant increase of TSH in females. Therefore an effect on circulating thyroid hormones levels is not expected.

However, it has been pointed out that early thyroid hormones disruption (during pregnancy or early life) may lead to neuro-cognitive impairments like effects on the IQ or development impairments (Haddow *et al*., 1999). The sensitivity of developing fetuses to hormonal level, combined to the fact that DINCH is intended to replace phthalates in medical devices in neonatal services, leads to identify a remaining uncertainty when a very sensitive population, i.e. premature babies, may be exposed to DINCH. This potential risk was identified also in the publication by Bhat et al. (2014) in which the MoS for newborn was pretty weak. The risk for this type of sensitive population has to be carefully assessed since the number of premature births is increasing these days due to a growing number of IVF for instance. However, this remaining uncertainty is related to a use that is outside the scope of REACH. Therefore there is no justification to put this substance on CoRAP in order to get additional information on this specific use in medical devices.

Based on these information, and taking into account that DINCH is developed as a substitute for phthalates, we believe that the data in hands are sufficient to state that DINCH is safe for the uses covered by REACH regulation and that no further action is required under this regulation.

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