

The Director General

Maisons-Alfort, 23 August 2016

OPINION

of the French Agency for Food, Environmental and Occupational Health & Safety

on "plastic toys and children's equipment intended for children under three years of age"¹

ANSES undertakes independent and pluralistic scientific expert assessments.

ANSES's public health mission involves ensuring environmental, occupational and food safety as well as assessing the potential health risks they may entail.

It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with the necessary information concerning these risks as well as the requisite expertise and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its opinions are made public.

This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 23 August 2016 shall prevail.

On 6 September 2013, ANSES issued an internal request to conduct the following expert appraisal: Plastic toys and children's equipment intended for children under three years of age.

1. BACKGROUND AND PURPOSE OF THE REQUEST

Exposure to multiple chemicals found in consumer products during critical periods of child development (*in utero*, perinatal, *etc.*) is mentioned among the hypotheses for explaining the increase in the incidence of certain diseases such as obesity, neurodevelopmental disorders, effects on the reproductive tract, *etc.* Children, especially those under 36 months of age, constitute a specific population that is particularly vulnerable. Indeed, from birth until adulthood, children undergo major physiological changes likely to modulate the toxicokinetics of chemical substances, and are relatively "more exposed" than adults to many chemicals, considering the ratio between exposure and body weight.

¹ Cancels and replaces the Opinion of 15 June 2016. See Annex 1.

Several studies based on observation of the behaviour of children aged 0 to 36 months show that plastic is the material most commonly put in the mouth, followed by textiles. In addition, plastic toys account for the majority of toys purchased in France. The internal request thus focused primarily on plastic toys and children's equipment intended for infants and children up to three years of age.

On the basis of these elements and considering Actions 17 and 20 of the 2009-2013 National Environmental Health Action Plan (PNSE 2²), ANSES issued an internal request with a view to assessing the health risks associated with chemical substances present in plastic toys and children's equipment intended for infants and children up to three years of age.

A review of the work subsequent to Directive 2009/48/EC (2009-2015) and the regulations, along with an industry study, were carried out for all types of toys and children's equipment.

Composition and migration tests, commissioned by ANSES, were conducted on plastic toys and children's equipment intended for children under three years of age, in order to search for plasticisers (phthalates and their substitutes³). A national sector survey and a quantitative health risk assessment were then carried out on the phthalates and their substitutes found in these tests. Several studies based on observation of mouthing behaviour in children aged 0 to 36 months confirm that, during this period, children put a great diversity of objects into their mouths. Thus, the health risk assessment focused on the study of migration in saliva following the mouthing of toys.

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French Standard NF X 50-110 "Quality in Expert Appraisals – General Requirements of Competence for Expert Appraisals (May 2003)".

The expert appraisal fell within the sphere of competence of the Expert Committee (CES) on "Assessment of the risks related to chemical substances" until December 2013, and was then entrusted to the CES on "Assessment of chemical risks of consumer items and products". ANSES entrusted the expert appraisal to several rapporteurs, also members of the aforementioned CESs and the Working Group on Assessment of substances and processes subject to authorisation in human food, according to their fields of expertise. The methodological and scientific aspects of the work were presented to the two CESs between 21 February 2013 and 25 March 2016. The work was adopted by the CES on "Assessment of chemical risks of consumer items and products" at its meeting on 25 March 2016.

ANSES analyses the links of interest declared by the experts prior to their appointment and throughout the work, in order to avoid potential conflicts of interest with regard to the matters dealt with as part of the expert appraisal.

The experts' declarations of interests are made public via the ANSES website (www.anses.fr).

In order to gather the opinions of the different stakeholders, a series of hearings took place between May 2013 and February 2014 with consumer associations (French National Consumer Institute, UFC-*Que Choisir* consumers' group, Women in Europe for a Common Future), manufacturer groups (French Federation of Toy and Childcare Industries, Federation of Trade and Retail Companies) and the French public authorities (Consumer Safety Commission, SQUALPI⁴).

² PNSE 2 - Action 17: Reduce the exposure of children and pregnant women or women of childbearing age to the most hazardous substances. Reduce the exposure of children and pregnant women to substances of concern.

Action 20: Improve the way in which the special sensitivity of children, pregnant women or women of childbearing age is taken into account in expert risk assessments.

³ Any substance that plays a technological role similar to that of phthalates in the materials.

⁴ Quality Sub-directorate for Industry and Standards at the Ministry of the Economy, Industry and the Digital Sector

3. ANALYSIS AND CONCLUSIONS OF THE CES ON "ASSESSMENT OF CHEMICAL RISKS OF CONSUMER ITEMS AND PRODUCTS"

Toys are regarded as products designed, whether or not exclusively, for use in play by children under 14 years of age or intended for this purpose, within the meaning of Decree 2010-166 of 22 February 2010 on the safety of toys, transposing Directive 2009/48/EC⁵. The latter stipulates that toy manufacturers shall carry out an analysis of the chemical, physical, mechanical, electrical, flammability, hygiene and radioactivity hazards that the toy may present, as well as an assessment of the potential exposure to such hazards. In terms of safety with regard to hazards of a chemical nature, the Directive prohibits the use of CMR substances in categories 1A, 1B or 2 in toys or structurally separate parts, except if they meet several criteria such as the inaccessibility of the substances even by inhalation, concentrations below a certain threshold, *etc.*

The European toy market is the world's biggest. It has grown over the last few years by around 3 to 6% per year, despite a decline in southern Europe. The categories of toys sold most widely in the European Union (EU) are pre-school and infant toys, followed by dolls, outdoor toys and board games/puzzles (more than half of all sales in the EU). In France, the best-selling toys in 2014, all ages combined, were construction toys, dolls, board games and puzzles, infant toys and outdoor toys. Taking into account the scope of the request (toys made of plastic) and the target population (children under 36 months of age), the work focused on the following toy categories: infant toys, dolls and construction toys.

According to the regulations, **childcare articles** are products intended to ensure or facilitate seating, bathing, sleeping, transportation, and the movement and physical protection of children under four years of age. Nevertheless, it should be noted that many of the products regarded by the public as childcare articles are not actually considered as such within the meaning of the regulations (e.g. teething rings, pacifiers, *etc.*). They have been called "children's equipment" in the framework of this study.

■ Bibliographical summary of the work relating to toys and children's equipment

Several methodological reports relating to the assessment of chemical risks associated with the use of toys were identified. The 2008 report by the RIVM⁶ entitled "Chemicals in Toys. A general methodology for assessment of chemical safety of toys with a focus on elements" constitutes the reference report used as the starting point for drafting the "Toys" Directive (2009/48/EC) (RIVM, 2008). Precise methodological points have also been addressed in different opinions by the SCHER⁷ (SCHER, 2010a and b, 2015).

Many studies have already been carried out by national and international organisations on the different types of toys in order to assess the exposure of children and characterise the health risks. Only the work subsequent to Directive 2009/48/EC has been studied here. Most of this work assessed exposure to chemical substances present in toys *via* composition, migration or emission tests, and conducted health risk assessments and advocated the reduction of exposure *via* the creation or reduction of regulatory thresholds for composition in the materials. Few recent studies have been conducted on childcare articles.

⁵ Directive 2009/48/EC of the European Parliament and Council of 18 June 2009 on the safety of toys

⁶ Rijksinstituut voor Volksgezondheid en Milieu (Netherlands National Institute for Public Health and the Environment)

⁷ Scientific Committee on Health and Environmental Risks of the European Union

The analysis of this work revealed a wide diversity of types of toys and children's equipment. Their materials (hard/soft plastic, wood, textiles, metals, *etc.*) and the substances they are composed of vary a great deal.

■ Substances assessed in plastic toys and children's equipment

The experts chose to examine chemicals added intentionally to the composition of the materials to confer certain properties to the toys and children's equipment. The choice thus focused on the addition of chemical substances to plastic toys. Indeed, various substances are present in the formulations of materials constituting the different plastic toys and childcare articles available on the market. Without this being an exhaustive list, they include the following substances: phthalates and substitutes, flame retardants, short-chain chlorinated paraffins, bisphenol A, metals, *etc.*

PVC is one of the most widely used plastics in the area of toys. The plasticisers used most often in PVC are phthalates. **Phthalates and their substitutes have therefore been targeted in this internal request.**

Tests of the composition of phthalates and their substitutes in a limited sample of toys and children's equipment (bibs, teething rings, pacifiers), followed by migration testing in a saliva simulant were conducted at ANSES's request (DGCCRF, 2013 and 2014). These tests were only conducted on new toys. Out of 31 toys and items of children's equipment tested, only the PVC toys contained plasticisers, with the exception of one elastomer toy (ATBC). The presence of these substances was not identified in the children's equipment. The plasticisers found included two prohibited phthalates (DEHP used as a principal plasticiser associated with DINP in a toy purchased at a street market, and low levels of DEHP attributed to its presence as an impurity of DEHTP in three toys), and some of their substitutes (ATBC, DEHTP, DINCH, DOIP, TXIB) were quantified. Subsequently, it was shown that all the substances found migrated in a saliva simulant.

The CES decided to conduct a health risk assessment for the substances detected in the composition and migration tests conducted by the DGCCRF's laboratories in 2013 and 2014. The following phthalate substitutes are concerned: 1,2-cyclohexane dicarboxylic acid diisonyl ester (DINCH), diethylhexyl-terephthalate (DEHTP), bis(2-ethylhexyl) isophthalate (DOIP), acetyl-tributyl-citrate (ATBC) and 2,2,4-trimethyl-1,3-pentanediol diisobutyrate (TXIB). This selection of substances of interest takes into account the positions expressed by the associations and industrial federations from the sector during the hearings.

DEHP and DINP were not selected for the health risk assessment (HRA), as their uses are subject to restriction measures in toys and childcare articles under application of the REACH Regulation⁸.

- **Assessment of the health risks associated with the mouthing of plastic toys containing phthalate substitutes: ATBC (CAS No 77-90-7), DINCH (CAS No 166412-78-8), DEHTP (CAS No 6422-86-2), TXIB (CAS No 6846-50-0) and DOIP (CAS No 137-89-3)**

⁸ The REACH regulation restricts the use of certain phthalates (DEHP, DBP, BBP) to concentrations of less than 0.1% in toys and childcare articles. For three other phthalates (DINP, DIDP, DNOP), this restriction is applicable for toys and childcare articles that can be put in the mouth by children (Decree No. 2006-1361 of 9 November 2006, today included in Annex XVII of the REACH Regulation).

o Hazards

ATBC has low acute toxicity. The data available on ATBC do not show any skin irritation or sensitisation, nor any mutagenic, carcinogenic or reprotoxic effect. ATBC does not present oestrogenic or androgenic activity. However, there are doubts concerning activation of the PXR-receptor pathway which could affect the metabolism of steroid hormones. Therefore, no conclusion can currently be reached on the endocrine-disrupting nature of ATBC because no robust data are available on potential effects such as those on thyroid function or on other organs or functions. Subchronic and chronic toxicity studies in rodents show:

- effects on body weight (decrease at 300 and 1000 mg/kg/d),
- liver effects (increase in liver weight, hypertrophy of the liver, hepatocellular hypertrophy and/or cellular necrosis of hepatocytes at 1000 mg/kg/d),
- kidney effects (increase in kidney weight and variation of urinary composition at 1000 mg/kg/d),
- biochemical changes (from 300 mg/kg/d),
- haematological effects (from 300 mg/kg/d), which, according to the authors, may not be associated with the treatment and remain to be verified.

The authors consider that some of the effects are an adaptive response to metabolism (hypertrophy of the liver, some biochemical changes, some haematological effects). The experts have reservations about these author conclusions.

DINCH has low acute toxicity. It does not have a skin or eye irritant effect, nor a sensitising effect. Subchronic, chronic, and two-generation studies show:

- liver effects (increase in liver weight, in serum γ GT concentrations and decrease in serum bilirubin concentrations),
- kidney effects (increase in kidney weight),
- thyroid effects (increase in serum thyroid stimulating hormone (TSH) levels, in thyroid weight, hyperplasia/hypertrophy by proliferation of follicle cells and an increase in the incidence of colloid substance alteration).

The kidney effects were considered relevant in humans by EFSA⁹ and NICNAS¹⁰ (EFSA, 2006; NICNAS, 2008 and 2012).

DINCH does not induce any effect on reproduction or development (ANSES, 2015a). In its analysis of the best risk management option (RMOA) carried out in application of the REACh Regulation, ANSES concluded that DINCH may have endocrine activity, in view of the various effects observed on the thyroid. Furthermore, the available data are inconclusive with regard to a possible anti-androgenic activity (ANSES, 2015a).

DINCH is not genotoxic. In a two-year combined study of chronic toxicity and carcinogenicity in rats, only thyroid adenomas were observed and these are associated with a mode of action of DINCH that is specific to rodents. "ANSES considers that the carcinogenic effects of DINCH on the thyroid gland in rats are not relevant for humans. It should be noted that these effects have not been assessed in other species than rats" (ANSES, 2015a). DINCH is not considered to be carcinogenic to humans.

DEHTP has low acute toxicity *via* the oral route. It has a low skin and eye irritant potential. It is not considered genotoxic or carcinogenic.

Several studies have been conducted to assess the toxicity of DEHTP in rats and mice after repeated exposure *via* the oral route. They show effects on certain haematological parameters (concentration of haemoglobin, haematocrit, mean corpuscular haemoglobin concentration

⁹ European Food Safety Authority

¹⁰ National Industrial Chemicals Notification and Assessment Scheme (Australia)

(MCHC), mean corpuscular volume (MCV)), on body weight (increase or decrease), an increase in liver weight and effects on the eye with retinal degeneration of the external nuclear layer. A NOAEL¹¹ of 1500 ppm (79/102 mg/kg/d in males/females) can be derived on the basis of the effects on the eye (Deyo, 2008).

In the framework of an RMOA carried out in application of the REACH Regulation, ANSES concluded that no reproductive toxicity was observed and that no alert relating to a possible endocrine-disrupting effect was observed regarding DEHTP (ANSES, 2015b).

TXIB has low toxicity *via* the oral, respiratory or dermal routes. It is a mild skin irritant in guinea pigs but no irritation was observed in rabbits. TXIB has no skin sensitiser effect in guinea pigs or humans. It has no eye irritant effect in rabbits. By the respiratory route, TXIB is considered a sensory irritant (feeling of irritation of the eyes and upper airways).

TXIB is not mutagenic *in vitro*. No *in vivo* genotoxicity or carcinogenicity data are available. Subchronic and chronic studies highlight effects on the liver and kidneys. The observed liver effects are not always consistent between studies and are considered by the authors as adaptive in two out of four studies (Astill *et al.*, 1972; Krasavage *et al.*, 1972). In addition, the study by Krasavage *et al.* (1972) showed that the liver effects (increase in ASAT¹², in the relative weight of the liver and the activity of microsomal enzymes) were reversible. Nevertheless, despite doubts about the harmful nature of these effects and their reversibility, these effects are considered by the CES as critical, considering all the available studies (LOAEL¹³ = 150 mg/kg bw/d).

Two of the three studies on reproduction and development, conducted in rats, revealed effects on reproduction: a decrease in the number of implantation sites and the number of *corpora lutea*, a decrease in the total weight and size of the litter 4 days after birth and in the number of live young at birth for the study of screening of toxicity to reproduction and development with an assessment of sperm motility (NOAEL = 276/359 mg/kg bw/d in males/females) and a decrease in the average weight of the foetuses in the study of prenatal development (NOAEL = 343 mg/kg/d).

With regard to **DOIP**, no study on toxicity was identified. Nevertheless, some safety data sheets indicate that DOIP causes reprotoxic effects (proposal for classification as 1B by the manufacturer).

o Dose-response relationship

For each substance, a review of the toxicity reference values (TRVs) as well as the critical doses selected by national, European and international organisations, was carried out for the oral route. Selection of the established TRVs was based on their analysis considering the relevance of the choices made (critical effect, key study, critical dose, uncertainty factors) and the transparency of the way in which the TRV was established.

For the present health risk assessment, only children aged 0 to 3 years were specifically targeted. The experts consider that the TRVs apply to the entire population regardless of age, and including sub-groups of the population such as children. If there are data showing that children are more sensitive than adults to the effects of certain substances, these must be taken into account in the establishment of the TRV (ANSES, 2016a). The CES analysed the selected TRVs in order to verify that they were applicable to this specific age sub-group. To do this, the CES followed the approach adopted in the framework of the infant total diet study (iTDS, 0-3 years) (ANSES, 2016b to be published). Thus, the CES reviewed the toxicological data specific to children taken into account in the establishment of each of these TRVs (studies of perinatal and post-natal toxicity, studies of

¹¹ No Observed Adverse Effect Level

¹² Aspartate aminotransferase

¹³ Lowest Observed Adverse Effect Level

developmental toxicity, reproductive studies conducted on several generations, *etc.*). If there is no TRV, a selection was made from among the existing critical doses according to the same criteria. The TRV or the critical doses selected are shown in the table below.

Table 1: TRV and critical dose selected for the health risk assessment and applicability to children under three years of age

Substance	TRV / Critical dose selected (source)	Critical effect (source study)	Critical dose	Uncertainty factors	Applicability to children aged 0 to 3 years
ATBC	TRV = 1.0 mg/kg bw/d EFSA (2005)	General toxicity (moderate effect on body weight and a few biochemical parameters) 90-day studies in rats with <i>in utero</i> exposure, a two-generation reproductive study in rats (Chase and Willoughby, 2002; Robins, 1994)	NOAEL 100 mg/kg/d	100 UF _A 10 UF _H 10	Yes A two-generation study (Robbins, 1994) was taken into account when establishing the TRV.
DINCH	TRV = 0.4 mg/kg bw/d (NICNAS, 2012)	Renal toxicity Combined study of toxicity and of carcinogenesis in rats conducted by BASF (2005)	NOAEL 40 mg/kg/d LOAEL 200 mg/kg/d	100 UF _A 10 UF _H 10	Yes A two-generation study (BASF, 2003) and a toxicity study on pre- and post-natal development (BASF, 2004) were taken into account when establishing the TRV.
DEHTP	TRV = 1 mg/kg bw/d EFSA (2008)	Effects on the retina and the nasal cavity in rats (Deyo, 2008: combined chronic toxicity and carcinogenicity study)	NOAEL 79 mg/kg/d LOAEL 324 mg/kg/d	100 UF _A 10 UF _H 10	Yes A two-generation study (Faber et al., 2007a) was considered when establishing the TRV.
TXIB	No TRV established NOAEL = 30 mg/kg bw/d	Liver toxicity Combined study of repeated toxicity and screening of toxicity to reproduction and development in rats (Japan MHLW, 1993)	NOAEL 30 mg/kg bw/d	-	Yes Two combined studies of repeated toxicity and screening of toxicity to reproduction and development (Japan MHLW, 1993 and Eastman Chemical, 2001) were taken into account.
DOIP	Absence of data				

NOAEL = No Observed Adverse Effect Level; LOAEL= Lowest Observed Adverse Effect Level; UF_H = inter-individual uncertainty factor; UF_A = inter-species uncertainty factor

○ **Assessing exposure**

In this expert appraisal, **assessment concerns the exposure** of children under three years of age to previously identified substances in toys when these are put into the mouth.

The oral route of exposure is one of the starting assumptions of the health risk assessment (HRA). Exposure from mouthing can take place *via*:

- saliva,
- the direct ingestion of part of the toy (or particles that become loose during chewing).

In these two routes, two substance transfer mechanisms can be involved: diffusion and dissolution either by saliva or the gastric juices. Exposure is dependent on phenomena of wear.

The regulations covering toys intended for children under three years of age stipulate that they should not contain small removable parts that may present a choking risk. These parts should not therefore be accessible and ingested directly. In addition, liquid toys or those consisting of brittle material, with a layer of paint or textile fibres that can be easily scraped off and swallowed, were not taken into account in the definition of the selected toys. Thus, the direct ingestion of part of the toy was not taken into account.

The study population was divided into different age groups to take into account the behavioural and physical development of children between 0 and 3 years, especially in connection with the phenomenon of mouthing: 0 - 12 months; 13 - 24 months and 25 - 36 months.

The daily exposure dose (DED expressed in mg/kg/d) is calculated according to a probabilistic approach¹⁴ that helps better understand the variability of exposure within a population. Probability distributions were assigned to these different parameters with the exception of the mouthing surface area.

$$DED = \frac{F \times S \times D}{Bw} \quad (1)$$

where D = duration of contact [min/d], F = flow of migration [μ g/min/cm²], S = surface area in contact with the mouth [cm²], bw = body weight [kg]

All types of toys combined, the highest daily exposure dose concerned ATBC. The DEDs for TXIB, DINCH and DEHTP were relatively similar and a factor of 10 lower than that of ATBC. Lastly, the lowest DED values corresponded to DOIP.

¹⁴ For the calculations of the DED, a probabilistic approach was preferred to a deterministic exposure assessment. The probabilistic approach involves taking into account the variability and uncertainty of the determinants of exposure through statistical distributions in order to assess all the observed or expected exposure situations.

Table 2: Results of the DED (in µg/kg bw/d) for the three age groups

	Age group	0 – 12 months	13 – 24 months	25 – 36 months
ATBC	median	12.9	3.75	3.79
	95 th percentile	74.6	22.5	15.73
DEHTP	median	0.34	0.10	0.09
	95 th percentile	2.43	0.81	0.61
DINCH	median	1.64	0.50	0.50
	95 th percentile	25.2	8.48	6.12
DOIP	median	0.03	0.01	0.01
	95 th percentile	0.16	0.04	0.03
TXIB	median	0.37	0.1	0.1
	95 th percentile	9.42	3.27	2.62

Among children aged between 1-2 years and 2-3 years, the results show broadly similar exposure that is lower than for the 0-1 year age group. This is explained by the fact that children in this last age category generally spend more time putting objects in their mouth.

o **Risk characterisation**

Only threshold effects were selected at the hazard identification stage (no effects without a proven threshold). The level of risk is therefore expressed by the hazard quotient (HQ), which is the ratio between the DED and the TRV. The value of the DED is the 95th percentile of the distribution of values of the DED.

It should be noted, however, that it was not possible to select a TRV from the hazard characterisation for TXIB. In order to assess the health risks in the absence of a TRV, the adopted approach involved first selecting a MOEref (Reference Margin of Exposure), without a unit. The MOEref represents a margin of minimal exposure in humans with respect to an experimentally obtained critical dose (e.g. NOAEL, LOAEL or BMD in animals). The MOEref is then compared to a margin of exposure (MOE) calculated according to the ratio of the critical dose in animals divided by the value of the 95th percentile of the DED.

Table 3: Results of the risk assessment for the three age groups

Substances		ATBC	DEHTP	DINCH	TXIB
		HQ*			MOEref/MOE*
Age group	0-1 year	0.075	0.002	0.042	0.09
	1-2 years	0.023	0.0008	0.021	0.033
	2-3 years	0.016	0.0006	0.015	0.026

* Calculated from the 95th percentile of the DED, MOEref = UF_A x UF_H x UF_S = 10 x 10 x 3 = 300

Concerning the health risk assessment in connection with exposure to three of the identified phthalate substitutes (ATBC, DINCH, DEHTP) present in the PVC toys tested, the results based on a realistic exposure scenario do not show a health risk for children aged 0 to 3 years exposed *via* the mouthing of toys.

Concerning TXIB, the results of the calculation of the reference margin of exposure do not show a health risk. The health risk assessment for TXIB relied on the choice of a low critical dose based on an effect considered by the authors as adaptive (Astill *et al.*, 1972; Krasavage *et al.*, 1972) and whose harmful nature is controversial.

An analysis of the uncertainties was carried out and focused on the context and formulation of the question, the identification of the hazards, the dose-response relationship, the estimate of exposure and the characterisation of risks. It noted several unknowns in terms of impact on the HRA. However, **the hypotheses made for conducting this HRA are mainly optimistic. Thus, in the current state of knowledge and according to the methodology used, the results of the health risk assessment do not show a health risk for children under three years of age mouthing the tested toys containing these substitutes (ATBC, DEHTP, DINCH and TXIB). Moreover, the results of the HRA carried out for the four substances mentioned above are consistent with those of other HRAs carried out by other organisations (RIVM, 2009 and US CPSC, 2014).**

With regard to **DOIP**, the health risk could not be assessed due to the absence of data on the substance's hazards. The CES is concerned that this substance has been found in toys (DGCCRF, 2013, UFC-Que Choisir, 2011). In addition, some safety data sheets indicate that DOIP causes reprotoxic effects (proposal for classification as 1B by the manufacturer).

Moreover, exposure to these same substances *via* other sources of exposure was not taken into account. Therefore, the hypothesis according to which an accumulation of sources could lead to a different conclusion regarding the emergence of a health risk cannot automatically be ruled out. The results highlight the importance of ensuring the absence of other concomitant sources of exposure, to avoid the risk of exceeding the reference value from the adding together of all these sources (other objects, food, dust, *etc.*). Indeed, several studies show the presence of these substances (except for DOIP) in various media (indoor air, dust, food, *etc.*).

The CES stresses that other substances, whose effects may combine with those of the studied substances, may be present in plastic toys.

- **Endocrine activity of extracts from migration**

In addition, ANSES commissioned a specific study from the OFI¹⁵ (OFI, 2015). Its aim was to combine migration tests performed on 18 toys with *in vitro* tests of activation of hormonal receptors (oestrogenic, androgenic, thyroid, PPAR γ ¹⁶). The results of this study are consistent with those obtained in the framework of the tests carried out by the DGCCRF (DGCCRF, 2013 and 2014) and also identified the presence of tributyl citrate (TBC) and diethyl phthalate (DEP) in some of the toys tested.

No androgenic, thyroid or PPAR γ activity was detected, but oestrogenic activities were identified in some samples. Nevertheless, these results should be considered with caution because, in some extracts, the oestrogenic activities identified could not be attributed to the identified substances.

¹⁵ Austrian Research Institute for Chemistry and Technology

¹⁶ Peroxisome proliferator-activated receptor

■ Recommendations

- Regarding public access to information:
 - The CES recommends improving access to reliable information in French about consumer product recalls on an institutional website.

- Regarding the toy sector:
 - The CES reiterates that many substances whose use is restricted or prohibited, mainly phthalates, are still found in many toys marketed in Europe (RAPEX alerts¹⁷). Thus, the CES reiterates the value of the controls in the toy sector in order to avoid the presence on the French market of toys that do not comply with the regulations, and recommends at the very least maintaining such control pressure.
 - The CES recommends integrating, in particular in the "Toys" Directive, the obligation to perform migration tests in a saliva simulant before toys for children under three years of age can be placed on the market. The standards from the NF EN 71 series should make it mandatory to perform migration tests in a saliva simulant before toys for children under three years of age can be placed on the market.

- Regarding the substances:
 - No published data are currently available for DOIP. The CES recommends avoiding its use before knowledge on its toxicity has first been acquired. More generally, the CES reiterates the importance of not using substances in products, in particular in toys and children's equipment, without knowledge of their toxicity and impact on the environment.
 - The CES recommends supplementing knowledge of the toxicity of TXIB to clarify the choice of critical effect.

- Regarding the methodology:
 - The CES recommends validating the protocol for migration tests by conducting *in vivo* measurements in children from the same age group who intentionally put the same toys in their mouths (e.g. saliva samples from kindergarten children, etc.).
 - The CES recommends performing tests on worn, used, old or artificially aged toys in order to obtain information on the evolution of migration, the degradation of the material, the fragmentation of the toy by the child during chewing, the alteration of the toy's surface in contact with saliva, and the emergence of newly-formed compounds.

- Regarding the health risk assessment:

¹⁷ Rapid Alert System for dangerous non-food products. Since 2004, it has facilitated the early exchange of information between the Member States and the European Commission on the measures taken to prevent or restrict the marketing or use of consumer products posing a serious risk to consumer health and safety, with the exception of foodstuffs and medical pharmaceutical devices.

- The CES recommends conducting a HRA for all substances likely to be found following migration in a saliva simulant, such as tributyl citrate (TBC) or diethyl phthalate (DEP) (OFI, 2015).
- Only migration in a saliva simulant *via* the mouthing of toys was investigated in this study. However, other routes of exposure could be considered in connection with the use of a plastic toy. The CES recommends conducting additional studies in order to assess the contribution of each route to the exposure of children during contact with a plastic toy. For example, studies have in particular drawn the CES's attention to dermal exposure to substances likely to migrate from the plastic material.
- In addition, some of these substances have been found in other media (objects, air, dust, food, *etc.*), and the CES reiterates the value of determining the exposure levels of children *via* these media with a view to an aggregated assessment.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety endorses the CES's conclusions and recommendations. ANSES's decision to assess the health risks associated with the presence of phthalates in toys is primarily related to the fact that the phthalates and their substitutes present in PVC are frequently found in toys and that phthalates are the plasticisers most often used in toys. Nevertheless, the presence of other chemical substances of interest in toys justifies an assessment of the associated risks (bisphenol A or BPA, chlorinated paraffins, flame retardants, *etc.*). These substances may have already undergone risk assessments. This is particularly the case with BPA, assessed in 2015 by EFSA, which concluded that exposure *via* toys was negligible¹⁸. Recent legislative measures have been taken at European level by setting a migration limit of 0.1 mg/L in toys intended for children under three years of age for all toys intended to be put in the mouth¹⁹. At French national level, the Act on the modernisation of our health system of 26 January 2016²⁰ supplements the Public Health Code by prohibiting the manufacture, sale, offering for sale, exhibition and importation of toys or games containing BPA that do not comply with the concentration limit or the migration limit for this substance defined by decree of the Ministers for Health, Consumer Affairs, Industry and the Environment.

ANSES stresses that for the five substances that underwent a detailed assessment, in the current state of knowledge and according to the methodology used, the results of the risk assessment that was conducted do not show a health risk for children under three years of age. However, for one of them, DOIP, no data relating to its toxicity are currently available, which means that no conclusion can be drawn regarding the absence of risk. In addition, the health risk assessments conducted by the experts, on the basis of the available data, did not take all the other potential sources into account.

¹⁸ EFSA (2015) Scientific opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs: Part I – Exposure assessment, Part II – Toxicological assessment and risk characterisation. EFSA Journal 2015; 13(1):3978

¹⁹ Enacted on 23 June 2014 (Annex II of Directive 2009/48/EC on the safety of toys). This provision is applicable from 21 December 2015. This limit was transposed into French law in 2015 (Decree of 8 January 2015 amending the Decree of 24 February 2010 laying down the procedures for application of Decree No. 2010-166 of 22 February 2010 on the safety of toys)

²⁰ Act No. 2016-41 of 26 January 2016 on the modernisation of our health system. Article 59.

For this reason, in its work programme on endocrine disruptors, ANSES has also planned in the near future to undertake an assessment of the cumulative health risks associated with exposure to certain phthalates.

In addition, the composition and migration tests commissioned by ANSES helped identify regulated (DEHP, DINP) or non-regulated (DOIP, DEP) phthalates in the toys tested. It should be noted that many toys containing such substances are identified in the European Rapid Alert System, RAPEX.

Two non-regulated phthalates were found in toys tested in the framework of the study commissioned by the Agency:

- DEP, which is registered in the framework of the REACH Regulation, was recently assessed by Germany and Portugal²¹. This assessment shows that the available data are sufficient to conclude that DEP's classification is not justified and that DEP does not have an endocrine-disrupting effect.
- DOIP, which is pre-registered in the framework of the REACH Regulation. Depending on the possible registration of DOIP, the Agency recommends remaining vigilant to the content of the registration dossier, as the last phase of registration is planned for 2018 (1-100 tonnes/year).

Lastly, tributyl citrate (TBC) was found in toys tested by the OFI. This substance underwent an analysis of the best risk management option (RMOA) in application of the REACH Regulation in 2015 as part of the National Endocrine Disruptor Strategy (SNPE) of the Ministry of Ecology, Sustainable Development and Energy (ANSES, 2016²²).

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²¹ BAUA and DGS (2015) Conclusion Document. August 2015. Available from: <http://www.echa.europa.eu/documents/10162/a5c64025-d83a-4952-8476-ac396ee9acc9>

²² ANSES (2016) Opinion of the French Agency for Food, Environmental and Occupational Health & Safety on the assessment of the substances included in the Agency's 2015 work programme in the framework of the National Endocrine Disruptor Strategy (SNPE): ATBC (acetyl-tributyl-citrate, CAS No 77-90-7), TBC (tributyl citrate, CAS No 77-94-1), BHT (butylated hydroxytoluene, CAS No 128-37-0), terephthalic acid (CAS No 100-21-0), methyl salicylate (CAS No 119-36-8) and iprodione (CAS No 36734-19-7)

KEYWORDS

Toys, childcare articles, children's equipment, plasticisers, phthalates, substitutes, children, DINCH, ATBC, DEHTP, TXIB, DOIP, mouthing, endocrine disruptors, sensitive population, window of susceptibility

ANNEX 1

Date	Version	Page	Description of the change
15/06/2016	01		First signed version of the ANSES opinion
August 2016	02	12	Following the feedback meeting organised in June 2016, the recommendation on <i>"increasing the controls in the toy sector in order to avoid the presence on the French market of toys that do not comply with the regulations"</i> was amended as follows: <i>"The CES reiterates the value of the controls in the toy sector in order to avoid the presence on the French market of toys that do not comply with the regulations, and recommends at the very least maintaining such control pressure."</i>
		12	Following the feedback meeting organised in June 2016, the recommendation on <i>"integrating in the "Toys" Directive or in the NF 71 standards the obligation to perform migration tests in a saliva simulant before toys for children under three years of age can be placed on the market."</i> was amended as follows: <i>"The CES recommends integrating, in particular in the "Toys" Directive, the obligation to perform migration tests in a saliva simulant before toys for children under three years of age can be placed on the market. The standards from the NF EN 71 series should make it mandatory to perform migration tests in a saliva simulant before toys for children under three years of age for children under three years of age can be placed on the market."</i>
		14	Following the feedback meeting organised in June 2016, the paragraph relating to the RAPEX alert was simplified by deleting the figures extracted from the RAPEX statistics that related not to all the toys on the market or to a representative sample of the marketed toys, but only to toys identified as hazardous by the control authorities of the Member States.