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Probabilistic Risk Assessment of Consumer Exposure to Reproductive and Developmental Toxicants

Emmanuelle Durand, Carole Leroux, Guillaume Perouel, Claire Beausoleil, Céline Dubois, Lauranne Verines-Jouin, Christophe Rousselle, Valérie Pernelet-Joly and François Pouzaud*

Department of Risk Assessment, French Agency for Food, Environmental and Occupational Health & Safety (ANSES), France

***Corresponding author**

François Pouzaud, Department of Risk Assessment, French Agency for Food, Environmental and Occupational Health & Safety (ANSES), 14 rue Pierre et Marie Curie - 94701 Maisons-Alfort Cedex, France, Tel: +33-1-56-29-56-45; Email: francois.pouzaud@anses.fr

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Abstract

In 2009, the French Health Ministry requested the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) to assess the risks for consumers regarding exposure to suspected endocrine disruptors (EDs) and/or reproductive toxicants (R2s). For the purpose of the study consumer products containing the selected EDs were identified from a national sector survey among manufacturers and available bibliographic data. For each product, use patterns and exposure scenario were defined for workers and general populations including vulnerable population. A scientific review of the effects on reproduction (fertility/development) and endocrine-disrupting potential was conducted in order to select critical doses for these target populations. Toxicological reference doses (TRs) were calculated as the ratio between critical doses and uncertainty factors. Both direct consumer exposure to EDs in consumer products and indirect exposure by the intake of contaminated air and house dust were considered. For each scenario, uptake doses were modelled through a probabilistic approach based on a one-dimensional Monte Carlo simulation.

Finally, the statistical distributions of doses through direct and indirect exposure were compared to TRs to assess the risk. Probabilistic exposure assessment was preferred to the deterministic approach because it includes uncertainty and variability in some parameters and therefore allows a more realistic description of consumer exposure. It also provides the opportunity to assess the final consumer exposure uncertainty by sensitivity analysis.

The method described was applied tofiveR2s and/or EDs: n-hexane, toluene, cis-CTAC, orthophenylphenol (OPP) and methyl-tert-butylether (MTBE).

Results showed that exposure situations posing a potential risk for embryonic or foetal development may exist, due to occupational or non-occupational exposure of pregnant women to certain consumer products containing toluene, n-hexane or cis-CTAC. Situations at risk for reproduction have also been brought to light, although ANSES emphasizes that strong uncertainties exist with regard to the risk situation identified for MTBE.

INTRODUCTION

In the last few decades, various scientific studies have drawn attention to the possible effects of chemicals found in the environment on human health and more specifically on reproductive function. Endocrine disruptors (EDs) and reproductive toxicants can be used in a wide variety of products. Substances classified as CMR substances in group 1A and 1B under Commission regulation (EC) n°1272/2008 are banned for use in consumer products. Currently, there are no restrictions to the use of reproductive toxicants of group 2 (R2s) and/or suspected EDs in consumer products, except as otherwise provided for in the Reach regulation or other sectoral regulations (e.g. Commission regulation (EC) no 790/2009 for cosmetics). Therefore the health risks for consumer exposed to EDs and/or

R2s are of specific concern and should be assessed more precisely. In this context, the French Health Ministry requested ANSES in 2009 to identify and characterize potential exposure situations at risk to health and associated with usual consumer products and/or items containing certain chemicals classified as R2s or identified as being potential EDs by the European Commission.

Mixtures and articles containing R2s and/or EDs to be considered for health risk assessment (HRA) were prioritized after a French sector survey. Finally, five of the reproductive toxicants and/or suspected EDs contained in those consumer products available to the "general population" were selected.

The objective of this work is to apply the principles of HRA for the evaluation of n-hexane, toluene, *cis*-CTAC, OPP and MTBE, with particular emphasis on the description of exposure probabilistic assessment. The methodology and the conclusions of the five evaluations discussed in this work are published on ANSES website [1].

It should be noted that exposure through use of cosmetics, drugs or phytopharmaceutical products and the intake of contaminated food was not considered in the framework of ANSES expertise assessment.

METHODS

Consumer health risk regarding exposure to EDs/R2s was assessed according to the general 4-steps methodology developed by the NRC in 1983: 1) hazard identification, 2) dose-response assessment, 3) exposure assessment, and 4) risk characterization [2,3].

When dealing with reproductive toxicants, HRA specific adjustments were necessary to take into account certain key parameters such as the existence of vulnerable populations (pregnant women, children) in conjunction with windows of susceptibility related to the different phases of human life (*in utero* development for example) or delayed effects. Moreover, discontinuous exposure situations due to more or less use of consumer products required also specific considerations.

Hazard identification and dose-response assessment

An analysis of the available scientific studies published up to 2013 on the effects of these five substances was performed with a special emphasis on reproductive effects (i.e. fertility or developmental) [4-8]. This led to the identification of critical effects considered relevant to the HRA. Key studies and dose descriptors such as NOAELs and LOAELs to be used for the HRA were selected considering the quality of the data set (based on Klimischcriteria [9] and for assessment of study reliability and data extraction). The reliability and plausibility of the effects observed and their relevance to humans were also evaluated. In general, the OECD's test guidelines and GLP studies were preferred but all relevant toxicological information, including non-standard academic research studies, were considered.

Subsequently, the target populations to be considered for the HRA (the general population and workers) were examined in relation to the periods of exposure in the key studies:

-the exposure of pregnant women was characterized to assess the risk to embryo-foetal development.

- adults or children exposure (male or female) was characterized to assess the risk to reproduction.

Finally, toxicological references doses[1] (TRs) were calculated for each critical doses, taking into account uncertainty factors (UFs) (e.g. interspecies and intraspecies UFs). ANSES considered the default hypothesis that a threshold dose does exist for chemical substances causing an effect on reproduction and/or development, except if data tend to show that there is no threshold [10].

The selection of TRs was based on a conservative approach, insofar as the critical dose ultimately selected was the value providing the greatest protection. Because of the lack of available studies, it was not always possible to derive a TR for each of the effects considered.

Exposure assessment

Both the general population and workers using consumer products were considered in the exposure assessments. Two complementary approaches were developed to characterize direct exposure from the use of products and indirect exposure from background concentrations in environmental media.

Direct exposure, caused by the use of the considered product, was assessed through a three steps approach involving 1) identification and selection of consumer products containing EDs/R2s, 2) selection of data to construct exposure scenario and assess consumer exposure, and 3) calculation of uptake doses. Furthermore, a sensitivity analysis was conducted to identify the most influential parameters on the doses calculated. Consumer products (mixtures and articles) containing R2s/EDs were identified from a national sector survey conducted between August 2010 and May 2011 among manufacturers. Additional information was gathered from the available bibliographic data and databases on consumer product composition registered between 2000 and 2012. Data on workers exposure were also identified in Colchicdatabase. Using this inventory, the products to be considered for risk assessment were selected, considering the likelihood of consumer exposure and data availability to quantify exposure (e.g. data on composition, recommendations for use, measured data, etc.). Exposure scenarios were developed for each product selected, taking into account the use patterns of products, frequency of use, target population (children, workers, general population), relevant routes of exposure (i.e. inhalation, dermal contact, ingestion) and physico-chemical properties of the substances. Subsequently, integrated exposure to EDs/R2s on the day of the event (i.e., the day the product was used) was modelled through a probabilistic approach by a one-dimensional Monte Carlo simulation in order to take into account the variability of input parameters of the scenarios (e.g. anthropometric data, housing characteristics, amount of the product, concentration of the compounds in the product). Probability distributions for each parameter were constructed from available data of all the

1 Toxicological reference dose is defined as the ratio between the critical dose (NOAEL or LOAEL) and uncertainty factors (UFs), when compared with exposure to reproductive toxicants, they can qualify or quantify a risk to human health. They are specific to a substance, duration of exposure (acute, intermediate or chronic), a route of exposure (inhalation, oral, dermal), a type of effect and a population (ANSES, 2007).

relevant literature, with priority given to French data. Finally, a sensitivity analysis was conducted in order to determine the relative influence of each parameter on exposure and to have a better idea on the global level of confidence in the final results. This analysis also allowed highlighting gaps regarding the available information for influential parameters.

Indirect exposure through contact with media contaminated by multiple and/or undefined sources was assessed via a probabilistic approach using bibliographic data on EDs/R2s concentrations in air (indoor/outdoor) and house dust. French data were selected when available.

Uptake doses from direct and indirect exposure were calculated separately. Integrated doses (i.e. the sum of the corresponding doses for each route of exposure) were calculated when multiple routes of exposure were considered and converted into internal doses when appropriate. Aggregate exposure from concomitant use of consumer products was not specifically characterized in this study but was put into perspective with regard to HRA results.

Risk characterisation

The method developed for the HRA described below was identical for all five substances. The TRs calculated for each of the critical doses selected and each target population were compared with the probabilistic distributions of exposure doses for the HRA. When appropriate, TRs were converted into internal doses (iTRs) to take into account the toxicokinetic differences for the different routes of exposure.

Considering the windows of susceptibility of EDs, risk assessment for chemicals with intermittent exposure was discussed regarding the reversibility of effects, chemical toxicokinetics and frequency of exposure. For prenatal exposure, ANSES assumed that developmental toxicity could occur following a single exposure event.

Regarding other reproductive effects, risk assessment was considered relevant only if repeated uses lead to chronic exposure (e.g. if the product is used at least once a week). In this case, as for developmental effects, appropriate TRs were compared to probabilistic distributions of exposure doses to assess the risk.

According to the methodology developed by ANSES [3], the results of HRA for each substance and exposure scenario were considered as follows (Figure 1):

Situation 1: The 95th percentile of the probabilistic distribution of exposure doses was above the TR: it was considered that risk situations could not be ruled out. A higher level of confidence was given for HRA results estimated from measured exposure situations, compared to those estimated from modelled exposure.

Situation 2: The 95th percentile of the probabilistic distribution of exposure doses was below the TR: risk was considered negligible. However, when the 95th of the exposure distribution exceeded 10% of the TR, the exposure associated with the use of the product was considered significant and was highlighted in the HRA results. For these products, it was estimated that concomitant exposure to the substance through other sources of exposure (e.g. use of several different products containing the substance on the same day) could lead to situation 1.

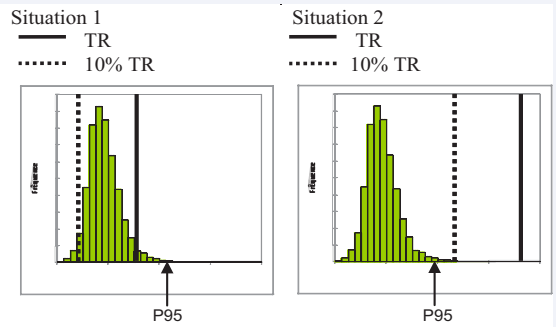

Figure 1 Interpretation of results (exposure dose distribution and toxicological reference dose) relating to a given chemical substance.
TR: Toxicological reference doses.
P95: The 95th percentile of the probabilistic distribution of exposure doses.

RESULTS AND DISCUSSION

Hazard identification

The critical effects, TRs and iTRs considered for the HRAs are presented in (Table 1) [11-19].

This work was conducted using all the available publications on these substances, targeting data on the effects on reproductive function and on their modes of action that could involve an endocrine-disrupting mechanism of action. Regarding the substances classified as R2 (i.e., n-hexane, toluene and *cis*-CTAC), it should be noted that only few studies have been published since the earlier European assessments. Those ultimately selected were considered to be of sufficient quality to conduct the HRA. For all five substances, identification of reproductive hazards was based on animal studies since no reliable studies on humans were available. However, since there was no data indicating that these effects were specific to animals, it was assumed that they could be extrapolated to humans. Several reproductive effects were taken into account for n-hexane and MTBE. Only developmental effects were considered for toluene, *cis*-CTAC and OPP. The available studies for these substances were considered suitable for HRA, although some studies were outdated due to the few recent studies or non-standard academic research studies. However, regarding MTBE, uncertainties remain concerning the results of the Biles *et al*., (1987) [19] study, showing a non-monotonic dose-response relationship, with an observable effect for the two lowest doses but no effect observed at the highest dose.

Moreover, critical non-reproductive toxicity effects occurring at the lowest dose (e.g. neurotoxicity for toluene and n-hexane) were also considered for HRA. These results are not discussed in this paper.

Exposure assessment

Identification of consumer's products containing EDs or R2s was rather difficult given the lack of data on associated formulations. Therefore, the products selected for HRA were only

Table 1: Key studies used for the HRA of five chemicals with developmental and reproductive toxicity effects.

Substance	Critical effects observed in animals	Key study	Exposure route	Starting point /Uncertainty factors (UFs)	Toxicological reference dose (TR) or internal TR (iTR)	
					General population	Occupational population
OPP (CAS n° 90-43-7)	Developmental effect (Increased incidence of litters with foetal resorption, without maternal toxicity)	[11]	oral	NOAEL 25 mg. $kg^{-1}bw.d^{-1}$ UFs=100	iTR=0.25	iTR=0.25
Toluene (CAS n° 108-88-3)	Developmental effect (Decrease in weight of offspring)	[12]	inhalation	NOAEC 1875 $mg.m^{-3}$ UFs=100	TR*=4.7	TR*=14.1
n-hexane (CAS n°110-54-3)	Reprotoxicity effect (Decrease in testicular weight, atrophy of seminiferous tubules)	[13]	inhalation	LOAEC 3524 $mg.m^{-3}$ UFs=300 or 150	TR*=9	TR*=74
	Developmental effect (Increased number of foetal resorptions, and early and late resorptions)	[14]	inhalation	LOAEC 700 $mg.m^{-3}$ UFs=300	TR*=2	TR*=6
cis-CTAC (CAS n° 51229-78-8)	Developmental effect (malformations (eye, facial and skeletal anomalies)).	[15]	oral	red UFs=300	iTR=0.017	iTR=0.017
MTBE (CAS n°1634-04-4)	Reprotoxicity effect (Increase in the percentage of abnormal sperm, ↑ (40%) in the level of LH at D28)	[16]	oral	LOAEL 400 $mg.kg^{-1}bw.d^{-1}$ UFs=300 or 150	iTR=1.3	iTR=2.6
	Change in levels of circulating hormones (↓ in level of testosterone, ↑ in level of corticosterone at D28)	[17]	oral	NOAEL 400 $mg.kg^{-1}bw.d^{-1}$ UFs=100 or 50	iTR=4	iTR=8
	Developmental effect (Decrease in weight of newborns and delayed ossification)	[18]	inhalation	NOAEC 3600 $mg.m^{-3}$ UFs= 100	TR*=9	TR*=27
	Reprotoxicity effect (Decrease in survival index of newborns on PND4)	[19]	inhalation	LOAEC 900 $mg.m^{-3}$ UFs= 300 or 150	TR*=0.53	TR*=4.5

those with sufficient data to quantify consumer exposure.

Regarding direct exposure assessment, measurements at workplaces from the Colchic database were used to assess worker exposure to EDs/R2s during painting (toluene) and professional use of adhesive (n-hexane, toluene). Measurements at petrol service stations were used to assess the exposure of workers and the general population to n-hexane, toluene and MTBE associated with petrol vapour emissions. Measured data on exposure to toluene, n-hexane, *cis*-CTAC and OPP in other products were not available. Results from mathematical models used to assess exposure to these mixtures were considered suitable for HRA.

Regarding indirect exposure assessment via the intake of contaminated environmental media and house dust, no French data were available for EDs/R2s, except for toluene.

The data used for direct and indirect exposure assessment are summarized in (Table 2) [20-27]. Probabilistic distributions of exposure parameters and exposure doses are not presented in this paper.

Risk assessment

Ultimately, it was only possible to assess risks to adults (female or male) and to the unborn children of pregnant women, due to the lack of toxicological reference doses for the other populations or age groups of interest (young children, adolescents, etc.).

Exposure situations posing a potential reproductive risk for adults or a potential risk for embryonic or foetal development due to occupational or non-occupational exposure of pregnant women to certain products containing toluene, n-hexane or *cis*-CTAC are summarized in (Table 3). Significant exposure situations (i.e., those exceeding 10 % of the TR) are also highlighted in (Table 3).

Regarding HRA results, the study was only able to identify a limited amount of information on consumer products containing EDs/R2s and associated formulation. Because of this, the data used for HRA are neither representative of the French market nor exhaustive with regard to all the products containing EDs/R2s, especially for substances used as preservatives in a large number of mixtures. Since these data are essential in order to characterize population exposure and the possible risks to health, an update to the inventory of consumer products available on the French market and their associated formulations is needed to complete this work. However, in spite of these limits, experimental data were judged sufficiently robust to conduct the HRA. ANSES considers that exposure situations posing a potential risk for embryonic or foetal development may exist, due to occupational or non-occupational exposure of pregnant women to certain products (Home-improvement products, cleaning and maintenance products, repellents) containing toluene (Liquid glues, liquid paints, spray paints, varnishes, paint strippers for wood, spray degreasing agents/lubricants for metal, paints

Table 2: Data on uses and environmental contamination for OPP, n-hexane, toluene, *cis*-CTAC and MTBE selected for the HRA.

	Direct Exposure assessment				Indirect exposure assessment	
Substance (General information)	**Method**	**Products considered for HRA**	**95th of exposure on day of event (mg.m^{-3} OR mg.kg^{-1}.j^{-1}) (general public)**	**95th of exposure on day of event (mg.m^{-3} OR mg.kg^{-1}.j^{-1}) (workers)**	**Method**	**95th of exposure**
OPP (Use for its biocidal properties as a disinfectant and preservative).	Routes of exposure: inhalation and dermal contact Modelling of exposure concentrations in air and quantities of OPP on the surface of the skin. Calculation of internal exposure doses (mg. kg^{-1}.j^{-1})	Insecticides	6,3.10^{-4} (PW) ; 5,3.10^{-4} (W) ; 5,4.10^{-4} (M)	NC	Indoor and outdoor air Settled dust [20], [21]	5,0.10^{-4} (PW) ; 5,5.10^{-4} (W) ; 4,5.10^{-4} (M)
		Household disinfectant surface cleaners (liquid)	7,0.10^{-5} (PW) ; 7,2.10^{-5} (W) ; 6,3.10^{-5} (M)	7,6.10^{-3} (PW) ; 4,6.10^{-3} (W) ; 4,9.10^{-3} (M)		
		Household disinfectant surface cleaners (wipes)	1,1.10^{-6} (PW) ; 1,2.10^{-6} (W) ; 2,0.10^{-6} (M)	6,9.10^{-5} (PW) ; 4,4.10^{-5} (W); 4,4.10^{-5} (M)		
		Household disinfectant surface cleaners (spray)	1,3.10^{-4} (PW); 1,4.10^{-4} (W); 1,2.10^{-4} (M)	1,1.10^{-1} (PW); 6,0.10^{-2} (W); 6,0.10^{-2} (M)		
		Bathroom cleaning products	1,4.10^{-4} (PW); 1,2.10^{-4} (W); 1,3.10^{-4} (M)	NC		
		Room air fresheners	3,0.10^{-2} (PW) ; 2,0.10^{-2} (W) ; 2,2.10^{-2} (M)	NC		
		Car air fresheners	9,7.10^{-4} (PW); 8,1.10^{-4} (W); 8,8.10^{-4} (M)	9,7.10^{-4} (PW); 8,1.10^{-4} (W); 8,8.10^{-4} (M)		
		Metal degreasing agents	8,0.10^{-2} (PW) ; 8,0.10^{-2} (W) ; 8,0.10^{-2} (M)	NC		
Toluene Use as a solvent or as an intermediate in chemical synthesis.	-Route of exposure: inhalation - Modelling of exposure concentrations in air (mg.m-3) - Exposure measurement data (French data extracted from Colchic INRS 2013): - Liquid paints, paint thinners and varnish: occupational population. - Liquid glues: occupational population - Fuel: general and occupational population.	Adhesives (glues)	6,5 mg.m^{-3} (PW, W and M)	78 mg.m^{-3} ((PW, W and M)	Indoor and outdoor air [22] French OQAI data, 2003-2005	0,07 mg.m^{-3} (PW, W and M)
		Adhesives (spray)	8,5.10^{-3} mg.m^{-3} ((PW, W and M)	NC		
		Paints (liquid)	7,7. mg.m^{-3} (PW, W and M)	52 mg.m^{-3} ((PW, W and M)		
		Paints (spray),	0,3 mg.m^{-3} (PW, W and M)	0,7 mg.m^{-3} (PW, W and M)		
		Paint thinners	[10 – 96] mg.m^{-3} (PW, W and M)	52 mg.m^{-3} ((PW, W and M)		
		Paint (hobbies)	0,15 mg.m^{-3} (PW, W and M)	NC		
		Wood varnish,	21 mg.m^{-3} (PW, W and M)	52 mg.m^{-3} ((PW, W and M)		
		Paint strippers for wood	42 mg.m^{-3} (PW, W and M)	560 mg.m^{-3} (PW, W and M)		
		Wood maintenance products	8,8.10-4 mg.m-3 (PW, W and M)	NC		
		Spray degreasing agents for metal	0,9 mg.m^{-3} (PW, W and M)	49 mg.m^{-3} (PW, W and M)		
		Spray for car plastic	6,2 mg.m^{-3} (PW, W and M)	329 mg.m^{-3} (PW, W and M)		
		Fuel	1,7.10-2 mg.m^{-3} (PW, W and M)	2,0 mg.m^{-3} (PW, W and M)		
n-hexane Use as a solvent in consumer goods.		Adhesives (glue, spray), Adhesive thinners, Paints (liquid, spray), Metal Lubricant and Degreasing agents, Car air freshener (solid form and spray), Car plastic renovators, Stain remover liquid for textiles (liquid, spray), Textile waterproofing products, Waxes/varnishes, Insecticide, Fuel	Route of exposure: inhalation Modelling of exposure concentrations in air. Exposure measurement data (French data extracted from Colchic INRS 2013): - Liquid glues and glue thinners: occupational population - Fuel: general and occupational populations.		General and occupational populations: paint strippers for wood, glues and glue thinners. Sensitivity analysis (most sensitive parameter): 1/ mass concentration 2/ air exchange rate and duration of use	Indoor and outdoor air [23] (European data) Sensitivity analysis (most sensitive parameter): concentration in indoor air

	Direct Exposure assessment				Indirect exposure assessment	
Substance (General information)	**Method**	**Products considered for HRA**	**95th of exposure on day of event (mg.m^{-3} OR mg.kg^{-1}.j^{-1}) (general public)**	**95th of exposure on day of event (mg.m^{-3} OR mg.kg^{-1}.j^{-1}) (workers)**	**Method**	**95th of exposure**
Cis-CTAC Use as a preservative in numerous products, and in certain repellents in particular.		Textile treatment products (spray) (insect repellent and ironing spray), Textile treatment products (insect repellent), Repellents for skin application (gel, spray), Adhesives, Paints, Detergents, Waxes/varnishes	Route of exposure: dermal Modelling of quantities of *cis*-CTAC on the surface of the skin. Calculation of internal exposure doses		General population: repellents in gel for skin application. Occupational population: liquid glues. Sensitivity analysis (most sensitive parameter): 1/ mass concentration 2/ frequency of use	No data identified
MTBE Use as an additive in petrol.	Route of exposure: inhalation Exposure measurement data (French data extracted from Colchic INRS 2013): - Fuel: general and occupational populations.	Fuel			Sensitivity analysis (most sensitive parameter): MTBE concentration in the petrol station air.	Indoor and outdoor air Finnish and Belgian data: [24-27]. Sensitivity analysis (most sensitive parameter): concentration in indoor air

Abbreviations: HRA: Health Risk Assessment, OD: Odd Ratio, PW: Pregnant Women, W: Women.

Table 3: Summary of results of HRA associated to the use of products containing one of the following substances.

Products and uses		**Substances**	**Target population**	**95th percentile (mg/m^3) or (mg/kg/j)**	**TRs Developmental toxicity**	**TRs Reproductive toxicity**	**RCRs Developmental toxicity**	**RCRs Reproductive toxicity**	**Risk of in utero developmental effects associated with the use of a product by pregnant women.**	**Risk of a reproductive toxicity effects (other than an effect on foetal development) associated with the use of a product by adults.**
	Liquid glues	Toluene	GP (PW)	6,5 mg.m^{-3}	4,7 mg.m^{-3}	No data	1,4	Not concerned	situations presumed at risk	Not concerned
			OP (PW)	78 mg.m^{-3}	14,1 mg.m^{-3}	No data	5,5	Not concerned	situations at risk	
		n-hexane	GP (PW)	51 mg.m^{-3}	2 mg.m^{-3}	Not considered	26	Not concerned	situations presumed at risk	Not considered
			OP (PW and M)	17,6 mg.m^{-3}	6 mg.m^{-3}	74mg.m-3	2,9	0,23	situations at risk	situations with significant exposure
		cis-CTAC	GP (PW)	1,1.10^{-2} mg.kg^{-1}.j^{-1}	0,017 mg.kg^{-1}.j^{-1}	No data	0,65	Not concerned	situations with significant exposure	Not concerned
			OP (PW)	1,1.10^{-2} mg.kg^{-1}.j^{-1}	0,017 mg.kg^{-1}.j^{-1}	No data	0,65	Not concerned	situations with significant exposure	Not concerned
	Liquid paints	Toluene	GP (PW)	7,7 mg.m-^{3}	4,7 mg.m^{-3}	No data	1,6	Not concerned	situations presumed at risk	Not concerned
			OP (PW)	52 mg.m^{-3}	14,1 mg.m^{-3}	No data	3,7	Not concerned	situations at risk	Not concerned
		n-hexane	GP (PW)	9,8 mg.m^{-3}	2 mg.m^{-3}	Not considered	4,9	Not concerned	situations presumed at risk	Not considered
			OP (PW and M)	73 mg.m^{-3}	6 mg.m^{-3}	74 mg.m^{-3}	12	0,99	situations presumed at risk	situations with significant exposure for adult male
	Spray paints	Toluene	OP (PW)	1,7 mg.m^{-3}	14,1 mg.m^{-3}	No data	0,12	Not concerned	situations with significant exposure	Not concerned

Products and uses		Substances	Target population	95th percentile (mg/m³) or (mg/kg/j)	TRs Developmental toxicity	TRs Reproductive toxicity	RCRs Developmental toxicity	RCRs Reproductive toxicity	Risk of in utero developmental effects associated with the use of a product by pregnant women.	Risk of a reproductive toxicity effects (other than an effect on foetal development) associated with the use of a product by adults.
		n-hexane	OP (PW and M)	19 $mg.m^{-3}$	6 $mg.m^{-3}$	74 $mg.m^{-3}$	3,2	0,26	situations presumed at risk	situations with significant exposure for adult male
	Varnishes	Toluene	GP (PW)	21 $mg.m^{-3}$	4,7 $mg.m^{-3}$	No data	4,5	Not concerned	situations presumed at risk	Not concerned
			OP (PW)	52 $mg.m^{-3}$	14,1 $mg.m^{-3}$	No data	3,7	Not concerned	situations at risk	Not concerned
		cis-CTAC	GP (PW)	$5,3.10^{-3}$ $mg.kg^{-1}.j^{-1}$	0,017 $mg.kg^{-1}.j^{-1}$	No data	0,31	Not concerned	significant exposure situations	Not concerned
HOME-IMPROVEMENT PRODUCTS			OP (PW)	$5,3.10^{-3}$ $mg.kg^{-1}.j^{-1}$	0,017 $mg.kg^{-1}.j^{-1}$	No data	0,3	Not concerned	significant exposure situations	Not concerned
	Paint strippers for wood	Toluene	GP (PW)	42 $mg.m^{-3}$	4,7 $mg.m^{-3}$	No data	8,9	Not concerned	situations presumed at risk	Not concerned
			OP (PW)	560 $mg.m^{-3}$	14,1 $mg.m^{-3}$	No data	40	Not concerned	situations presumed at risk	Not concerned
		n-hexane	GP (PW)	30 $mg.m^{-3}$	2 $mg.m^{-3}$	Not considered	15	Not considered	situations presumed at risk	Not considered
			OP (PW and M)	295 $mg.m^{-3}$	6 $mg.m^{-3}$	74 $mg.m^{-3}$	49	4,0	situations presumed at risk	situations presumed at risk
	Liquid degreasing agents/ lubricants for metal	n-hexane	GP (PW)	20 $mg.m^{-3}$	2 $mg.m^{-3}$	Not considered	10	Not considered	situations presumed at risk	Not considered
		OPP	OP (PW)	$8,0.10^{-2}$ $mg.kg^{-1}.j^{-1}$	0,25 $mg.kg^{-1}.j^{-1}$	No data	0,32	Not concerned	situations with significant exposure	Not concerned
	Spray degreasing agents/ lubricants for metal	n-hexane	GP (PW)	0,26 $mg.m^{-3}$	2 $mg.m^{-3}$	Not considered	0,13	Not considered	situations with significant exposure	Not considered
			OP (PW and M)	23 $mg.m^{-3}$	6 $mg.m^{-3}$	74 $mg.m^{-3}$	4,3	0,31	situations presumed at risk	situations with significant exposure
		Toluene	GP (PW)	0,9 $mg.m^{-3}$	4,7 $mg.m^{-3}$	No data	0,19	Not concerned	Situations with significant exposure	Not concerned
			OP (PW)	49 $mg.m^{-3}$	14,1 $mg.m^{-3}$	No data	3,5	Not concerned	situations presumed at risk	Not concerned
	Paint thinners	Toluene	GP (PW)	10 $mg.m^{-3}$	4,7 $mg.m^{-3}$	No data	2,1	Not concerned	situations presumed at risk	Not concerned
			OP (PW)	52 $mg.m^{-3}$	14,1 $mg.m^{-3}$	No data	3,7	Not concerned	situations at risk	Not concerned
	Glue thinners	n-hexane	GP (PW)	41 $mg.m^{-3}$	2 $mg.m^{-3}$	Not considered	21	Not concerned	situations presumed at risk	Not considered
			OP (PW and M)	17,6 $mg.m^{-3}$	6 $mg.m^{-3}$	74 $mg.m^{-3}$	2,9	0,24	situations at risk	situations with significant exposure
	Plastic renovators	Toluene	GP (PW)	6,2 $mg.m^{-3}$	4,7 $mg.m^{-3}$	No data	1,3	Not concerned	situations presumed at risk	Not concerned
			OP (PW)	329 $mg.m^{-3}$	14,1 $mg.m^{-3}$	No data	23	Not concerned	situations presumed at risk	Not concerned
		n-hexane	GP (PW)	0,28 $mg.m^{-3}$	2 $mg.m^{-3}$	Not considered	0,14	Not considered	situations with significant exposure	Not considered
			OP (PW and M)	3,1 $mg.m^{-3}$	6 $mg.m^{-3}$	74$mg.m^{-3}$	0,52	0,08	situations with significant exposure	Not concerned*
	Car air fresheners sprays	n-hexane	GP (PW)	0,3 $mg.m^{-3}$	2 $mg.m^{-3}$	Not considered	0,15	Not Concerned	situations with significant exposure	Not considered
			OP (PW)	0,3 $mg.m^{-3}$	2 $mg.m^{-3*}$	Not concerned*	0,15	Not concerned*	situations with significant exposure	Not concerned*

Products and uses		Substances	Target population	95th percentile (mg/m³) or (mg/kg/j)	TRs Developmental toxicity	TRs Reproductive toxicity	RCRs Developmental toxicity	RCRs Reproductive toxicity	Risk of in utero developmental effects associated with the use of a product by pregnant women.	Risk of a reproductive toxicity effects (other than an effect on foetal development) associated with the use of a product by adults.
CLEANING & MAINTENANCE PRODUCTS	Stain removers for textiles (liquid)	n-hexane	GP (PW)	2,4 $mg.m^{-3}$	2 $mg.m^{-3}$	9 $mg.m^{-3}$	1,2	0,27	situations presumed at risk	situations with significant exposure
			OP (PW and M)	61 $mg.m^{-3}$	6 $mg.m^{-3}$	74 $mg.m^{-3}$	10	0,82	situations presumed at risk	situations with significant exposure for adult male
	Textile waterproof-ing products (spray)	n-hexane	GP (PW)	2,4 $mg.m^{-3}$	2 $mg.m^{-3}$	Not concerned	1,2	Not considered	situations presumed at risk	Not considered
			OP (PW and M)	95 $mg.m^{-3}$	6 $mg.m^{-3}$	74 $mg.m^{-3}$	15,8	1,3	situations presumed at risk	situations with significant exposure for adult male
	Textile treatment products (liquid)	*cis*-CTAC	GP (PW)	5,9.10-3 $mg.kg^{-1}.j^{-1}$	0,017 $mg.kg^{-1}.j^{-1}$	No data	0,35	Not concerned	Situations with significant exposure	Not concerned
	Detergents, household cleaners (liquid)	*cis*-CTAC	OP (PW)	3,4.10-3 $mg.kg^{-1}.j^{-1}$	0,017 $mg.kg^{-1}.j^{-1}$	No data	0,2	Not concerned	situations with significant exposure	Not concerned
	Detergents, household cleaners (spray)	OPP	OP (PW)	$1,1.10^{-1}$ $mg.kg^{-1}.j^{-1}$	0,25 $mg.kg^{-1}.j^{-1}$	No data	0,44	Not concerned	situations with significant exposure	Not concerned
	Wood maintenance products (waxes, floor polishes) (spray)	n-hexane	GP (PW)	0,23 $mg.m^{-3}$	2 $mg.m^{-3}$	Not considered	0,12	Not considered	Situations with significant exposure	Not considered
			OP (PW and M)	11 $mg.m^{-3}$	6 $mg.m^{-3}$	74 $mg.m^{-3}$	1,8	0,15	situations presumed at risk	situations with significant exposure
	Fuel - exposure in service stations	MTBE	OP (PW and adults)	11 $mg.m^{-3}$	27 $mg.m^{-3}$	4,5 $mg.m^{-3}$	0,41	2,4	situations with significant exposure	situations at risk for adults
FUEL		n-hexane	OP (PW)	1,4 $mg.m^{-3}$	6 $mg.m^{-3}$	Not concerned*	0,23	0,019	situations with significant exposure	Not concerned*
		Toluene	OP (PW)	2,0$mg.m^{-3}$	14,1$mg.m^{-3}$	No data	0,14	Not concerned	situations with significant exposure	Not concerned
REPELLENTS	Repellents for skin application (liquid/gel)	*cis*-CTAC	GP (PW)	$2,2.10^{-2}$ $mg.kg^{-1}.j^{-1}$	0,017 $mg.kg^{-1}.j^{-1}$	No data	1,3	Not concerned	situations presumed at risk	Not concerned
	Repellents for skin application (spray)	*cis*-CTAC	GP (PW)	$7,6.10^{-3}$ $mg.kg^{-1}.j^{-1}$	0,017 $mg.kg^{-1}.j^{-1}$	No data	0,45	Not concerned	Situations with significant exposure	Not concerned

Abbreviations: Not concerned or Not concerned* = no data to assess the risk or situation at risk negligible, Not considered = frequency of use of product considered irrelevant to assess sub-chronic reproductive risk, *exposure and TR on 24h, GP: General population, OP: occupational population, RCR: Risk Characterization Ratio, PW: Pregnant women, M: Adult male.

thinners, plastic renovators), n-hexane (Liquid glues, liquid paints, spray paints, paint strippers for wood, liquid degreasing agents/lubricants for metal, spray degreasing agents/lubricants for metal, glue thinners, plastic renovators, car air freshener sprays, stain removers for textile (liquid), textile waterproofing products spray), wood maintenance products (waxes, floor polishes) (spray), or *cis*-CTAC (Liquid glues, repellents for skin application (liquid/gel). The results of the HRA showed also that exposure in adults (men and women) when dispensing fuel or filling tanks (from a petrol tanker) could lead to situations likely to cause effects on reproduction in the exposed individuals.

No risk regarding other consumer products or indirect exposure via environmental media or the intake of contaminated house dust was expected.

CONCLUSION

Exposure resulting from the use of consumer products varies greatly from one individual to another due to the many possible

conditions of use of these products, differences in product composition and inters individual physiological variation parameters. In this context, the HRA method developed by ANSES (available on ANSES website [3] based on probabilistic exposure assessment is eminently suitable as it covers as many exposure situations as possible. Moreover, the review and the use of several mathematical models and probabilistic distribution for associated parameters are of particular interest, because representative exposure data are generally not available.

Several recommendations were proposed for the five substances for which some situations of concerns were identified, such as informing consumers of the presence of these substances in products, avoiding the use of products listed in (Table 3) by pregnant women, and providing information on hygiene measures and good practices to limit exposure. ANSES also issues specific recommendations for each substance, in order to increase knowledge on the hazard of these substances and their mode of action, on the identification of safe substitutes, and on the conditions of population exposure. Cumulative and aggregate exposure to several consumer products containing EDs/R2s is of primary interest for ANSES and will be further addressed.

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Conflict of Interest

The authors take full responsibility for the drafting and content of this paper and have no competing interests to declare. Their affiliations are shown on the cover page.

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