anses
French agency for food, environmental and occupational health & safety

State of current knowledge
Request No 2009-SA-0331

Maisons-Alfort, 24 March 2015

Reprotoxic substances and/or endocrine disruptors:

Memo

relating to the state of current knowledge of uses, exposure sources and toxicity

for several perfluorinated compounds and phthalates

Presentation of the issue raised and organisation of the expert appraisal

In June 2009, the Agency received a formal request from the Directorate General for Health (DGS) (Request No 2009-SA-0331) for a health risk assessment (HRA) of exposure to category 3[1] (R3) reprotoxic (according to Directive 67/548/EC) and/or endocrine disrupting (ED) substances found in consumer products marketed in France. This request covered the general population, including vulnerable populations and people in the workplace handling so-called "consumer" products in the context of their professional activity (excluding production, processing, distribution and disposal). The substances subject to the expert appraisal included a list of ten in the class of phthalates and two in the class of perfluorinated compounds.

These substances are as follows:

- Perfluorinated compounds: perfluorooctane sulfonate (PFOS) (CAS No 1763-23-1, 29081-56-9, 2795-39-3), perfluorooctanoic acid (PFOA) (CAS No 335-67-1).

- Phthalates: butylbenzyl-phthalate (BBP) (CAS No 85-68-7), di-(2-ethylhexyl)phthalate (DEHP) (CAS No 117-81-7), diisodecyl phthalate (DIDP) (CAS No 26761-40-0), di-n-butyl phthalate (DBP) (CAS No 84-74-2), diisononyl phthalate = 1,2-Benzenedicarboxylic acid, diisononyl ester (DINP) (CAS No 28553-12-0), diisopentyl phthalate (DIIP) (CAS No 131-18-0), mono-n-butyl phthalate (CAS No 131-70-4), dipropyl phthalate (CAS No 131-16-8), diisobutyl phthalate (DIBP) (CAS No 84-69-5), di-n-hexyl phthalate (CAS No 84-75-3).

[1] Substances classified as category 3 reprotoxic according to Directive 67/548/EEC are now classified as toxic to reproduction, category 2 according to (EC) Regulation no. 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures, known as the CLP Regulation. In this document, substances are classified based on the CLP Regulation.

Other perfluorinated compounds and phthalates not appearing on this list may however be found in consumer goods and products and in various compartments of the environment.
ANSES therefore considered, in agreement with its expert appraisal bodies (Working Group (WG) on Endocrine disruptors, Expert Committees (CESs) on Assessment of the risks related to chemical substances and Characterisation of substance hazards and toxicity reference values), that a summary should be made of the available data on an expanded list of chemical compounds from these two classes (see below), in order to document uses, current regulations, exposure and risks. The Agency also considered that the sources of potential exposure to these substances should include food, water, air and dust.

This memo concisely describes the main sections of the two reports resulting from the collective expert appraisal (one on several perfluorinated compounds and the other on several phthalates), summarising the data that are available or currently being acquired on uses, contamination levels in various products and environmental compartments, and potential risks related to these substances.

The ultimate aim of this work was to characterise the main toxic effects of exposure to these compounds and determine the primary sources of human exposure. It made it possible to identify substances for which a health risk assessment is justified in light of their widespread use and/or persistence in the human body or the environment and in light of their potential toxicity, particularly to reproductive function and development.

Results of the expert appraisal

1. Perfluorinated compounds

PFOS and PFOA
Since May 2009, PFOS and PFOA have been included on the list of substances covered by the Stockholm Convention on Persistent Organic Pollutants (POPs). Their production, placing on the market and use, whether on their own, in preparations or as constituents of articles, are prohibited, subject to derogation (Regulation (EC) 850/2004 on persistent organic pollutants amending Directive 79/117/EEC).

PFOS was identified as a priority hazardous substance in Annex X of the Directive of the European Parliament and of the Council of 12 August 2013[2]. Today, levels of PFOS in the environment result more from past activities and uses than from current production sites. The main manufacturer of this compound (3M) phased out its production in 2002. It is considered that PFOS is no longer produced in Europe or North America. However, there is a derogation of use in Europe for certain applications (Directive 2006/1122/EC of 12 December 2006), and PFOS continues to be produced in other countries including China.

Since 2 October 2013, PFOA has had the R1B harmonised classification. PFOA is primarily used to produce its ammonium salt (APFO), used as a surfactant in the production of the two main fluoropolymers: polytetrafluoroethylene (PTFE) and polyvinylidene fluoride (PVDF).

Moreover, PFOA can be an unintended by-product of the production of these fluoropolymers, and substances such as fluorotelomers can be broken down into perfluorinated carboxylic acids or perfluorinated sulfonic acids. Fluorotelomers can also be broken down into PFOA.

[2] Directive 2013/39/EU of the European Parliament and of the Council of 12 August 2013 amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy.

Other perfluorinated compounds covered in this expert appraisal (see table below):

Class	Abbreviation	CAS Number	Compound name
Perfluorinated carboxylic acids (PFCAs)	PFBA	375-22-4	Perfluorobutanoic acid
	PFPA	2706-90-3	Perfluoropentanoic acid
	PFHxA	307-24-4	Perfluorohexanoic acid
	PFHpA	375-85-9	Perfluoroheptanoic acid
	PFOA	335-67-1	Perfluorooctanoic acid
	NH4-PFOA	3825-26-1	Perfluorooctanoic acid ammonium salt
	PFNA	375-95-1	Perfluorononanoic acid
	PFDA	335-76-2	Perfluorodecanoic acid
	PFUnA	2058-94-8	Perfluoroundecanoic acid
	PFDoA	307-55-1	Perfluorododecanoic acid
	PFTrDA	72629-94-8	Perfluorotridecanoic acid
	PFTeDA	376-06-7	Perfluorotetradecanoic acid
Perfluorosulfonic acids (PFSAs)	PFBS	375-73-5	Perfluorobutane sulfonate
	PFPS	2706-91-4	Perfluoropentane sulfonate
	PFHxS	355-46-4	Perfluorohexane sulfonate
	PFHpS	375-92-8	Perfluoroheptane sulfonate
	PFOS	1763-23-1	Perfluorooctane sulfonate
	PFDS	335-77-3	Perfluorodecane sulfonate
Other	PFHxPA	40143-76-8	Perfluorohexylphosphonic acid
	PFOPA	40143-78-0	Perfluorooctylphosphonic acid
	PFDPA	52299-26-0	Perfluorodecylphosphonic acid
	PFOSA	754-91-6	Perfluorooctanesulfonamide
	PPVE	1623-05-8	Perfluoropropylvinyl ether
	EtFOSA	4151-50-2	N-ethyl perfluorooctanesulfonamide
	MeFOSA	31506-32-8	N-methyl perfluorooctanesulfonamide

In this rest of this memo, polyfluoroalkylated and perfluoroalkylated substances are referred to by the acronym PFAS.

Most articles containing perfluorinated compounds are manufactured outside of the European market and it is difficult to obtain specific information regarding perfluorinated compounds in imported articles.

Recent data show a significant decrease in perfluorinated compounds in products on the market over the last few years. However, PFOS can still be found in some products. In particular, recent US-EPA data suggest that carpet-care liquids, treated-floor waxes and sealants, treated food contact paper, and sealant tapes and pastes are the most significant sources of perfluorinated compounds, including PFOA, from the ten categories of articles studied in the United States (source: US-EPA[3]). Furthermore, according to these authors, short-chain perfluorinated compounds (C4 to C7) seem to be used more than long-chain perfluorinated compounds (C8 to C12), but this trend will need to be confirmed by market studies.

Levels of perfluorinated compounds in various products and media

A decrease in levels of PFOS and PFOA in the environment (food, air, dust) since 2002 is reported in a Scandinavian study[4]; however, this has not been the case for short-chain sulfonated derivatives. That said, the lack of physico-chemical data and analytical references for

[3] 4.4.2 US- EPA: Trends of Perfluoroalkyl Acid Content in Articles of Commerce – Market Monitoring from 2007 through 2011 (August 2012)

[4] Nordic Council of Ministers* (2013) Per- and polyfluorinated substances in the Nordic Countries. Use, occurence and toxicology. pp. 230.

compounds other than PFOS and PFOA is a barrier to studying these substances in humans and the environment.

Regarding food contamination, a low level of food contamination was observed in the French Total Diet Study (TDS2, ANSES, 2011b[5]). Concentrations below the limit of detection were reported in 98% of the samples tested in this study. Fish, and more particularly freshwater fish, are the most contaminated foodstuffs (specific sampling of freshwater fish with the ICAR-PCB study[6] and of seafood with the CALIPSO study[7]). Therefore, heavy consumers of freshwater fish have the highest levels of exposure, followed by heavy consumers of seafood.

Regarding contamination in water intended for human consumption (WIHC): PFASs are not included in the required health monitoring parameters for WIHC. Current French national data are based on the work of ANSES's Nancy Laboratory for Hydrology (NLH), published in the May 2011 report relating to national campaigns on the occurrence of perfluorinated alkyl compounds in untreated and distributed water. Other "exceptional" sampling and analysis campaigns, whose results have not yet been published, have been undertaken at the request of the Directorate for Water and Biodiversity (DEB) of the Ministry of Ecology, Sustainable Development and Energy (MEDDE):

- in 2011 on groundwater in metropolitan France by the French Bureau of Geological and Mining Research (BRGM);
- in 2012 on surface water in overseas *départements* and metropolitan France, and on groundwater in overseas *départements*.

Regarding contamination in air (indoor and outdoor) and dust: the results of the literature search show that:

- most of the studies identified in the literature involve PFOS and PFOA. Of the other perfluorinated compounds studied, PFOSA, PFBS, PFHxS, PFHxA, PFHpA, PFNA, 6:2 FTOH, 8:2 FTOH, 10:2 FTOH, MeFOSA, EtFOSA, MeFOSE and EtFOSE are those covered by the most publications;

- the data on contamination in indoor air and dust are primarily related to homes. A few studies also present contamination data for other indoor environments (offices, shops, etc.). The ranges of concentrations measured in these two media are fairly wide;

- several publications presenting contamination data for outdoor air study the long-distance transport of perfluorinated compounds. In these studies, measurements were taken in isolated rural areas. The ranges of concentrations measured in outdoor air are fairly wide. There are more publications on neutral perfluorinated compounds, which are more volatile;

- only two studies presenting contamination data for house dust and outdoor air in France were identified in the scientific literature for PFOS, PFOA, PFHxS, MeFOSA, EtFOSA, MeFOSE, EtFOSE (outdoor air and dust), PFOSA (dust only), PFBS, PFNA, PFDA, PFDS, 6:2 FTOH, 8:2 FTOH and 10:2 FTOH (outdoor air only).

[5] ANSES (2011b) French Total Diet Study 2 (TDS2). Volume 1. Inorganic contaminants, minerals, persistent organic pollutants, mycotoxins and phyto-oestrogens. ISBN 978-2-11-128112-7. 305 p.
[6] ICAR-PCB: National study of PCB concentrations in consumers of freshwater fish, undertaken in 2009. Denys S1, *et al.* Toxicol Lett. 2014 Dec 1;231(2):233-8.
[7] CALIPSO: Dietary consumption of fish and seafood, and concentration levels of trace elements, pollutants and omega 3, undertaken in 2004.

Calculations of aggregate exposure, undertaken with the aim of determining the main sources of exposure to certain perfluorinated compounds, are given in the expert appraisal report. The exposure media taken into account in these calculations are as follows:

- Food and beverages – exposure by ingestion
- Dust deposited in indoor environments – exposure by ingestion
- The air compartment – exposure by inhalation

Results from the calculation of the Daily Exposure Dose (DED) presented in the expert appraisal report can be taken into account to assess the contribution of the various exposure routes (average scenario).

Note that the quality of the data used for these calculations differs from one medium to another:

- dietary exposure data are for individuals in France, while contamination data for air and dust have been taken from the literature.

Biosurveillance data

Regarding biosurveillance studies, their direct comparison is difficult due to discrepancies in several methodological points related to the quantitative measurement of PFASs in biological matrices. Detection limits, management of non-detected values, and consideration of the linear and branched forms of certain compounds are in particular critical points that can affect results for distributions of concentrations measured in the population.

PFOS and PFOA are the two main biomarkers of exposure to perfluorinated carboxylic acids (PFCAs) mentioned in the literature. Of all perfluorinated compounds, these two are also the most subject to routine testing. Depending on the study, they contribute to 75-90% of the exposure profile, which nonetheless depends on many other tested substances. Other compounds such as PFHxS, PFNA and PFDA are also frequently tested for and detected in many studies. PFDoA, PFUnA, PFHpA and PFTrDA make up another set of substances detected mainly in studies undertaken in Asia. There is relatively high variability in relative proportions between the various tested PFASs, in particular depending on the geographic origin of the collected samples. Other representatives of this class of substances, in particular their precursors (PFOSA/PFOSE derivatives, fluorotelemers), are tested for and/or detected much less frequently.

In the serum of adult subjects, the levels of PFOA and PFOS observed internationally generally range from a few µg/l to several tens of µg/l. Foetal and post-natal exposure has also been demonstrated. However, levels measured in umbilical cord blood are approximately 1.2 to 3 times lower than those measured in maternal blood, depending on the substance in question. In breast milk, observed concentrations are more than ten times lower than those measured in maternal serum.

Rates of transfer from mother to foetus (umbilical cord blood, amniotic fluid) or to infant (breast milk) vary between substances, in particular based on their structural, physico-chemical and pharmaco-kinetic properties. For example, this transfer is more significant for PFOA than for PFOS. Branched forms, short chains and carboxylate functional groups promote this transfer, compared to linear forms, long-chain forms and those containing sulfonate groups.

A downward trend in biological concentrations of PFOS has been observed in the general population. On several continents, this has been the case since 2002, when one of the main production companies stopped manufacturing it. However, this trend has not been observed for PFOA, for which the published studies show conflicting results. Furthermore, biological concentrations due to other substances in the class of perfluorinated compounds (PFNA, PFHxS) have been increasing in the past decade.

Studies on biological concentrations of these various compounds show conflicting results and highlight various influencing factors such as age and gender. The diversity of exposure sources, the variability of exposure profiles over time, and individual polymorphisms for certain pharmaco-kinetic parameters are just some of the factors that contribute to this non-convergence in observations.

While the volume of available data appears relatively significant for PFOS and PFOA, the characterisation of this class of substances in all its diversity, from technical formulations to degradation products, needs to be improved in order to better understand this class of contaminants in all its complexity. This could be achieved for example by taking precursor forms (fluorotelomers, PFOSE/PFOSA derivatives) into account more systematically and by distinguishing between linear and branched forms.

The results of two studies undertaken in France (the ELFE study[8] and the ANR CONTREPERF project) are expected in 2015 and should shed light on concentration levels in mothers and their children.

Toxicity data

Epidemiological studies have reported a possible effect of perfluorinated compounds on the fertility of couples (increased risk of unwanted childlessness) but have not been able to specifically attribute this to PFOS or PFOA. An effect on sperm morphology was suggested in a single human study and indicates the need to undertake new studies using a longitudinal approach. As for the other health events falling within the scope of this expert appraisal, the data are too limited to be able to characterise a potential effect of perfluorinated compounds.

Recent **experimental studies** have confirmed the effects of PFOS and PFOA. The mammary gland seems to be the organ with the highest susceptibility to PFOA, particularly during *in utero* exposure. The peripubescent period is also a time of susceptibility to the effects of perfluorinated compounds. Very few compounds in the class of perfluorinated compounds, other than PFOS and PFOA, have been covered by studies assessing their toxicity. It is worth noting that there are differences in susceptibility to perfluorinated compounds between animal species. Since the expert appraisal by Inserm (2011), new studies have been published on the toxicity of perfluorinated compounds. These studies will be covered in an ANSES expert appraisal.

Tolerably Daily Intake (TDI) values of 150 ng/kg/day for PFOS and of 1500 ng/kg/day for PFOA were proposed by EFSA in 2008. These values, which are currently being evaluated by ANSES, appear significantly higher than the exposure values evaluated and available in the literature (Inserm, 2011[9]).

2. Phthalate compounds

Phthalates are used in the production of certain consumer goods, especially in products using plastic materials such as PVC. Some uses are subject to sector-specific regulations; these include toys, rubber materials and articles in contact with foodstuffs, food products and beverages, biocidal and plant protection products, cosmetic products, construction and decoration products, and childcare articles. Growing interest in long-chain phthalates (more than seven carbon atoms) can be observed. Recent data show a significant decrease in the use of short-chain phthalates, for which the regulations have resulted in European-level restrictions on

[8] http://www.elfe-france.fr/index.php/fr/

[9] Inserm collective expert appraisal report on "Reproduction and the environment" published in 2011 relying on the available scientific data from the second half of 2010; section VIII deals with perfluorinated compounds

use in products in the last few years. Long-chain phthalates, which still have few restrictions, thus seem to be an alternative to short-chain compounds.

In addition to the list of ten phthalates mentioned in the DGS request (see above), ANSES considered, based on hearings with plastics industry representatives and researchers specialising in reproductive toxicology, that other compounds should be covered by the expert appraisal, whether from a toxicological viewpoint or as regarding their uses.

These substances are as follows: di-propyl-heptyl phthalate (DPHP) (CAS No 53306-54-0), diisoundecyl phthalate (DIUP) (CAS No 26761-40-0), dicyclohexyl phthalate (DCHP) (CAS No 84-61-7), diisooctyl phthalate (DIOP) (CAS No 27554-26-3), ditridecyl phthalate (DTDP) (CAS No 119-06-2), di-n-heptyl phthalate (DHPP) (CAS No 3648-21-3), di-iso-heptyl phthalate (DiHP) (CAS No 71888-89-6), di-n-octyl phthalate (DnOP) (CAS No 117-84-0), di-undecyl phthalate (DUP) (CAS No 3648-20-2), diallyl-phthalate (DAP), butyl-octyl phthalate (BOP) (CAS No 84-78-6), dibenzyl phthalate (DBzP) (CAS No 523-31-9), dipropyl phthalate (DiPrP) (CAS No 605-45-8).

In France, an industry study was undertaken by ANSES that highlighted the following points:

- Short-chain phthalates: no specific uses were identified for mono-n-butyl phthalate (MnBP), dipropyl phthalate (DPP), di-n-hexyl phthalate (DnHP) or di-n-pentyl phthalate (DnPP). Note that mono-n-butyl phthalate (MnBP) is a biological metabolite of DBP and BPP, which explains why no uses were identified for this compound in the industry study. According to the manufacturer responses in the industry survey, di-2-ethylhexyl phthalate (DEHP), dibutyl phthalate (DBP), di-isobutyl phthalate (DIBP) and butyl benzyl phthalate (BBP) are mainly used as plastifiers, which are then used in various rubber articles, glues, interior fittings (floor and wall coverings, cables, shower curtains, coated fabrics, etc.), plastic bags and diary covers.
- Long-chain phthalates: several uses were identified for di-isononyl phthalate (DINP), di-isodecyl phthalate (DIDP) and di-propylhelptyl phthalate (DPHP). These are used in particular in rubber and in many other industry sectors and products (glues, sealants, etc.).

This trend will need to be confirmed by an updated industry study dealing more specifically with compounds for which there is little available information.

Levels of phthalates in various products and media

Regarding contamination in food and in water intended for human consumption, the data already available or currently being acquired for certain compounds in the class of phthalates will indicate whether or not they are found in foods and in WIHC. The results of current studies will enable a better quantification of dietary exposure including exposure from drinking water. However, a number of latest-generation phthalates have not been addressed in such studies. Work is being undertaken at the Agency under the guidance of the Nancy Laboratory for Hydrology in order to characterise national levels of phthalates in distributed water and bottled water.

Regarding contamination in air (indoor and outdoor) and dust, there are French data on homes and schools for BBP, DBP, DEHP, DiBP and DiNP. Di-ethyl phthalate (DEP), di-methyl phthalate (DMP) and di-methyl ethyl phthalate (DMEP) (not targeted in the DGS request) were also measured in these studies. By 2015-2016, other ongoing studies will provide nationwide data on exposure to these phthalates for primary residences on the one hand and for preschools and elementary schools on the other hand (continental France in both cases). Furthermore, few data on contamination in outdoor air were identified in the scientific literature.

Regarding phthalates that have not been measured in these media in France:

- Considering that little information was obtained in the industry study for DnPP, DnHP, DPP and DPHP, use of these substances in France will need to be confirmed in order to assess the need to acquire exposure data. This recommendation also applies to phthalates that have not been subject to an industry study (DiUP, DCHP, DiOP and DTDP).
- Regarding DiDP, measurements in air and dust in France can already be recommended in light of the results of the industry study.
- Pending French measurements, consideration could be given to assessing the quality of studies available in other countries and possibly extrapolating their results to the French situation, in order to use them for future expert appraisal work.

Biosurveillance data

Some phthalate compounds can generate common metabolites that can be complicated to monitor through biosurveillance studies.

- All of the available exposure data should make it possible to identify at-risk populations, e.g. people with behaviour, eating habits or professional activities resulting in potentially at-risk situations of exposure.
- Data are available regarding biological concentrations in the French population for DEHP, DBP, etc. (ELFE study). However, the characterisation of this class of substances in all its diversity, from technical formulations to degradation products, needs to be improved in order to better understand this class of contaminants in all its complexity[10].

Toxicity data

Long-chain phthalate substances are generally considered to be less toxic than short-chain compounds (<C8), even though few studies document their effects on the environment and on humans. However, the data are still highly lacking in this area.

- Regarding experimental studies, recent studies examining the effects of phthalates on the male reproductive system raise some issues:
  While toxicity reference values for phthalates are often based on the anti-androgenic effect of these products in foetal male rats, a growing number of data show that anti-androgenic activity in the foetal testis is not affected by phthalates in humans. This raises questions regarding the relevance of extrapolating experimental data obtained in rats to humans.

- A review of *in vivo* studies on the possible impact of phthalates on obesity and metabolism suggests that an exhaustive analysis of the literature will need to be undertaken to clarify the obesogenic potential of phthalates and the impact on the occurrence of other metabolic disorders. Lastly, some studies suggest that there may be later effects in adulthood after neonatal exposure; this is referred to as the Developmental Origins of Health and Disease (DOHaD) approach, where effects can occur even after several generations, indicating a transgenerational modification to the epigenome. Such possibilities should be explored to confirm or refute these results.

- Furthermore, ubiquitous exposure provides justification for taking into account the effects related to combined exposure to several of these substances.

[10] http://www.elfe-france.fr/index.php/fr/

Conclusions and outlook

The use of certain compounds in the classes of perfluorinated compounds and phthalates is regulated through application of the REACh Regulation and/or sector-specific regulations. Some other compounds in these two classes have not yet been assessed in a regulatory framework at European level.

The survey of available data on certain substances shows they are used for a wide variety of purposes, resulting in the contamination of several environmental compartments and foods.

This therefore raises the issue of assessing exposure to certain substances in the general population and in workers, as well as potential health risks.

The results of the expert appraisal studies in progress at ANSES, dealing in particular with food contamination (iTDS, CONTREPERF studies), and of biosurveillance studies undertaken elsewhere in France will lead the Agency to assess the contribution of various media to internal exposure, and assess the risks to human health using an aggregate approach taking into account all exposure routes.

The perfluorinated compounds in question include PFOS and PFOA, and for phthalates, they include DEHP, BBP and DIDP. This will involve in particular comparing observed exposure levels with reference values where applicable.

Some substances do not currently have toxicity reference values (TRVs), even though their toxicity has been documented. Therefore, ANSES will mandate the Expert Committee on Characterisation of substance hazards and toxicity reference values with a view to proposing TRVs taking into account their reprotoxic and/or ED effects. The perfluorinated compounds in question include PFHxA, PFHxS, PFBA and PFBS, and for phthalates, they include DIBP, DnOP and DIOP.

The Director General

Marc Mortureux