

COLLECTIVE EXPERT APPRAISAL: SUMMARY AND CONCLUSIONS

Related to the establishment of a Toxicity Reference Value based on the reprotoxic effects of nonylphenols

AFSSET Solicited Request No. 2003/AS03

Only the French language version of this document shall prevail.

Overview of the question

AFSSET's work programme on reprotoxic TRVs included organisation of a pilot phase to ensure implementation of the recommended development method. Reprotoxic TRVs were developed as part of the submissions for linuron, di-n-butyl phthalate (DnBP), benzyl butyl phthalate (BBP), nonylphenols, toluene and ethylene glycol ethyl ether (EGEE).

On 25 July 2007, the Directorate General for Health (DGS) requested that AFSSET validate these TRVs through a collective expert appraisal.

Organisation of the expert appraisal

AFSSET entrusted validation of these TRVs to the Expert Committee (CES) for "Assessment of risks linked to chemical agents". This CES mandated a *rapporteur* to conduct an expert appraisal of nonylphenol, which was carried out in accordance with the French Standard NF X 50-110 "Quality in Expertise Activities - General Requirements of Competence for Expert Appraisals".

Description of the method

Based on the document "*Construction d'une VTR reprotoxique pour le nonylphénol* [Development of a reprotoxic TRV for nonylphenol]" prepared by the toxicology laboratory team at the University of Western Brittany¹, the *rapporteur* assessed the compliance of the method used compared with the recommendations of the Working Group on the following points: i) information retrieval and ii) toxicity profile, in order to select the critical effect and source study to use. He then gave his opinion about the choices made in light of the available data.

The establishment of TRVs differs depending on the assumption made or data acquired on the substance's mechanism of toxic action. Currently, the default hypothesis is to consider a monotonic relationship between exposure, or dose, and effect, or response. On the basis of current knowledge and conventions, it is generally accepted that for reprotoxic effects, toxicity is expressed only above a threshold dose (with the exception of germ cell mutagenicity). Nevertheless, this assumption may be questioned if warranted by the available data.

¹ Annex 2 of the reference document for the development of a TRV based on reprotoxic effects

Mathematically, the establishment of a TRV is therefore defined as follows²:

$$TRV = \frac{\text{Critical dose}}{UF} \text{ where} \quad \begin{array}{l} \text{Critical dose} = \text{NOAEL, LOAEL or BMDL} \\ UF = \text{globally applied uncertainty factor} \end{array}$$

In practice, establishment of the TRV involves the following four steps:

- choice of the critical effect;
- choice of a good quality scientific study usually enabling establishment of a dose-response (or dose-effect) relationship;
- choice or establishment of a critical dose from experimental doses and/or epidemiological data;
- application of uncertainty factors to the critical dose to account for uncertainties.

This method is detailed in the reference document for the establishment of a TRV based on reprotoxic effects (AFSSET, December 2006), and establishment of the TRV for nonylphenol is based on this method.

As a result of its internal discussions, the CES has reached a decision about the choice of the critical dose and uncertainty factors. The CES emphasised the need to refer back to the supplemental studies which, while they are not directly used to identify the critical dose, are useful for choosing uncertainty factors (toxicokinetic studies, availability of other NOAELs or LOAELs, etc.).

Results of the collective expert appraisal

Summary of toxicity data

This part is based on a summary of the work carried out by the submitter in 2006 as part of the pilot phase. For more information, the reader can refer to the “*Document de référence pour la construction d’une valeur toxicologique de référence fondée sur des effets reprotoxiques – annexe 2*” [Reference document for the development of a Toxic Reference Value based on reprotoxic effects – Annex 2]. The report is based on monographs written previous to this work by national organisations and on literature published subsequent to these monographs.

Nonylphenols make up a family of compounds with the chemical formula $C_6H_4(OH)C_9H_{19}$ with a benzene ring and a nine-carbon linear or branched chain. Branched nonylphenols have a main chain of up to eight carbon atoms at the most; the degree of branching and their positions vary widely depending on the isomers. The primary compounds are:

- linear 4-nonylphenol, 4-n-nonylphenol or p-nonylphenol (CAS No. 104-40-5),
- branched 4-nonylphenol (CAS No. 84852-15-3),
- n-nonylphenol (mixture of isomers with a linear alkyl chain) (CAS No. 25154-52-3),
- branched nonylphenol (mixture of isomers with a branched alkyl chain) (CAS No. 90481-04-2).

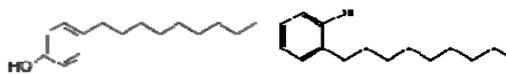
² NOAEL: “no observed adverse effect level”; LOAEL: “lowest observed adverse effect level”; BMDL: “benchmark dose lower confidence level”

LINEAR NONYLPHENOL

Linear 4-nonylphenol
(CAS No.104-40-5)



n-nonylphenol, mixture of isomers with a linear alkyl chain
(CAS No.25154-52-3)

**BRANCHED NONYLPHENOL**

Branched 4-nonylphenol
(CAS No.84852-15-3)



Branched nonylphenol ramifié, mixture of isomers with a branched alkyl chain
(CAS No.90481-04-2)

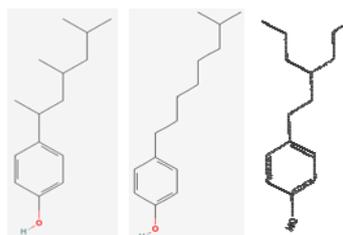


Figure 1 : Chemical formulas of the primary compounds

The data reported below refer to both the linear and branched forms. In this expert summary, the term nonylphenol, if not specified, covers all types of nonylphenol.

Nonylphenol is mainly used for manufacturing surfactants (NP polyethoxylates) contained in consumer products (household products, personal care products, etc.), and for producing resins or plastics, including food-grade plastics. The general population can be exposed during the use of common consumer products. The route of exposure may thus be respiratory (household products), dermal (personal care products), or oral (due to the migration of nonylphenol into food from food contact materials or drinking water). The European evaluation conducted on linear and branched nonylphenols (CAS Nos. 84852-15-3 and 25154-52-3) in 2002 concluded that the main route of exposure is oral (EU, 2002).

Since 2004 (the 29th Adaptation to Technical Progress [ATP]) branched 4-nonylphenol (CAS No. 84852-15-3) and n-nonylphenol (CAS No. 25154-52-3) have been classified by the European Union as Category 3 substances that are reprotoxic to development and reproduction in humans (R63: possible risk of harm to the unborn child and R62: possible risk of impaired fertility). Both of these compounds are also classified as harmful (R22: harmful if swallowed), corrosive (R34: causes burns), and dangerous for the environment (R50/53: very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment).

Toxicokinetics

Few toxicokinetic data are currently available. In animals, absorption of nonylphenol through the digestive tract would be rapid and most likely high. Primary metabolism occurs through glucuro- and sulfo-conjugation. The main means of excretion are in the faeces and urine. Nonylphenol has been found unchanged in the bile of rats exposed to high doses, evidence of metabolic saturation or excretion of the parent compound concomitant with metabolism. In humans, bioavailability by oral route has been estimated at approximately 20%. The metabolites shown in rats and humans are qualitatively identical between these species.

Health effects

Following chronic exposure by oral route, renal effects have been shown at low doses (15 mg/kg body weight/day) in rats. Reprotoxic and developmental effects have also been shown for exposures of the same order of magnitude and it would seem appropriate to take these effects into account for the establishment of specific reprotoxic TRVs.

No human data are available.

- *Nephrotoxic effects*

A repeated dose toxicity study (90 days) conducted in rats by oral route showed a decrease in weight gain and food intake, as well as histological evidence of damage to the liver (cell necrosis) and kidneys (mineralisation recorded during a second anatomopathology examination) at a dose of 140 mg/kg bw/d of branched 4-nonylphenol (CAS No. 84852-15-3) (Canadian Medical Association [CMA], 1997, Cunny *et al.*, 1997). A NOAEL of 50 mg/kg bw/d was identified.

During a three-generation study (US National Toxicology Program [NTP], 1997, Chapin *et al.*, 1999) in which Sprague-Dawley rats were exposed by oral route to branched 4-nonylphenol (CAS No. 84852-15-3), a decrease in weight gain and increase in kidney weight were observed at 50 mg/kg bw/d. In addition, from 15 mg/kg bw/d for all generations, degenerative lesions and no dose-dependent renal tubule dilation were noted.

- *Reprotoxic effects*

The reprotoxic effects of nonylphenol have been reported in rats exposed over several generations or during exposure *in utero*. The effects observed at lower doses were disruption of the reproductive system of neonates (early vaginal opening, and decreased ovarian weight and sperm count), almost certainly without functional impairment of reproduction and fertility, and changes in the epididymides due to exposure during gestation [EU, 2002].

These reprotoxic effects in neonates were observed alongside changes in the liver and kidneys of parents when several generations were exposed (Nagao *et al.*, 2001). On the basis of current knowledge, it is not possible to establish a causal link between the general toxicity observed in the Filial (F) 0 generation (histological evidence of hepatic and renal changes) and the reprotoxicity shown in generation F1. As a precaution, a TRV based on reprotoxic effects may be proposed.

From a review of the literature, and based on the latest data, several good quality reprotoxicity studies conducted in animals have been selected. They are considered representative of the reprotoxic effects observed and are summarised below. Other studies were conducted by the intraperitoneal route. They were not considered relevant for the establishment of a reprotoxic TRV because the method of administration (intraperitoneal route) is not representative of actual conditions of exposure in the embryo.

- Pre- or postnatal toxicity studies

The initial study conducted in Wistar rats exposed to nonylphenol from the 9th to the 15th gestation day showed no toxicity for development up to 300 mg/kg bw/d (Initiative Umweltrelevante Altstoffe [Initiative of the Advisory Committee on Existing Chemicals of Environmental Relevance] 1992).

The second study was conducted in Wistar rats exposed *in utero* to linear 4-nonylphenol (CAS No. 104-40-5) by oral gavage of the dam from the 11th to the 18th gestation day to doses of 0, 3, 15 and 75 mg/kg bw/d (Hossaini *et al.*, 2001). The effects were observed after birth in F1 at Day (D) 11, D21 and D110. At D110, a dose-dependent decrease in absolute weight of the right epididymis was observed from an exposure of 15 mg/kg bw/d. A NOAEL of 3 mg/kg bw/d was identified.

In the third study, Sprague-Dawley rats were exposed from the 7th gestation day (GD7) to the 10th postnatal week, by oral gavage, to linear 4-nonylphenol (De Jager *et al.* 1999). The authors observed mortality and a decrease in absolute weight of the testicles and epididymis, a decrease in seminiferous tubule diameter and basal epithelium thickness at 100 mg/kg bw/d, in the presence of mortality. A decrease in sperm count was also observed, but at 250 mg/kg bw/d. No NOAEL could be identified.

Recently, Moon *et al.* (2007) conducted a study on the effects of oral exposure to a mixture of branched isomers of nonylphenol, at doses of 0, 10 and 100 mg/kg bw/d, on mammary gland development in Long Evans rats. The dams were exposed to branched nonylphenol from the 15th to the 19th gestation day and the effects were observed in F1 females at the 4th, 22nd, 33rd, 41st and 66th postnatal day (D4, D22, D33, D41 and D66, respectively). At 100 mg/kg bw/d, the observed effects were an increase in uterine weight (D41), an increase in rates of branching of the primary to the secondary ducts (D4), an increase in the number of alveolar buds and differentiation of terminal end buds in alveolar buds (D33). From 10 mg/kg bw/d, a decrease in primary branching from the mammary gland collecting duct and delayed mammary epithelium migration to the lymph node (D22) was observed.

Endocrine effects were also observed at D41 with a decrease in pituitary luteinising hormone (LH), an increase in the number of oestrogen receptors in the stroma and epithelium of the mammary glands and in the uterus, and an increase in the number of prolactin receptors in the mammary glands at the dose of 100 mg/kg bw/d. An increase in the number of progesterone receptors in the epithelium of the mammary glands and in the uterus at 10 mg/kg bw/d and a decrease at 100 mg/kg bw/d could be noted. At 10 and 100 mg/kg bw/d, a decrease in pituitary thyroid stimulating hormone (TSH) was observed. Thus, by taking all these effects into account, a LOAEL of 10 mg/kg bw/d can be proposed. No NOAEL was identified.

- Study of toxicity over several generations

In the NTP study (1997) published by Chapin *et al.* in 1999, Sprague-Dawley rats were exposed by oral route to 0, 15, 50 and 160 mg/kg bw/d (0, 200, 650 and 2000 parts per million [ppm]) of branched 4-nonylphenol (CAS No. 84852-15-3). Exposure was continued over three generations (from Week 7 for F0 to Week 8 for F3). Fertility and mating were normal. Lengthening of the oestral cycle at 160 mg/kg bw/d (in F1 and F2) and early vaginal opening at 50 and 160 mg/kg bw/d (in F1, F2 and F3) were noted, as well as decreased ovarian weight (with no histological evidence of damage), decreased epididymal sperm density and spermatid count in F2. The explanation for these changes in sperm is uncertain. Disruption of the reproductive system appeared to be minor and had no impact on fertility. A NOAEL for reprotoxic effects was identified at 15 mg/kg bw/d. These effects were also accompanied by a general toxicity with a decrease in weight gain and an increase in kidney weights at 50 and 160 mg/kg bw/d. The NOAEL observed in this study was 15 mg/kg bw/d for effects on reproduction.

In the study by Nagao *et al.* (2001), Sprague-Dawley rats were exposed to a mixture of linear isomers of nonylphenol (CAS No. 25154-52-3) by oral gavage at doses of 0, 2, 10 and 50 mg/kg bw/d.

In the latter dose group (50 mg/kg bw/d), a decrease in body weight was shown in the parental generation, but it was not significant. An increase in liver and kidney weights, associated in the parental generation (F0) with histological changes (centrilobular hypertrophy, eosinophilic bodies), was also observed at this dose. The authors concluded that there was no clear toxicological significance, which was also suggested in other studies (Cunny *et al.*, 1997).

In F0 and F1 females, a significant decrease in absolute and relative ovarian weights was observed at 50 mg/kg bw/d without associated histological evidence of damage. In F1 generation females, a statistically significant decrease in serum LH (5.5 ng/mL *versus* 7.2 ng/mL in control batches, $p < 0.05$) and early vaginal opening (at postnatal day [PND] 31.5 on average *versus* 33.4 in the controls, $p < 0.01$) was observed at the highest dose tested. A statistically significant decrease ($p < 0.05$) in the number of young per litter (11.5 *versus* 13.5 on average in

the controls) and in the number of implantation sites (12.5 *versus* 14.9 on average in the controls) was observed at 50 mg/kg bw/d in the F2 generation. An increase in testosterone levels in males and uterus weight in females of the parental generation (F0) was reported at 2 mg/kg bw/d, but was not observed at higher doses. An increased prostate weight in males before weaning and a decrease in levels of follicle stimulating hormone [FSH] in adult males were observed at 2 mg/kg bw/d in generation F1. These effects were not demonstrated at higher doses (10 and 50 mg/kg bw/d). The authors propose a NOAEL of 10 mg/kg bw/d for these reprotoxic effects.

All animal studies selected were conducted according to strict protocols (following OECD or equivalent guidelines). These studies were therefore given a Klimisch rating of 1 and can be considered in the establishment of a TRV.

Mechanism of action

Only the mechanism of action related to reprotoxic effects was investigated. A uterotrophic response and an early vaginal opening were clearly shown during *in vivo* studies in immature or ovariectomised female rats, confirming the oestrogenic activity of nonylphenol. Studies conducted *in vitro* confirm this activity, which would be 10^3 to 10^6 times lower than that of 17- β -oestradiol [EU, 2002].

The uterotrophic assay in the female rat is a recognised test that predicts endocrine disrupting effects in humans. Thus, in light of all available data, the reprotoxic effects observed in animals could also be observed in humans.

Analysis and assessment of the choices for establishment of the TRV

Since there are several forms of nonylphenol, the CES recommended developing two TRVs: one for the forms with a linear alkyl chain and the other for forms with a branched alkyl chain.

Branched nonylphenol (CAS Nos. 90481-04-2 and 84852-15-3)

- *Choice of the critical effect*

Branched nonylphenol has shown oestrogenic activity in both *in vitro* (10^3 to 10^6 times lower than that of oestradiol) and *in vivo* studies. The various studies reviewed showed oestrogenic activity during exposure *in utero* over several generations. These studies highlighted the effects on the ovaries (decreased ovarian weights without histological damage) and on the sperm of offspring (decreased epididymal sperm density and spermatid count), early vaginal opening, and effects on mammary gland development (a decrease in primary branching of the mammary gland collecting duct and delayed mammary epithelium migration to the lymph node at the 22nd day after birth). These effects are consistent with the oestrogenic activity shown. They may be considered as critical effects due to:

- their biological plausibility and the link shown with the mechanism of action of nonylphenol; and
- the good scientific quality of the studies demonstrating these effects.

It should be noted that effects on the mammary gland appear to be the most sensitive markers since they are observed at the lowest doses (LOAEL = 10 mg/kg bw/d). **The CES has thus chosen effects on the mammary gland as the critical effect.**

- *Source study*

Two previously described studies (Chapin *et al.*, 1999; Moon *et al.*, 2007) can be considered for the branched nonylphenol compounds. A comparative table of these two studies is given in Annex 3.

The choice of the study by **Moon *et al.* (2007)** for the establishment of a reprotoxic TRV for branched nonylphenol is based on:

- taking into account the most sensitive toxic effect: a LOAEL of 10 mg/kg bw/d was highlighted in the study by Moon *et al.* (2007) for effects on mammary glands while the

fertility study by Chapin *et al.* (1999) showed a NOAEL of 15 mg/kg bw/d for other oestrogenic effects. Chapin *et al.* did not study the effects on mammary glands. The choice of the study by Moon *et al.* provides protection against the effects that appeared at the highest doses in the Chapin study.

- the quality of the study was considered acceptable by the experts, even though it did not follow all the OECD recommendations (OECD Test Guideline 414).
- *Choice of the critical dose*

Of the two selected studies, the one which allowed effects to be observed at lower doses (Moon *et al.*, 2007) was used by the experts to derive the critical dose.

The LOAEL of 10 mg/kg bw/d derived from this study was therefore proposed as the critical dose.

No benchmark dose (BMD) was proposed from this study due to the methodological difficulties encountered in choosing the level of response given the context of continuous responses.

- *Choice of uncertainty factors*
 - UF_A: inter-species variability: the factor used is the maximum factor of 10 because there are no data in humans.
 - UF_H: intra-species variability: the factor 10 is chosen by default when using studies conducted in animals, to take into account the greater variability within the human species.
 - UF_L: use of a LOAEL: According to the method of developing TRVs based on toxic effects for reproduction and development, AFSSET recommends a factor of 3 or 10 depending on the case. The CES proposes a factor of 3 because the LOAEL from the study by Moon is lower than those established in other studies, suggesting that the effects selected are very sensitive.
 - UF_D: insufficiency of data: not applicable, as data were judged to be sufficient.

Linear nonylphenol (CAS Nos. 25154-52-3 and 104-40-5)

- *Choice of the critical effect*

Linear nonylphenol has shown oestrogenic activity in both *in vivo* and *in vitro* studies, 10³ to 10⁶ times lower than that of oestradiol. Multigenerational studies of good scientific quality have identified **effects on vaginal opening and on the ovaries** from 50 mg/kg bw/d, with no functional change in reproduction. These effects are consistent with the oestrogenic activity identified. They may be considered as critical effects due to:

- their biological plausibility and the link shown with the mechanism of action of nonylphenol; and
- the good scientific quality of the studies showing these effects.

- *Source study*

The two studies chosen, described above (see the section on reprotoxic effects), concerning linear nonylphenol are those by Hossaini *et al.* (2001) and by Nagao *et al.* (2001). A table comparing these two studies is given in Annex 4.

These two studies are of good quality (Klimisch 1). In the study by Hossaini *et al.* (2001), only the decrease in absolute weight of the right epididymis was reported by the authors as being statistically significant. Consequently, the study will not be considered for the establishment of the TRV. Thus, the study by **Nagao *et al.* (2001)**, which showed oestrogenic activity in female F1 rats exposed to linear nonylphenol, was chosen as the key study for developing the TRV.

- *Choice of the critical dose*

In the chosen study (Nagao *et al.*, 2001), decreased serum LH and ovarian weight, and early vaginal opening were observed at 50 mg/kg bw/d, the dose corresponding to the LOAEL.

It is important to emphasise that other biological changes appear at the lowest dose. Indeed, a decrease in FSH was observed in F1 generation males at 2 mg/kg bw/d, but not at higher doses (224 ng/mL vs. 302 ng/mL in the control batches). The authors note that the data on hormone levels must be interpreted with care until newer studies can confirm their results. Similarly, an increase in the relative and absolute weight of the prostate and seminal vesicle was reported for the single dose of 2 mg/kg bw/d (respectively, 12.8±2 mg vs. 11.4±2.2 mg in the controls and 76.4±13.6 mg vs. 68.4±12.9 mg in the controls).

The CES has chosen the NOAEL of 10 mg/kg bw/d proposed by the authors as the critical dose.

No benchmark dose (BMD) was proposed from this study due to the methodological difficulties encountered in choosing the level of response given the context of continuous responses.

However, the CES believes the pair of LOAEL / NOAEL values can be considered for establishment of the TRV. The minor difference between the two values supports the accuracy of the TRV.

- *Choice of uncertainty factors*

- UF_A: inter-species variability: the factor chosen is the maximum factor of 10 because there are no data in humans.
- UF_H: intra-species variability: the factor 10 is chosen by default when using studies conducted in animals, to take into account the greater variability within the human species.
- UF_L: use of a LOAEL: not applicable.
- UF_D: insufficiency of data: in the chosen study (Nagao *et al.*, 2001) numerous effects were examined but not those on the mammary gland. Nevertheless, these effects seem to occur at much lower levels, of about 10 mg/kg bw/d as shown by the Moon *et al.*, 2007 study on branched nonylphenol. Thus, the CES proposes a factor of three due to the lack of data on the mammary gland.

The Expert Committee (CES) for “Assessment of risks linked to chemical agents” accepted the report of the collective expert appraisal at its meeting on 22 January 2009 and informed the Directorate General of AFSSET.

Conclusions and recommendations of the collective expert appraisal

- ▶ Nonylphenol is a family of compounds that have been the subject of several reprotoxicity studies in rodents. Two TRVs have been developed, one for linear compounds and one for branched compounds.
- ▶ No human data are available.
- ▶ The standard assumption is to consider the effects observed in rats as relevant for humans and that oestrogenic-type effects can be considered as critical effects. The mechanism advanced (oestrogenic action) is plausible and correlated to the effects shown.
- ▶ Although the objective is to develop a reprotoxic TRV, other effects, such as nephrotoxic effects, are likely to occur at comparable dose levels.

- ▶ The European report decided on a NOAEL of 15 mg/kg bw/d for reproductive effects based on the NTP, 1997 study. The studies chosen here, to develop the TRV, are more recent and thus could not have been taken into account in the European report.

The CES thus proposes establishing two TRVs, one for linear and one for branched nonylphenols, specifically for the effects on development and reproduction. Given the demonstrated effects on development, which indicate endocrine disruption and whose window of critical exposure corresponds to the gestation period, the TRV will be applicable for sub-chronic exposure.

-- Branched nonylphenol CAS Nos. 90481-04-2 and 84852-15-3 --			
Critical effect	Critical dose*	UF**	TRV
Effects on mammary gland development Study of developmental toxicity by oral exposure in Long Evans rats Moon <i>et al.</i> , 2007	LOAEL = 10 mg/kg bw/d No BMDL established	300 UF _A 10 UF _H 10 UF _L 3	TRV = 0.03 mg/kg/d Confidence level Data collection: high Study: high Critical dose: average (No NOAEL) TRV: average

*Time conversion factors, allometric coefficients: NIL.

**UF = uncertainty factors. UF: overall uncertainty factor (applied), UF_A: inter-species variability, UF_H: individual variability

-- Linear nonylphenol Nos. CAS 25154-52-3 and 104-40-5 --			
Critical effect	Critical dose*	UF**	TRV
Decreased serum LH, early vaginal opening (F1) Toxicity study in two generations of Sprague Dawley rats exposed by oral gavage Nagao <i>et al.</i> , 2001	LOAEL = 50 mg/kg bw/d NOAEL = 10 mg/kg bw/d No BDML established	300 UF _A 10 UF _H 10 UF _D 3	TRV = 0.03 mg/kg/d Confidence level Data collection: average (Lack of mammary gland study) Study: high Critical dose: high TRV: average

*Time conversion factors, allometric coefficients: NIL.

**UF = uncertainty factors. UF: overall uncertainty factor (applied), UF_A: inter-species variability, UF_H: individual variability

Recommendations of the CES

The CES emphasises that the same information is not available with which to establish TRVs for both types of nonylphenol. In fact, the TRV for branched nonylphenol is based on effects on development of the mammary gland (Moon *et al.*, 2007) whereas these effects were not investigated specifically for linear nonylphenol in the study by Nagao *et al.* Thus, the CES recommends scientific monitoring, which would enable the TRV for linear nonylphenol to be re-evaluated as new data are published that take this type of effect into account.

The CES did not wish to apply an allometric adjustment³ to the critical dose because this type of adjustment has not yet undergone extensive study in France and the reference document for developing the TRVs based on reprotoxic effects has not yet addressed this issue. The need for a better understanding of animal-human transposition and of the UF_A uncertainty factor led to the recommendation that further consideration be given to this aspect.

Lastly, the CES recommends studying the effects of different nonylphenol isomers in isolation to assess the influence of the length of the main chain and enable a comparison of the toxic effects of exposure to these structurally similar chemicals.

Maisons-Alfort, 06 March 2009

On behalf of the Expert Committee (CES) for
"Assessment of risks linked to chemical agents",

Chairman of the CES

M. Michel Guerbet

³Some agencies occasionally recommend "human equivalent" critical doses or concentrations by applying adjustments that take into account differences in body surface areas during oral exposure or other specific physiological parameters of the respiratory route. These adjustments have not yet been adequately discussed within the French Working Groups.