COLLECTIVE EXPERT APPRAISAL:
SUMMARY AND CONCLUSIONS

Regarding the "expert appraisal for recommending occupational exposure limits for chemical agents"

Assessment of health effects and methods for the measurement of exposure levels in workplace atmospheres for

butylbenzyl-phthalate (CAS n° 85-68-7)

This document summarises the work of the Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee) and the Working Groups on health effects and on metrology.

Presentation of the issue

On 12 June 2007, AFSSET, which became ANSES in July 2010, was requested by the Directorate General for Labour to conduct the expert appraisal work required for setting occupational exposure limit values (OELVs) for butylbenzyl-phthalate.

France does not currently have any (8-hour or 15-minute) exposure limit values for butylbenzyl-phthalate.

The Directorate General for Labour asked ANSES to assess this substance and, if necessary, propose occupational exposure limits based on health considerations for butylbenzyl-phthalate.

Scientific background

The French system for establishing OELVs has three clearly distinct phases:

- Independent scientific expertise (the only phase entrusted to ANSES);
- Proposal by the Ministry of Labour of a draft regulation for the establishment of limit values, which may be binding or indicative;
- Stakeholder consultation during the presentation of the draft regulation to the French Steering Committee on Working Conditions (COCT). The aim of this phase is to discuss the effectiveness of the limit values and if necessary to determine a possible implementation timetable, depending on any technical and economic feasibility problems.

The organisation of the scientific expertise phase required for the establishment of Occupational Exposure Limits (OELVs) was entrusted to AFSSET in the framework of the 2005-2009 Occupational Health Plan (PST) and then to ANSES after AFSSET and AFSSA merged in 2010.

The OELs, as proposed by the Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee), are concentration levels of pollutants in

workplace atmospheres that should not be exceeded over a determined reference period and below which the risk of impaired health is negligible. Although reversible physiological changes are sometimes tolerated, no organic or functional damage of an irreversible or prolonged nature is accepted at this level of exposure for the large majority of workers. These concentration levels are determined by considering that the exposed population (the workers) is one that excludes both children and the elderly.

These concentration levels are determined by the OEL Committee experts based on information available from epidemiological, clinical, animal toxicology studies, etc. Identifying concentrations that are safe for human health generally requires adjustment factors to be applied to the values identified directly by the studies. These factors take into account a number of uncertainties inherent to the extrapolation process conducted as part of an assessment of the health effects of chemicals on humans.

The Committee recommends the use of three types of values:

- 8-hour occupational exposure limit (8h-OEL): this corresponds to the limit of the time-weighted average (TWA) of the concentration of a chemical in the worker's breathing zone over the course of an 8-hour work shift. In the current state of scientific knowledge (toxicology, medicine, epidemiology, etc.), the 8h-OEL is designed to protect workers exposed regularly and for the duration of their working life from the medium- and long-term health effects of the chemical in question;
- Short-term exposure limit (STEL): this corresponds to the limit of the time-weighted average (TWA) of the concentration of a chemical in the worker's breathing zone over a 15-minute reference period during the peak of exposure, irrespective of its duration. It aims to protect workers from adverse health effects (immediate or short-term toxic effects such as irritation phenomena) due to peaks of exposure;
- Ceiling value: this is the limit of the concentration of a chemical in the worker's breathing zone that should not be exceeded at any time during the working period. This value is recommended for substances known to be highly irritating or corrosive or likely to cause serious potentially irreversible effects after a very short period of exposure.

These three types of values are expressed:

- either in $mg.m^{-3}$, i.e. in milligrams of chemical per cubic metre of air and in ppm (parts per million), i.e. in cubic centimetres of chemical per cubic metre of air, for gases and vapours;
- or in $mg.m^{-3}$, only for liquid and solid aerosols;
- or in $f.cm^{-3}$, i.e. in fibres per cubic centimetre for fibrous materials.

The 8h-OELV may be exceeded for short periods during the working day provided that:

- the weighted average of values over the entire working day is not exceeded;
- the value of the short term limit value (STEL), when it exists, is not exceeded.

In addition to the OELs, the OEL Committee assesses the need to assign a "skin" notation, when significant penetration through the skin is possible (Anses, 2014). This notation indicates the need to consider the dermal route of exposure in the exposure assessment and, where necessary, to implement appropriate preventive measures (such as wearing protective gloves). Skin penetration of substances is not taken into account when determining the atmospheric limit levels, yet can potentially cause health effects even when the atmospheric levels are respected.

The OEL Committee assesses the need to assign an “ototoxic” notation indicating a risk of hearing impairment in the event of co-exposure to noise and the substance below the recommended

OELs, to enable preventionists to implement appropriate measures (collective, individual and/or medical) (Anses, 2014).

The OEL Committee also assesses the applicable reference methods for the measurement of exposure levels in the workplace. The quality of these methods and their applicability to the measurement of exposure levels for comparison with an OEL are assessed, particularly with regards to their compliance with the performance requirements in the NF-EN 482 Standard and their level of validation.

Organisation of the expert appraisal

ANSES entrusted examination of this request to the Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee). The Agency also mandated:

- The Working Group on health effects to conduct the expert appraisal work on health effects;
- The Working Group on metrology to assess measurement methods in workplace atmospheres.

Several ANSES employees contributed to this work and were responsible for scientific coordination of the different expert groups.

The methodological and scientific aspects of the work of these WGs were regularly submitted to the Expert Committee.

The report produced by the two Working Groups takes account of observations and additional information provided by the Committee members.

This expert appraisal was therefore conducted by experts with complementary skills. It was carried out in accordance with the French Standard NF X 50-110 “Quality in Expertise Activities”.

Preventing risks of conflicts of interest

ANSES analyses interests declared by the experts before they are appointed and throughout their work in order to prevent potential conflicts of interest in relation to the points addressed in expert appraisals.

The experts’ declarations of interests are made public on ANSES's website (www.anses.fr).

Description of the method

For the assessment of health effects:

A summary report was prepared by the Working Group on health effects and submitted to the OEL Committee, which commented on it and added to it.

The data and information in this report were primarily taken from the "European Union risk assessment report. Benzyl butyl phthalate" of the European Commission published in 2007 (EC, 2007) and the INSERM collective expert assessment report entitled "Reproduction et Environnement. Expertise collective" published in 2011 (INSERM, 2011). They were

supplemented by a review of the literature on Medline and Toxline conducted primarily between December 2010 (end of the INSERM1 report bibliography) and July 2012.

For assessment of methods for measuring exposure levels in workplace:

A summary report was prepared by the Working Group on metrology and submitted to the OEL Committee, which added its own comments.

The summary report presents the various protocols for measuring butylbenzyl-phthalate in workplace atmospheres grouped together based on the methods they use. These methods were then assessed and classified based on the performance requirements set out particularly in the French Standard NF EN 482: "Workplace atmospheres - General requirements for the performance of procedures for the measurement of chemical agents" and the decision-making criteria listed in the methodology report (Anses, 2014).

A list of the main sources consulted is detailed in the methodology report (Anses, 2014).

These methods were classified as follows:

- Category 1A: the method has been recognized and validated (all of the performance criteria in the NF-EN 482 Standard are met);
- Category 1B: the method has been partially validated (the essential performance criteria in the NF-EN 482 Standard are met);
- Category 2: the method is indicative (essential criteria for validation are not clear enough);
- Category 3: the method is not recommended (essential criteria for validation are lacking or inappropriate).

A detailed comparative study of the methods in Categories 1A, 1B and 2 was conducted with respect to their various validation data and technical feasibility, in order to recommend the most suitable method(s) for measuring concentrations for comparison with OELs.

The collective expert appraisal work and its conclusions and recommendations were adopted on 13 May 2014 by the OEL Committee (term of office 2014-2017).

The collective expert appraisal work and the summary report were submitted to public consultation from 12/03/2015 to 13/05/2015. The people or organizations who contributed to the public consultation are listed in appendix of the report (only available in French). The comments received were reviewed by the OEL Committee who adopted this version on 7 March 2016.

Results of the collective expert appraisal on health effects

Butylbenzyl-phthalate (BBzP) is a phthalate used primarily as a plasticiser in products containing polyvinyl chloride (PVC). It is also used for the production of other polymers found in sealants, glues, paints, coatings and inks.

Kinetics and metabolism

No data on the toxicokinetics of BBzP in humans or animals after exposure by inhalation were found in the literature. For other routes of exposure (oral and dermal), the human data are limited.

[1] French National Institute for Health and Medical Research

No quantitative data on the absorption of BBzP by inhalation were identified in the literature. Dermal absorption of BBzP is slow. A study in rats shows that 30% to 40% of the amount applied on the skin is absorbed (permeation flow (J): 0.15 to 0.3 µg.cm^{-2}.min^{-1} according to EC, 2007).

The few available data on other phthalates indicate that they are distributed throughout all the body's tissues, with no real preference for a particular organ or retention in a given tissue. There is no evidence of any accumulation of the substance or its metabolites (EC, 2007).

There is only one study that can be used to characterise BBzP metabolism in humans. According to this study, mono-benzyl-phthalate (MBzP) is the main BBzP metabolite found in urine. Indeed, 67% and 78% of ingested BBzP (depending on the administered dose: 253 or 506 µg respectively) were excreted in urine in the form of MBzP. Mono-n-butyl-phthalate (MnBP) was not detected in urine for the lowest dose and its excretion was only 6% at the highest dose.

In rats, BBzP absorbed orally is primarily metabolised into MnBP and MBzP under the action of esterases in the intestinal wall and liver. Unlike in humans, MnBP is the main urinary metabolite of BBzP in rats. The other identified metabolites are hippuric acid, benzyl alcohol and n-butanol.

The half-life of BBzP in humans is not known, but the available data seem to indicate that it is less than 24 hours. Urinary excretion appears to be the preferred route in humans (up to 84% of the administered dose of BBzP can be found in the urine as the two metabolites).

Furthermore, in rats, the excretion kinetics of BBzP metabolites after oral administration are dose-dependent. Indeed, urinary excretion rates are lower when orally administered doses are higher. Furthermore, the excretion levels for these two metabolites have been found to be higher in adult rats than in immature rats.

General toxicity

Toxicity in humans

In the context of establishing an OEL for BBzP, it is important to underline the fact that the available data regarding effects in humans, more particularly after exposure by inhalation, are very limited.

Acute toxicity

No data on the acute toxicity of BBzP were identified in the literature.

Irritation

Mild irritation was observed in 12% of the volunteers who agreed to wear a skin patch containing 10% BBzP (Mallette and Von Haam, 1952 cited by EC, 2007). However, no signs of irritation or sensitisation were found in volunteers after dermal application of a patch containing BBzP (Hammond *et al*., 1987).

Chronic toxicity

Two workplace studies in workers exposed by inhalation to mixtures of several phthalates were reported in the literature (Milkov *et al*., 1973; Nielsen *et al*., 1985). Although undertaken in the workplace, these studies were not specific to BBzP (they dealt with exposure to phthalate mixtures) and cannot be used to identify a dose-response relationship between BBzP exposure and a health effect.

Reproductive toxicity

Several studies have attempted to link phthalate exposure to reproductive system abnormalities (indicators: sperm parameters, early puberty, endometriosis, hormones, etc.) in adults within the general population. These studies do not specifically deal with BBzP (co-exposure to several substances) and cannot be used to identify a dose-response relationship between BBzP exposure and a given effect. Therefore, none of these studies can be used to establish an OEL for BBzP.

Few studies have assessed the possible role that exposure to phthalates may play in female reproductive toxicity. In the specific case of MBzP, two studies did not show any relationship between urinary concentrations of MBzP and endometriosis or uterine leiomyomata in adult women (Itoh *et al*., 2009; Weuve *et al*., 2010).

Several studies have investigated the effects of exposure to phthalates, including BBzP, on *in utero* development. The results of the publication by Swan *et al*., 2005 showed decreased anogenital distance in newborn boys. This study cannot be used for the establishment of an OEL because it does not include measurements of atmospheric BBzP concentrations. Other studies with larger population sizes are necessary to confirm these initial results (INSERM, 2011).

Carcinogenic effects - genotoxicity

No human carcinogenicity studies specific to BBzP were identified in the literature.

In a case-control study by Aschengrau *et al.* (1998), no connection was found between increased incidence of breast cancer and occupational exposure to BBzP (exposure to several oestrogenic compounds).

Toxicity in animals

There are many more data from animal testing than there are for humans. However, it is important to note that the most commonly considered route of exposure is the oral route. Due to the large number of studies, the reader is invited to refer to the collective expert appraisal report for a detailed description of them.

Acute toxicity

No data on the acute toxicity of BBzP by inhalation were identified in the literature.

Irritation

Mild eye irritation lasting 48 hours was observed during a Draize test in rabbits. The results of tests undertaken on rabbit skin show that BBzP is not a skin irritant.

Subchronic toxicity

Three studies on subchronic toxicity by inhalation in Sprague-Dawley rats are described in the review by Hammond *et al*., 1987. The adverse effects observed in the studies by inhalation were

essentially limited to chromodacryorrhoea (porphyrin secretion reflecting a state of stress in rats) and red tears in animals of both sexes at high concentrations (no other details were provided). In the most relevant study (over a 13-week period), the authors reported a statistically significant increase in relative liver and kidney weights (with no other histopathological changes) at the highest concentration (789 $mg.m^{-3}$) in rats of both sexes. A decrease in blood glucose concentrations was also observed in males exposed to 789 $mg.m^{-3}$.

In rats, repeated oral exposure to BBzP results in decreased weight gain, an increase in the relative weight of certain organs (particularly the liver and kidneys) and pathological pancreatic lesions at the lowest doses (120 to 380 mg/kg/day). These lesions affect both the endocrine pancreas (with enlargement, cell vacuolation and peripheral congestion of the Langerhans islets) and the exocrine pancreas (with pyknotic nuclei, acinar atrophy and peri-acinar inflammatory cell infiltration). At higher doses, the following are observed: haematological effects, hepatic peroxisome proliferation, degeneration or lesions in the liver (observed in Wistar rats but not in Sprague-Dawley rats), kidneys and reproductive organs in males, and effects on fertility. In mice and Beagle dogs, only a decrease in body weight gain was observed in the experimental studies.

Reproductive toxicity

Effects on fertility and reproductive organs

Studies in male rats exposed orally to BBzP show toxic effects on male reproduction including lesions in reproductive organs, lowering of sperm concentrations and decreased fertility. These effects are generally observed at doses greater than or equal to 500 mg/kg/day, except in the ten-week NTP study (1997). Indeed, in this study, a decrease in epididymal sperm concentrations was observed from the dose of 200 mg/kg/day (in F0 males). It was not combined with any histopathological changes and fertility was not impaired at this dose. However, at the higher dose (2200 mg/kg/day), lesions in the testes and epididymis, a decrease in sperm concentrations and impaired fertility were observed.

No studies were identified showing a link between BBzP exposure in non-gestating adult females and effects on the reproductive system.

Effects on development

Several studies show that BBzP and its two main metabolites (MnBP and MBzP) have embryotoxic and teratogenic effects in rats and mice. The incidence of these effects varies with the dose and stage of development. The NOAEL[2] values identified for foetal toxicity with oral exposure before the 15th day of gestation, in rats and mice, range from 182 to 500 mg/kg/day. The lowest value is the one determined from the study by Price (1990, cited in NTP-CERHR, 2003) in CD-1 mice.

The strongest effects observed in the male reproductive system due to the anti-androgenic activity of BBzP were found in several recent studies covering the period of sexual differentiation in rats. In a study where the period of exposure in pregnant females range from the 6th to the 20th day of gestation, a Benchmark Dose (BMD) 1% of 163 mg/kg/day ($CI_{95\%}$[3] = 95 to 280 mg/kg/day) was determined for delayed testicular migration and a BMD 5% of 172 mg/kg/day ($CI_{95\%}$ = 126 to 271 mg/kg/day) was determined for a decrease in relative testis weight. The multi-generational study by Tyl *et al*. (2004) resulted in the lowest NOAEL (50 mg/kg/day) based on a decrease in anogenital distance in male offspring observed at 250 mg/kg/day. Therefore, the measurement

[2] No Observed Adverse Effect Level
[3] 95% confidence interval

of anogenital distance currently appears to be the most sensitive marker. It also reflects changes in the development of the male reproductive system due to the anti-androgenic activity of this substance. However, the exposure conditions in this study are not relevant for the establishment of an OEL.

Some studies have demonstrated that *in utero* exposure to high doses of a phthalate alters Leydig cells in rats. For example, inhibition of testosterone secretion and decreased InsL3 (relaxin/insulin-like 3) expression were found in foetal male rats exposed to BBzP (Wilson *et al*., 2004; Howdeshell *et al*., 2008). The consequences of inhibited foetal testosterone production have been clearly identified. For example, various masculinisation defects are described: decreased anogenital distance, the retention of mammary areola or nipples in males, reduced penile length, lower prostate weight and an increase in hypospadias and cryptorchidism (INSERM, 2011).

InsL3 is a hormone that, among other things, induces growth of the gubernaculum testis, a ligament responsible for testicular descent. It therefore seems logical to link, at least partially, the cryptorchidism induced by *in utero* exposure to phthalates to inhibited secretion of this Leydig-cell hormone.

Carcinogenic effects – genotoxicity

In rats, an NTP study (1982) showed an increase in the incidence of lymphocytic leukaemia in female F344 rats exposed to BBzP (dose: 720 mg/kg/day). However, a more recent NTP study (1997) exposing rats of the same strain for two years did not confirm these results (no increase in the incidence of leukaemia). This study showed an increase in the incidence of acinar cell adenoma and adenoma combined with carcinoma and of pancreatic acinar cell hyperplasia in male rats exposed to 500 mg/kg/day. Non-dose-dependent renal lesions were also observed in females.

In mice, a study similar to that in rats undertaken by the NTP did not show any increase in tumour incidence in animals exposed to BBzP (doses: 780 and 1560 mg/kg/day) compared to the controls (NTP, 1982 cited by EC, 2007).

Several phthalates including BBzP are known to induce peroxisome proliferation in the liver of rats and mice, which results in structural modifications after observation with an electronic microscope and changes in the enzymatic activities associated with peroxisomes. A possible relationship between peroxisome proliferation and the occurrence of hepatic tumours in rodents was suggested (Lapinskas, 2005).

However, the results of carcinogenesis studies in animals do not appear consistent with this mechanism of action.

BBzP is not genotoxic with the exception of low clastogenicity in mouse bone marrow cells (*in vivo* test). Based on the results of the many studies on the genotoxicity of BBzP, it is not mutagenic (EC, 2007).

In 1999, the IARC concluded that BBzP could not be classified as carcinogenic to humans (group 3) due to the lack of data in humans and limited evidence in animals (IARC, 1999).

Establishment of OELs

8h-OEL

Choice of critical effects

Since there are no available data in humans that can be used to establish an OEL for BBzP, the toxic effects on the male reproductive system observed in rats appear the most relevant to be taken into consideration.

The results of experimental studies show that the strongest effects are observed in the male reproductive system and are related to the anti-androgenic activity of BBzP. Several studies indicate that *in utero* exposure corresponds to the most susceptible period for these effects. However, the available data, particularly the lowest NOAEL identified in the multi-generational study[4] by Tyl *et al.* (2000), cannot be used to establish an OEL.

Choice of key study and identifying point of departure

Of the experimental studies in animals on the reprotoxic effects of BBzP, the ten-week study by the NTP (1997) exposing male F344 rats to BBzP through feed resulting in a NOAEL[5] of 200 mg/kg/day is the most robust. Indeed, this study was undertaken in a population of adult rats within which a critical effect transposable to workers was identified (impairment of reproductive organs and fertility). Moreover, the study is of good quality and the chosen range of doses is wide enough to provide a coherent benchmark dose. Furthermore, the fact that this benchmark dose is a NOAEL instead of a LOAEL[6] gives the study even more validity. In addition, the significant difference between the NOAEL and the LOAEL is also a safety factor. Lastly, the choice of this effect and this study is supported by the fact that most of the NOAELs (or BMDs) determined with oral exposure in rodents are around 200 mg/kg/day, for both general toxicity (Hammond *et al*., 1987) and reprotoxicity (Piersma *et al.*, 2000; Price *et al.*, 1990 cited in CERHR 2003). Therefore, this study was chosen to establish an OEL.

Route-to-route extrapolation

In rodents, gastro-intestinal absorption of BBzP is close to 100% (INSERM, 2011).

Since no data are available, it is considered by default that absorption by inhalation in rodents is 100%. Since no other data are available, the OEL Committee considers by default that these absorption percentages are the same in humans.

According to ECHA (2012), the respiratory volume of a rat for 8 hours of exposure (expressed in kilograms of body weight) is 0.38 $m^3.kg^{-1}$. It corresponds to a "standard" respiratory volume of 6.7 m^3 for a human of 70 kg.

This leads to:

$$NOAELestimated\ inhaled(mg.m-3)\ = \text{NOAELoral rat} \times \frac{1}{0{,}38} \times \frac{100}{100} \times \frac{6{,}7}{10}$$

Applying this calculation to the data in the study by the NTP (1997) leads to a NOAEL for the worker by inhalation of 352.6 $mg.m^{-3}$.

Choice of adjustment factors (AF)

[4] The exposure conditions in this study are not relevant for the establishment of an OEL.
[5] As the significant effect was observed with only one dose, it was not possible to calculate a BMD
[6] Lowest Observed Adverse Effect Level

The OEL Committee proposes applying the following adjustment factors:

- inter-species variability (AF_A): 3 justified by allometric scaling, which eliminates the kinetics component. Based on a comprehensive review of the literature, INSERM concludes that there are not sufficient data to affirm that humans are more susceptible than rats or vice versa.
- inter-individual variability (AF_H): 3. Due to the lack of quantitative data on inter-individual variability, the value of 3 was assigned by default to this factor in order to take into account variability within the population of workers.
- differences in exposure time: transposition from subchronic to chronic exposure (AF_S): 3

Although the route of exposure is not the most suitable for establishing an OEL, it is not necessary to apply an adjustment factor for route-to-route extrapolation. Indeed:

- since the effect is systemic, the calculations were made based on a scenario that considers that both oral absorption and absorption by inhalation are equal to 100%;
- the NOAEL was re-calculated to be adapted to the lung volumes of rats and the work hours of workers;
- No effects specific to a route of exposure were identified.

Critical effect	Critical dose	AF	8h-OEL
Impairment of reproductive organs and fertility (NTP, 1997)	**NOAEL = 200 mg.kg^{-1}.day^{-1}** Route-to-route extrapolation: **$NOAEL_{inhaled\ HED}$ = 352.6 mg. m^{-3}**	**27** AF_A 3 AF_H 3 AF_S 3	13 mg.m^{-3}

15min-STEL

There are no data on the effects of acute exposure in humans. The available data on acute exposure in animals are not relevant for the establishment of a 15min-STEL (oral and dermal exposure).

Thus, in order to limit the size and number of exposure peaks and in accordance with its methodology (AFSSET, 2009), the OEL Committee recommends not exceeding five times the value of the 8h-OEL, i.e. 65 mg.m^{-3}, over a 15-minute period with occupational exposure to BBzP.

"Skin" notation

No quantitative data on the dermal penetration of BBzP in humans were found in the literature.

Lacking data in humans, experimental data were taken into account.

Based on the information in the *in vivo* study in rats by Elsisi *et al. (*1989) as a first approximation, a skin permeation flow (J) can be estimated from the following data:

- a deposited dose of 5 to 8 mg.cm^{-2} (the dose is not precisely known);

- a percentage of the dose excreted within seven days of 30% (figure in the text and value from Figure 1 in the publication by Elsisi *et al.* 1989);
- a percentage of the dose in muscles and fat of 4.6% and 0.17% (Table 1 in the publication by Elsisi *et al.* 1989).

The flow (J) estimated from these data corresponds to:

- J = 5 to 8 mg.cm^{-2} x (30% + 4.6% + 0.17%) / (100 x 7 days x 24 hours x 60 minutes)
- J = 0.2 to 0.3 µg.cm^{-2}.min^{-1} i.e. 12 to 18 µg.cm^{-2}.h^{-1}

The calculated flow thus corresponds to the values of 0.15 to 0.30 µg.cm^{-2}.min^{-1} reported by European Commission (EC, 2007).

The amount absorbed, for exposure to a concentration equivalent to the 8h-OEL over an 8-hour working period, considering 100% absorption by inhalation (as used for the route-to-route extrapolation) and a volume of inhaled air of 10 m^3 corresponds to:

- 13 (mg/m^3) x 10 (m^3) = 130 mg

The amount absorbed by the hands and forearms (2000 cm^2) after exposure for one hour corresponds to:

- 18*10^{-3} (mg.cm^{-2}.h^{-1}) x 2000 (cm^2) = 36 mg

In accordance with the methodological document of the OEL Committee, the criteria of ECETOC[7] were applied to determine a relative uptake by dermal route in relation to inhalation.

The amount of compound absorbed by the hands and forearms (2000 cm^2) after exposure for 1 hour must account for over 10 % of the systemic dose absorbed by inhalation over one 8-hr work day on exposure to the 8h-OEL (ECETOC, 1993).

The dose absorbed by the dermal route would thus correspond to 28% of the dose absorbed by inhalation.

However, it should be noted that this result has a limitation. Indeed, this absorption percentage was extrapolated from experimental data in animals. And yet it is known that dermal penetration of phthalates is species-dependent since it is influenced by esterase activity, which can differ between animals and humans (Payan *et al.*, 2001; Hopf *et al.*, 2014).

For other phthalates, such as di-butyl-phthalate (DBP) in particular, the dermal absorption flow calculated from *in vitro* data in animals can be much greater (40 times greater) than that calculated for humans (Beydon *et al.*, 2010; Scott *et al.*, 1989).

For di(2-ethylhexyl) phthalate (DEHP), however, it was calculated that the dermal absorption flow obtained from *in vitro* data in animals was only four times greater than that calculated for humans (Barber *et al.*, 1992; Scott *et al.*, 1989).

Considering the extrapolations performed from results obtained for other phthalates, dermal penetration could be lower in humans than the study by Elsisi suggests. However, it is possible that the dermal route may contribute to over 10% of the systemic burden. Therefore the OEL Committee recommends assigning the skin notation for this substance.

[7] European Centre for Ecotoxicology and Toxicology of Chemicals

Results of the collective expert appraisal on measurement methods in workplace atmospheres

The following table presents the two measurement methods that were identified and evaluated.

Table 1: Summary table of methods for measuring BBzP in workplace atmospheres

No.	Method	Similar protocols
1	Sampling in a cellulose acetate filter and silica gel tube - Desorption in methanol - High-performance liquid chromatography analysis (HPLC/UV detector)	DFG method 2**:** 2006 and IFA: method 8387: 2009
2	Sampling in a polyurethane foam tube and quartz fibre filter - Desorption in toluene - gas chromatography analysis (flame ionisation detector or electron capture detector)	MétroPol: sheet 96: 2006[8]

The following two graphs present the ranges for which the various methods were tested and their limits of quantification in light of the 8h-OEL and the pragmatic 15min-STEL recommended by the OEL Committee.

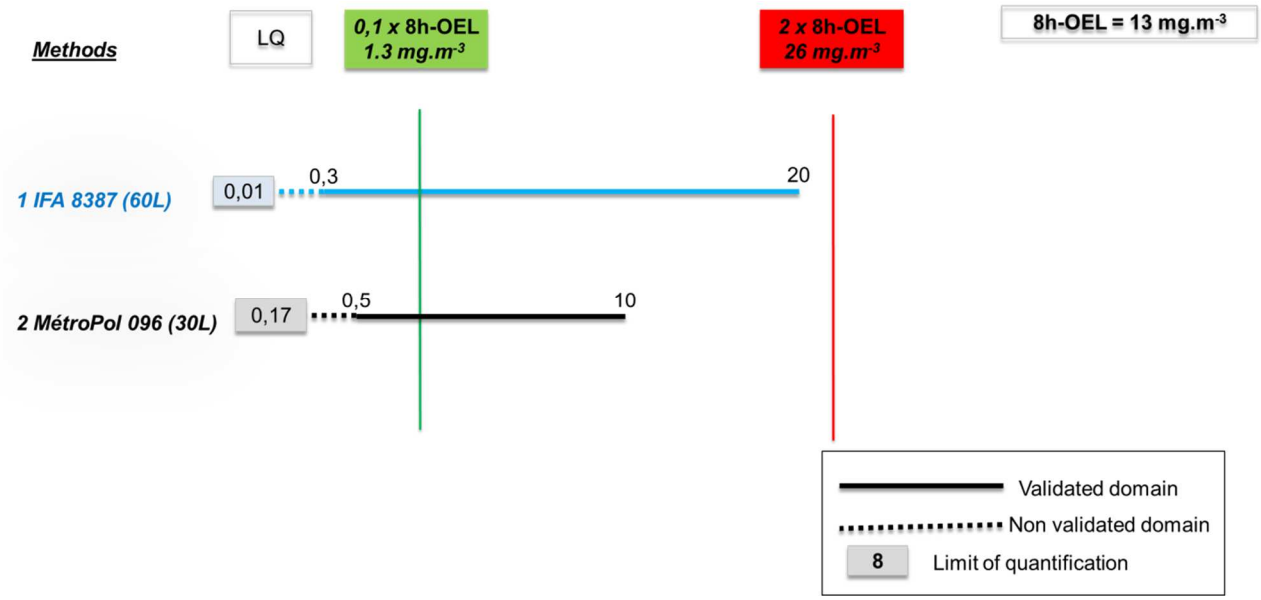

Figure 1: Ranges of validity and limits of quantification for the various compared methods from 0.1 to 2 times the 8h-OEL recommended by the OEL Committee for BBzP

[8] This reference was modified by INRS when updating its MétroPol database in November 2015 (after the assessment carried out within the framework of this expertise): http://www.inrs.fr/ Publications / bdd / metropol.html

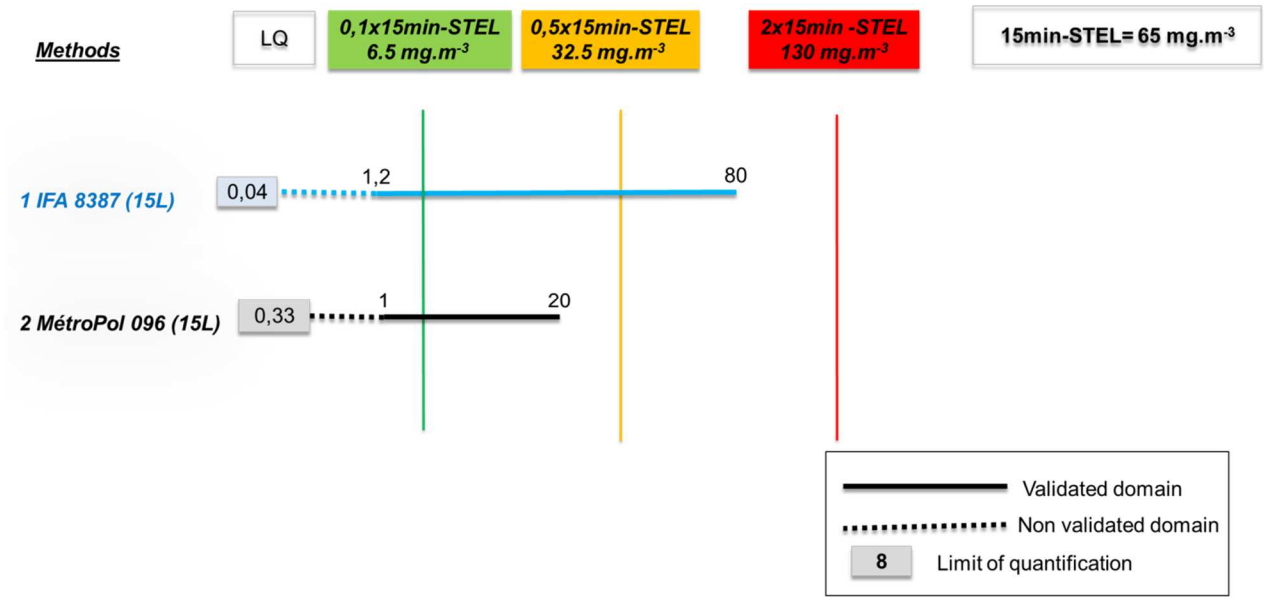

Figure 2: Ranges of validity and limits of quantification for the various compared methods from 0.1 to 2 times the pragmatic 15min-STEL recommended by the OEL Committee for BBzP

Conclusion and recommendations

Method 1 described by the DFG[9] protocol (IFA 8387) involves taking a sample from a device made of a cellulose acetate filter and a silica gel tube and then analysing by liquid chromatography with a UV detector after desorption of the samples with methanol.

The full sampling device described in the DFG protocol can, by placing a closed 37mm cassette upstream of the silica gel tube, at the recommended flow rate of 1 $L.min^{-1}$, collect the inhalable fraction of the aerosol, according to the NF-EN 481 Standard, and therefore sample the mixed phase (aerosol + gas) of the compound.

These methods are classified in category 3, due to the inadequacy and incompleteness of the published data, especially on the sampler capacity, making it impossible to fulfil all of the requirements in the NF EN 482 Standard.

However, considering the very low volatility of BBzP (0.0012 Pa at 20°C.) and an implementation not requiring the use of dispersive process (e.g. high pressure spraying), which is usually the case, it is unlikely or even impossible, that levels of concentration corresponding to twice the recommended OELs (26 and 130 $mg.m^{-3}$) can be achieved. Based on these hypotheses, the proposed methods could be used to control occupational exposure to BBzP, on the condition of full validation (including long-term sampling for the control of the 8-hour OEL and determination of measurement uncertainties).

Conclusions of the collective expert appraisal

Based on the data that are currently available, the Committee recommends setting an 8h-OEL of 13 $mg.m^{-3}$. This recommendation is intended to protect against effects on the male reproductive

[9] Deutsche Forschungsgemeinschaft

system related to the anti-androgenic activity of BBzP (impairment of reproductive organs and fertility in particular) and MBzP (the main metabolite in humans). This value is also protective for all other effects in the general population of workers.

Based on the data currently available, no 15min-STEL can be recommended for BBzP. Therefore, in accordance with its methodology, the OEL Committee recommends not exceeding 5 times the value of the 8h-OEL (i.e. 65 $mg.m^{-3}$) over a 15-minute period.

The OEL Committee recommends assigning a "skin" notation.

Regarding the assessment of methods for measuring BBzP in workplace atmospheres, the Committee does not recommend measurement method. Indeed, although the two measurement methods identified allow to reach the tenth of the 8h-OEL or of the 15min-STEL, they have not been validated up to 2 times these limit values. The Committee recommend to validate both methods identified on domains of concentration higher than currently, and for sampling time at least 4 hours.

However, considering the very low volatility of BBzP (0.0012 Pa at 20°C.) and an implementation not requiring the use of dispersive process (e.g. high pressure spraying), which is usually the case, it is unlikely or even impossible, that levels of concentration corresponding to twice the recommended OELs (26 and 130 $mg.m^{-3}$) can be achieved. Based on these hypotheses, the proposed methods could be used to control occupational exposure to BBzP, on the condition of full validation.

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