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 measuring exposure levels in the workplace atmosphere for di-n-butyl-phthalate (CAS n° 84-74-2)

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 di-n-butylphthalate (DnBP).

France currently has an indicative mean eight-hour exposure value for di-n-butylphthalate of 5 $mg.m^{-3}$. This value was set in the Circular[1] of 13 May 1987 of the Ministry of Labour (not published in the OJ).

The Directorate General for Labour requested ANSES to re-assess this value and, if necessary, propose new occupational exposure limits based on health considerations for di-n-butyl-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.

[1]Supplementing and amending the Circular of 19 July 1982 on the acceptable values for concentrations of certain hazardous substances in workplace atmospheres.

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 and animal toxicology studies. 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). This body 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 groups were regularly submitted to the OEL Committee. The final report takes account of all their observations.

This expert appraisal was therefore conducted by groups of 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 Risk Assessment Report of the European Commission published in 2003 and the INSERM collective expert appraisal report entitled "Reproduction et Environnement" published in 2011. They were supplemented by a review of the literature on Medline and Toxline published primarily between December 2010 (end of the INSERM report bibliography) and January 2012.

For the assessment of methods for measuring exposure levels in workplace atmospheres

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 di-n-butylphthalate 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.

A list of the main sources consulted is detailed in the methodology report.

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 10 October 2013 by the OEL Committee (term of office 2010-2013)

The collective expert appraisal work and the summary report were submitted to public consultation from 27/08/2014 to 28/10/2014. No comments were received. The OEL Committee (term of office 2014-2017) adopted this version on 14 december 2015.

Results of the collective expert appraisal on the health effects of di-n-butylphthalate

Di-n-butylphthalate (DnBP) is a phthalate used as a plasticiser for commonly used products. Phthalates are used in most rigid, semi-rigid and flexible articles made from polyvinyl chloride (PVC). Some products, such as plastic bags, window frames, food packaging, plastic raincoats, shower curtains, boots, garden hoses, certain medical devices and blood storage containers can contain up to 50% phthalates.

Kinetics and metabolism

Data on the toxicokinetics of DnBP in humans are very limited, more particularly after exposure by inhalation (for which there are also few data available for animals).

No data on the absorption of DnBP by inhalation were identified in the literature. Skin contact does not appear to be a major route of absorption for this substance (permeation flow of 0.07 $\mu g.cm^{-2}.h^{-1}$). In rodents, gastro-intestinal absorption is close to 100%.

Distribution in the body is rapid and depends on the route of exposure. In a study exposing rats by inhalation to concentrations of 0.5 and 50 $mg.m^{-3}$ for 6 hours per day over periods of 3 and 6 months, the target organs identified were the brain, lungs, liver, kidneys and testicles (Kawano, 1980). After oral exposure in rats, no significant accumulation was observed (William and Blanchfield, 1975; Tanaka *et al*., 1978). Furthermore, DnBP and its metabolites are capable of crossing the placental barrier in rats.

In rats exposed orally, DnBP is hydrolysed into mono-n-butyl phthalate (MnBP), either in the intestinal mucosa before being absorbed by the gastro-intestinal tract or after absorption, by pancreatic lipase. The side chain of MnBP may then be oxidised. Urinary metabolites are mainly the glucuroconjugated derivative of MnBP and free MnBP (approximately 66-70% of metabolites) and oxidised derivatives of MnBP. Free phthalic acid may also be formed but to a lesser extent. In humans, similar percentages of total (free and conjugated) MnBP in 24-hour urine have been found in volunteers exposed orally (approximately 64 to 73% of metabolites).

Phthalate metabolites are rapidly eliminated in the urine; their half-life ranges from 8 to 48 hours depending on the phthalate. MnBP is the main metabolite of DnBP identified in the urine of rats and humans. It is a good indicator of exposure for people occupationally exposed to DnBP.

In rats, DnBP undergoes an enterohepatic cycle since over one-third of the absorbed dose is excreted through the bile and reabsorbed by the intestines, which explains its low faecal excretion (< 10%).

General toxicity

Toxicity in humans

Acute toxicity

No data on the acute toxicity of DnBP by inhalation were identified in the literature, undoubtedly due to the low volatility of DnBP.

Chronic toxicity

Two workplace studies report neurological disruptions in workers chronically exposed to DnBP by the respiratory route. However, there are many methodological biases that significantly limit the use of these results for the assessment of health risks related to the substance.

Reproductive toxicity

Several studies have examined the relationships between phthalate exposure and reproductive system abnormalities (indicators: sperm parameters, early puberty, endometriosis, hormones, etc.) in adults. In most studies, the authors do not look into a specific phthalate but rather several phthalates and their metabolites (INSERM, 2011).

Most of the studies undertaken in human adults show a relationship between urinary concentrations of phthalates (or their metabolites) and the alteration of sperm parameters, including sperm concentration and morphology, as well as increased DNA fragmentation in male gametes. However, a few studies do not show any effects of phthalates on sperm parameters. Furthermore, one exposed/unexposed study shows a relationship between high concentrations of MnBP and low testosterone concentrations (Pan *et al*., 2006; INSERM, 2011). None of these studies are really specific to DnBP or capable of identifying a dose/response relationship linking

DnBP exposure to impaired sperm quality. Therefore, none of these studies can be used to establish an OEL for DnBP.

Few studies have assessed the possible role that exposure to phthalates may play in female reproductive toxicity. The evidence of a possible link between phthalates and endometriosis as reported in a few studies is insufficient. The effects of phthalate exposure on ovulatory function and certain hormone levels (oestradiol, progesterone, LH, FSH) suggested in animal studies have not been described for women (INSERM, 2011). No specific effects of DnBP have been found.

Several studies have investigated the effects of exposure to phthalates, including DnBP, on *in utero* development. The results of the publications by Swan (2005 and 2008) show decreased anogenital distance in newborn boys, which suggests that phthalates act on the androgenisation of foetuses. Other studies with larger population sizes are necessary to confirm these initial results (INSERM, 2011). These studies cannot be used for the establishment of an OEL because they do not include measurements of atmospheric DnBP concentrations.

Carcinogenic effects - genotoxicity

No studies have been published that can be used to assess the carcinogenicity of DnBP in humans.

Toxicity in animals

The data from animal testing are much more extensive than those for humans. However, it is important to note that the most commonly considered route of exposure remains 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

By inhalation, the LC_{50} in rats is greater than 15.68 $mg.L^{-1}$ after 4 hours of exposure and equal to 25 $mg.L^{-1}$ in mice after 2 hours of exposure (Voronin, 1975; Greenough et al. 1981 cited by EC, 2003).

Subchronic and chronic toxicity

Local respiratory effects (non-inflammatory lesions of the upper airways) were found from 1.18 $mg.m^{-3}$ in 'nose-only' exposed rats in the study by Gamer *et al.*, 2000 (unpublished study cited by ECHA, 2012a).

The subchronic toxicity of DnBP with oral exposure in rodents has been covered in 10 publications including 2 for mice and 8 for rats. Several of these studies report changes in haematological (decrease in hematocrit counts and the number of erythrocytes) and biological (increase in serum levels of albumin and glucose, decrease in triglycerides) parameters and an increase in the weight of certain organs (liver, kidney). An increase in markers of hepatic peroxysome proliferation has also been noted in some studies. A possible relationship between peroxysome proliferation and the occurrence of hepatic tumours in rodents has been suggested (Lapinskas, 2005). However, several studies have shown that this was species specific. Therefore, these effects are considered non-transposable to humans.

Reproductive toxicity

Effects on fertility and reproductive organs

Several types of effects are observed in adult males after exposure to DnBP: structural and functional testicular effects and reduced male fertility likely as a result of these effects. The effects described include, among other things, a decrease in the weight of testicles and accessory sex glands, seminiferous tubule degeneration, a decrease in testicular zinc and iron concentrations, a decrease in blood testosterone levels but an increase in testicular testosterone levels, hyperplasia of the interstitial cells, reduced numbers of spermatocytes, detachment of germ cells and a decrease in the enzymatic activity (succinate dehydrogenase) of Sertoli cells.

It appears that the adult testicles of rats and rabbits are much less sensitive to the effects of phthalate exposure than foetal and postnatal testicles (INSERM, 2011).

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

Effects on development

Most of the effects of *in utero* exposure in animals involve foetal testicles and have been observed in gavage studies. These studies report effects on the three main types of testicular cells: Leydig cells, Sertoli cells and germ cells. Many studies consistently report: Leydig cell aggregation and decreased testosterone and Insl3 (relaxin/insulin-like 3) production in these cells; an increase in the diameter of spermatic cords; the appearance of multinucleated gonocytes (foetal germ cells) (INSERM, 2011).

DnBP administered to gestating rats inhibits the steroidogenic activity of foetal testicles in various strains of rats. 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).

Embryotoxic and teratogenic effects have been observed in animals. The strongest effects have been on the development of the male reproductive system related to the anti-androgenic activity of DnBP. The lowest doses associated with an effect have been observed in rats. An NOAEL of 10 $mg.kg^{-1}.day^{-1}$ based on a decrease in testicular testosterone concentrations (observed at 50 mg/kg/day) can be deduced after *in utero* exposure.

The adverse effects on fertility are a decrease in fertility signs, the gestation period, the number of live foetuses per litter, newborn weight and maternal weight, testicular lesions in newborns and delayed male puberty.

Carcinogenic effects – genotoxicity

There are no relevant long-term carcinogenesis studies available in laboratory animals. Several phthalates including DnBP are known to induce peroxysome proliferation in the liver of rats and mice, which results in structural modifications after observation with an electron microscope and changes in the enzymatic activities associated with peroxysomes. A possible relationship between peroxysome proliferation and the occurrence of liver tumours in rodents was suggested (Lapinskas, 2005). These carcinogenic effects observed in rodents are considered non-transposable to humans.

Based on the results of the many studies on the genotoxicity of DnBP, it is considered non-genotoxic (EC, 2003).

Establishment of OELs

8h-OEL

Choice of the critical effect

Since no human data are available that can be used to establish an OEL for DnBP, it seems relevant to use data on the most susceptible animal species, i.e. male rats, during what seems to be the most susceptible period, i.e. *in utero* exposure. The effects on the development of the male reproductive system linked to the anti-androgenic activity of DnBP are both histological and functional.

According to the data in the literature, testicular differentiation takes place on the 14.5th day of gestation in rats and the 43rd day in humans (Shepard, 1998). And yet, pregnant women are likely to be occupationally exposed to DnBP in the first trimester of pregnancy. It can be considered that there is good consistency for reprotoxic effects in animals and humans. Therefore, the reprotoxic effects of DnBP appear to be the most relevant to be taken into account for the establishment of an OEL.

Choice of the key study and identification of the Point of Departure (POD)

Of the experimental studies undertaken in animals on the reproductive toxicity of DnBP, the study by Lehmann (2004) exposing rats orally between the 12th and 19th days of gestation expresses the lowest NOAEL and shows the strongest effect. Therefore, this study has been chosen to establish the OEL.

The critical effect chosen from all of the expected effects on the male reproductive system shown in this study is the reduction in testosterone concentrations in foetal testes. The identified NOAEL is 10 mg.kg^{-1}.day^{-1}.

Route-to-route extrapolation

In rodents, gastro-intestinal absorption of DnBP 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 (2012b), the respiratory volume of a rat for an 8 hours exposure (expressed in kilogram 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 70kg. As a reminder, the respiratory volume of a worker is estimated at 10 m^3.

We obtain :

$$NOAEL_{\text{estimated inhaled}}\ (mg.m^{-3}) = NOAEL_{\text{oral rat}} \times \frac{1}{0,38} \times \frac{6,7}{10}$$

Applying this calculation to the data in the study by Lehmann (2004) leads to a NOAEL for the worker by inhalation of 17.6 mg.m^{-3}.

Choice of adjustment factors (AFs)

The OEL Committee proposes applying the following adjustment factors:

- inter-species variability (AF_A): 3 justified by the allometric adjustment, 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. Studies in non-human primates are not sufficient to determine the relevance of the animal model and the effects observed in rodents should be taken into account.
- inter-individual variability (AF_H): 3. Lacking quantified data on inter-individual variability, the value of 3 has been assigned to this factor by default.

Although the route of exposure is not the most suitable for establishing an OEL, it is not necessary to apply a 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 working hours of workers.

Critical effect	Critical dose	**CF**	**8h-OEL**
Reduction in testosterone concentrations in foetal testes (Lehman et al., 2004)	**NOAEL = 10 mg.kg^{-1}.day^{-1}** Allometric adjustment Route-to-route extrapolation **$NOAEL_{inhaled\ HEC}$ = 17.6 mg. m^{-3}**	**9** AF_A 3 AF_H 3	**1.95 mg.m^{-3} rounded to an 8h-OEL of 2 mg.m^{-3}**

15 min-STEL

For humans, no data on irritation induced after exposure to DnBP were identified in the literature. For animals, by inhalation, the study by Gamer *et al*., 2000 (cited by EC, 2003, and ECHA, 2012a) describes local respiratory effects not associated with inflammation. Therefore, the risk assessment report considers that irritation is not transposable to workers.

However, given the reprotoxicity of this substance, special attention should be paid to women of childbearing age, to avoid exposure peaks during specific windows of exposure. In these conditions and in accordance with its methodology, the OEL Committee recommends not exceeding 5 times the value of the 8h-OEL, i.e. 10 mg.m^{-3}, over a 15-minute period with occupational exposure to DnBP.

"Skin" notation

The in vitro study by Scott *et al*., 1987 reports a skin permeation flow value of 0.07 µg.cm^{-2}.h^{-1} determined after applying undiluted DnBP onto human skin.

In accordance with the OEL Committee's methodological document, applying ECETOC criteria[2] to determine a relative contribution for skin contact in relation to inhalation at an exposure level corresponding to the 8h-OEL (2 mg.m^{-3}) gives a contribution of 0.7%. Therefore, the OEL Committee does not recommend assigning a skin notation for this substance.

[2] 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).

Conclusion

Recommended 8h-OEL: 2 $mg.m^{-3}$;

No proposed 15 min-STEL;

However, it is recommended to not exceed, over a 15-minute period, a pragmatic 15 min-STEL of 10 $mg.m^{-3}$ corresponding to 5 times the recommended 8h-OEL;

No 'Skin' notation assigned.

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

Assessment of methods for measuring di-n-butylphthalate in the workplace atmosphere

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

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

No.	Methods	Protocols
1	Sampling in a polyurethane foam tube - Desorption in toluene - Gas chromatography analysis (FID or EC detector)	MétroPol: sheet 96: 2006
2	Sampling in an OVC tube - Desorption in toluene - Gas chromatography analysis (FID detector)	OSHA 104: 1994
3	Sampling in a cellulose ester membrane - Desorption in CS_2 - Gas chromatography analysis (FID detector)	NIOSH NMAM 5020, issue 2: 1994
4	Sampling in a cellulose nitrate filter - Desorption in a water/acetonitrile mixture - Liquid chromatography analysis (UV detector)	IRSST: method 308.-1
5	Sampling in a cellulose acetate filter and silica gel tube - Desorption in methanol - Liquid chromatography analysis (UV detector)	DFG method 2**:**2006 and IFA: method 8387: 2009

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 15 min-STEL recommended by the OEL Committee.

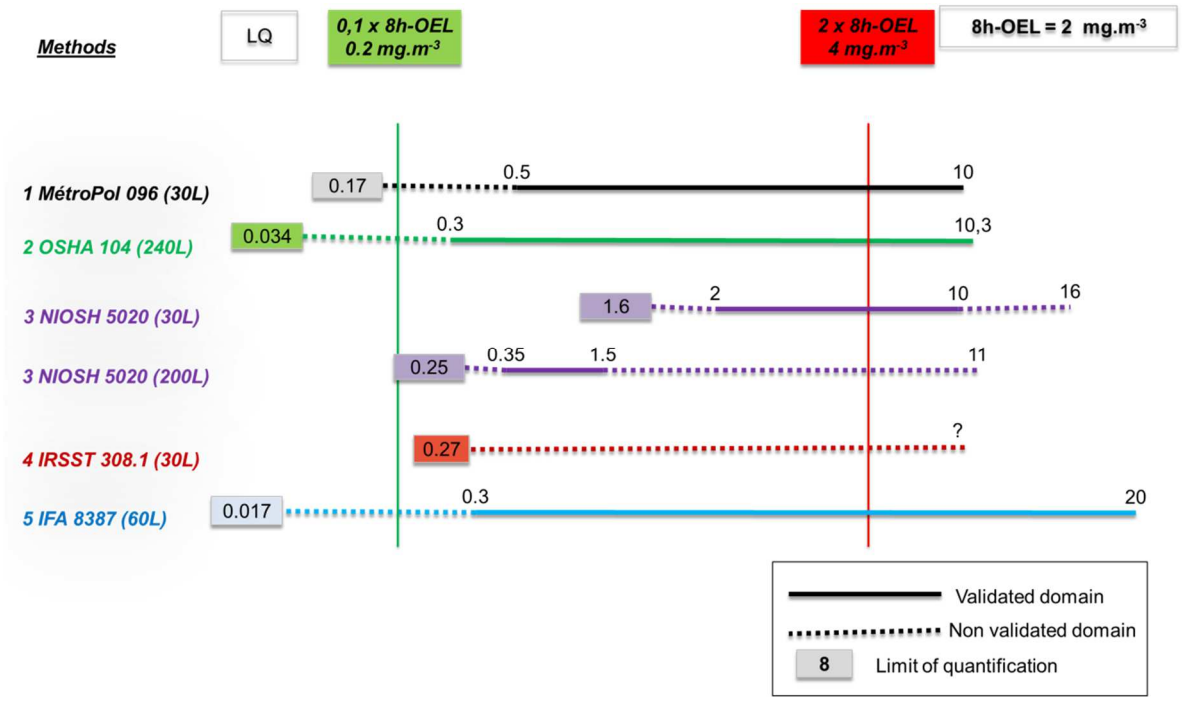

Figure 1: Ranges of validity and limits of quantification for the various compared methods from 0.1 to 2 times the 8h-OEL recommended by the OEL Committee for DnBP

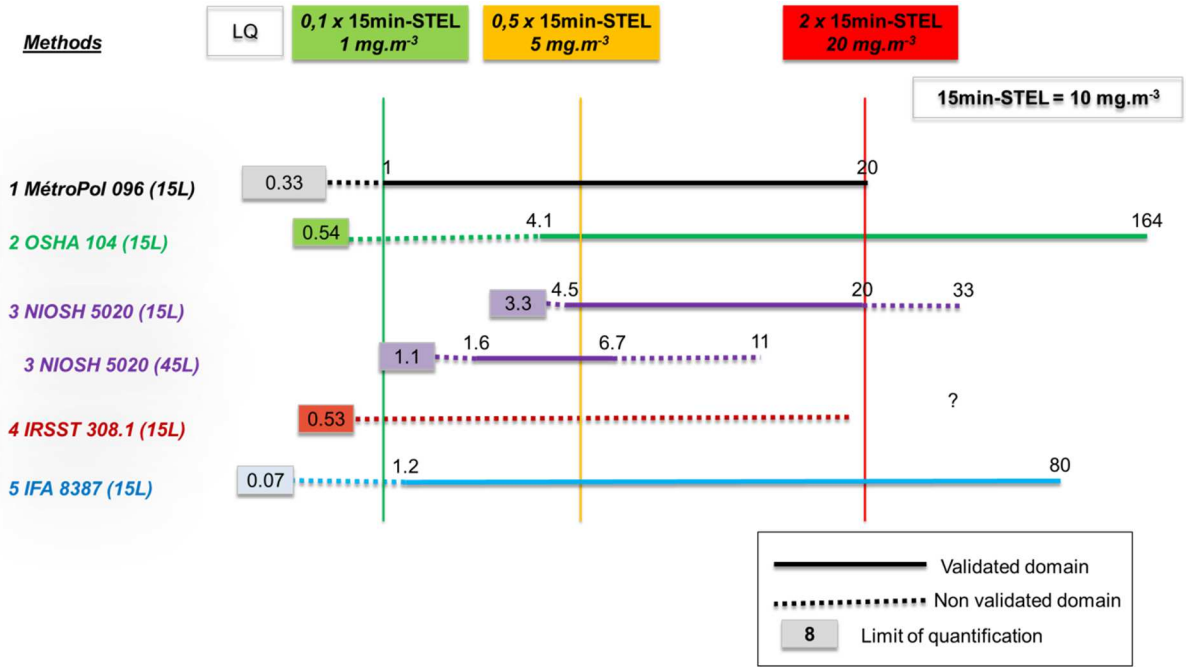

Figure 2: Ranges of validity and limits of quantification for the various compared methods from 0.1 to 2 times the pragmatic 15 min-STEL recommended by the OEL Committee for DnBP

Conclusion and recommendations

Two methods have validation criteria that comply with the requirements of the NF-EN 482 Standard and thus can be used to determine di-n-butylphthalate concentrations for comparison with the 8h-OEL and pragmatic 15 min-STEL recommended by the OEL Committee:

- **Method 2 described by the OSHA 104 Protocol** which involves taking a sample in an OVS tube, made of a glass fibre filter and 2 sections of Tenax (140/70 mg), and then analysing by gas chromatography (FID detector) after desorption of the samples with toluene.
- **Method 5 described by the DFG protocol** (or IFA 8287 method) which involves taking a sample in a unit made of a cellulose acetate filter (diameter 37 mm) and a silica gel tube (ORBO 502-Supelco) and then analysing by liquid chromatography (DAD detector) after desorption of the samples with methanol.

However, these two methods are not equivalent.

In order to choose the most suitable method, it is first necessary to verify whether the compound is in the form of an aerosol, a gas phase or a mixed phase (aerosol + gas):

- When there is a mixed phase of di-n-butylphthalate (aerosol + gas) or only an aerosol of this compound, the complete sampling method 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.
- However, in this case, the protocol given by OSHA may not be suitable since the fraction of the aerosol sampled by the OVS tube is not known. Therefore, the OSHA protocol would only be suitable if there were certainty of only having the gas phase of di-n-butylphthalate.

Furthermore, the validation criteria for these methods mean that they cannot be classified at the same level irrespective of the type of OEL to be checked. Thus:

- When di-n-butylphthalate is in gas form only:
    - Method 2 is partially validated for technical control in a regulatory framework of the 8h-OEL and of the pragmatic 15 min-STEL recommended by the OEL Committee and for the monitoring of short term exposure.
- When di-n-butylphthalate is in a mixed phase or in aerosol form only:
    - Only method 5 can sample the inhalable fraction. It is partially validated for regulatory comparison with the pragmatic 15 min-STEL recommended by the OEL Committee but is indicative for technical control in a regulatory framework of the 8h-OEL recommended by the OEL Committee since the validation data were obtained by doping and passage of an air flow for 1 hr.
- When di-n-butylphthalate is in aerosol form only:
    - Method 3 described by the NIOSH NMAM 5020 which involves a sampling in cellulose ester membrane followed by a gas chromatography analysis (FID detector) after desorption in CS_2 allows inhalable fraction sampling. It is partially validated for the monitoring of short-term exposure. However, it does not achieve a tenth of the pragmatic 15min-STEL recommended by the OEL Committee or a tenth of the 8h-OEL. It is therefore not adapted for technical control in a regulatory framework of the 15-min STEL and of the 8h-OEL.

The other methods, i.e. the INRS MétroPol 96 Method and the IRSST 308-1 Method are classified in category 3, on account of the insufficiency and incompleteness of the published data, making it impossible to fulfil all of the requirements in the NF-EN 482 Standard.

The group therefore recommends the following methods:

<table>
<tr><th rowspan="2">Method</th><th rowspan="2">Protocol</th><th colspan="3">Category</th></tr>
<tr><th>for regulatory technical control of the 8h-OEL</th><th>for regulatory technical control of the 15 min-STEL[3]</th><th>for monitoring short-term exposure</th></tr>
<tr><td>Method 2: active sampling in an OVS tube – desorption in toluene – GC analysis/FID</td><td>OSHA 104: 1994</td><td colspan="3">1 B

<u>If gas phase only</u></td></tr>
<tr><td rowspan="2">Method 5: active sampling in a cellulose acetate membrane followed by a silica gel tube – methanol desorption – HPLC analysis/UV</td><td rowspan="2">IFA 8387: 2009
DFG method 2: 2006</td><td>2</td><td colspan="2">1 B</td></tr>
<tr><td colspan="3"><u>If a mixed phase (aerosol + gas) or aerosol</u></td></tr>
<tr><td rowspan="2">Method 3 : sampling on in a cellulose ester membrane - Desorption in CS_2 - Gas chromatography analysis (FID detector)</td><td rowspan="2">NIOSH NMAM 5020</td><td colspan="2"><u>3</u></td><td><u>1B</u></td></tr>
<tr><td colspan="3"><u>If aerosol phase only</u></td></tr>
</table>

Conclusions of the collective expert appraisal

Based on the data currently available, the Committee recommends setting an 8h-OEL of 2 mg.m^{-3}. This recommendation is intended to protect against effects on the foetal development of the male reproductive system due to the anti-androgenic activity of DnBP during in utero exposure (testicular damage in particular). This value is also protective for all other effects in the general population of workers.

Based on the data currently available, no 15 min-STEL can be recommended for DnBP. Therefore, in accordance with its methodology[4], the Committee recommends not exceeding 5 times the value of the 8h-OEL (i.e. 10 mg.m^{-3}) over a 15-minute period.

[3] Validation and performance criteria for methods for monitoring STELs are defined in the NF EN 482 Standard from 0.5 to 2 times the STEL. Under the French regulations, for the technical control of the exposure limit, the measurement method must be able to measure one-tenth of the 15min-STEL (Ministerial Order of 15 December 2009 on technical monitoring of occupational exposure limits in the workplace atmosphere and conditions for accrediting the organisations in charge of monitoring, published in the French Official Journal of 17 December 2009). As such, when a method cannot measure one-tenth of the 15min-STEL, it cannot be classified in category 1A or 1B for regulatory control of the 15min-STEL. However, it may be classified in category 1A or 1B solely for assessing occupational exposure.

[4] For more details, refer to the collective expert report for setting occupational exposure limit values for chemical agents from December 2008 on recommendations relating to occupational exposure limits in order to limit the size and number of exposure peaks over the working day (Part 1)

The Committee does not recommend a 'skin' notation.

As for the assessment of methods for measuring DnBP in the workplace, two measurement methods are recommended depending on the physical form of DnBP and the type of OEL to be controlled:

- when DnBP is in gas form only, the OEL Committee recommends Method 2, partially validated for technical control of the 8h-OEL in a regulatory framework.
- When DnBP is in a mixed phase or an aerosol only, the OEL Committee recommends Method 5, which is indicative for technical control of the 8h-OEL in a regulatory framework.

Moreover, for follow-up to the recommendations on the value that should not be exceeded over a 15-minute period to limit exposure peaks, there are two partially validated methods for short term exposure assessment: Method 2 for exposure to the gas form only and Method 5, recommended in the presence of a mixed phase or aerosol. It should be noted that Method 3 is partially validated for the monitoring of short-term exposure when DnBP is in aerosol form but is not validated for the regulatory technical control of this value.

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