COLLECTIVE EXPERT APPRAISAL:

SUMMARY AND CONCLUSIONS

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

On the evaluation of biomarkers of exposure and recommendation for biological limit values for 2-methoxypropanol (1PG2ME or PGME$_\beta$; CAS 1589-47-5) and 2-methoxypropyl acetate (1PG2MEA or PGMA$_\beta$; CAS 70657-70-4)

This document summarises the work of the Expert Committees on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee) and on health reference values (HRV Committee) and the Working Group on biomarkers (Biomarkers WG).

Presentation of the issue

On 3 February 2012, Anses received a formal request from the French Directorate General for Labour (DGT) to conduct the expert appraisal work required for recommending biological monitoring in the workplace for 2-methoxy-1-propanol and its acetate, 2-methoxypropyl acetate.

There are two isomers of propylene glycol monomethyl ether (PGME): 1-methoxy-2-propanol (2PG1ME or PGME$_\alpha$, CAS No. 107-98-2) and 2-methoxy-1-propanol (1PG2ME or PGME$_\beta$, CAS No. 1589-47-5); the respective acetates are 1-methoxy-2-propanol acetate (2PG1MEA or PGMAα, CAS No. 108-65-6) and 2-methoxypropyl acetate (1PG2MEA or PGMA$_\beta$, CAS No. 70657-70-4).

In this report, 1-methoxy-2-propanol and its acetate will be referred to respectively as PGME$_\alpha$ and PGMA$_\alpha$ while 2-methoxy-1-propanol and its acetate will be referred to as PGME$_\beta$ and PGMA$_\beta$.

Since PGME$_\beta$ and its acetate are classified as reprotoxic (Category 1B) under the CLP Regulation[1], a concentration of at least 0.3% PGME$_\beta$ and/or PGMA$_\beta$ in the commercial form of PGME results in a 1B reprotoxic classification[2].

France does not currently have any occupational exposure limits for PGME$_\beta$ and its acetate. However, since 2007, PGME$_\alpha$, as well as its acetate, have binding limit values, i.e. an 8h-OEL of 50 ppm and a 15min-STEL of 100 ppm[3].

1 REGULATION (EC) No 1272/2008 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006

2 Maximum concentrations of beta impurities in commercial mixtures decreased from 5% to 0.5% in 1998 (with this substance's classification as an R2 reprotoxic substance) and then to 0.3% with the implementation of the CLP Regulation in 2008

3 *Article R.4412-149 of the French Labour Code*

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In an opinion published in 2008 (AFSSET 2008[4]), AFSSET recommended, to "*limit the risk of occupational exposure, strengthening biological surveillance in the workplace by developing markers for 2-methoxypropionic acid (2-MPA), the main metabolite of 1PG2ME and its acetate, and by systematically measuring urinary levels, instead of atmospheric levels, to be able to assess the overall exposure of workers*".

The DGT thus asked ANSES to assess the relevance of recommending monitoring one or more biomarkers and the elaboration of biological limit values for the selected biomarker(s)

Scientific background

Biological monitoring of exposure in the workplace has emerged as a complementary method to atmospheric metrology for assessing exposure to chemical agents. Biological monitoring assesses a worker's exposure by including all the routes by which a chemical penetrates the body (lung, skin, digestive tract). It is particularly worthwhile when a substance has a systemic effect, and:

- when routes other than inhalation contribute significantly to absorption,
- and/or when the pollutant has a cumulative effect,
- and/or when the working conditions (personal protection equipment, inter-individual differences in respiratory ventilation, etc.) determine large differences in internal dose that are not taken into account by atmospheric metrology.

With regard to prevention of chemical risk in the workplace, the French Labour Code provides for the use of biological monitoring of exposure and biological limit values.

Committee definitions

Biomarker of exposure (BME): parent substance, or one of its metabolites, determined in a biological matrix, whose variation is associated with exposure to the targeted agent. Biomarkers of early and reversible effects are included in this definition when they can be specifically correlated to occupational exposure.

Biological limit value (BLV): This is the limit value for the relevant biomarkers.

Depending on the available data, the recommended biological limit values do not all have the same meaning:

- if the body of scientific evidence is sufficient to quantify a dose-response relationship with certainty, the BLVs will be established on the basis of health data (no effect for threshold substances or risk levels for non-threshold carcinogens);
- in the absence of such data for substances with threshold effects, BLVs are calculated on the basis of the expected concentration of the biomarker of exposure (BME) when the worker is exposed to the 8-hour OEL. For carcinogens, in the absence of sufficient quantitative data, the biological limit value is calculated on the basis of another effect (pragmatic BLV). These latter values do not guarantee the absence of health effects, but aim to limit exposure to these substances in the workplace.

[4] French Agency for Environmental and Occupational Health Safety (AFSSET). (2008). Les éthers de glycol. Synthèse des connaissances sur les expositions de la population générale et professionnelle en France. September 2008, available (in French) via the following link: https://www.anses.fr/fr/system/files/CHIM2003et0016Ra-3.pdf

Whenever possible, the Committee also recommends biological reference values (BRVs). These correspond to concentrations found in a general population whose characteristics are similar to those of the French population (preferentially for BMEs) or in a control population not occupationally exposed to the substance under study (preferentially for biomarkers of effects).

These BRVs cannot be considered to offer protection from the onset of health effects, but do allow a comparison with the concentrations of biomarkers assayed in exposed workers. These values are particularly useful in cases where it is not possible to establish a BLV (ANSES, 2017).

Organisation of the expert appraisal

ANSES entrusted examination of this request to the OEL Committee then the “health reference values” Committee. The Agency also mandated the Working Group on biomarkers (Biomarkers WG) for this expert appraisal.

The methodological and scientific aspects of the work of this group were regularly submitted to the Expert Committees. The report produced by the working group takes account of observations and additional information provided by the Committee members.

This expert appraisal was therefore conducted by a group 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

One rapporteur of the Biomarkers WG and one ANSES employee produced a summary report on biomarkers of exposure and the recommendation of biological limit values (BLVs) and biological reference values for the BME(s) considered relevant.

The summary report on the BMEs for $PGME_{\beta}$ (and its acetate) was based on bibliographical information taking into account the scientific literature published on this substance until end of 2018. The bibliographical research was conducted in the following databases: Medline, Scopus and the Public Health Database.

The scientific articles selected for evaluating biomonitoring data on $PGME_{\beta}$ were identified using the following keywords: “propylene glycol methyl ether”, “biomarker”, “biomonitoring”, “biological monitoring”, “urine”, “blood”, “occupational”, “analysis method”.

The rapporteur reassessed the original articles or reports cited as references whenever he considered it necessary, or whenever the Committee requested it.

The report, the summary and conclusions of the collective expert appraisal work were adopted by the “health reference values” Committee (2017-2020) on 18 October 2019.

The collective expert appraisal work and the summary report were submitted to public consultation from 28/02/2020 to 28/04/2020. No comments were received. The Health Reference Values Committee (term of office 2017-2020) adopted this version on 25 June 2020.

Result of the collective expert appraisal

Toxicokinetics data

Absorption

There are very few data on the absorption of $PGME_{\beta}$. However, like any glycol ether, it is readily absorbed by the oral and respiratory routes.

$PGME_{\beta}$ can be absorbed by the lungs in aerosol form.

Regarding the oral route, a study in animals reported rapid absorption of $PGME_{\beta}$ (Tmax in blood <1h) (Carney *et al.* 2003).

Distribution

There are no data available for humans.

In animals, $PGME_{\beta}$ is distributed in the blood and skin, with lower quantities being distributed in other tissues (liver, kidneys, brain, testicles and fat) after oral exposure (Miller *et al.* 1986).

It is acknowledged that it crosses the placental barrier.

Metabolism

In humans, the conversion of $PGME_{\beta}$ into 2-methoxypropionic acid or 2-MPA (the main metabolite of $PGME_{\beta}$, not produced *via* the metabolism of $PGME_{\alpha}$) is similar to that observed in animals (Miller *et al.* 1986), occurring at a rate of around 70% (Devanthéry *et al*. 2003).

Figure 1 shows the metabolic pattern of $PGME_{\beta}$ and its acetate. PGMA was rapidly hydrolysed (carboxylases) to produce PGME and acetic acid in rats in an *in vitro* study (Stott *et al*. 1985).

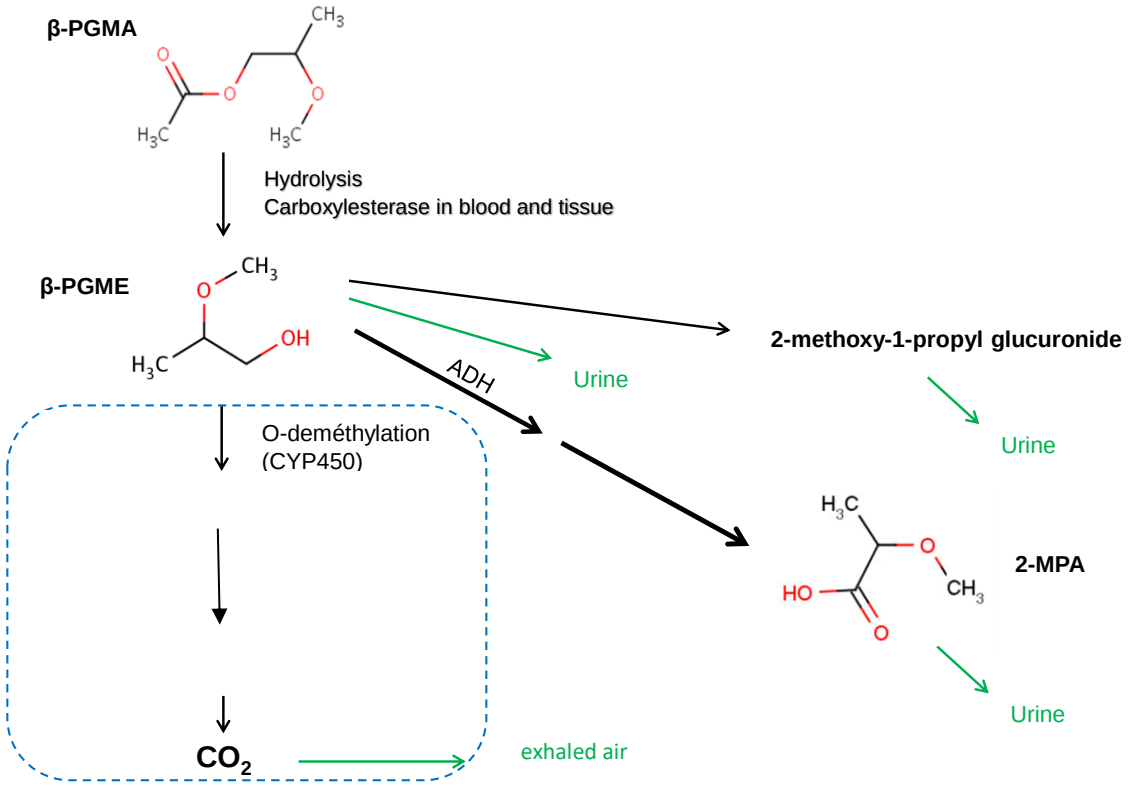

Figure 1: Metabolic pattern of $PGME_{\beta}$ (adapted from Miller *et al*. 1986)

Excretion

In a study undertaken in volunteers (n = 6) exposed to concentrations of 15, 50 and 95 ppm PGME (with 0.3% $PGME_{\beta}$) in vapour form (dermal and respiratory exposure), the authors calculated a urinary excretion percentage of 63-68% of the absorbed dose (for concentrations of 95 and 50 ppm respectively). To estimate dermal exposure, the six volunteers immersed one hand (unspecified exposed surface area[5]) in an aqueous solution of $PGME_{\alpha}$ (10%). The concentrations of 2-MPA measured in urine ranged from a value below the limit of detection (LOD = 0.10 mg/L) to 2.01 mg/L (for the six volunteers having immersed their hand in the PGME solution with 10% $PGME_{\beta}$).

The authors attributed the presence of 2-MPA in the volunteers' urine before exposure to past exposure (occupational and/or environmental) and to the long elimination half-life of the metabolite (Devanthéry *et al*. (2003).

In a field study, Laitinen (1997) reported a half-life of 15h for urinary 2-MPA.

In the study by Miller *et al*. (1986), the authors reported that the main metabolite of $PGME_{\beta}$ was urinary 2-MPA. They also detected $PGME_{\beta}$ (small quantities) in urine, in glucuroconjugated form. They did not detect free $PGME_{\beta}$ or propylene glycol.

[5] *of around 500 to 700 cm² (Berode et al. 1985)*

Selection of biomarkers of exposure and effect

Biomarkers of exposure (BME)

The analysis of the data in the literature led to two potential BMEs being identified:

- urinary 2-MPA
- urinary $PGME_{\beta}$

However, due to a lack of data on urinary $PGME_{\beta}$, this BME was not selected.

The advantages of 2-MPA, the only BME for which data are available, are described below:

- there are correlations between urinary concentrations of 2-MPA and atmospheric concentrations of PGME;
- relationships between 2-MPA concentrations and health effects have been reported;

This BME presents also disadvantages :

- there are large inter-individual variations;
- more generally, simultaneous exposure to alcohol is likely to partially inhibit the formation and elimination of the acid metabolites of glycol ethers.

Urinary 2-MPA, the main metabolite of $PGME_{\beta}$, seems relevant as a BME for the biological monitoring of occupational exposure to β isomer of PGME and its acetate.

Biomarkers of effect

No biomarkers of early effects were found in the literature.

Information on biomarkers of exposure identified as relevant for the biomonitoring of exposed workers

Name	**Urinary 2-Methoxypropionic acid (2-MPA)**
Other substances giving rise to this biomarker	DPGME and TPGME[6]
Concentrations measured in exposed workers or volunteers (with exposure levels and sampling times)[7]	• **Field studies:** Laitinen (1997b) N=26 (painters) with < 2.5% $PGMA_{\beta}$ M (8h) : 5.46 ± 9.52 ppm Med : 1.03 ppm $[2\text{-MPA}]_{urine}$ (ES): LOD = 0.1 mg/L AM (± SD) : 1.27 ± 1.6 mmol/mol creat (*i.e*. 1.17 ± 1.47 mg/g creat) Med : 0.53 mmol/mol creat (*i.e.* 0.48 mg/g creat) Anundi *et al.* (2000) N= 38 (graffiti removers including 2 women) $[PGMA]_{atm}$ (% de $PGME_{\beta}$ NR) : AM ± SD: 5.2 ± 6.2 mg/m^3 (1.4 ± 1.7 ppm) GM: 2.82 mg/m^3 and Max : 32.78 mg/m^3 $[2\text{-MPA}]_{urine}$ (ES): LOD = 0.24 µmol/L (*i.e*. 0.02 mg/L) AM : 6.81 µmol/L (*i.e*. 0.71 mg/L) Ben-Brik *et al.* (2004)* France 2000-2001 N= 54 (municipal employees of Paris) $[PGMA]_{atm}$ with 0.5-5% PGMEβ: NS $[2\text{-MPA}]_{urine}$: two samples collected per subject one month apart (ES/EW) LOD = 0.05 mg/L AM (± SD) : 1st urine sample : 1.24 ± 0.80 mmol/mol creat (*i.e*. 1.14 ± 0.74 mg/g creat) 2nd urine sample: 1.33 ± 0.98 mmol/mol creat (*i.e*. 1.22 ± 0.90 mg/g creat) Multigner *et al.* (2007)* France 2000-2001[8] N= 45 (municipal employees of Paris) $[PGMA]_{atm}$ with 0.5-5% $PGME_{\beta}$: NS 2-MPA (ES/EW) : LOD = 0.05 mg/L Med: 1.21 mg/g creat. (< LOD-5.14)

[6] Regarding the specificity of this BME, the authors of the ECETOC (2005) report suggest that dipropylene glycol monomethyl ether (DPGME) and tripropylene glycol monomethyl ether (TPGME), which are also isomer mixtures, may lead to the formation of 2-MPA. The INRS (2010c) reported that DPGME may theoretically lead to the formation of 61% $PGME_{\beta}$ and 39% $PGME_{\alpha}$ (considering 100% metabolic cleavage); a study in rats and rabbits (Breslin *et al.*, 1996) did not seem to confirm these percentages.

[7] *Values as reported by the authors. No publications specified whether the reported concentrations were those of free or total 2-MPA.*

[8] *These were the same subjects as in the study by Ben-Brik et al. 2004*

Concentrations measured in exposed workers or volunteers (with exposure levels and sampling times)	<u>Crucq and Pereira (2016)</u> N= NS (Bodywork painters)(46 samples) $[PGMA]_{atm}$ and % de $PGME_{\beta}$: NS $[2\text{-}MPA]_{urine}$ (sampling time NS) : LOD : NS AM : 0.35 mg/L Med : 0.13 mg/L and Max : 2,63 mg/L • **Studies on volunteers:** <u>Devanthéry *et al.* (2003)</u> N= 6 $[PGMA]_{atm}$ (0.3% $PGME_{\beta}$) : 15, 50 and 95 ppm (6h exposure). $[2\text{-}MPA]_{urine}$: Urine was collected every 2h (outside the chamber) and *ad lib* following exposure (until the next morning) LOD = 0.10 mg/L AM (±SD) : 0.73 (± 0.12) mg/L for exposure to 50 ppm AM (±SD) : 2.21 (± 0.35) mg/L for exposure to 95 ppm. A 15 ppm $[2\text{-}MPA]_{urine:}$ < 0.30 mg/L.
Conversion factor (with molecular weight)	2-MPA molecular weight: 104.1 Creatinine molecular weight: 113.12 1 mg/L = 9.6 µmol/L 1 µg/g creatinine = 1.087 µmol/mol creatinine
Concentration in the general population[9]	<u>Ben-Brik *et al.* (2004)*</u>: N= 55 (municipal employees not occupationally exposed) $[2\text{-}MPA]_{urine}$ MA (± SD) : 1st urine sample: 1.02 (±0.52) mmol/mol creat (*i.e.* 0.94 ± 0,48 mg/g creat) 2nd urine sample: 1.12 ± 0.98 mmol/mol creat (*i.e.* 1.03 ± 0.9 mg/g creat) <u>Multigner *et al.* (2007)*:</u> N= 53 (municipal employees not occupationally exposed) $[2\text{-}MPA]_{urine}$ 100% of samples above the LOQ (0.05 mg/L), Med: 1.12 mg/g creat. and Max : 2.50 mg/g creat.

[9] *Or failing this, in a non-occupationally exposed control population; 95th percentile or failing this the median or the mean (number of people in the study if this information is available)*

Concentration in the general population[9]	PELAGIE (*Perturbateurs Endocriniens : Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance*) - France, 2002-2006 3421 pregnant women Exposure assessed via self-questionnaires and job-exposure matrix 2-MPA (samples collected on morning) : LOQ = 0,05 mg/L[10] **1-** *Labat et al. (2008)*: pilot study N=200 subjects (selected based on their occupational exposure[11]) $[2\text{-MPA}]_{urine:}$ 22.5% (45/200) > LOQ GM: 0.43 mg/g creat (Max 8.75 mg/g creat.) **2-** *Cordier et al. (2012)*:* case-control study **N=** 94 cases and 580 controls $[2\text{-MPA}]_{urine}$: 5% des controls > LOQ Med : < LOQ (Max = 0.72 mg/L) **3-** *Garlantézec et al. (2012)**: **N= 451** $[2\text{-MPA}]_{urine:}$ 6% > LOD, Med < 0.05 mg/L (Max 0.72 mg/L). Calculated GM: 0.15 mg/L (for values greater than or equal to the LOD[11]) **4-** *Garlantézec et al. (2013)**: **N= 519** $[2\text{-MPA}]_{urine:}$ 6.9% > LOD Med < LOD and Max 0.76 mg/L. Calculated Med: 0.13 mg/L (for values greater than or equal to the LOD[12]) Frömme (2013) Germany: N= 44 ((31 women and 13 men) LOQ: 0,01 mg/L $[2\text{-MPA}]_{urine}$: 34% > LOQ, Med: 0.01 mg/g creat (< 0.01 mg/L), Max: 0.13 mg/g creat (0.08 mg/L) P95: 0.04 mg/g creat (0.02 mg/L). Nisse *et al.* (2017)* France 2008-2010: IMEPOGE (blood and urinary levels of various environmental pollutants in the general population) N = 120 subjects (men and women) $[2\text{-MPA}]_{urine:}$ 70% > LOD LOD = 0.01 mg/L and LOQ = 0.05 mg/L Warenbourg *et al.* (2017)*: Case-control study of the EDEN (Study of the pre- and postnatal determinants for child development and health in France, 2002-2006) and PELAGIE 1-EDEN : N = 67 and LOQ 0,05 mg/L N= 29 cases and 86 controls $[2\text{-MPA}]_{urine}$: 25.4% > LOD and Med < LOD 2-PELAGIE : N = 48 and LOQ = 0.05 mg/L $[2\text{-MPA}]_{urine}$: 2.1% > LOQ and Med < LOQ.

Concentrations in the general population[9]	ESTEBAN (2019) France (2014-2016) N=500 (adults aged from18 to 74 years) $[2\text{-MPA}]_{urine}$: 59.2% > LOQ LOQ = 0.01 mg/L and LOD = 0.003 mg/L GM (CI 95) = 0.014 (0,012-0.017) mg/L and Med : 0.013 mg/L GM (CI 95) = 0.018 (0.016-0.021) mg/g cr. and Med : 0.016 mg/g creat P95 (CI 95): 0.113 (0.071 – 0.222) mg/L P95 (CI 95) : 0.147 (0.105 – 0.188) mg/g creat	
Recommended limit values for exposed workers (INRS, 2014)	USA - ACGIH (BEI)	NS
	Germany - DFG (BAT)	
	Québec - IRSST (BME)	
	Finland - FIOH (BAL)	
	Other value(s):	France: biomarker proposed but value not determined** Switzerland: NS Belgium: NS

Mean (M); Arithmetic mean (AM); Geometric mean (MG); Median (Med) ;Standard deviation (SD); Maximal value (Max); 95th Percentile (P95), Confidence interval (CI) ; End of shift (ES); End of week (EW); Limit of detection (LOD)
** the analyses were undertaken by the same analytical laboratory* (Laboratory for Toxicology and Genetic Disease - *Lille Regional University Hospital)*
*** according to Biotox: "In subjects not occupationally exposed, urinary concentrations of 2-MPA were below 0. 30 mg/L (limit of detection of 0. 1 mg/L)"*

Study of the relationship between concentrations of 2-MPA in urine and health effects

In 2012, Cordier *et al.* assessed occupational exposure to solvents in pregnant women as part of a case-control study (with 94 cases and 580 controls) nested within the PELAGIE cohort. Malformations were studied by teams of obstetricians and paediatricians (two years of monitoring enabled subsequent malformations to be identified). Ninety-four children were found to have major malformations.

The authors assessed occupational exposure via three methods:

- A job-exposure matrix
- A self-questionnaire
- Measurements of urinary biomarkers

The authors reported that the risk of foetal malformations increased linearly with occupational exposure to solvents assessed via the matrix or self-questionnaire. They specified that non-occupational exposure was also assessed via a questionnaire but was not associated with a risk of major malformations.

For 2-MPA, an OR of 2.9 (95% CI: [1.2-6.8]) was observed for all malformations (when the concentration of 2-MPA was above the LOQ (0.05 mg/L)). The authors did not report statistically

[10] *Only the study of Labat et al 2008, pilot study of PELAGIE, reports a LOQ of 0,05 mg/L; the other articles present this value as a LOD but the authors have been contacted and have specified that it was a LOQ*

[11] *The authors were contacted and specified that for the PELAGIE pilot study (Labat et al. 2008), the subjects were selected based on their occupational exposure to solvents to undertake the analyses with the highest urinary metabolite levels*

[12] *The subjects in the Garlantézec et al. 2012 and 2013 studies were similar*

significant ORs for the risk of major malformations with other metabolites of glycol ethers. They indicated that they had made adjustments (maternal age at inclusion, level of education, alcohol and tobacco consumption and folic acid supplementation).

Only the study by Cordier et al. 2012 in pregnant women makes it possible to highlight a statistically significant increase in fetal malformations following exposure to $PGME_{\beta}$ (see Appendix 2 in the French report).
However, since the point of departure (POD) that could be identified as LOAEL corresponds to the LOQ of the study (0.05 mg/L) and that 2-MPA is detected in less than 5% of the samples, this study cannot be used to recommend a biological limit value given the too great uncertainties that it would generate.

Study of the relationship between concentrations of 2-MPA in urine and atmospheric concentration

The study by Laitinen *et al.* (1997b) undertaken in silkscreen workers (n = 54) enabled a linear correlation to be established between excreted 2-MPA and occupational exposure to $PGMA_{\alpha}$:

$Y = 0.16 x + 0.26 \quad R^2 = 0.78$ (n = 26)

where “y” represents urinary 2-MPA in mmol/mol creatinine and “x” is weighted exposure over eight hours to $PGMA_{\alpha}$ in ppm.

Although the concentration of the β-isomer in the mixture used was estimated, it is not possible to explicitly deduce a relationship with this isomer, which is the subject of this report.

Anundi *et al.* (2000) conducted a study in Sweden focusing on graffiti removers (n = 38, 36 men and two women). 2-MPA was detected in almost all of the urine samples, including those of 18 controls not occupationally exposed. The arithmetic mean urinary concentration of 2-MPA was 6.81 µmol/L (0.71 mg/L), while the atmospheric concentration of $PGME_{\alpha}$ for the graffiti removers was 2.82 mg/m^3 or 0.77 ppm (geometric mean). Concentrations of 2-MPA were significantly higher in the 38 graffiti removers than in the 18 office workers considered as unexposed (p = 0.0002).

In the study by Dévanthéry *et al.* (2003), urinary concentrations of 2-MPA before exposure to PGME varied between a value below the limit of detection of 0.10 mg/L and 0.30 mg/L. Urinary concentrations of 2-MPA had peaked at the end of exposure, ranging from 1.19 to 3.29 mg/L (for exposure to 50 and 95 ppm PGME containing 0.5% $PGME_{\beta}$). The urinary concentrations of 2-MPA showed a correlation with exposure to PGME.

The proportions of β isomer found in the commercial form of PGME have varied considerably from one product to another, and $PGME_{\beta}$ has no OEL. Thus, the studies reporting correlations between atmospheric $PGME_{\alpha}$ and 2-MPA do not make it possible to deduce with certainty a relationship between $PGME_{\beta}$ and 2-MPA. Therefore, a biological limit value cannot be derived for exposure to the β isomer.

Establishment of BLVs and choice of biological reference value

Biological limit value (BLV)

As no study allows with certainty the recommendation of a BLV based on health effects following an occupational exposure to $PGME_{\beta}$ and the establishment of a correlation between atmospheric $PGME_{\alpha}$ and 2-MPA, it is not possible to date to recommend a biological limit value.

Biological reference value (BRV)

The ESTEBAN cross-sectional study (Health Study on the Environment, Biomonitoring, Physical Activity and Nutrition) carried out on a representative sample of the adult population residing in France (which results were published in November 2019) identifies a value of 95th percentile of 0.113 mg/L for the age group 18 to 74 years (N = 500 included between April 2014 and March 2016). The analytical method used for the measurements carried out in this cohort presents a LOD of 0.003 mg/L and a LOQ of 0.01 mg/L (Esteban, 2019).

Concerning 2-MPA, a BRV of 0.10 mg/L (0.15 mg/g creat) is therefore recommended.

Conclusions of the collective expert appraisal

2-MPA in urine – End of shift:

BLV based on a health effect	**None**
BLV based on exposure to the 8-OEL	**None**
Biological reference value	**0,10 mg/L (0,15 mg/g creat)**

This BRV can not be considered to offer protection from the onset of health effects but do allow a comparison with the concentrations of biomarkers assayed in exposed workers

The study by Cordier et al. (2012) reporting developmental effects that could be associated with low levels of exposure to 2-methoxy-1-propanol or its acetate, the experts recommend reducing the exposure to these substances to the lowest possible level .

Sampling method and factors that may affect the interpretation of results

Sampling should be carried out at the end of the shift, preferably at the end of the week. It is advisable to rapidly transport samples at a temperature of 4°C or less. Urine samples should be kept at -20°C until they are analysed.

Regarding the interpretation of the results, simultaneous exposure to alcohols is likely to partially inhibit the formation and elimination of the acid metabolites of glycol ethers.

Biometrology

Some analytical methods described in the literature have been listed and are shown in the table below for 2-MPA. The objective of this section is not to recommend a measurement method, but to provide information on certain characteristics of the analytical methods.

	Method 2	**Method 3**	**Method 3**
Analytical technique References	NCI GC-MS after esterification with PFBBr** Labat *et al.*, 2008	GC-MS analysis, after acid hydrolysis and derivatisation with MTBSTFA Frömme *et al.*, 2013	GC-MS/MS buffer solution TBHAS, acetone derivation with PFBBr ESTEBAN 2019
pH adjustment	6	5-7	
Limit of detection	0.01 mg/L	NS	0,003 mg/L
Limit of quantification	0.05 mg/L	0.01 $mg \cdot L^{-1}$	0,01 mg/L
Fidelity	Repeatability (%CV) < 10 for 0.5 mg/L	NS	
Precision	NS	NS	
Reference standard	2-pentoxyacetic acid	Pentafluorophenoxyacetic acid	
Interlaboratory quality control programme	No	No	

* MTBSTFA: *N-tert*.-butyldimethylsilyl-*N*-methyltrifluoroacetamide
** PFBBr: Pentafluorobenzyl bromide

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