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COLLECTIVE EXPERT APPRAISAL:

3

SUMMARY AND CONCLUSIONS

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

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On the evaluation of biomarkers of exposure and recommendation for biological limit values for 2-methoxypropanol (1PG2ME or PGME_β; CAS 1589-47-5) and 2-methoxypropyl acetate (1PG2MEA or PGMA_β; CAS 70657-70-4)

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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 Groups on biomarkers (Biomarkers WG).

12

13 Presentation of the issue

14 On 3 February 2012, Anses received a formal request from the French Directorate General for
 15 Labour (DGT) to conduct the expert appraisal work required for recommending biological
 16 monitoring in the workplace for 2-methoxy-1-propanol and its acetate, 2-methoxypropyl acetate.
 17 There are two isomers of propylene glycol monomethyl ether (PGME): 1-methoxy-2-propanol
 18 (2PG1ME or PGME_α, CAS No. 107-98-2) and 2-methoxy-1-propanol (1PG2ME or PGME_β, CAS
 19 No. 1589-47-5); the respective acetates are 1-methoxy-2-propanol acetate (2PG1MEA or PGMA_α,
 20 CAS No. 108-65-6) and 2-methoxypropyl acetate (1PG2MEA or PGMA_β, CAS No. 70657-70-4).
 21 In this report, 1-methoxy-2-propanol and its acetate will be referred to respectively as PGME_α and
 22 PGMA_α while 2-methoxy-1-propanol and its acetate will be referred to as PGME_β and PGMA_β.

23 Since PGME_β and its acetate are classified as reprotoxic (Category 1B) under the CLP
 24 Regulation¹, a concentration of at least 0.3% PGME_β and/or PGMA_β in the commercial form of
 25 PGME results in a 1B reprotoxic classification².

26 France does not currently have any occupational exposure limits for PGME_β and its acetate.
 27 However, since 2007, the main isomer, PGME_α, as well as its acetate, have binding limit values,
 28 i.e. an 8h-OEL of 50 ppm and a 15min-STEL of 100 ppm³.

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

29 In an opinion published in 2008 (AFSSET 2008⁴), AFSSET recommended, to “*limit the risk of*
 30 *occupational exposure, strengthening biological surveillance in the workplace by developing*
 31 *markers for 2-methoxypropionic acid (2-MPA), the main metabolite of 1PG2ME and its acetate,*
 32 *and by systematically measuring urinary levels, instead of atmospheric levels, to be able to assess*
 33 *the overall exposure of workers”.*

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

36

37 **Scientific background**

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

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

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

50 Committee definitions

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

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

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

- 58 - if the body of scientific evidence is sufficient to quantify a dose-response relationship
 59 with certainty, the BLVs will be established on the basis of health data (no effect for
 60 threshold substances or risk levels for non-threshold carcinogens);
- 61 - in the absence of such data for substances with threshold effects, BLVs are calculated
 62 on the basis of the expected concentration of the biomarker of exposure (BME) when
 63 the worker is exposed to the 8-hour OEL. For carcinogens, in the absence of sufficient
 64 quantitative data, the biological limit value is calculated on the basis of another effect

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>

65 (pragmatic BLV). These latter values do not guarantee the absence of health effects,
66 but aim to limit exposure to these substances in the workplace.

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

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

74

75 **Organisation of the expert appraisal**

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

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

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

85

86 **Preventing risks of conflicts of interest**

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

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

91

92 **Description of the method**

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

96 The summary report on the BMEs for PGME_β (and its acetate) was based on bibliographical
97 information taking into account the scientific literature published on this substance until end of
98 2018. The bibliographical research was conducted in the following databases: Medline, Scopus
99 and the Public Health Database.

100 The scientific articles selected for evaluating biomonitoring data on PGME_β were identified using
101 the following keywords: “propylene glycol methyl ether”, “biomarker”, “biomonitoring”, “biological
102 monitoring”, “urine”, “blood”, “occupational”, “analysis method”.

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

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

107

108 **Result of the collective expert appraisal**

109

110 **Toxicokinetics data**

111 **Absorption**

112 There are very few data on the absorption of PGME_β. However, like any glycol ether, it is readily
 113 absorbed by the oral and respiratory routes.

114 PGME_β can be absorbed by the lungs in aerosol form.
 115 Regarding the oral route, a study in animals reported rapid absorption of PGME_β (Tmax in blood
 116 <1h) (Carney *et al.* 2003).

117

118 **Distribution**

119 There are no data available for humans.

120 In animals, PGME_β is distributed in the blood and skin, with lower quantities being distributed in
 121 other tissues (liver, kidneys, brain, testicles and fat) after oral exposure (Miller *et al.* 1986).

122 It is acknowledged that it crosses the placental barrier.

123

124 **Metabolism**

125 In humans, the conversion of PGME_β into 2-methoxypropionic acid or 2-MPA (the main metabolite
 126 of PGME_β, not produced *via* the metabolism of PGME_α) is similar to that observed in animals
 127 (Miller *et al.* 1986), occurring at a rate of around 70% (Devanthery *et al.* 2003).

128 Figure 1 shows the metabolic pattern of PGME_β and its acetate. PGMA was rapidly hydrolysed
 129 (carboxylases) to produce PGME and acetic acid in rats in an *in vitro* study (Stott *et al.* 1985).

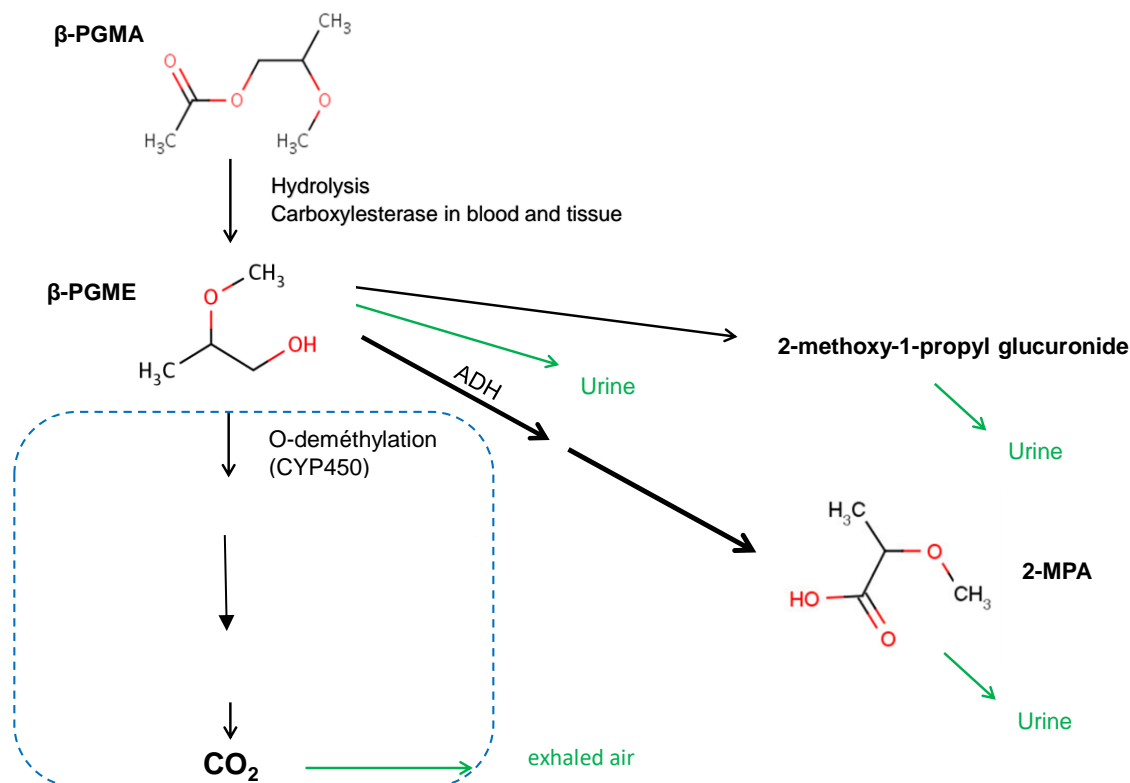


Figure 1: Metabolic pattern of PGME_β (adapted from Miller *et al.* 1986)

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133

134 **Excretion**

135 In a study undertaken in volunteers ($n = 6$) exposed to concentrations of 15, 50 and 95 ppm PGME
 136 (with 0.3% PGME_β) in vapour form (dermal and respiratory exposure), the authors calculated a
 137 urinary excretion percentage of 63-68% of the absorbed dose (for concentrations of 95 and 50
 138 ppm respectively). To estimate dermal exposure, the six volunteers immersed one hand
 139 (unspecified exposed surface area⁵) in an aqueous solution of PGME (PGME with 10% PGME_β).
 140 The concentrations of 2-MPA measured in urine ranged from a value below the limit of detection
 141 (LOD = 0.10 mg/L) to 2.01 mg/L (for the six volunteers having immersed their hand in the PGME
 142 solution with 10% PGME_β).

143 The authors attributed the presence of 2-MPA in the volunteers' urine before exposure to past
 144 exposure (occupational and/or environmental) and to the long elimination half-life of the
 145 metabolite. In a field study, Laitinen (1997) reported a half-life of 15h for urinary 2-MPA.

⁵ of around 500 to 700 cm^2 (Berode *et al.* 1985)

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

149

150 **Selection of biomarkers of exposure and effect**

151 ***Biomarkers of exposure (BME)***

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

- 153 - urinary 2-MPA
- 154 - urinary PGME_β

155 However, due to a lack of data on urinary PGME_β, this BME was not selected.

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

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

160 This BME presents also disadvantages :

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

164

165 **Urinary 2-MPA, the main metabolite of PGME_β, seems relevant as a BME to be used for the**
 166 **β isomer of PGME and its acetate.**

167

168 ***Biomarkers of effect***

169 No biomarkers of early effects were found in the literature.

170

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

Name	Urinary 2-Methoxypropionic acid (2-MPA)
Other substances giving rise to this biomarker	DPGME and TPGME ⁶

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_β and 39% PGME_α (considering 100% metabolic cleavage); a study in rats and rabbits (Breslin *et al.*, 1996) did not seem to confirm these percentages.

<p>Concentrations measured in exposed workers or volunteers (with exposure levels and sampling times)⁷</p>	<ul style="list-style-type: none"> • Field studies: <p><u>Laitinen (1997b)</u> 26 painters: exposure to 5.5 ± 9.5 ppm PGMA (mean, and median of 1.03) with < 2.5% PGMA_β 2-MPA: arithmetic mean of 1.3 ± 1.6 mmol/mol creat. at end of shift and median of 0.53 mmol/mol creat.</p> <p><u>Anundi et al. (2000)</u> 38 graffiti removers (including two women): arithmetic mean exposure to 5.2 ± 6.2 mg/m³ (1.4 ± 1.7 ppm) PGME_α with an unspecified percentage of PGME_β; a geometric mean and a maximum value respectively of 2.82 and 32.78 mg/m³ 2-MPA: arithmetic mean of 6.81 μmol/L (0.71 mg/L) (end of shift)</p> <p><u>Ben-Brik et al. (2004)*</u> France 2000-2001 54 municipal employees of Paris: for unspecified exposure to PGME_α with 0.5-5% PGME_β 2-MPA: two samples collected per subject: arithmetic means of 1.24 ± 0.80 (1st urine sample) and 1.33 ± 0.98 mmol/mol creat. (2nd urine sample) at end of week and end of shift (samples collected one month apart)</p> <p><u>Multigner et al. (2007)*</u> France 2000-2001⁸ 45 municipal employees of Paris: for unspecified exposure level to PGME_α with 0.5-5% PGME_β. 2-MPA: median of 1.21 mg/g creat. (< LOD-5.14) (end of week and end of shift)</p> <p><u>Cruçq and Pereira (2016)</u> Bodywork painters (n = ? – 46 samples): for unspecified exposure level to PGME, with an unspecified percentage of PGME_β 2-MPA: arithmetic mean of 0.35 mg/L and median of 0.13 mg/L (max 2.63 mg/L) (sampling time not specified)</p> • Studies on volunteers: <p><u>Devanthery et al. (2003)</u> Six volunteers exposed to 15, 50 and 95 ppm PGME containing 0.3% PGME_β. 2-MPA: 0.73 ± 0.12 and 2.21 ± 0.35 mg/L for exposure to 50 and 95 ppm respectively. At 15 ppm, the excreted levels were lower than the background level, which could reach 0.30 mg/L. Urine was collected every 2h (outside the chamber) and <i>ad lib</i> following exposure (until the next morning)</p>
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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

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	<p><u>Ben-Brik et al. (2004)*</u>: 55 municipal employees not occupationally exposed 2-MPA: arithmetic means of 1.02 ± 0.52 to 1.12 ± 0.98 mmol/mol creat.</p> <p><u>Multigner et al. (2007)*</u>: 53 municipal employees not occupationally exposed 2-MPA: 100% of samples above the LOQ (0.05 mg/L), median of 1.12 mg/g creat. and maximum value of 2.50 mg/g creat. France 2000-2001.</p> <p><u>PELAGIE (Perturbateurs Endocriniens : Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance)</u> - France, 2002-2006 3421 pregnant women Exposure assessed via self-questionnaires and job-exposure matrix</p> <p>1- <u>Labat et al. (2008)</u>: pilot study in 200 subjects (selected based on their occupational exposure¹⁰) 22.5% (45/200) above the LOQ of 0.05 mg/L, geometric mean of 0.43 mg/g creatinine and maximum value of 8.75 mg/g creat.</p> <p>2- <u>Cordier et al. (2012)*</u>: case-control study (94 cases and 580 controls) 5% (30/580) above the LOD¹¹ of 0.05 mg/L, median < LOD and maximum value of 0.72 mg/L</p> <p>3- <u>Garlantézec et al. (2012)*</u>: 6% (31/451) above the LOD of 0.05 mg/L, median < 0.05 mg/L and maximum value of 0.72 mg/L. Calculated geometric mean of 0.15 mg/L for values greater than or equal to the LOD¹¹</p> <p>4- <u>Garlantézec et al. (2013)*</u>: 6.9% (29/519) above the LOD¹¹ of 0.05 mg/L, median < LOD and maximum value of 0.76 mg/L. Calculated median of 0.13 mg/L for values greater than or equal to the LOD¹²</p>

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)

¹⁰ 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

¹¹ The authors were contacted and specified that this was a limit of quantification (see Labat et al. 2008, PELAGIE pilot study)

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

<p>Concentrations in the general population</p>	<p><u>Frömme (2013):</u> German general population: n = 44 (31 women and 13 men) 2-MPA: 34% > LOQ of 0.01 mg/L, median of 0.01 mg/g creat. (< 0.01 mg/L), maximum value of 0.13 mg/g creat. (0.08 mg/L) and 95th percentile of 0.04 mg/g creat. (0.02 mg/L).</p> <p><u>Nisse <i>et al.</i> (2017)*:</u> IMEPOGE (blood and urinary levels of various environmental pollutants in the general population) survey in France, 2008-2010 n = 2000 subjects (men and women) 2-MPA detected (> 0.01 mg/L) in 70% of the urine collected from 120 subjects but no possible quantification (< 0.05 mg/L)</p> <p><u>Warenbourg <i>et al.</i> (2017)*:</u> Case-control study of the EDEN (Study of the pre- and postnatal determinants for child development and health in France, 2002-2006) and PELAGIE n = 29 cases and 86 controls</p> <ul style="list-style-type: none"> ▪ 1-EDEN: 25.4% (17/67) above the LOD of 0.05 mg/L, with a median < 0.05 mg/L ▪ 2-PELAGIE: 2.1% (1/48) above the LOD, with a median < LOD. 	
<p>Recommended limit values for exposed workers (INRS, 2014)</p>	<p>USA - ACGIH (BEI)</p> <p>Germany - DFG (BAT)</p> <p>Québec - IRSST (BME)</p> <p>Finland - FIOH (BAL)</p>	<p>NS</p>
	<p>Other value(s):</p>	<p>France: biomarker proposed but value not determined**</p> <p>Switzerland: NS</p> <p>Belgium: NS</p>

173

174 * the analyses were undertaken by the same analytical laboratory (Laboratory for Toxicology and Genetic Disease - Lille Regional
 175 University Hospital)

176 ** according to Biotox: "In subjects not occupationally exposed, urinary concentrations of 2-MPA were below 0.30 mg/L (limit of
 177 detection of 0.1 mg/L)".

178

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

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

185 The authors assessed occupational exposure via three methods:

- 186 - A job-exposure matrix
- 187 - A self-questionnaire
- 188 - Measurements of urinary biomarkers

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

193 For 2-MPA, an OR of 2.9 (95% CI: [1.2-6.8]) was observed for all malformations (when the
 194 concentration of 2-MPA was above the LOQ (0.05 mg/L)). The authors did not report statistically
 195 significant ORs for the risk of major malformations with other metabolites of glycol ethers. They
 196 indicated that they had made adjustments (maternal age at inclusion, level of education, alcohol
 197 and tobacco consumption and folic acid supplementation).

198
 199
 200 Study of the relationship between concentrations of 2-MPA in urine and atmospheric concentration

201 The study by Laitinen *et al.* (1997b) undertaken in silkscreen workers (n = 54) enabled a linear
 202 correlation to be established between excreted 2-MPA and occupational exposure to PGMA:

203 $Y = 0.16 x + 0.26 \quad R^2 = 0.78 \quad (n = 26)$

204 where “y” represents urinary 2-MPA in mmol/mol creatinine and “x” is weighted exposure over
 205 eight hours to PGMA_α in ppm

206 Anundi *et al.* (2000) conducted a study in Sweden focusing on graffiti removers (n = 38, 36 men
 207 and two women). 2-MPA was detected in almost all of the urine samples, including those of 18
 208 controls not occupationally exposed. The arithmetic mean urinary concentration of 2-MPA was
 209 6.81 μmol/L (0.71 mg/L), while the atmospheric concentration of PGME_α for the graffiti removers
 210 was 2.82 mg/m³ or 0.77 ppm (geometric mean). Concentrations of 2-MPA were significantly higher
 211 in the 38 graffiti removers than in the 18 office workers considered as unexposed (p = 0.0002).

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

217 **The proportions of β isomer found in the commercial form of PGME have varied**
 218 **considerably from one product to another, and PGME_β has no OEL. Thus, the studies**
 219 **reporting correlations between atmospheric PGME_α and 2-MPA do not make it possible to**
 220 **deduce with certainty a relationship between PGME_β and 2-MPA. Therefore, a biological**
 221 **limit value cannot be derived for exposure to the β isomer.**

222

223

224

225

226 **Establishment of BLVs and choice of biological reference value**

227 Biological limit value (BLV)

228 Only the study by Cordier *et al.* (2012) in pregnant women showed a statistically significant
229 increase in malformations following exposure to PGME_β, despite the low urinary levels measured.

230 Based on this study's results (described above), the limit of quantification of 0.05 mg·L⁻¹ of urinary
231 2-MPA was identified as the LOAEL for the developmental effects (major malformations) of
232 PGME_β.

233 Since the study's subjects were pregnant women, it did not appear relevant to apply an inter-
234 individual adjustment factor, because this is the most susceptible population group in the
235 workplace. After application of a LOAEL-to-NOAEL adjustment factor of 3, the recommended
236 biological limit value is 0.017 mg·L⁻¹ rounded up to 0.02 mg·L⁻¹.

237 **The Committee recommends for urinary 2-MPA with sampling at end of shift a BLV of**
238 **0.02 mg·L⁻¹.**

239

240 Biological reference value (BRV)

241 Recent studies undertaken with large cohorts (Warembourg *et al.* 2017, Nisse *et al.* 2017) could
242 not be used because the levels of detection were too low, whereas earlier studies are certainly
243 not representative of current exposure.

244 **Therefore, no BRV can be recommended for 2-MPA.**

245

246

247 **Conclusions of the collective expert appraisal**

248 2-MPA in urine – End of shift:

BLV based on a health effect	0.02 mg·L⁻¹
Biological reference value	None

249

250 **The limits of quantification of the analytical methods should be improved to enable urinary**
251 **2-MPA to be appropriately quantified.**

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258 **Sampling method and factors that may affect the interpretation of results**

 259 Sampling should be carried out at the end of the shift, preferably at the end of the week. It is
 260 advisable to rapidly transport samples at a temperature of 4°C. If urine samples are transported
 261 at ambient temperature, it is preferable to acidify them at the time of sampling. Upon arriving at
 262 the laboratory, urine samples should be kept at -20°C until they are analysed.

263 Sampling conditions and alcohol consumption can interfere with 2-MPA measurement results.

264

 265 **Biometrology**

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

Urinary 2-MPA			
	Method 1	Method 2	Method 3
Analytical technique	GC-MS analysis, after acid hydrolysis and derivatisation with MTBSTFA*	NCI GC-MS after esterification with PFBBr**	GC-MS analysis, after acid hydrolysis and derivatisation with MTBSTFA
References	DFG, 2006	Labat <i>et al.</i> , 2008	Frömme <i>et al.</i> , 2013
pH adjustment		6	5-7
Limit of detection	0.05 mg·L ⁻¹	0.01 mg·L ⁻¹	NS
Limit of quantification	NS	0.05 mg·L ⁻¹	0.01 mg·L ⁻¹
Fidelity	Repeatability (%CV): 6.6 and 2.9 for 1 and 20 mg·L ⁻¹ , respectively	Repeatability (%CV) < 10 for 0.5 mg·L ⁻¹	NS
Precision	Recovery rate (%): 87.5, 82.5 and 79.9 for 1, 10 and 50 mg·L ⁻¹ , respectively	NS	NS
Reference standard	Pentafluorophenoxyacetic acid	2-pentoxyacetic acid	Pentafluorophenoxyacetic acid
Interlaboratory quality control programme	No	No	No

 269 * MTBSTFA: *N-tert.*-butyldimethylsilyl-*N*-methyltrifluoroacetamide

270 ** PFBBr: Pentafluorobenzyl bromide

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