COLLECTIVE EXPERT APRAISAL:

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 and biological reference values for dimethylformamide (CAS n°68-12-2)

This document summarises the work of the Expert Committee on "Health reference values" and the Working Group on biomarkers (Biomarkers WG).

Presentation of the issue

Within the framework of the European research program HBM4EU, a joint effort of thirty countries, guidance values for biomonitoring (or Human Biomonitoring Guidance Values (HBM-GVs)) are recommended for the general population and workers. These values are proposed for substances of interest identified as priorities. Dimethylformamide (DMF) has been the subject of proposals for guidance values within the HBM4EU program (see HBM4EU: Deliverable Report D5.9 - 3rd substance specific derivation of EU-wide health-based guidance values[1]).

The methodology applied within the framework of the HBM4EU project (Apel *et al.,* 2020) for the identification of the biomarkers of exposure (BME) of interest and the proposal of biological values for workers is partly based on Anses methodology (ANSES, 2017).

As part of the memorandum of understanding on occupational exposure limits and biological limit values (OELs and BLVs) established in July 2018 between Anses and the Directorate General for Labor (DGT), Anses was asked to recommend biological values for DMF. This document has been drawn up in response to this request, on the basis of the assessment previously carried out by Anses employees as part of the HBM4EU research program for the recommendation of biological values for DMF in the workplace.

Currently, France has a binding 8h-OEL for DMF of 15 $mg.m^{-3}$ (5 ppm) and a binding short-term limit value over 15 minutes (or VLCT-15min) of 30 $mg.m^{-3}$ (10 ppm).

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,

[1] Available on HBM4EU website: https://www.hbm4eu.eu/work-packages/deliverable-5-9-3rd-substance-specific-derivation-of-eu-wide-health-based-guidance-values/ ; accessed on December 2021

- 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.

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 Expert Committee on “Health reference values”. The Agency also mandated the Working Group on biomarkers of exposure (WG on BME) 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 the website: https://dpi.sante.gouv.fr/.

Description of the method

Two ANSES employees and two experts from the WG on BME produced the report on the BME and the recommendation of human biomonitoring guidance values for workers (HBM-GV_{Worker}), for the BME selected as relevant in the context of the HBM4EU research program. To this end, a review of the studies provided by the IARC (IARC, 2018), ECHA (ECHA, 2019), ACGIH (ACGIH, 2017 and 2018), DFG (DFG, 2006 and 2019) and SCOEL (SCOEL, 2006) was conducted with a search for more recent studies on the following databases: Medline, Scopus.

The scientific articles selected for the evaluation of DMF biological monitoring data were identified based in particular on the following keywords: "Dimethylformamide", "DMF", "guidance value", "toxicity reference value (TRV)", "biomarker of exposure", "biomonitoring", "toxicokinetic*", "health effects", "liver", "carcinogenicity", "reprotoxic effects".

In this document, only the results of the collective expert appraisal are detailed. The toxicological profile and data on DMF exposure can be found in the HBM4EU Deliverable Report D5.9.

The summary and conclusions of this collective expert appraisal work (in French) were adopted by the Expert Committee on "Health reference values" on 30/06/2022.

The collective expert appraisal work was submitted to public consultation from 06/09/2022 to 06/10/2022. No comments were received. The Health Reference Values Committee adopted this version on 8 December 2022.

Result of the collective expert appraisal

Choice of BME(s)

The table below (Table 1) details the advantages and limits of each BME identified in literature for DMF exposure.

Table 1: Advantages and limits of the relevant BME

Analyte	Matrix	Advantages	Limits
NMF total (tNMF)	**Urine**	- Half-life adapted to estimate daily exposure - Database available -Specific - Undetectable in the general population - Dose response with health effects - Good correlation with airborne DMF - Non invasive	- Delayed excretion after skin absorption - Influenced by alcohol consumption
AMCC	**Urine**	- Half-life enabling to estimate weekly exposure - Database available - Dose response with health effects - Good correlation with airborne DMF - Directly linked to MIC*, causing the hepatotoxic effects - Non invasive	Environmental source of exposure (active or passive smoking) that may cause interferences*
MCVal	Blood	- Very stable, assess long term exposure - Directly linked to MIC formation - Dose response with health effects - Good correlation with airborne DMF	- Limited database - Probably influenced by smoking - Invasive
DMF	**Urine**	Specific	- Very limited database - Very short half-life (2 h) - Low excreted levels for high absorbed doses
Formamide	**Urine**	None	- No data available on correlation with DMF exposure or its health effects - Not specific, can be found in absence of DMF exposure

*methylisocyanate

**tobacco smoke are a source of MIC, precursor of AMCC

Total NMF (which is the sum of N-hydroxymethyl-N-methylformamide (HMMF) and NMF) and AMCC measured in urine are recommended by several agencies/organisations (SCOEL, DFG, ACGIH) as BMEs for biomonitoring of occupational DMF exposure. These two BMEs have many advantages; they are the best studied in the context of assessing DMF exposure and its health effects in the workplace. The many advantages of these two BMEs make it possible to retain them for deriving BLVs or BRVs. Their measures are not redundant because they provide different informations: total NMF measured at the end of the shift on any day of the week reflects the exposure of the day while AMCC measured at the end of the shift and at the end of the week is an indicator of weekly exposure. It also has the advantage of being an indicator of the production of methylisocyanate (MIC), at the origin of DMF hepatotoxic effects.

The MCVal has the advantage to reflect DMF exposure of the previous months and is a direct indicator of the hepatotoxic risk. However, the lack of data does not allow to retain it currently for the derivation of a BLV.

Regarding the other potential BMEs, formamide and DMF in urine, the available data do not allow the characterization of associations of these BMEs levels with the health effects of DMF or with atmospheric exposure.

Consequently, only tNMF and AMCC in urine are retained as relevant BMEs for the biomonitoring of occupational exposure to DMF.

Proposal for biological limit values

Choice of critical effect

Many studies conducted at the workplace make it possible to establish dose-response relationships between tNMF concentration and health effects. Among these health effects linked to occupational exposure to DMF, the most sensitive effects, retained as critical effects, are the effects on liver. These effects are assessed by measuring liver enzymes such as ALT, AST and γGT. In several published studies, “Antabuse” effects[2] were observed in the absence of liver damage in workers exposed to DMF. However, the great inter-individual variability of alcohol intolerance and the indirect nature of this effect (which requires the intake of alcohol to manifest itself), makes it unsuitable for setting a reference value to protect all workers exposed to DMF. The choice of DMF hepatotoxicity as the critical effect is a consensus among the various agencies or organisations recommending OELs and limit values for biological indicators in the workplace.

DMF is a reprotoxic substance but studies conducted in animals report points of departure (PODs) for these effects at higher levels than those observed for hepatic effects. Regarding the carcinogenic effects, it should be reminded that:
- there is insufficient evidence of DMF genotoxicity;
- the two clusters of testicular cancers published do not constitute sufficient proof of the carcinogenicity of DMF in humans and that, in animals (rats and mice), the only tumors induced by DMF are hepatic and that they are always preceded by hepatotoxic effects. From these observations, it can be deduced that a BLV offering protection against hepatic damage also most likely protects against a possible risk of cancer.

[2] Antabuse effects are effects occurring when ethanol is taken a few hours to a few days after contact with N,N-dimethylformamide and consisting of peripheral vasodilation, predominantly on the face, neck and in the upper part of the trunk, responsible for hypotension, tachycardia, headaches and dizziness, and frequently accompanied by sweating, vomiting and a feeling of chest tightness

Choice of key study(ies) and POD

Urinary total NMF

The database provides many studies that can be selected as key studies. However, for methodological reasons (error in the units of measurement, inappropriate analytical methods leading to an overestimation of the results), the following studies were not retained: Lyle *et al.*, 1979, Catenacci *et al.*, 1984 and Fiorito *et al.,* 1997. Despite the interest of the results reported by Lauwerys *et al.* (Lauwerys *et al.*, 1980) and Wrbitzky *et al.* (Wrbitzky and Angerer, 1998 and Wrbitzky, 1999), these studies conducted on European populations cannot be retained either for the following reasons:
- the non-representativity of the subjects in the study by Lauwerys *et al.:* In this study the authors do not report any effect on the liver enzymes of workers exposed to DMF (N=22) up to 40-50 mg/g cr of tNMF. They emphasize that the recruitment selection criteria (not specified in the article), were quite strict. According to ACGIH, these criteria could lead to a selection bias, implying that the results may not be representative of those of other workers (ACGIH, 2017)
- the uncertainty on the effects on liver related to alcohol consumption not taken into account in two publications of the same study conducted in a cohort of 126 workers (Wrbitzky and Angerer, 1998; Wrbitzky, 1999): The authors report an increase in serum concentrations of liver enzymes in the exposed group (vs. controls) with a mean tNMF concentration in urine of 9.1 mg/g cr (14.9 mg/L). However, if the different work areas in the company were taken into account, an excess risk of liver damage was observed, unexpectedly, only in the area where the exposures were the lowest (with an average concentration of tNMF of 4.5 m/g cr); this discordant result was probably explainable by a higher alcohol consumption specifically in this group. In the other three zones, no effect on hepatic enzyme activity was observed for tNMF concentrations of 6.7, 11.6 and 16 mg/g cr.

Finally, among the studies reporting dose-response relationships between urinary tNMF concentrations and the risk of elevated serum concentrations of liver enzymes, the following studies were retained as key studies:

- the only study conducted on a European population, among the studies retained with consideration of alcohol consumption, the recent study by Kilo *et al.*, did not report any hepatotoxic effect in workers (N=220 workers) exposed to DMF whose average urinary concentration of tNMF was 7.7 mg/L (standard deviation: 8.8 mg/L) , compared to a control group (N=175) (Kilo *et al.,* 2016).

- the other three selected studies were conducted in Asia:

- despite a low number of subjects, Sakai *et al*., reported no effect on hepatic enzymes from exposure to DMF in 10 workers (followed during 2.5 years) for an average concentration of tNMF in urine of 24.7 mg/g cr (Sakai *et al.*, 1995),
- He *et al.*, in a cohort of 79 workers, did not find increase in liver enzymes in the most exposed subjects when workers were divided into 2 groups (concentrations > or < 15 mg/g cr) (He *et al*., 2010),
- more recently, Wu *et al*. were able to measure liver enzyme activity in a cohort of 698 workers exposed to DMF (vs. 188 controls). Their results showed an excess risk of liver damage only appearing in the third tertile of the distribution of urinary concentrations of tNMF (> 3.88 mg/L; median 9.59 mg/L) and the $BMDL_{10}$ for the risk liver damage was 14 mg/L (Wu *et al.*, 2017).

Urinary AMCC

Urinary AMCC is a relevant BME according to the database, because, on the one hand, it makes it possible to assess the cumulative exposure of the previous days and, on the other hand, it is linked to the formation of MIC, metabolite responsible of hepatotoxic effects.

Studies reporting relationships between urinary AMCC levels and liver effects are fewer in numbers than for tNMF and also show less consistent results.

However, studies selected as key studies for the calculation of a BLV for tNMF can be considered relevant for the derivation of a BLV for AMCC.

- the European study by Kilo *et al.,* carried out on a large number of subjects (220 exposed versus 175 controls), did not report any effect on hepatic enzymes whereas the average urinary concentration of AMCC in the urine of exposed workers was 9.4 mg/g cr (standard deviation: 10.4 mg/g cr) (Kilo *et al.,* 2016).
- the four studies, conducted in Asia, indicate that:
  - No effect on liver in 10 workers exposed to DMF during 2.5 years (average urinary concentration of AMCC: was 22.0 (± 4.6) mg/g cr; 2.2-110 mg/g cr) (Sakai *et al*., 1998);
  - A significant increase of the number of individuals with elevated liver enzyme activity was observed in the most exposed group when the subjects were divided into two groups (those with urinary concentration of AMCC greater than or less than 40 mg/g cr) (He *et al.*, 2010);
  - In another study with 72 exposed and 72 non exposed workers, the authors report an increase in liver enzymes in exposed subjects (presenting an average concentration in urinary AMCC of 28.3 mg/L) compared to non exposed workers (He et al., 2015);
  - In the study involving the largest number of workers (698 exposed to DMF and 188 controls) and which is also one of the most recent (Wu *et al.,* 2017), the results show an excess of risk of liver damage in the second and third tertiles of the distribution of urinary concentrations of AMCC, with median values of 44 mg/L (16.95-86.82 mg/L)) and 148 mg/L (>86.62 mg/L) respectively. The median of urinary concentrations of AMCC in the lowest exposed group (and in which no hepatotoxic effect was observed) was 2.2 mg/L (<16.95 mg/L). The authors report a $BMDL_{10}$ of 155 mg/L.

In conclusion for the two selected BMEs, tNMF and AMCC in urine, it seems difficult to retain only one study. It is therefore more relevant to select several studies as key studies, for the derivation of BLVs. This choice is, in particular, motivated by:

- the ethnic variability of DMF metabolism and the different geographical origins of the available studies (involving Asian and European population);

- methodological differencies in the studies, in particular for the definition of liver test abnormalities, which varies from one study to another (*i.e.* with the choice of the increase of one or two liver enzymes depending on the authors).

Thus, the following studies are selected for deriving BLVs for biomonitoring of occupational DMF exposure: Sakai *et al.*, 1995; He *et al.*, 2010; Kilo *et al.*, 2016; Wu *et al.*, 2017.

Identification of a POD and proposition of BLVs

The Table 2 reports the results with dose-effect relationships from the key studies for tNMF and AMCC in urine.

Table 2: Summary of the PODs (median and mean) reported in key studies

Reference and subjects	NOAEL/LOAEL/ BMDL	Urinary t NMF Sampling time		Urinary AMCC Sampling time	
		mg.g^{-1} cr	**mg.L^{-1}**	**mg.g^{-1} cr**	**mg.L^{-1}**
Sakai *et al.*, 1998 10 workers Japan	NOAEL	Mean±SD = 24,7 ± 5,4 ES	NR	Mean±SD = 22 ± 4,6 ES	NS
He *et al.*, 2010 79 workers China	NOAEL	GM = 15 ES/EW	NR	NR	NS
	LOAEL	NR	NR	GM = 40 ES/EW	NS
He *et al.*, 2015 72 exposed workers et 72 non exposed China	NOAEL	NR	NR	NR	NS
	LOAEL	NR	NR		Mean±SD = 28,32±8,07 (Sampling time : NR)
Kilo *et al.*,2016 220 workers et 175 non exposed Germany	NOAEL		Mean±SD = 7,8 ± 8,8	Mean±SD = 9,4 ± 10,4	
Wu *et al.*, 2017 698 workers et 188 non exposed China	NOAEL[3]		Med (max) = 1,8 (<4)		Med (max) = 2,2 (<17)
	LOAEL[18]		Med (min) = 9,6 (>4)		Med (min) = 44 (>17)
	$BMD_{95}L_{10}$		14		155

Med : Median ; SD : Standard deviation ; GM : Geometric mean ; Min : minimal value; Max : maximal value; NS : not specified

On the basis of these studies, concerning:

- **urinary tNMF**: the NOAELs are between 1.8 (Max<4) and 7.8 (SD± 8,8) mg.L^{-1} and between 15 and 24.7 (SD ± 5,4) mg.g^{-1} cr, with a LOAEL of 9.6 (Min>4) mg.L^{-1} and a $BMD_{95}L_{10}$ of 14 mg.L^{-1}. Taking into account the highest NOAEL and the lowest LOAEL (i.e 7.8 and 9.6 mg.L^{-1} respectively), **the value of 10 mg.L^{-1}, as proposed in the framework of HBM4EU project appears to be sufficiently protective of the critical effects (i.e. DMF hepatotoxicity). This value is selected as BLV for the protection of the health of workers exposed to DMF.**

- **urinary AMCC**: the NOAELs are 2.2 (<16. mg.L^{-1}) and between 9.4 (SD± 10.4) and 22 (SD± 8.1) mg.g^{-1} cr, while for the LOAELs the corresponding values are between 28 and 44 (Min>17) mg.L^{-1} and 40 mg.g^{-1} cr. Taking into account the highest NOAEL and the lowest LOAEL (2.2 et 28 mg.L^{-1} ou 22 et 40 mg.g^{-1} cr), **the values of 20 mg.L^{-1} or 25 mg.g^{-1} cr seem to be sufficiently**

[3] Calculs réalisés par le GT IBE

protective against the critical effects (liver effects). These values are selected as BLV for the protection of the health of workers exposed to DMF.

Proposal of biological reference values (BRV)

Urinary tNMF

There is no data on urinary tNMF levels in the general population. It should also be noted that total NMF is not detected in the urine of unexposed workers or in controls from field studies (Kilo *et al.*, 2016).
No BRV is therefore recommended for total NMF in urine.

Urinary AMCC

There are many studies reporting measurements of urinary AMCC concentration in unexposed workers and in the general population. Among these data, the NHANES study of the CDC (or Centers of Disease Control (CDC, 2021) campaign (2013-2014) allows to identify values for the 95th percentile according to smoking status, in adults. Thus, the recommended BRVs for the AMCC are:
- for non-smokers: 0.473 mg.L^{-1} rounded to **0.5 mg.L^{-1}** or 0.391 mg.g^{-1} of cr rounded to **0.4 mg.g^{-1} cr**
- for smokers: 1.580 mg.L^{-1} rounded to **1.6 mg.L^{-1}** or 1.190 **mg.g^{-1} of cr** rounded to **1.2 mg.g^{-1} cr**

Conclusions of the collective expert appraisal

The biological values recommended for monitoring occupational exposure to DMF are:

Urinary total NMF at the end of the shift:

BLV based on a health effect	**10 mg.L^{-1}**
BLV based on an 8h-OEL exposure	None
Biological reference value (BRV)	None

Urinary AMCC at the end of week and end of shift:

BLV based on a health effect	**20 mg.L^{-1} ou 25 mg.g^{-1} cr**
BLV based on an 8h-OEL exposure	None
Biological reference value (BRV)	**Non smokers : 0,5 mg.L^{-1} or 0,4 mg.g^{-1} cr** **Smokers : 1,6 mg.L^{-1} or 1,2 mg.g^{-1} de cr**

As a reminder, BRV can not be considered as protective against health effects but do allow a comparison with the concentrations of biomarkers measured in exposed workers (by comparison with the levels of impregnation of the general adult population)

It is important to point out that the “Antabuse” effects induced by exposure to DMF combined with alcohol consumption could occur at lower levels than the hepatic effects. Consequently workers exposed to DMF must be informed of the risk and of the need not to consume alcoholic beverages during periods of exposure and at least for a week after stopping them.

In addition, in view of the interest of this BME for workers biomonitoring, it is recommended to conduct new studies at workplace on relationships between AMCC concentrations in urine and health effects, in particular the elevation of serum concentrations of liver enzymes, in order to provide data allowing the consolidation of AMCC BLV.

Sampling methods and factors that may influence the results

For the urinary measurement of tNMF, a sample at the end of shift, regardless of the day of the week, is recommended. The samples must be collected in a polypropylene tube (10 mL of urine), without preservative and stored for transport at + 4°C (7 days).

Regarding the AMCC, a sample at the end of the week and end of the shift will be preferred.

Biometrology

Some analytical methods described in the literature have been listed in the table below for the selected IBE.

Table 3: Review of analytical methods for the measurement of urinary total NMF

	URINARY TOTAL N-METHYLFORMAMIDE (NMF)		
	Method 1	Method 2	Method 3
Reference	Kawai *et al.,* 1992	He *et al.,* 2010	Will *et al.*, 2016 (DFG)
Analytical technique	GC-FTD (Flame Thermoionic detector) Temperature in the injector port at 200°C-250°C	GC-MS-EI (Temperature in the injector port at 220°C)	GC-MS-EI (Temperature in the injector port at 300°C)
Standardisation (ISO/AFNOR)	Adjustment : creatinine, specific gravity	Adjustment : creatinine Exclusion criteria >3.4 g/L ou <0.3 g/L	Adjustment : creatinine Exclusion criteria >3.4 g/L ou <0.3 g/L
Limit of detection	Not specified	0,5 mg/L	0,1 mg/L
Limit of quantification	Not specified	Not specified	0,3 mg/L
Linearity zone	Not specified	Not specified	0,1 – 200 mg/L
Possible preparation of the sample and its duration	Extraction with methanol	Liquid liquid extraction with ethyl acetate	Thermolysis for 2 hours at 120°C to transform HMMF into NMF then extraction with ethanol
Analytical interference	Not specified	Not specified	Yield : 97,4% No interference observed
Quality control Reference Standard	Not specified	Not specified	Validation parameters evaluated according to the Bundesärztekammer Guidelines (German Medical Association) Participation to inter-laboratory tests G-EQUAS

Table 4: Review of analytical methods for the measurement of urinary AMCC

URINARY N-ACETYL-S-(N-METHYLCARBAMOYL)CYSTEINE (AMCC)		
	Method 1	Method 2
Reference	Imbriani et *al.,* 2002	Seitz et *al.,* 2018
Analytical technique	HPLC with UV@196nm detection	SPE-LC-MS/MS
Standardisation (ISO/AFNOR)		creatinine adjustment
Limit of detection	0,9 mg/L (calculated)	0,005 mg/L
Limit of quantification	5 mg/L (low point in range)	Not specified
Linearity zone	Until 1 g/L	Not specified
Possible preparation of the sample and its duration	SPE 95.4%+/- 1.7%	Acidification and 10 min centrifugation Online SPE
Analytical interference	Negligible (internal standard necessary)	MS/MS with 2 transitions +internal d_3-AMCC standard
Quality control Reference Standard	3 QC precision 2 QC accuracy	Use of an internal d_3-AMCC standard Participation to the German External Quality Assurance Scheme (GEQUAS)

From an analytical point of view, based on the elements provided in this document it is recommended to use the following analytical methods for each of the BME:
- the method described in the study by Will *et al.* (Will *et al.*, 2016) (GC-MS-EI with port temperature 300°C) for urinary tNMF,
- the method used in the study by Seitz *et al.* (Seitz *et al.*, 2018) (SPE-LC-MS/MS) for urinary AMCC.

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