

2-Butanone Oxime, a Chemical of Concern in the Working Environment

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ABSTRACT

Employers of the companies where carcinogenic chemicals are being processed or used are obliged to ensure safe working conditions for their employees. Butan-2-one oxime, commonly present in alkyd paints or silicone sealants may pose such a risk due to its reclassification as a category 1B carcinogen. Therefore, in Poland new maximum admissible concentrations (MAC) value of 1 mg/m³ was proposed by interdepartmental Commission for maximum admissible concentrations and intensities for agents harmful to health in the working environment. Assessing exposure to this compound requires a method to be developed for its determination in the workers' breathing zone, which was the aim of the presented study. A method was developed for determining the aerosol concentrations of 2-butanone oxime in the air at workplaces, in the range of 1/10 to 2 of the MAC value, i.e. from 0.1 mg/m³ to 2 mg/m³. The method involves trapping the airborne aerosol of 2-butanone oxime onto a sampler - a glass tube with silica gel, its extraction with methanol and analysis of the resulting solution using gas chromatography with flame ionization detector in the presence of co-substances. Validation parameters were determined according to the guidelines of EN 482. The limit of detection at 6.79 ng/ml and the relative total uncertainty of 11.19% was determined. The method can be used by environmental occupational hygiene laboratories to measure concentrations of butan-2-one oxime in the air.

Keywords: butane-2-one oxime, MEKO, working environment, gas chromatography, workplace air, carcinogenic substance, determination method.

INTRODUCTION

Butane-2-one oxime, known as MEKO (CAS No: 96-29-7), becomes a category 1B carcinogen since March 2022 (Regulation (UE) 2020/1182). Revised MEKO carcinogenicity category has resulted in legal consequences for the companies. As it was indicated by Kupczewska-Dobecka (2022), the main changes cover the compliance with REACH restriction concerning its placing on the market for sale, but also new obligations such as keeping a register of work that requires contact with MEKO or its mixtures (containing MEKO in concentrations $\geq 0.1\%$); a register of workers exposed to this compound and carrying out measurements in the range and frequency specified in the regulations (Kupczewska-Dobecka, 2022). 2-Butanone oxime is commonly used in paints,

alkyd and epoxy resins, as well as polyurethanes and in the formulation of primers, lacquers, varnishes and protective coatings. It is a well-known anti-skinning agent in the paint industry in alkyd paints, primers, wood preservatives and building materials. This compound is also used as a reagent for the production of cross-linking agents used in neutral silicone (Fortmann et al., 1998). Currently, there is no practical substitute for MEKO for general purpose, researched and with a well-conducted risk assessment that would prevent paint skinning (Kupczewska-Dobecka, 2022). Thus, new requirements for employers may become problematic especially in the initial period of transition.

According to the harmonised classification and labelling approved by the European Union, the substance is not only a Category 1B

carcinogen, but also toxic if swallowed, causes organ damage and serious eye damage. It is harmful by skin contact and may cause skin irritation or allergic skin reaction, drowsiness or dizziness (REGULATION (EC) No 1272/2008). There is an association between MEKO concentrations and an increased incidence of liver tumors (Kupczewska-Dobecka, 2022; Kupczewska-Dobecka and Dobecki, 2023).

2-Butanone oxime, belongs to a class of organic chemicals containing an R-C(=NOH)-R grouping, formally created by condensation of hydroxylamine with a ketone (ketoximes). Known methods of producing MEKO such as nitrohydrogenation, electrochemical or hydroxylamine have drawbacks, especially the use of toxic oxidising agents and harmful reaction by-products. Therefore, much work has been devoted to finding a more efficient and cleaner production of MEKO. Zhang et al. (2017) described the ammoximation of MEK, using ammonia and hydrogen peroxide on TS-1 catalysts in a ceramic membrane reactor. The optimization of the process for the preparation of methyl ethyl ketone oxime by ammoximation of MEK and modeling of the reaction unit was also described by the authors (Zhang et al., 2021).

As the oximes are volatile, a significant concentration in the gas phase at industrial workplaces may be expected (Kempter, 1999). MEKO can be released in significant quantities into the air, including the air of the working environment. The International Agency for Research on Cancer identifies MEKO as one of the main substances to which workers may be exposed during painting (Kupczewska-Dobecka, 2022). Butan-2-one oxime can also be released from building products such as paints or filler compounds and silicone sealants used to increase the thermal insulation of buildings and to waterproof household elements. Butan-2-one oxime may be also emitted during the curing process of silicone materials mainly used in enclosed spaces that are exposed to continuous or cyclic contact with water (e.g., kitchen, bathroom, garage) (Klewicz et al., 2020). A study of the emission profile and dynamics of two types of commercial neutral silicone sealants (Klewicz et al., 2020) indicated that MEKO may pose a risk to workers who work and stay in rooms containing sealants or silicone coatings. At the same time, it can pose a risk to these rooms' residents due to its residual emissions resulting from e.g. sorption and desorption processes in the silicone matrix. He et al. (2019) confirmed that the

emission process is tightly coupled with the curing process. The authors used MEKO to validate the developed model that can predict the VOCs emission process for adhesives.

In Poland, the scale of the problem of occupational exposure to MEKO is currently unknown, as such studies have not yet been conducted (Kupczewska-Dobecka and Dobecki, 2023). In contrast, occupational exposure studies were carried out in Germany between 1998 and 2011 and the range of butan-2-one oxime concentrations at workplaces (stationary measurements and in the worker's breathing zone) from different industries ranged from 1.1 to 4.7 mg/m³ (Van Gelder, 2013).

The most reliable results of occupational risk assessment for chemical substances are obtained by using their concentrations' measurements at workplace air and establishing relations of the obtained results to the values of occupational exposure limits. This method is commonly used in Poland, as well as in other countries, to assess exposure due to legally binding values of occupational exposure limits for the work environment, as recommended by the Labour Code (Dz.U. 2023 poz. 1465) and the Regulation of the Minister of Health of 2 February 2011 on tests and measurements of factors harmful to health in the work environment (Dz.U. 2023 poz. 419). However, so far, there are no legally binding hygiene standards for this substance. Butane-2-one oxime, due to its classification, is a substance on the priority list of the Advisory Committee on Safety and Health at Work (ACSH) for establishing binding values in accordance with the Directive 2004/37/EC. Hygienic standards for butan-2-one oxime have been established in Germany (1 mg/m³), Denmark (83 mg/m³) and Ireland (10 mg/m³). Maximum admissible concentrations – short term exposure limit (MAC-STEL) values have also been established in Germany (8 mg/m³) and in Ireland (33 mg/m³). In Poland, Group of Experts for Chemical Agents has developed documentation, along with proposals for MAC-STEL values for MEKO to the Interdepartmental Commission for Maximum Admissible Concentrations and Intensities for Agents Harmful to Health in the Working Environment. The proposed limit values concern MAC at the level of 1 mg/m³, and in order to protect workers from the irritating effects of the substance, MAC-STEL value, which was proposed at 3×MAC, i.e. 3 mg/m³ (Skowroń et al., 2023). These values are still a proposition and have not been established in Poland yet.

In order to assess the risk associated with occupational exposure to chemicals in the working environment based on measurements of their concentrations, it is necessary to develop selective determination methods with adequate sensitivity and precision. The analytical procedures used for the quantification of chemicals in air must ensure that they can be quantitatively extracted from the air and that their concentrations are measured within a range of 0.1 to 2 of the MAC value. There is no method for the determination of 2-butanone oxime that meets such criteria. Reports on the detection of MEKO in air samples date back to the 1990s. Fortmann et al. (1998) for detection of MEKO in paints applied a modification of NIOSH Method 2010, in which air samples were collected on silica gel cartridges, consisting of two sections (150 and 75 mg) of activated silica gel, extracted with methanol and analysed by GC/MS. In the aforementioned German study, the method developed by Lichtenstein et al. (2012) was applied by adsorption of MEKO onto Chromosorb 106, 16 hours of its extraction with methanol and determination of the compound by gas chromatography. In contrast, Kempter (1999) developed a liquid chromatography method with UV/Vis detection for the determination of oximes in air samples using pre-column derivatisation with a hydrazine reagent. The aim of the work presented here was to develop a method for the

determination of MEKO by individual dosimetry for the assessment of exposure in workplace air.

MATERIALS AND METHODS

For the determination of MEKO in air samples, a gas chromatograph with flame ionization detector (GC-FID) (Agilent Technologies 7820A, China) and HP 1 Column (50 m × 0.32 mm × 0.52 μm) (Hewlett Packard, USA) were used (Fig. 1). For weighing of standards: analytical balance Sartorius TE214S (Sartorius Corporation, USA), for storage Refrigerator-Freezer ARDO CO23B-2H (Merloni, Poland) were used. The following reagents of at least p.c. purity were used in the study: 2-butanone oxime (Sigma-Aldrich), Methanol (Riedel de Haen, Germany), Carbon disulfide (Honeywell, UK), Dimethylformamide (DMF) (POCh, Poland), Xylene (Sigma-Aldrich), Naphthalene (Sigma-Aldrich), Isobutanol (ACROS Organics), Ethyl acetate (Sigma-Aldrich) and Ethylbenzene (Fluka).

AIR SAMPLING

Adsorbent tubes containing 2 layers of suitable sorbent were used for air sampling: non-activated silica gel (Analyst Service-Production

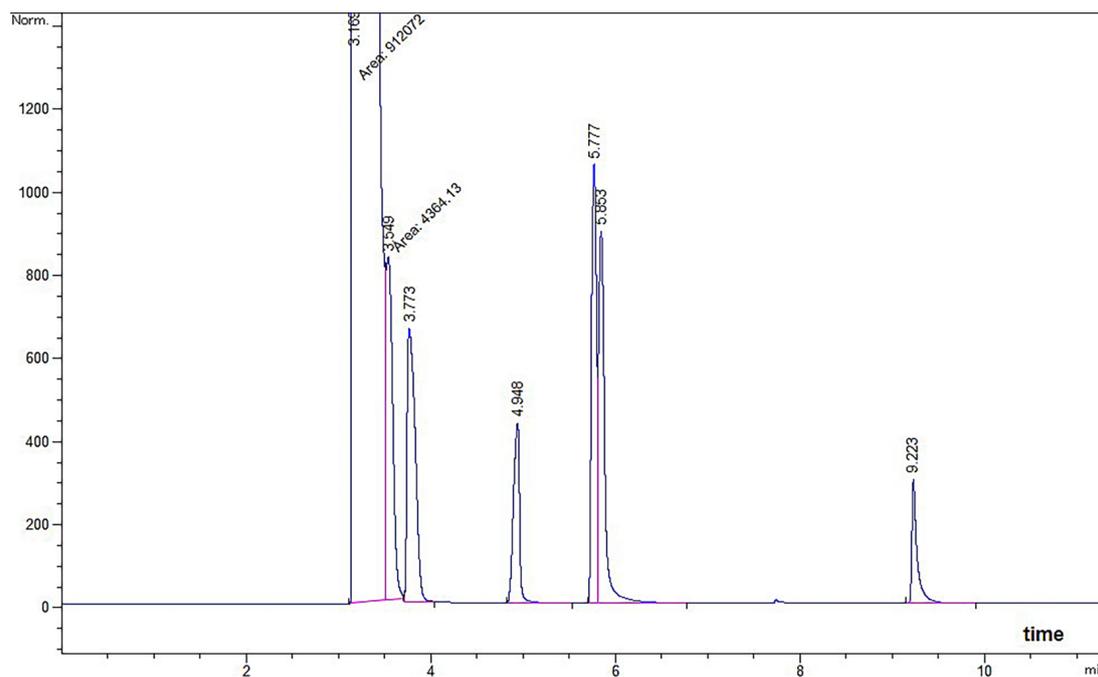


Figure 1. Chromatogram of the MEKO standard in the presence of co-eluting substances

Plant, Poland), activated carbon, (Analyst Service-Production Plant, Poland), Supelco ORBO 506 activated silica gel Anasorb CMS (SKC, USA), XAD 7 (SKC, USA) and Chromosorb 106 (SKC, USA). Forced air flow using GilAir Plus air sampling aspirators (Gillian Sensidyne, USA) was applied.

DETERMINATION OF MEKO BY GC-FID TECHNIQUE

Based on a literature review, a preliminary study was carried out to determine the parameters for the chromatographic determination of the butan-2-one oxime. Studies related to column selection (dimensions and filling) and chromatographic analysis parameters (carrier gas flow rate, column temperature) were undertaken. Chromatographic separation of the mixture of co-substances and MEKO was carried out using a gas chromatograph with a flame-ionization detector FID on an HP-1 column, 50 m × 0.32 mm × 0.52 μm, under the conditions of an oven temperature program: initial temperature of 70°C (1 min), temperature increment of 10°C/min to a final temperature of 180°C (3 min). The temperature of the dispenser was 280°C, the sample divider was 5:1 and the flow rate of carrier gas (helium) was 1.5 ml/min.

Under the conditions described above, 2-butanone oxime can be determined in the presence of co-occurring compounds, which are components of, for example, alkyd paints, such as xylenes, naphthalene, isobutanol, ethyl acetate, ethylbenzene (Fig.1).

RESULTS AND DISCUSSION

During the method development for determination of MEKO in the air of the working environment, assumptions were made to enable further research. The concentration range of the determined substances was assumed at the multiplicity level of 0.1–2 the maximum allowable concentration values allowable concentration (0.1–2 mg/m³) and 0.5–2 of the maximum admissible – short term concentration (1.5–6 mg/m³), the volume of the air sample taken to assess compliance with MAC value of 24 liters, and the volume of the air sample taken for comparison with the value of the maximum allowable short term concentration: 3 liters. The above assumptions were used to carry

out preliminary studies related to the selection of a suitable sampler and solvent allowing desorption/extraction from the medium applied.

ESTABLISHING THE SOLVENT FOR MEKO RECOVERY/EXTRACTION

For the development of the method, three solvents were selected, i.e. methanol (MeOH), carbon disulfide (CS₂) and DMF in MeOH (1%). A solution was prepared with a concentration of 4.89 mg/ml of 2-butanone oxime, respectively, in each of these solvents, and then solutions with equivalent concentrations of 0.1, 0.5 and 1 of MAC value, respectively, under the assumptions outlined above (i.e., 2.4, 12 and 24 μg/ml). These solvents were selected based on a review of the literature and methods for the determination of butan-2-one and butan-2-one oxime. Analysis of the chromatograms for each solution showed higher peak areas for MEKO in solutions in methanol than in carbon disulfide, and similar retention times of DMF and MEKO under the accepted chromatographic determination conditions. Therefore, methanol was chosen for further studies.

DETERMINING THE SAMPLER FOR AIR SAMPLING

Since 2-butanone oxime exists in air in gaseous form, sorbent-filled samplers were chosen. Based on a literature review of the determination of MEKO and methyl ethyl ketone MEK (NIOSH 2500; NIOSH 2555; OSHA 1004; Lichtenstein. 2012), sorbents such as activated carbon, activated silica gel (Supelco ORBO 509), inactivated silica gel, Anasorb CMS, XAD 7 and Chromosorb 106 were selected for preliminary studies. Two longer layers of each sorbent from the sorption tubes were poured into desorption vials. Then, 10 μL of oxime solution with a concentration of 4.89 mg/ml was injected onto each sorbent. It was allowed to dry, after an hour 1 ml of solvent was added on top and then the samples were shaken for 30 minutes on a shaker. Two control solutions and blank samples were prepared simultaneously. Figure 2 shows the histogram of the recoveries of 2-butanone oxime from the tested sorbents using MeOH as the desorption solvent. The best results were obtained using non-activated silica gel, and the recovery rate for 2-butanone oxime in this

case was 100%. For the selected sampler, studies were conducted to establish sampling conditions (air flow and aspirator) that will ensure quantitative extraction of 2-butanone oxime from air.

According to the principles of individual dosimetry, samples should be taken for at least 75% of the working shift's duration. For this purpose, 10 µL each of a 2.0 mg/ml MEKO solution was applied to silica gel (first layer of sorbent) placed in glass tubes and air was passed through, at a constant flow rate of 400 ml/min for 1 hour, 200 ml/min for 2h and 65 ml/min for 6h, respectively. After this time, the two sorbent layers were separately covered with 1 ml of MeOH and the contents were shaken for 30 minutes. 2-butanone oxime was determined in solutions taken from the above of both sorbent layers placed in desorption vials separately and in the reference solutions obtained by introducing 10 µl of a 2.0 mg/ml MEKO solution into 1 ml of solvent. Measurements were repeated 3

times. Detailed test results are shown in Table 1. The content of the substance on the second layer of the sorbent (in % of the amount determined on the first layer) at a flow rate of 400 ml/min exceeds 16%. Thus, we can assume that the sampler in form of a glass tube filled with an inactivated silica gel is suitable for extracting 2-butanone oxime from air at a flow rate of no more than 200 ml/min.

RECOVERY STUDY

To evaluate the recovery rate from the sorbent, 10 µl of 2-butanone oxime solution in MEOH at concentrations of, respectively: 0.243, 1.215 and 2.43 mg/ml were added to 18 desorption vials (6 each) containing non-activated silica gel. The vials were filled with 1 ml of methanol and after an hour, shaken for 30 minutes. The resulting extracts were analysed chromatographically under

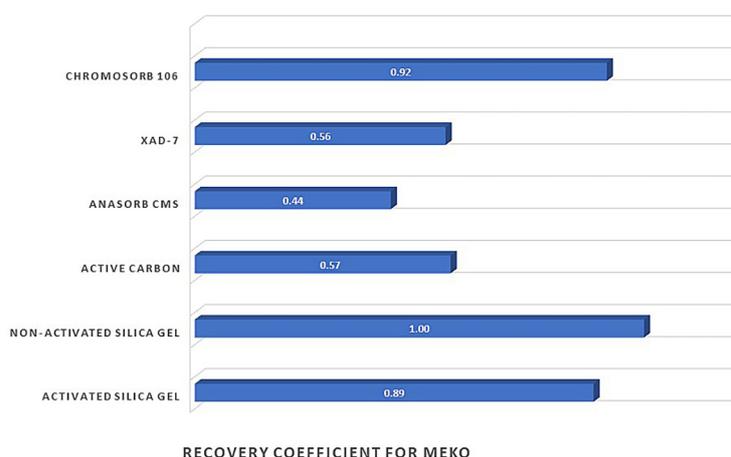


Figure 2. Histogram of MEKO recoveries from the sorbents tested using different solvents

Table 1. Verification results of the adopted air sampling method

Number of sample	Air flow [ml/min]	Sampling time [h]	The approximate concentration of the substance in the air [mg/m ³]	Average area of the peaks in the solutions after desorption		The content of the substance in the second layer [in % of the amount determined in the first layer]
				layer I	layer II	
1	400	1	1	39.5	10.2	25.82
2				39.5	9.09	23.01
3				39.8	6.7	16.83
1	200	2	1	48.4	nd	0
2				48.1	nd	0
3				47.9	nd	0
1	65	6	1	48.4	0.865	1.79
2				48.5	0.97	2.00
3				49.0	1.14	2.33

Note: nd – not detected.

the established conditions. Two reference solutions were prepared simultaneously, with concentrations of 2.43, 12.15 and 24.3 $\mu\text{g/ml}$, respectively. Using the peak areas on the chromatograms of the tested solutions, desorption coefficients were calculated. The obtained average desorption coefficient for MEKO was 0.99, which meets the requirements of PN-EN ISO 22065.

DETERMINATION OF CALIBRATION PARAMETERS OF THE MEASUREMENT/ANALYTICAL SYSTEM

Verification of analytical signals for different concentrations of the analyte in the test solutions was performed for standard solutions of 2-butanone oxime in MeOH. The concentration of these solutions was determined based on the following assumptions: the concentration range of the standard solutions at the assumed measurement range of 0.1–2 mg/m^3 for the volume of air taken for analysis of 24 liters, and the volume of 1 ml of solvent used for extraction was: 2.4–48.0 $\mu\text{g/ml}$. Three series each of calibration solutions were prepared and analyzed by gas chromatography with flame ionization detection. 2 μl each of the calibration solutions with increasing concentrations were injected. Two determinations were made for each concentration. Then the dependence of the peak area of the test substance on its concentrations in the standard solutions was plotted. The slope coefficient “b” of the calibration curve (Figure 3) with the equation $y = bx + a$, characterizing the sensitivity of the method is 2.492. The linearity of the calibration curve is

characterized by the value of the correlation coefficient. The correlation coefficient R is 0.9997. Table 2 shows the results of calibration determinations. The repeatability of the calibration determinations was also determined by analyzing 3 series of eight solutions of MEKO in methanol with concentrations of: 2.43 $\mu\text{g/ml}$, 12.15 μg and 24.3 $\mu\text{g/ml}$, respectively. The standard deviation and coefficients of variation were calculated from the peak areas obtained on the chromatograms. The coefficients of variation for successive concentration levels did not exceed 5% and amounted to 0.64%; 1.21%; 1.12% respectively.

STORAGE TESTS OF THE PREPARED SOLUTIONS AND SAMPLES

To test the stability of the standard solutions, MEKO solutions of 24.3 $\mu\text{g/ml}$ and 12.15 $\mu\text{g/ml}$ were left in the refrigerator. The results of testing the solutions durability after one, two, three, six and nine days of storage in the refrigerator are shown in Table 3. Based on these results we can assume that MEKO solutions stored at about 4°C are stable for up to nine days. The storage of the collected air samples was also tested according to their storage time in the refrigerator and freezer. The storage possibilities of the air samples taken was tested on the day the 2-butanone oxime was applied to the silica gel, and after one, two, six and nine days of storing the samples in the refrigerator and freezer. Based on the obtained variations of peak area results (Table 3), it was concluded that the samples should be stored up to nine days in the refrigerator.

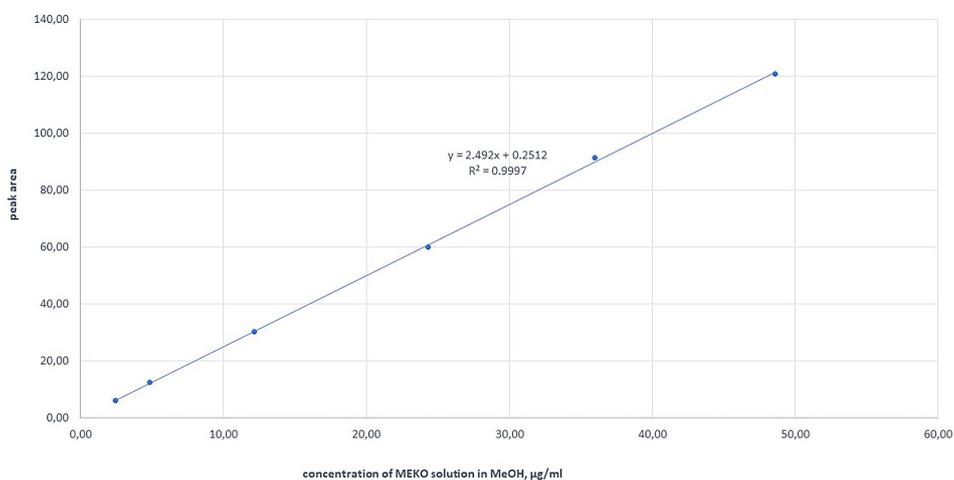


Figure 3. Calibration curve for butanone oxime

Table 2. Results of calibration determinations of butanone oxime

Parameter	Measurement series		
	I serie	II serie	III serie
Mean peak area for MEKO solution of 2.4 $\mu\text{g mL}^{-1}$	6.29	6.25	6.23
Mean peak area for MEKO solution of 4.9 $\mu\text{g mL}^{-1}$	12.50	12.25	11.73
Mean peak area for MEKO solution of 12.2 $\mu\text{g mL}^{-1}$	30.35	30.35	29.52
Mean peak area for MEKO solution of 24.3 $\mu\text{g mL}^{-1}$	60.15	61.60	60.84
Mean peak area for MEKO solution of 36.0 $\mu\text{g mL}^{-1}$	91.25	89.40	88.83
Mean peak area for MEKO solution of 48.6 $\mu\text{g mL}^{-1}$	120.70	121.75	118.67
Calibration curve $y = ax + b$	$y = 2.49x + 0.25$	$y = 2.5x + 0.18$	$y = 2.45x + 0.2$
Correlation coefficient, r	0.9999	1	0.9999
The average value of the calibration factor	2.5		
Standard deviation of the calibration factor	0.04		
Coefficient of variation of the calibration factor (%)	1.6		

Table 3. Stability of air samples and MEKO solutions stored under different conditions

Storage time	Area of peaks	Variation of peak area after storage [%]
Air samples stored in freezer		
0 day	53.43	–
1 day	52.45	–1.82
2 days	50.00	–6.41
6 days	55.15	3.23
9 days	58.95	3.39
Air samples stored in refrigerator		
0 day	53.43	–
1 day	56.10	5.01
2 days	51.00	–4.54
6 days	55.20	3.32
9 days	51.63	–3.37
MEKO solution stored in refrigerator		
0 day	61.65	–
1 days	63.90	3.65
2 days	62.30	1.05
3 days	63.83	3.53
6 days	63.90	3.65
9 days	59.43	–3.61

METHOD VALIDATION

For the applied sampling and determination method using a gas chromatography with a flame ionisation detector, validation parameters were determined in accordance with PN-EN 482 and PN-EN ISO 22065. The measurement range of the method, repeatability, correlation coefficients of the calibration curves, limits of detection and limits of quantification of the measuring instrument, as well as relative uncertainties of complex

and expanded uncertainties were determined. The calibration curve for a measurement range of the method of 2.43–48.6 $\mu\text{g/ml}$ (0.1–2 mg/m^3 for a 24 l air sample) is linear (correlation coefficient $R = 1$). The uncertainty components of the sampling process were identified: i.e. uncertainty related to the stability of the aspirator, uncertainty of the rotameter, uncertainty of the timing of the air sample.

Uncertainty components of the analytical process included: uncertainty associated with the

preparation of calibration solutions, uncertainty associated with the determination of the desorption coefficient, uncertainty of the calibration curve determination and method repeatability.

The relative compound uncertainty of the measurement result X (u_{crel}) was calculated based on the uncertainty of the standard parameters affecting the value of the analysis result, according to the formula (Dobecki, 2012):

$$u_{crel} = \sqrt{u_{rel1}^2 + \dots + u_{reln}^2} \quad (1)$$

where: u_{reln} - standard uncertainty of parameter n , %; the relative expanded uncertainty, U (in %), was calculated (for a confidence level of 95 % and a coverage factor $k = 2$), according to equation:

$$U = k \cdot u_{crel} \quad (2)$$

The relative overall uncertainty is 11.19%, the expanded uncertainty is 22.39%. LOD and LOQ calculation was chosen based on the value of the standard deviation of the retention time peak area of the analyte under study obtained for a series of blank samples and the directional coefficient of the calibration curve. In this way, the smallest concentration of the substance that can be detected by the analytical technique used - the instrument detection limit was calculated. The detection limit of the analytical instrument was calculated as 3 times the detection limit. Limit of detection (LOD) is equal to 6.79 ng/ml and limit of quantification (LOQ) 20.36 ng/ml.

CONCLUSIONS

The role of the employer is to control the conditions in the working environment and to reduce possible occupational risks. The proposal for a permissible value in Poland came before a binding value was set in the EU. This gives employers the opportunity to measure MEKO concentrations at workplaces against the new MAC value. This is important when the legislation introduces specific employer obligations related to the presence of carcinogens at workplaces. The application of the method developed in the article presented here will make it possible to carry out an occupational risk assessment related to inhalation exposure to the carcinogen MEKO. The developed method for the determination of this substance meets the requirements for procedures

for the determination of concentrations of chemical agents at workplaces (PN-EN 482). Therefore, employers of establishments with exposure to MEKO will have to make every effort to ensure safe working conditions by, for example, modernising machinery, technological processes, applying collective protection measures and by introducing organisational changes, as well as using appropriate personal protection. Due to the harmful effects on the health of workers in contact with 2-butanone oxime, following the establishment of occupational exposure limits, measurements of this carcinogenic substance in the air at workplaces will have to be carried out at a certain frequency.

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