Formaldehyde analysis of seized cosmetic products by HS-GC-MS of methylal, ethoxymethoxymethane, and ethylal derivatives

Ettore Ferrari Júnior[1,2], Lívia Barros Salum[1], Robiedson Romeiro Damasceno[1], Bárbara Elisa Pereira Alves[1], Eloisa Dutra Caldas[2*]

[1]*Forensic Analysis Laboratory, Criminalistics Institute, Civil Police of the Federal District, Brasilia, Federal District, Brazil, [2]Laboratory of Toxicology, Department of Pharmacy, University of Brasilia, Brasilia, Federal District, Brazil*

Formaldehyde is a carcinogenic compound used as preservative in cosmetic products. In this study, a derivatization procedure using MeOH, EtOH and HCl (25:25:1), and incubation at 60ºC for 4 hours was optimized, and the derivatized products — methylal, ethoxymethoxymethane (EMM), and ethylal — were directly analyzed by headspace-gas chromatography-mass spectrometry (HS-GC-MS) to determine formaldehyde concentrations. The validated method provided good linearity of the standard curve, selectivity, recovery (89.6-106.6%), repeatability, and intermediate precision (RSD < 12%), with an LOD of 0.0015% and an LOQ of 0.005% for all derivatized analytes. The validated method showed to be fast, clean, and easy to implement in a laboratory. To the best of our knowledge, this is the first reported HS-GC-MS procedure to determine formaldehyde as methylal, ethylal, and EMM as derivatized compounds. The method was satisfactorily applied for the analysis of nine hair-straightener cream samples seized by the Civil Police of the Federal District, Brazil. Eight samples contained formaldehyde, at levels ranging from 0.33 to 4.02 %, higher than the legal levels, indicating the need to control the levels of this toxic compound in cosmetic products.

Keywords: Formaldehyde. Cosmetics. GC-MS. Acetals.

INTRODUCTION

Formaldehyde (methanal, HCHO) is a gas at ambient temperature, with various industrial uses, classified as a human carcinogen based primarily on its association with nasopharyngeal cancer and leukaemia (IARC, 2012). Formaldehyde is also an impurity present at very low concentrations (0.1 to 40 µg/g) in excipients of pharmaceutical formulations, formed from the breakdown of the polymeric chain of polyethylene glycol and polysorbates (Li *et al*., 2006; Wu *et al*., 2011). Furthermore, formaldehyde releasers are added to cosmetic, including hair-straightening products, and oral hygiene products

as a preservative, with the maximum permitted level of free formaldehyde at 0.2 and 0.1%, respectively, in Brazil and Canada (Anvisa, 2013; Health Canada, 2019). In Europe, the use of formaldehyde as a preservative in cosmetic products is prohibited (Commission Regulation (EU) 2019/831).

Low levels of formaldehyde in cosmetic products can provoke allergic contact dermatitis in sensitive individuals (De Groot *et al*., 2010; Hauksson *et al*., 2016), and exposure to hair-straightening containing formaldehyde at high levels may be lethal. One occupational death due to formaldehyde was reported in the Federal District (Magalhães, Caldas, 2018). More recently, the compound was suspected to be the cause of death of a woman after doing a keratin hair smoothing treatment (*escova progressiva*) in the State of São Paulo (Brasil, 2019). Most of these products contain methylene

glycol, which converts to formaldehyde under the high temperature used in the hair smoothing treatment (Golden, Valentini, 2014). Indeed, various studies have shown that hairdressers are chronically exposed to high concentrations of formaldehyde in the workplace (Chang *et al.*, 2018; Pexe *et al.*, 2019; Pierce *et al.*, 2011).

Various analytical methods to detect formaldehyde in cosmetic and pharmaceutical products have been reported, including the semi-qualitative chromotropic acid (CA) colorimetric method (Hauksson *et al.*, 2016; Malinauskiene *et al.*, 2015), spectrophotometry after derivatization with acetylacetone (Brandão, Ramos, Rodrigues, 2018), HPLC-UV after derivatization with 2,4-dinitrophenylhydrazine (Golden, Valentini, 2014; Soman, Qiu, Chan, 2008; Oiye *et al.*, 2016), HPLC separation followed by derivatization with 3,5-diacetyl-

1,4-dihydrolutidine spectrophotometry (Miralles *et al.*, 2018) and headspace-gas-chromatography (HS-GC) after derivatization with ethanol (Del Barrio *et al.*, 2006; Daoudy *et al.*, 2018). Under acidic conditions, methylal or ethylal can be prepared through the reaction of formaldehyde and methanol or ethanol, and etoxymethoxymethane (EMM) is formed when both alcohols are present (Cao *et al.*, 2009; Chopade, Sharma; 1997; Zhang, Zhang, Jian, 2011), as shown in Figure 1.

The objectives of this paper were to develop and validate a method for determining formaldehyde in cosmetic products by headspace-gas-chromatography-mass spectrometry (HS-GC-MS) after derivatization of formaldehyde with methanol and ethanol as well as to apply the method in real samples seized by the Civil Police of the Federal District, Brazil.
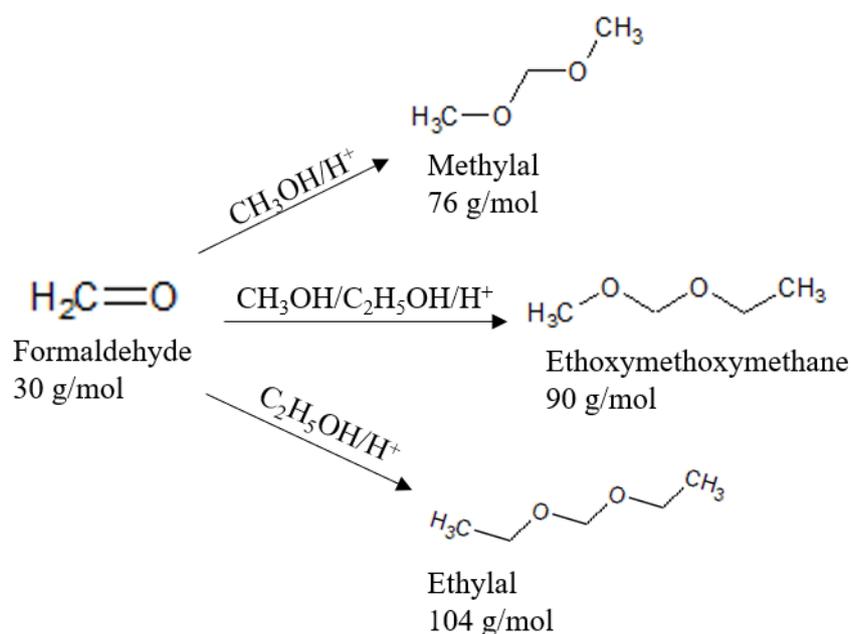

FIGURE 1 - Derivatization of formaldehyde by acid catalytic reaction using methanol, ethanol and methanol/ethanol, showing the formation of the acetals methylal, ethoxymethoxymethane and ethylal.

MATERIAL AND METHODS

Chemicals and reagents

Formaldehyde ACS grade (37%) and concentrated hydrochloride acid (HCl) were obtained from Dinâmica

(Brazil); methanol LC-MS grade (MeOH) was purchased from Sigma Aldrich (USA); and ethanol HPLC grade (EtOH) was obtained from Merck Millipore (Germany). A non-ionic cream base (formaldehyde-free) used for the preparation of cosmetics and medicaments was used as the blank matrix during method validation. According

to the Brazilian Pharmacopea, the cream base is made of water and oil (1:5.4) (Anvisa, 2012).

Headspace-Gas Chromatography-Mass Spectrometry conditions

HS-GC–MS analyses were performed using an Agilent 7890A gas chromatograph and 5975C mass spectrometer (Agilent Technologies, Santa Clara, CA, USA) system, controlled by Agilent Chemstation GC/MS Software (version E 02.02.1431).

An Agilent J&W VF-624ms fused-silica capillary GC column (30 m x 0.25 mm i.d., 1.4 µm film thickness) was used, with helium as a carrier gas at 1 mL/min. Inlet temperature was 250º C, and the headspace settings were as follows: injection volume, 250 µL; split ratio of 15:1; incubation temperature, 40°C; incubation time, 30 s, syringe temperature, 60°C; agitator speed, 500 RPM; fill speed, 100 µL/s. The GC oven temperature program started at 35°C and initial hold time of 5 min, increased to 40°C at a rate of 5°C/ min, hold 1 min; to 50°C at 10°C/min, hold 3 min. The total time run was 11 min, the solvent delay was set to 3.5 min, and the transfer line temperature at 250°C. Mass scan range was m/z 15–250. The identification of the derivatized products, ethylal, methylal, and ethoxymethoxymethane (EMM) (Figure 1), was confirmed by full scan analysis and NIST MS library. The quantification was performed by selected ion monitoring (SIM) mode, with the m/z 59, 103, and 31 for ethylal, m/z 45, 75, and 29 for methylal, and m/z 45, 59, and 89 for EMM; the first ions were used as quantifiers and the others two as qualifiers.

Optimization of derivatization step

In order to evaluate the efficiency of the derivatization step, four blank matrix samples fortified with formaldehyde at a final concentration of 0.2% were prepared in a 20 mL headspace vial and 2 mL of the following solutions were added: A1 = MeOH and HCl (50:1); A2 = EtOH and HCl (50:1); A3 = MeOH and EtOH (25:25), and A4 = MeOH, EtOH and HCl (25:25:1). Each sample was vortexed and kept for 30 min at 60ºC (water bath) before the HS-GC–MS analyses.

The kinetics of the reactions were evaluated using a formaldehyde fortified blank matrix (0.2%) prepared in A4 solution that was kept at 60ºC (water bath) for 5, 15 and 30 minutes, 1, 1.5, 2, 4, 6, 8, 12 and 24 hours. ANOVA (GraphPad Prism, V6.01) was used to evaluate any significant difference ($p < 0.05$) among the acetal instrument responses in relation to time.

Method validation

The method was validated for each derivatized product for matrix effect, linearity, selectivity, specificity, recovery, repeatability, intermediate precision, and dilution integrity according to the Brazilian Health Regulatory Agency (Anvisa, 2017).

Matrix effects (ME) were evaluated using 0.005, 0.05 and 0.2% formaldehyde concentrations, prepared in A4 solution only (M1) and in A4 solution with blank matrix (M2) (n = 3 for each), and expressed in % of the response ratio between the two preparations (ME = M2 x100/M1). No significant matrix effect was found when ME was lower than 10%.

Linearity of the standard curve was evaluated using seven different concentrations (0.005, 0.01, 0.05, 0.1, 0.2, and 0.5%) in triplicate. Each calibration point was prepared by weighing 300 mg of blank matrix fortified with formaldehyde in A4 solution. Selectivity was evaluated by analyzing 3 different blank matrices to evaluate the presence of interferents at the analyte retention times. Specificity of the method was evaluated by preparing samples with 300 mg of blank matrix and 1 mL of solutions A1, A2 or A4.

Recovery and repeatability were evaluated using the blank matrix fortified at three different formaldehyde concentrations, 0.005%, 0.01%, and 0.2%, prepared in A4 solution and analyzed on the same day. For intermediate precision, the whole procedure was repeated on another day by another analyst. LOD was estimated as $\mu + 3.3s$, where "μ" is the mean area of the 10 matrix blanks in A4 solution and "s" is the standard deviation. The LOQ of the method was defined as the lowest level at which the method was validated (repeatability and intermediated precision, RSD < 20%; recovery in the range of 80–120%).

Dilution integrity was evaluated to check the effect of dilution for samples that were out of the range of the standard curve. The blank matrix fortified with formaldehyde at concentrations of 10% and 15% in A4 solution was analyzed before and after 1:100 and 1:150 dilutions. The calculated concentration after dilution was compared with the concentration in non-diluted samples, and a ratio within ±20% was the acceptance criterion for this parameter.

Real sample for analysis

Nine hair-straightener creams seized by the Civil Police of the Federal District, Brazil, and suspected of adulteration with formaldehyde were analyzed using the validated method. Blank matrices fortified with 0.2% formaldehyde were included in the analysis batch to ensure method performance during a routine analysis (quality control sample, QC).

RESULTS AND DISCUSSION

Methylal, ethoxymethoxymethane (EMM), and ethylal formation

Figure 2 shows the chromatograms of blank samples spiked with formaldehyde and the A1, A2, A3,

and A4 solutions, kept for 30 min at 60ºC before HS-GC-MS analysis. Methylal was formed in A1 solution (MeOH and HCl), while methylal and ethylal were formed in A2 solution (EtOH and HCl) (Figure 2a). The formaldehyde standard solution (37 %, formalin) contains 6 to 15% of methanol, used as stabilizer (Cogliano *et al.*, 2004), which explains the formation of methylal under A2 conditions.

Only a small amount of methylal was formed in A3 solution (MeOH and EtOH), confirming the need for an acidic condition (Figure 2b). The optimum conditions for simultaneous derivatization of formaldehyde with both alcohols were achieved with A4 solution (MeOH:EtOH:HCl), where in addition to methylal and ethylal, EMM is formed (Figure 2b). The yields of methylal and ethylal were lower in A4 solution compared to when the reaction was conducted with only one of the alcohols (A1 and A2 solutions, respectively, Figure 2a). This result was expected, as there is competition for acetal formation with formaldehyde. The formation of EMM from formaldehyde, methanol and ethanol in a strongly acidic cationic resin was reported by Cao *et al.* (2009) when searching for co-solvents for methanol/gasoline blends. However, to the best of our knowledge, this is the first time that EMM is reported in the context of formaldehyde analysis in cosmetics.
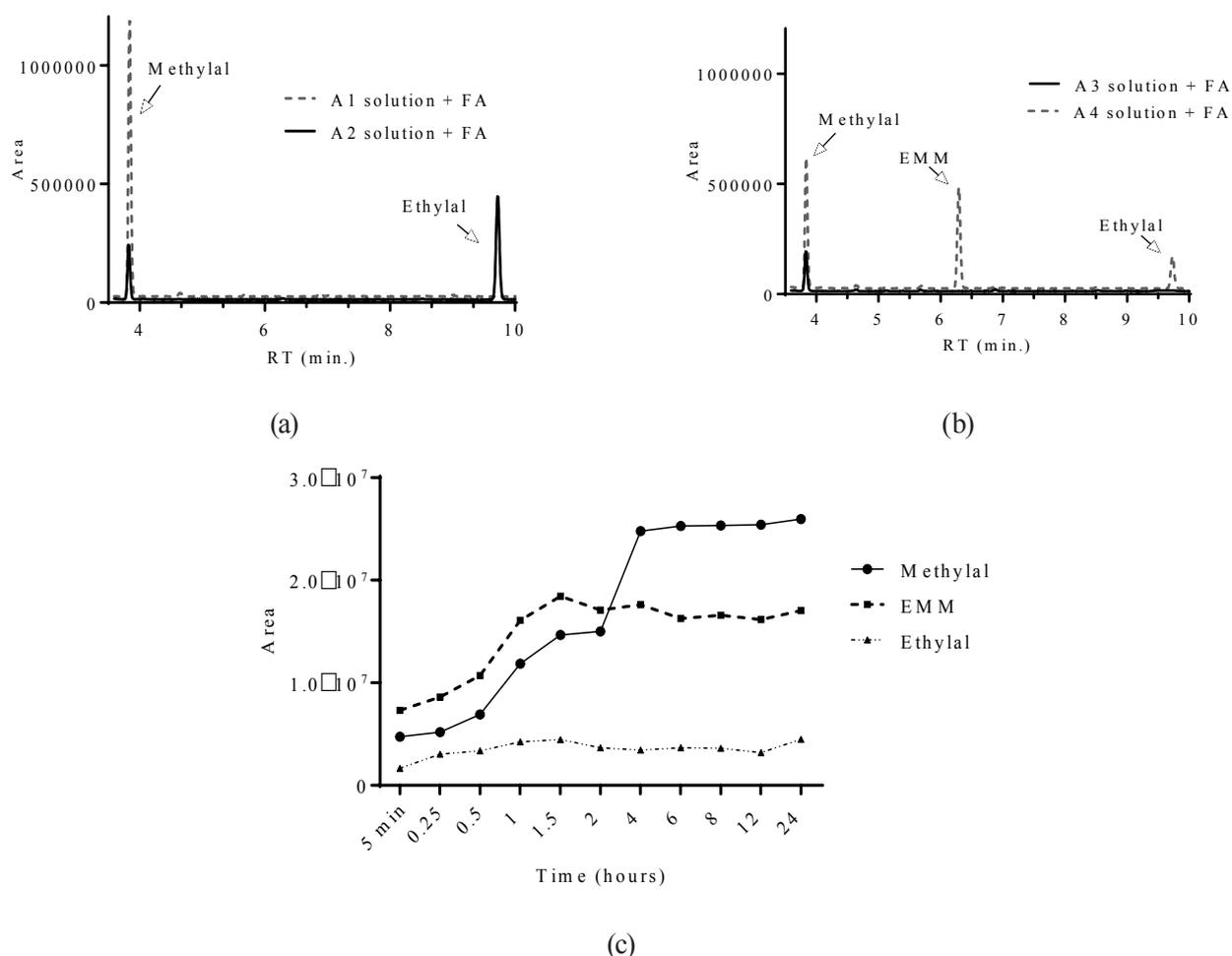
(a)

(b)

(c)

FIGURE 2 - HS-GC-MS **c**hromatograms of blank matrices spiked with formaldehyde (FA) at 0.2% in (a) A1 (MeOH:HCl, 50:1) and A2 (EtOH:HCl, 50:1) solutions; (b) A3 (MeOH:EtOH (25:25) and A4 (MeOH:EtOH:HCl, 25:25:1) solutions. (c) Kinetic for methylal, ethoxymethoxymethane (EMM), and ethylal formation at 60º C.

The kinetics of the in-matrix derivatization reaction was evaluated with formaldehyde in A4 solution incubated at 60ºC for 5 minutes up to 24 hours. Methylal formation was stabilized after 4 hours of incubation, EMM formation after 1.5 hour, and ethylal formation after 1 hour of incubation (Figure 2c). Incubation at 60ºC for 4 hours was the most appropriate derivatization conditions for performing HS-GC-MS formaldehyde analyses based on the formation of the three acetals. Although methylal formation stabilized later than the other two acetals, it gives the highest yield, as it can be seen in Figures 2c and may be the choice when very low levels of formaldehyde are investigated, such as when present as impurity in excipients of pharmaceutical formulations (Li *et al*., 2006;

Wu *et al*., 2011). The excess of the derivatizing agents (ethanol and/or methanol) and the plateau of the product responses indicate that the formaldehyde derivatization was completed in each of the cases.

Previous studies determined formaldehyde in pharmaceutical excipients by derivatization with acidified ethanol and ethylal analysis by HS-GC-MS (Del Barrio *et al*., 2006) or HS-GC-FID (Daoudy *et al*., 2018). Del Barrio *et al*. (2006) found the optimum condition for ethylal formation at 60ºC and 30 minutes, the longest heating time tested. Daoudy *et al*. (2018) found that ethylal formation plateaued after 25 minutes at 70ºC. In our study, the heating time plateau for ethylal was 1 hour, probably because of the competition of the other reactions in the system.

The optimized method, involving derivatization with A4 solution following incubation at 60°C for 4 hours and determination by HS-GC-MS, was further validated.

HS-GC–MS method validation

No matrix effect (< 10%, Table I) was found for methylal, ethylal, and EMM at the three concentration levels tested. Hence, the standard curve to quantify formaldehyde in the cosmetic samples was prepared in A4 solution incubated at 60 °C for 4 hours. Linearity of the standard curve was calculated by the least squares method and showed to be satisfactory for methylal, EMM and ethylal ($r^2 > 0.99$). No interfering peaks were observed in the chromatogram of a blank matrix, indicating that the method is selective. The LOD was set at 0.0015% formaldehyde. Dilution of highly concentrated samples to fit the standard curve did not impact the accuracy and precision of the analysis (variability within ± 20%; data not shown).

Recoveries were within the acceptable range at all concentrations tested for the three acetals (89.6 to 106.6 %), as were the repeatability and intermediated precision (< 12%; Table I), and the LOQ was set at the lowest validated level (0.005 %). The LOD/LOQ of the method complies with the legislation parameters for formaldehyde in oral hygiene and cosmetic products (0.1 and 0.2%, respectively), with the minimum level required for labeling (0.05%) (Anvisa, 2013; Commission Regulation (EU) 2019/831), and for the detection of illegal use in other products. Del Barrio *et al.* (2006) reported an LOQ of 0.2 µg/mL for HS-GC-MS formaldehyde determination in pharmaceutical recipients after derivatization using acidified ethanol, but the lowest validated level (recovery, intra and inter-day precision) was 50 µg/mL (0.005%), the LOQ of the present study for all three acetals.

TABLE I - Validation parameters for methylal, ethylal, and ethoxymethoxymethane (EMM) at three concentration levels (n=3 at each level)

Substance	Concentration, (%)	Matrix Effect, (%)	Recovery, (%)	Repeateability, RSD (%)	Intermediate Precision, RSD (%)
Methylal	0.005*	7.0	91.9	5.1	5.7
	0.05	2.2	103.1	3.6	5.1
	0.2	-7.0	99.7	5.8	5.2
Ethylal	0.005*	7.9	89.6	11.0	8.5
	0.05	2.3	90.6	6.1	5.7
	0.2	-7.9	92.7	5.9	5.1
EMM	0.005*	6.2	106.6	6.4	7.0
	0.05	2.2	97.5	4.6	4.2
	0.2	-2.6	96.4	5.9	4.3

* LOQ

Formaldehyde concentration in cosmetic product samples

The validated method was used to analyze hair-straightener cream samples seized by the Civil Police of the Federal District. Samples (300 mg) were weighed in a 20 mL headspace vial; 1 mL of A4 solution (MeOH:EtOH:HCl; 25:25:1) was added, vortexed, the vials incubated in a water bath at 60°C for 4 h, and analyzed by HS-GC–MS. Samples that showed

concentration above the working range of the method were diluted. One of the nine hair-straightener cream samples analyzed did not contain formaldehyde (< LOD), and the concentrations found in the eight positive samples are shown in Table II. The formaldehyde concentrations estimated from each acetal were similar, without a clear indication of higher or lower concentration according to the acetal measured, indicating that any acetal can be used in the determination. The mean calculated formaldehyde concentration levels in each sample ranged from 0.33 to 4.02 % (RSD< 3.4%), higher than the maximum level permitted in cosmetic products as a preservative (0.2%). Quality control (QC) samples showed satisfactory accuracy (RSD < 20%) for all acetals.

Various studies have investigated the levels of formaldehyde in shampoo, soaps, and creams, where it is normally found at levels up to 0.05% (Brandão, Ramos, Rodrigues, 2018; Miralles *et al*., 2018; Horev *et al*., 2015). However, very few studies have investigated formaldehyde in hair-straightening products. Oiye *et al*. (2016) analyzed five samples of these products sold in Brazil and found two samples containing levels of 0.02 and 0.03% and three samples at levels from 9.2 to 18.4%, much higher than those found in the present study. In the United Sates, the Environmental Working Group investigated 16 companies that make hair-straightening products that are commercialized in the country (EWG, 2011). Most companies did not admit that their products contain formaldehyde, but chemical analysis showed levels ranging from > 0.6 to 11.8 %, the highest levels found in Brazilian products (Anvisa, 2013). The products called keratine treatment or Brazilian blowout (*escova progressiva*) claim to be "formaldehyde-free", but the main chemical used is methylene glycol, which releases formaldehyde when heated during the treatment process, exposing the hairdressers to high concentrations of formaldehyde in the workplace (Golden, Valentini, 2014)

TABLE II - Formaldehyde concentration (%) in hair straightener cream samples analyzed by HS-GC-MS estimated from the derivatized products, methylal, ethoxymethoxymethane (EMM), and ethylal

Sample	Methylal (%)	Ethylal (%)	EMM (%)	Formaldehyde (%)*
1	1.99	1.97	1.96	1.97
2	3.13	3.33	3.20	3.22
3	0.39	0.38	0.39	0.39
4	2.01	2.04	2.00	2.02
5	3.90	4.00	4.17	4.02
6	0.35	0.33	0.34	0.33
7	3.17	3.29	3.38	3.28
8	2.73	2.77	2.79	2.76

*mean of the concentrations measured as methylal, ethylal, and EMM.

CONCLUSIONS

A method for formaldehyde analysis by HS-GC–MS was validated for cosmetic products. To the best of our knowledge, this is the first report of a method for formaldehyde determination that uses both methanol and ethanol resulting in three different derivatized compounds, which ensures that the method is reliable and robust. The method is easy to implement, can be successfully applied to the analysis of real samples, and has the potential to be used in formaldehyde determination in different products. The LOQ of 0.005% formaldehyde is suitable for detecting

the illegal use of formaldehyde in cosmetics, and it can also be applied when the compound is present as impurity in excipients of pharmaceutical products.

Analysis of Brazilian hair-straightening product samples showed formaldehyde levels up to 4%, which is much higher than what is allowed in Brazil and in other countries. These results reinforce the importance of analyzing cosmetic products from the market, even those that do not inform the presence of formaldehyde. In addition to being illegal not to declare the composition of the product, the presence of this toxic compound at high levels in cosmetics can cause health problems to the users. In the case of hair-straightening, it can also cause problems to professionals that apply these products, as normally the application includes blow-drying at high temperatures.

REFERENCES

Anvisa - Agência Nacional de Vigilância Sanitária; Formulário Nacional da Farmacopéia Brasileira, 2a ed. 2012. [Accessed July 18, 2022] Available at: https://www.gov.br/anvisa/pt-br/assuntos/farmacopeia.

Anvisa - Agência Nacional de Vigilância Sanitária. RDC nº 15, de 26/03/2013. Aprova o Regulamento Técnico "lista de substâncias de uso cosmético: acetato de chumbo, pirogalol, formaldeído e paraformaldeído" e dá outras providências. 2013. [Accessed July 18, 2022]. Available at: https://www.gov.br/anvisa/pt-br/assuntos/cosmeticos.

Anvisa - Agência Nacional de Vigilância Sanitária. RDC n° 166, de 24/07/2017. Dispõe sobre a validação de métodos analíticos e dá outras providências. 2017. [Accessed July 18, 2022]. Available at: http://antigo.anvisa.gov.br/documents/10181/2721567/RDC_166_2017_COMP.pdf/d5fb92b3-6c6b-4130-8670-4e3263763401

Brandão PF, Ramos RM, Rodrigues JA. GDME-based methodology for the determination of free formaldehyde in cosmetics and hygiene products containing formaldehyde releasers. Anal Bioanal Chem. 2018;410(26):6873–80.

Brasil, 2019. [Accessed July 18, 2022]. Available at: https://g1.globo.com/sp/sao-jose-do-rio-preto-aracatuba/noticia/2019/12/17/policia-abre-inquerito-para-apurar-morte-de-mulher-apos-fazer-escova-progressiva-em-ilha-solteira.ghtml.

Cao SJ, Hao AY, Sun HY, Sun T. A convenient preparation of ethoxymethoxymethane and its effect on the solubility of methanol/gasoline blends. Chinese Chem Lett. 2009;20(8):973–6.

Chang CJ, Cheng SF, Chang PT, Tsai SW. Indoor air quality in hairdressing salons in Taipei. Indoor Air. 2018;28(1):173–180.

Chopade SP, Sharma MM. Reaction of ethanol and formaldehyde: Use of versatile cation-exchange resins as catalyst in batch reactors and reactive distillation columns. React Funct Polym. 1997;32(1):53–65.

Cogliano V, Grosse Y, Baan R, Straif K, Secretan B, El Ghissassi F, et al. Advice on formaldehyde and glycol ethers. Lancet Oncol. 2004;5(9):528.

Commission Regulation (EU) 2019/831. Amending Annexes II, III and V to Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products. Official Journal of the European Union. 2019; L137, 29-63.

Daoudy BDAD, Al-Khayat MA, Karabet F, Al-Mardini MA. A robust static headspace GC-FID method to detect and quantify formaldehyde impurity in pharmaceutical excipients. J Anal Methods Chem. 2018;2018:13–7.

De Groot AC, White IR, Flyvholm MA, Lensen G, Coenraads PJ. Formaldehyde-releasers in cosmetics: relationship to formaldehyde contact allergy. Part 1. Characterization, frequency and relevance of sensitization, and frequency of use in cosmetics. Contact Dermatitis. 2010;62(1600-0536):2–17.

Del Barrio MA, Hu J, Zhou P, Cauchon N. Simultaneous determination of formic acid and formaldehyde in pharmaceutical excipients using headspace GC/MS. J Pharm Biomed Anal. 2006;41(3):738–43.

EWG - Environmental Working Group. Brands that hide formaldehyde; 2011. [Accessed July 18. 2022]. Available at: https://www.ewg.org/hair-straighteners/our-report/hair-straighteners-that-hide-formaldehyde/.

Golden R, Valentini M. Formaldehyde and methylene glycol equivalence: Critical assessment of chemical and toxicological aspects. Regul Toxicol Pharmacol. 2014;69(2):178–86.

Hauksson I, Pontén A, Isaksson M, Hamada H, Engfeldt M, Bruze M. Formaldehyde in cosmetics in patch tested dermatitis patients with and without contact allergy to formaldehyde. Contact Dermatitis. 2016;74(3):145–51.

Health Canada; Cosmetics Ingredient Hotlist. 2019. [Accessed July 18, 2022]. Available at: https://www.canada.ca/en/health-canada/services/consumer-product-safety/cosmetics/cosmetic-ingredient-hotlist-prohibited-restricted-ingredients/hotlist.html.

Horev L, Isaksson M, Engfeldt M, Persson L, Ingber A, Bruze M. Preservatives in cosmetics in the Israeli market conform well to the EU legislation. J Eur Acad Dermatology Venereol. 2015;29(4):761–6.

IARC. Working Group on the Evaluation of Carcinogenic Risks to Humans. Chemical agents and related occupations. IARC Monogr Eval Carcinog Risks Hum. 2012;100:9–562.

Li Z, Jacobus LK, Wuelfing WP, Golden M, Martin GP, Reed RA. Detection and quantification of low-molecular-weight aldehydes in pharmaceutical excipients by headspace gas chromatography. J Chromatogr A. 2006;1104(1–2):1–10.

Magalhães AFA, Caldas ED. Two health information systems to characterize poisoning in Brazil — a descriptive study. J Public Health. 2018;(March):1–9.

Malinauskiene L, Blaziene A, Chomiciene A, Isaksson M. Formaldehyde may be found in cosmetic products even when unlabelled. Open Med. 2015;10(1):323–8.

Miralles P, Chisvert A, Alonso MJ, Hernandorena S, Salvador A. Determination of free formaldehyde in cosmetics containing formaldehyde-releasing preservatives by reversed-phase dispersive liquid–liquid microextraction and liquid chromatography with post-column derivatization. J Chromatogr A. 2018;1543:34–9.

Oiye EN, Ribeiro MFM, Okumura LL, Saczk AA, Ciancaglini P, de Oliveira MF. Forensic investigation of formaldehyde in illicit products for hair treatment by DAD-HPLC: A case study. J Forensic Sci. 2016;61(4):1122–5.

Pexe ME, Marcante A, Luz MS, Fernandes PHM, Neto FC, Sato APS, et al. Hairdressers are exposed to high concentrations of formaldehyde during the hair straightening procedure. Environ Sci Pollut Res Int. 2019;26(26):27319–27329.

Pierce JS, Abelmann A, Spicer LJ, Adams RE, Glynn ME, Neier K, et al. Characterization of formaldehyde exposure resulting from the use of four professional hair straightening products. J Occup Environ Hyg. 2011;8(11):686–699.

Soman A, Qiu Y, Chan LQ. HPLC-UV method development and validation for the determination of low level formaldehyde in a drug substance. J Chromatogr Sci. 2008;46(6):461–5.

Wu Y, Levons J, Narang AS, Raghavan K, Rao VM. Reactive impurities in excipients: Profiling, identification and mitigation of drug-excipient incompatibility. AAPS PharmSciTech. 2011;12(4):1248–63.

Zhang X, Zhang S, Jian C. Synthesis of methylal by catalytic distillation. Chem Eng Res Des. 2011;89(6):573–80.