



Quality control of hydroalcoholic gels

Mohamed Habib Belmahi ^{a,b}, Zeineb Chelighem ^a, Soumia Tehami ^{a,b*}, Lamia Benseghir ^a

^a University 3 of Constantine Salah Boubnider, Faculty of medicine. Constantine, 25000, Algeria

^b University Hospital of Constantine. Constantine, 25000, Algeria

Abstract

The systematic use of alcohol-based hand sanitizers is the preferred method to prevent contamination and stop the spread of COVID-19. Increased demand for disinfectants has led to increased prevalence of adulterated alcohol-based disinfectants. The aim of this study is to assess the compliance and effectiveness of alcohol-based hand sanitizers marketed in Algeria.

This is a cross-sectional descriptive analytical study, carried out between the month of September and the month of October 2021, on hydro-alcoholic gels samples, randomly selected, present on the market. This work focuses on the qualitative analysis of the labelling and quantitative composition of the disinfectant gels by gas chromatography (GC-FID) to assess their ethanol content and methanol content to prevent the risk of fraud for each of them. As well as the assessment of irritating power by the Draize test.

30 hydro-alcoholic disinfectants were analysed, the average ethanol content of hydro-alcoholic gels was (47.25%±13.85) with a maximum of 79%. 82% of the results obtained do not agree with the who standard. Furthermore, the methanol content in all the hydro-alcoholic gels covered by the study is below the limit of quantification (0.01 g/L).

Hand sanitizer with adulterated alcohol is a serious public health risk, especially in the context of the COVID-19 outbreak. The precise determination of ethanol, isopropanol content is the key element in assessing the efficacy and safety of the product.

Keywords:

Alcohol-based hand sanitizer, Efficacy, Quantification, Impurity, GC-FID.

*Received March 24, 2024; accepted April 24, 2024

*Corresponding author

Email address: tehamisoumia25@gmail.com (Soumia Tehami).

Cited as: Belmahi M.H, Chelighem Z, Tehami S, Benseghir L. Quality control of hydroalcoholic gels. J. Mol. Pharm. Sci. 03 (01), 2024, 38-46.

1. Introduction

The COVID-19 pandemic is a major public health problem worldwide. To combat its spread, the World Health Organisation has recommended protective measures. These include hand hygiene, using alcohol-based disinfectants.

Demand for these products from healthcare professionals and the general public has increased considerably, but their availability has fallen considerably as the raw materials needed to manufacture them have become scarce. Disinfectants based on ethanol and isopropanol (2-propanol) have a degree of over 60%, as they are capable of denaturing microbial proteins and inactivating viruses.

Various countries, including Algeria, have taken a number of steps to increase availability, including relaxing the rules in force for the production of hydroalcoholic gels. Unfortunately, many non-specialist manufacturers have redirected their activities towards the production of hand sanitisers, which has led to the presence of many adulterated products.

Precise determination of the ethanol content in hydroalcoholic gels is essential to assess their efficacy and safety, and to detect fraudulent use of other alcohols (methanol) which are toxic to humans.

The aim of our study is to assess the conformity of hydroalcoholic gels available on the Algerian market by quantitative analysis of ethanol content using GC-FID. The secondary objectives are to assess the irritant power of hydroalcoholic gels and to search for impurities (methanol).

2. Material and methods

2.1. Sampling

This is a cross-sectional descriptive analytical study, carried out between September and October 2021.

The study focused on randomly selected samples of hydroalcoholic gels of different brands available on the market in the wilayas of Constantine and Mila. The main point of sale was pharmacies in the two wilayas.

2.1.1 Inclusion criteria

Any hydroalcoholic gel product sold in pharmacies in the wilayas of Constantine and Mila.

2.1.2 Non-inclusion Criteria

-Markets in other Algerian wilayas.

-Other ranges of hydro-alcoholic products (hydro-alcoholic solutions).

2.1.3 Information sheet

A rigorously completed information sheet accompanies each product. It contains the information about the gels shown on the packaging.

2.2 Determination of alcohols

2.2.1 Equipment

2.2.1.1 Gas chromatography coupled to a flame ionisation detector FID GC

the gas chromatography system used was a Perkin Elmer Clarus 580 with a flame ionisation detector (FID).

The injection system linked to the gas chromatography apparatus is a Perkin Elmer Turbomatrix 40 Head space (HS) sampler with a transfer line.

The carrier gases used is the nitrogen supplied by the PEAK SCIENTIFIC nitrogen generator.

An Elite-BAC-I capillary column [30m long, 0.32mm internal diameter, 1.8µm df] from RESTEK was used.

2.2.1.2 Densimeter

We measured the density of the hydroalcoholic gels using a RADWAG PS 600.R2 densimeter.

2.2.2. Methods

The method of analysis of alcohols (ethanol and methanol) used was previously validated in the toxicology laboratory of the Ibn Sina hospital in Annaba. Gas chromatography (GC) coupled with headspace extraction (HEX) with flame ionisation detection (FID) was used to determine the degree of various alcohols, namely ethanol, a component of hydroalcoholic products, and methanol. This analysis is part of the prevention of the risk of fraud and the verification of the conformity of hydroalcoholic gels.

2.2.2.1. Operating conditions

Table 1 shows the headspace conditions.

Tab. 1. Headspace (HS) conditions.

Temperature (°C)	Needle	70 °C
	Transfer line	80 °C
	Oven	60 °C
Time (min)	Injection	0,03 min
	Withdrawal	0,2 min
	Pressurisation	1 min
	Thermostat	22 min
	Cycle time	5 min
PPC	Pressure	16 psi

The chromatographic conditions are shown in the table 2.

Tab. 2. Chromatographic conditions.

Injector	Temperature	120 °C
	Nitrogen pressure	12 psi
	Split	Ratio: 10
Elite-BAC-1 Avantage capillary column (30m, 0.32mm, 1.8µm df)	Temperature	40 °C
	Analysis time	4 min
PPC	Temperature	250 °C
	Air / Hydrogen flow	450 mL / 45 mL
	Attenuation	- 4

The Detection, quantification limit and the linearity range are mentioned in the table 3.

Tab. 3. Detection and quantification limits.

Alcohol	Methanol	Ethanol
Detection limit (g/L)	0,005	0,002
Quantification limit (g/L)	0,01	0,01
Linearity range (g/L)	0,01 -5	0,01 - 5

2.2.2.2. Procedure

Prior to the actual analysis on GC-FID, we proceeded by: sample numbering, analysis of labelling, and measurement of the density of the hydroalcoholic gels

We assumed a dilution factor of 1/1000th so as not to exceed 1g/L.

2.2.2.3. Preparation of samples

To make the pre-dilutions for each sample after homogenisation of the hydroalcoholic product,

- Calculate the mass of a 10 mL volume of each sample.
- Place the weighed quantity of hydroalcoholic gels in a 50 mL graduated cylinder and add double-distilled water up to 50 mL.
- Shake manually.

Preparation of final dilutions at 1/1000 from the previous dilution.

Preparation of vials:

- Homogenisation before taking the test sample
 - Take 1 ml of the sample to be analysed from the dilutions.
 - Add 100 μ l of 1-Propanol internal standard solution.
 - Close the vials tightly with the septa.
 - Place the vials in the Headspace.
 - Set up the chromatographic conditions: Head pace and oven.
- Retention time of ethanol is 1,87min, and 1,52min for methanol (**Fig. 1**).

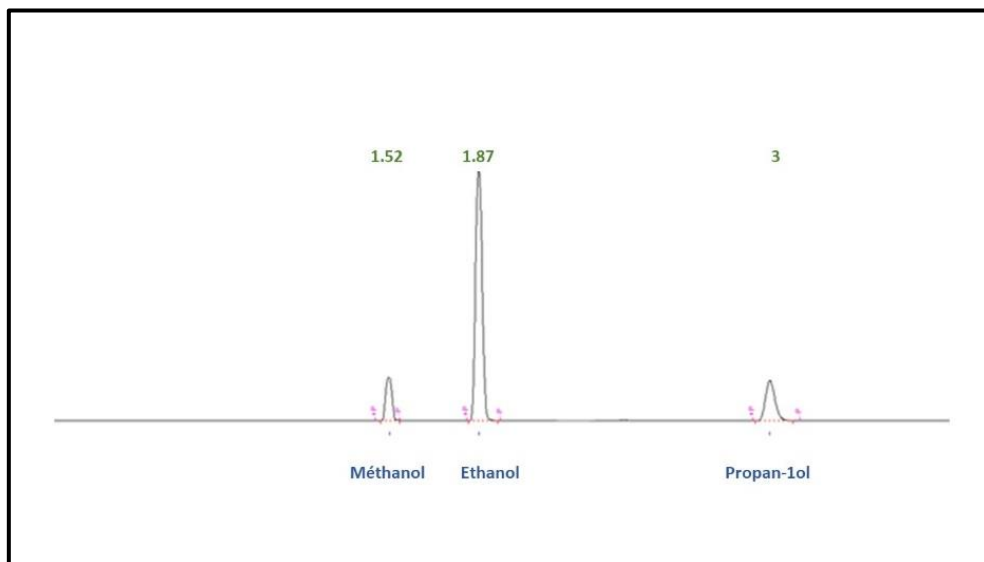


Fig. 1. Chromatogram of ethanol, methanol and propan-1-ol (internal standard).

2.2.2.4. Production of calibration curves

A/ Calibration curve for ethanol

The linearity study was carried out by analysing 5 standard ethanol solutions at the following concentrations: 0.2 g/L - 0.4 g/L - 1 g/L - 1.5 g/L - 2 g/L.

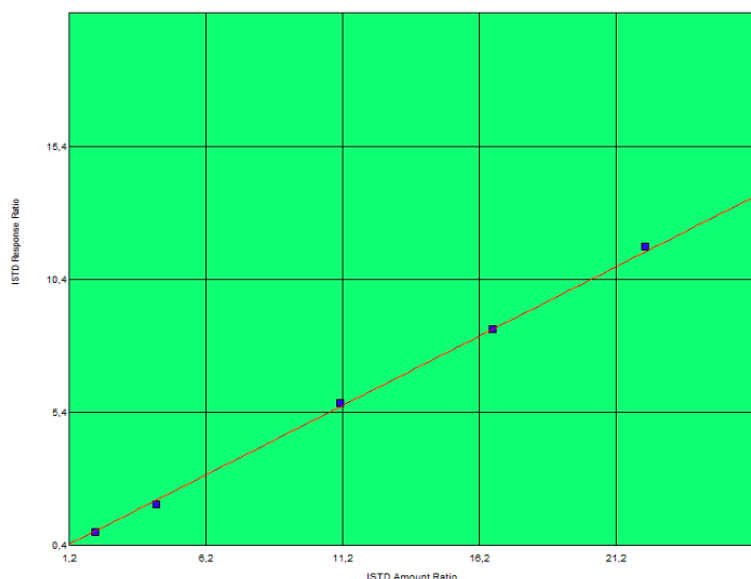


Fig. 2. Ethanol calibration curve.

B/ Methanol calibration curve

The linearity study was carried out by analysing 5 solutions of methanol prepared in water at the following concentrations: 0.25 g/L - 0.75 g/L - 1 g/L - 2 g/L - 3 g/L.

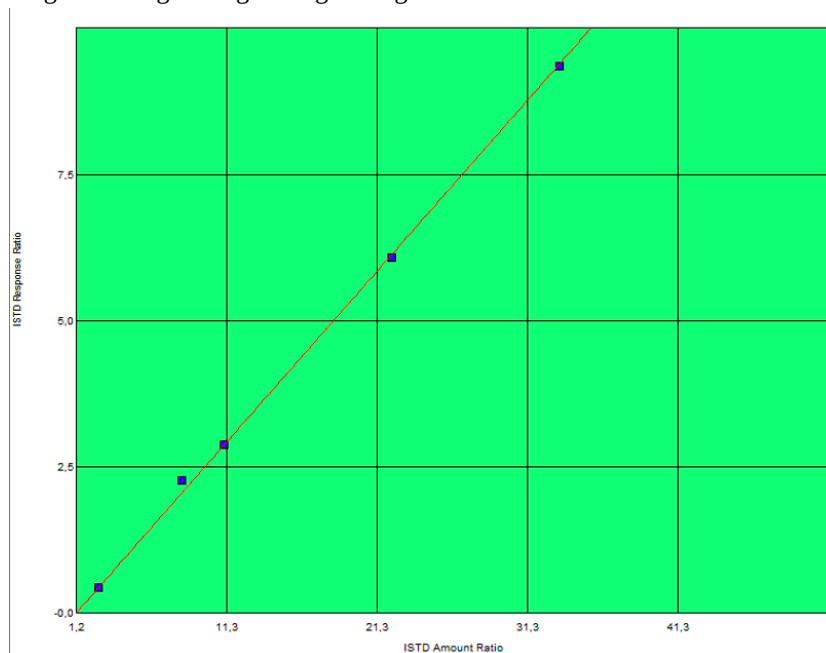


Fig. 3. Methanol calibration curve.

3. Results

3.1. Description of the sample's hydroalcoholic gels

We worked on 30 hydroalcoholic gels from Algerian production.

Of the 30 hydroalcoholic gels studied, only 8 indicated the alcoholic degree on their packaging.

90% carry instructions for use of the hydro-alcoholic gel on the packaging and 60% mention the storage conditions.

Only 10% of gels do not indicate the notion of cutaneous application only

63% of products state on the packaging "do not leave gels within the reach of children", the notion of flammability is indicated on only 53% of hydroalcoholic gels.

97%state the date of manufacture and use-by date on the packaging, 93%, bear the batch number.

According to the list of ingredients on the packaging of hydroalcoholic gels, the alcohol used in the composition is either ethanol (76%) or a mixture of two alcohols, ethanol and isopropanol (20%). Around 3% of gels do not indicate the type of alcohol used.

3.2. Results of the determination of the various Alcohols

3.2.1 Determination of ethanol

The results of the ethanol assay are shown in the table 4.

Tab. 4. Ethanol assay results.

N°	Ethanol content	Mentioned alcoholic degree %.	Norms (OMS)
1	68%	NM	60% -80%
2	59%	NM	
3	ND	NM	
4	66%	NM	
5	59%	NM	
6	22%	96%	
7	40%	NM	
8	45%	NM	
9	26%	NM	
10	45%	70%	
11	52%	NM	
12	64%	NM	
13	32%	NM	
14	34%	NM	
15	46%	NM	
16	39%	NM	
17	39%	90%	
18	58%	70%	
19	79%	80%	
20	48%	NM	
21	37%	NM	
22	52%	96%	
23	38%	NM	
24	52%	NM	
25	47%	96%	
26	27%	NM	
27	64%	NM	
28	39%	NM	
29	ND	70%	
30	46%	NM	

ND: not determined, NM: non mentioned.

3.2.2 Determination of methanol

The level of methanol obtained by assay in the various hydroalcoholic gels studied was below the limit of quantification (0.01 g/L).

4. Discussion

The emergence of the COVID-19 (coronavirus-2019) pandemic has become a major public health concern worldwide, requiring rigorous measures and controls to minimise its transmission [1].

The WHO has recommended the use of disinfectant products, in particular hydroalcoholic products for hand hygiene as a preventive measure, and has recommended two formulations, one ethanol-based and the second isopropanol-based. The health emergency caused by the pandemic led to an explosion in the production of disinfectant gels to cover the increased demand.

In order to prevent any shortage of these products, the various countries facilitated the production and marketing of hydroalcoholic gels and solutions, which led to an increase in the prevalence of adulterated alcohol-based hand sanitisers, including the production of hand sanitisers with an alcohol concentration of less than 60% and the illegal addition of methanol to hand sanitisers [2].

The evaluation of the labelling of the 30 hydroalcoholic gels studied from Algerian production showed that 90% of the products studied mentioned the instructions for use on the labelling in order to ensure complete effectiveness

and limit the risks of human contamination or fire and explosion during use. For best results, hands should be dry and visibly clean. It is essential to use the recommended quantities (a generous dab) with friction (25 to 30 seconds) until the product has evaporated away from the nostrils, to avoid inhaling alcohol, without rinsing [3]. It should also be borne in mind that using more gel increases the quantity of alcohol vapour generated, which increases the risk of ignition in the presence of a fire source [4].

Hydroalcoholic gel is composed mainly of ethanol, an extremely flammable substance with a flash point of 12°C for pure ethanol. This means that ethanol at room temperature is always a fire and explosion hazard [4]. For similar reasons, hydroalcoholic gels are classified as highly flammable products (bearing the "flame" pictogram), with slightly higher flash points, in the region of 18 to 25°C depending on the ethanol content [4]. This information is normally indicated on all hydro-alcoholic products on the market, unlike in our study where only half of the hydro-alcoholic gels (53%) indicated this on the labelling. Failure to comply with this recommendation can lead to inflammatory accidents, as in the case of a company employee whose hand caught fire after using a hand disinfectant and smoking a cigarette because he had not rubbed the disinfectant completely [5]. 60% mention the storage conditions that must be followed for the product to remain effective. These conditions have been issued by the French National Agency for Food, Environmental and Occupational Health and Safety (Anses), which states that exposure to heat could lead to "possible evaporation of the alcohol, which is the active substance. Excessive evaporation of the alcohol may reduce its content, thereby reducing the effectiveness of the solution"[6].

Keep the product away from heat and sunlight, close the container tightly after use and use the product fairly quickly after opening if the bottle is fitted with a metering pump [4].

Of the 30 products studied, 90% of the gels stated that they should be applied to the skin only and 63% said that they should not be left within the reach of children.

Health authorities worldwide and manufacturers have repeatedly reminded consumers that alcohol-based hand sanitisers are for external use only and should never be swallowed [7].

On the other hand, this powerful disinfectant, which was used on a massive scale during the coronavirus pandemic, was the cause of many accidental poisonings in children through ingestion or eye contact. However, these intoxications are mainly voluntary in adults, as a substitute for alcohol (ethanol) rather than for suicidal purposes [7].

Young children are exposed to serious eye injuries that can lead to blindness. In France, between 1 April 2020 and 24 August 2020, there was a 7-fold increase in paediatric cases of ocular exposure to hydroalcoholic gel compared with the same period in 2019. This increase was associated with an increasing number of hydroalcoholic gel devices available free of charge in public places [8]. According to the California Department of Ophthalmology in 2020, a 4-year-old girl was brought in by her parents following involuntary exposure of her right eye to disinfectant from a public place dispenser attached to an adult size. The child complained of severe photophobia. His right eyelid was oedematous [9].

In California in 2013, Aaron Bschnir reported the case of a 36-year-old man who died 7 days after ingesting an ethanol-based hand disinfectant. He was found apnoeic and pulseless in the waiting room of the emergency department, and his serum ethanol was 526 mg/dl. The case highlights the potential for significant toxicity following ingestion of a product found in all healthcare establishments [10].

After analysing the labelling of the hydroalcoholic gels studied, the majority of products (exactly 97%) mention an expiry date that must be respected by the user. According to the Anses, "the solution, in contact with air and skin, is likely to degrade". So once the product has been opened, it is advisable not to keep it for too long [6].

European regulations governing biocidal products do not impose any requirements on storage or shelf life once the product has been opened. However, care must be taken when storing and using these products, in order to guarantee their stability and efficacy and limit the risks to users [6]. Of the 30 hydroalcoholic gels studied, 93% bear the batch number on the packaging. It is compulsory to mention the batch number. In order to verify the conformity of hydroalcoholic gels already marketed in eastern Algeria, 30 hydroalcoholic gels were analysed using GC-FID.

According to the list of ingredients on the packaging of the 30 hydroalcoholic gels studied, the alcohol used in the composition of 23 products was ethanol alone, and for the remaining 6 products it was a mixture of two alcohols, ethanol and isopropanol. However, for sample number 12, the type of alcohol used was not mentioned. Of these products, only 8 (N° 6, 10, 17, 18,19,22,25,29) mention the alcohol content on the packaging.

According to our study, the maximum alcohol content is 79%. The average ethanol content of all the hydroalcoholic gels studied was $47.25\% \pm 13.85\%$. This result does not comply with standards required by the WHO for hydroalcoholic gels (60% - 80%).

However, the minority of hydroalcoholic gels analysed - exactly 5 products (1,4,12,19,27) – comply with standards, with an alcohol content of over 60%. Only 3 products (2,5,18) had an alcohol content close to 60%, while 20 products had an alcohol content below 60%.

Analysis of samples 3 and 29 (whose alcohol content was not determined) showed the presence of a peak with a retention time of 2.24, different from that for ethanol (1.89). The suspicion that the main component of these 2 gels is isopropanol, as the main alcohols used in the composition of hydroalcoholic gels are ethanol and/or propanol, which can be in the form of two isomers: 1-propanol and 2-propanol (isopropanol) [11]. After injection of pure isopropanol, a peak with a retention time of 2.24 was obtained, identical to that of the 2 gels. However, the method used does not allow the results obtained to be confirmed because the isopropanol assay method has not been validated.

It should be noted that a hand disinfectant containing less than 60% alcohol would be ineffective as a germicide and would not offer users any biocidal effect, leaving the public vulnerable to the contraction and spread of COVID-19 [2].

In our study, of the 8 products (N° 6, 10, 17, 18,19,22,25,29) mentioning the alcohol degree on the packaging, only product 19 had an alcohol degree compatible with the degree mentioned and only one product (18) had an alcohol degree close to 60% (58%).

For the 22 hydroalcoholic gels whose alcohol content was not mentioned, 4 products were compliant (1,4,12,27) with an alcohol content above 60%, while two products (2,5) had an alcohol content close to 60% (59%). According to the study by the toxicology laboratory at EHS Ibn Sina in Annaba, 7 samples mention the alcohol degree on the packaging, of which 5 products have an alcoholic degree compatible with the strength mentioned, and for the 13 hydroalcoholic gels for which the alcohol degree is not mentioned, 11 products comply [12].

In fact, other results point in the same direction as those obtained in our study. Sáenz et al (2021), analysed 24 marketed hydroalcoholic gels (15 produced by national and transnational companies, and nine collected from public areas, in use), only one brand of 15 gels complies with the quality requirements [13].

According to our study, only 18% of the products comply with the recommendations, unlike a study carried out at the national toxicology centre in Algiers (2020) where they found 69% [14].

This could be explained by increased demand, which has led to a shortage of the raw materials essential to the manufacture of hydroalcoholic gels, including ethanol. On the other hand, individuals and companies without adequate experience in chemistry and lacking the requisite knowledge and skills have seized the opportunity to improvise in the field.

Numerous reports worldwide have revealed that alcohol-based hand sanitisers sometimes contain undeclared methanol. Methanol should never be used in such a product, as oral, pulmonary and/or dermal exposure can lead to severe systemic toxicity and even death. The issue of methanol contamination was recently raised by the US FDA, which published a list of nearly 90 dangerous 'do not use' hand sanitisers containing methanol. Among the products tested, methanol content varied between 1 and 80% [15].

In our study none of our products contained methanol, a similar study at the national toxicology centre in Algiers by Chebli et al (2020) obtained the same result [85], unlike the study by Sáenz et al (2021) where the result was striking 25% of gels on the market contain methanol - a toxic substance - in alarming quantities, hundreds of times more than the FDA's upper limit requirement [13]. According to Ammar Abdulrahman Jairoun et al (2020), an inspection of disinfectants in Dubai found 6 disinfectants containing undeclared methanol out of 102 products tested [2]. The Arizona Poison and Drug Information Centre found an increase in exposures to hand sanitisers. Of these cases, 28% involved hand sanitisers contaminated with methanol [16].

5. Conclusion

With the onset of the COVID-19 pandemic around the world, demand for and consumption of hand sanitisers increased, leading to a sharp contraction in these products at all levels.

Assessment of the safety and composition of hydroalcoholic gels, and assurance of their safety by toxicologists before they are placed on the market, are essential for good consumer health prevention.

Evaluation of the conformity of hydroalcoholic gels marketed in eastern Algeria (30) by GC-FID revealed an average ethanol content of $47.25\% \pm 13.85\%$. This result does not comply with the standards required by the WHO for hydroalcoholic gels (60% - 80%), but 17% of these products are compliant.

The level of methanol in all the hydroalcoholic gels concerned by the study was below the limit of quantification (0.01 g/L). This dosage is necessary to prevent any attempt at fraud and to ensure consumer health safety. Instructions for use were mentioned in 90% of the products studied, but only 53% indicated the flammability risk of these gels. Storage conditions were mentioned in 60% of products. These notions are important to ensure efficacy and safety of use.

To obtain an effective, high-quality hydroalcoholic gel, the producer must comply with a number of production criteria, various evaluation tests must be carried out and the gel must be used in accordance with the recommendations.

References

- [1] Golin AP, Choi D, Ghahary A. Hand sanitizers: A review of ingredients, mechanisms of action, modes of delivery, and efficacy against coronaviruses. *Am J Infect Control*. sept 2020;48(9):1062-7.
- [2] Jairoun AA, Al-Hemyari SS, Shahwan M. The pandemic of COVID-19 and its implications for the purity and authenticity of alcohol-based hand sanitizers: The health risks associated with falsified sanitizers and recommendations for regulatory and public health bodies. *Res Soc Adm Pharm*. janv 2021;17(1):2050-1.
- [3] Jing JJJ, Pei Yi T, Bose RJC, McCarthy JR, Tharmalingam N, Madheswaran T. Hand Sanitizers: A Review on Formulation Aspects, Adverse Effects, and Regulations. *Int J Environ Res Public Health*. mai 2020;17(9):3326.
- [4] Institut national de recherche et de sécurité. Gel hydroalcoolique : se prémunir de tout risque d'incendie-explosion - Actualité - INRS [Internet]. [cité 7 nov 2021]. Disponible sur: <https://www.inrs.fr/actualites/risque-incendie-explosion-du-gel-hydroalcoolique.html>
- [5] Alain Bassett. Instant Hand Sanitizer Hazard [Internet]. 04:55:21 UTC [cité 3 nov 2021]. Disponible sur: <https://www.slideshare.net/alanbassett/instanthandsanitizerhazard>
- [6] Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail. Avis de L'anses relatif aux critères d'efficacité des désinfectants hydroalcooliques pour l'hygiène humaine et la garantie de cette efficacité tout au long de leur cycle de vie [Internet]. 2020 [cité 11 juill 2021]. Disponible sur: <https://www.anses.fr/fr/system/files/BIOC2020SA0067>
- [7] Chan APL, Chan TYK. Methanol as an Unlisted Ingredient in Supposedly Alcohol-Based Hand Rub Can Pose Serious Health Risk. *Int J Environ Res Public Health*. juill 2018;15(7):1440.
- [8] Gilles C.Martin,Gael Le Roux, Damien Guindolet. Pediatric Eye Injuries by Hydroalcoholic Gel in the Context of the Coronavirus Disease 2019 Pandemic | Ophthalmology | JAMA Ophthalmology | JAMA Network [Internet]. [cité 6 nov 2021]. Disponible sur: <https://jamanetwork.com/journals/jamaophthalmology/fullarticle/2775155>
- [9] Sonam Yangzes, Sartag Grewal, Tonyot Gailson. Hand Sanitizer–Induced Ocular Injury: A COVID-19 Hazard in Children | Cornea | JAMA Ophthalmology | JAMA Network [Internet]. [cité 6 nov 2021]. Disponible sur: <https://jamanetwork.com/journals/jamaophthalmology/fullarticle/2775159>
- [10] Schneir AB, Clark RF. Death caused by ingestion of an ethanol-based hand sanitizer. *J Emerg Med*. sept 2013;45(3):358-60.
- [11] World Health Organization, éditeur. WHO guidelines on hand hygiene in health care: first global patient safety challenge: clean care is safer care. Geneva, Switzerland: World Health Organization, Patient Safety; 2009. 262 p.
- [12] Laouar K, Mebirouk S F, Djafer R. détermination des alcools dans les gels hydro-alcooliques par la CPG-FID.
- [13] Sáenz L de la T, Lardizábal-Gutiérrez D, Estrada-Guel I, Paraguay-Delgado F. Methanol detection in commercial sanitizing gels, during the COVID-19 Pandemic. *TECNOCENCIA Chihuahua*. 3 juin 2021;15(1):16-25.
- [14] Chebli AI, Zebbiche Y, Seleyimi S, Cheradi S, Benaissa A, Hadjadj Aoul F z. Contrôle de qualité des produits désinfectants hydro alcooliques : expérience du Centre National de Toxicologie. *J Algér Pharm*. 2020;3(1):65-9.
- [15] Berardi A, Cenci-Goga B, Grisoldi L, Cossignani L, Perinelli DR. Analysis of Commercial Hand Sanitisers amid CoViD-19: Are We Getting the Products that We Need? *AAPS PharmSciTech*. 15 oct 2020;21(7):286.
- [16] Holzman SD, Larsen J, Kaur R, Smelski G, Dudley S, Shirazi FM. Death by hand sanitizer: syndemic methanol poisoning in the age of COVID-19. *Clin Toxicol Phila Pa*. nov 2021;59(11):1009-14.

