Chapter

Biotoxicological Monitoring of Organic Solvents in the Tunisian Footwear Industry

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Abstract

Organic solvents (OS) are widely used in Tunisian footwear industry; however, there are no data related to employees' exposure. The objective of this study was therefore to adjust analytical methods in our laboratory for exposure assessment purposes. The predominant solvents are acetone, cyclohexane, hexane, methyl ethyl ketone, and toluene. Eighteen companies benefited from 55 airborne and 190 urine samples. Quantification of solvents and their metabolites was achieved by analytical methods that were adapted and validated in our laboratory. Airborne solvents were determined using gas chromatography (GC-FID). Urinary solvents or metabolites were measured either by GC or high-performance liquid chromatography (HPLC). Validation criteria were determined and used to judge the methods reliability. For airborne solvents, the concentrations exceeding the threshold limit value are mainly for hexane. For urines, the hippuric acid concentrations exceeded the biological limit value in semi-industrial process. Surprisingly, trans, trans-muconic acid was found in industrial and artisanal processes even though benzene was not among the used products. GC and HPLC methods have been adjusted, optimized, and effectively used to quantify OS and their metabolites in airborne and urine samples. Thus, a process of occupational risk assessment via a biotoxicological and airborne monitoring for solvents is now set.

Keywords: solvent exposure, chromatographic methods, risk assessment, indoor air, biomonitoring

1. Introduction

In the modern world, chemicals are integrated almost into every part of human life and activity. Their handling especially in huge quantities represents in some cases a health risk. In this context, organic solvents are regarded among the main chemical pollutants of the family called volatile organic compounds [1, 2–5] commonly used in the industrial sectors. Indeed, these products are widely employed in several fields and included in the composition of various products such as paints, inks, glues, pesticides, degreasers, and thinners. However, due to their readily volatilization, these solvents can be easily released into the atmosphere during manufacturing, storage, transportation, and application, which facilitate their inhalation by human and causing thus adverse health effects. In some cases, the inhaled chemical even undergoes biotransformations and may create more or less reactive

intermediates leading to intoxication. Therefore, the assessment of human exposure to organic solvents in workplaces where they are handled in great quantities is of utmost importance for elucidation of human risks.

Among the chemical risks (CR) identified in Tunisian footwear manufacturing industry, organic solvents occupy by far the first place. However, despite the huge consumed quantities, exposure data of employees to these solvents in this area are almost absent. Actually, the prevention of occupational risks, especially for CR, is based on risk assessment following the procedures set by the regulations [4–8]. Nonetheless, the Tunisian health regulations [7, 8] have provided no requirement for entrepreneurs to conduct risk assessments via indoor air measurements in the workplaces or any biological exposure monitoring. We think that one of the reasons could be related to the lack of specialized laboratories in the field of metrology and health exposure assessment, since foreign companies engaged in such assessment are obliged to send their samples abroad.

To do so and overcome this shortcoming, the development of protocols and the validation of analytical methods to quantify the solvents and their metabolites in human fluids can partly solve the problem of exposure to OS. In the current case, the developed methods were used to evaluate the airborne content in terms of solvents such as acetone, cyclohexane, n-hexane, MEK, toluene, and trichloroethylene in shoe manufacturing companies in the city of Sfax. The detection and the quantification of their respective metabolites were also addressed.

Within this context, according to the guidelines, the most used technique is the gas chromatography (GC) coupled to a mass spectrometry detector [9–11]. The urinary metabolites of OS are also assessed by chromatographic methods; liquid chromatography (HPLC) [12, 13] and gas chromatography (GC) [14], each coupled to mass spectrometry, remain by far the most suitable methods for solvent and metabolite quantification. However, in our laboratory the GC is coupled with flame ionization FID detector. In this investigation, and as mentioned earlier, our main focus is to adapt the analytical method with our instrument and to validate GC-FID and HPLC methods to be used later on in routine analysis of OS and their respective urinary metabolites, in workplaces, such as shoe industry, with the ultimate aim to assess chemical exposures and health adverse impacts.

2. Material and methods

2.1 The shoe manufacturing process and sampling of the footwear companies

Actually, in Tunisia, the shoe industry, despite its mechanization, remains a labor industry where about 150 operations are required to make a pair of shoes. The shoe manufacturing steps are already presented in previous publications [15, 16].

The footwear manufacturing companies were identified and classified under three groups according to their manufacturing processes: industrial, semi-industrial, and artisanal. The classification is previously detailed [16] and briefly summarized in **Table 1**.

2.2 Selection of solvents and their metabolites to be quantified

Following the identification of solvents encompassed in the composition of products handled (glues, thinners, and strippers) in shoemaking conducted during the first half of 2008 in Sfax region, we were able to identify the most predominant solvents such as acetone, cyclohexane, hexane, methyl ethyl ketone, toluene, and

	Process	Industrial	Semi-industrial	Artisanal	Total
The discovered population (2005)	Companies	26	6	60	92
	Employees	751	48	350	1149
The selected sample (2008)	Companies	6	6	10	22
	Employees	122	48	60	230

Table 1.
Footwear companies.

a b

Figure 1
(a) Individual sampling of indoor air exposure. (b) Stationary sampling of the workplace's atmosphere.

trichlorethylene [4, 17, 18]. They were subjected to an airborne quantification in addition to their metabolites which were measured in urine worker samples [19]. Although benzene was not identified in the composition of the products, for security reasons, it was systematically investigated via its metabolite trans, trans-muconic acid in urine [7, 8, 20].

2.3 Sampling and analytical methods

The solvent exposure assessment was performed along 15 weeks, based on some former studies [5, 21, 22] and via several steps that are detailed in our previous publication [16].

To measure personal exposure, an air sampling holder was fixed near the respiratory zone of each volunteer worker (**Figure 1**) [23–27]. The sampling method and equipments have already been described [16]. These samples were taken in the middle of the week on Wednesdays or Thursdays depending on the type of the company's manufacturing process and installation locations (**Table 2**).

Result comparisons of the analyzed samples were carried out in reference to average values of exposure (*TLV*) calculated over a reference period of 8 hours/day and 39 hours/week (**Table 7**) [7, 8, 17, 28, 29].

In order to quantify solvent metabolites, 190 employees among 230 involved in shoe manufacturing, belonging to 22 companies, have benefited from urinary sampling. These samples were taken by the weekends and at the end of the work shifts:

Process manufacturing	Installation location	Leave weekly	Airborne sampling	Urinary sampling
Industrial	Industrial zone	Saturday (afternoon) and Sunday	Wednesday (Morning)	Friday (afternoon)
Semi-industrial				
Artisanal	The Medina (old town)	Sunday (afternoon) and Monday	Thursday (morning)	Saturday (afternoon)

NB.: Semi-industrial companies: some in the Medina and other industrial areas.

Table 2.
The moments of interventions in the companies.

Companies	Class	Identified	Planned	Realized	Airborne measurements	Urinary sampling
Industrial	1	26	6	4	17	105
Semi-industrial	2	6	6	5	23	60
Artisanal	3	60	10	10	15	25
	Total	92	22	18	55	190

Table 3.
Sample of participating companies to airborne and biomonitoring interventions.

on Friday or Saturday afternoon (**Tables 2** and **3**) [30–33]. These urine samples were performed with reference to the biological limit values (**Table 7**) [16, 34–36].

2.3.1 Toxicological analysis protocols

2.3.1.1 Dosing the target solvents in the indoor air

After desorption in 5 ml of carbon disulfide (Fluka®, Ref. 84710), the activated charcoal was analyzed by gas chromatography coupled with flame ionization detector (GC-FID) using an external calibration mode (**Tables 4** and **5**, **Figure 2**): (i) SHI MADZU® chromatograph, GC-9A, and (ii) capillary column Hewlett-Packard® HP-5MS (L = 60 m, inner diameter = 0.25 mm, film

Solvent		Acetone (C_3H_6O)	n-Hexane (C_6H_{14})	MEK (C_4H_8O)	Cyclohexane (C_6H_{12})	Trichlorethylene (C_2HCl_3)	Toluene (C_7H_8)	Benzene (C_6H_6)
Desorption	Solvent	Carbon disulfide						
	Amount (ml)	5 ml for validation area and 1.5 ml for the control area						
	Mode	Manual agitation						
	Stirring (min)	30 min at relatively low temperature						
	Materials	Volumetric flasks, rocking stirring, 10 ml vials of glass, micropipette						
Volatilization temperature		56.3°C	68.7°C	79.6°C	80.7°C	87.3°C	110.6°C	88°C
Method		GC-FID (Gas chromatography with flame ionization detection)						
External standard		Acetone (C_3H_6O)	n-Hexane (C_6H_{14})	MEK (C_4H_8O)	Cyclohexane (C_6H_{12})	Trichlorethylene (C_2HCl_3)	Toluene (C_7H_8)	Benzene (C_6H_6)

MEK: methyl ethyl ketone.

Table 4.
Preparation and analytical targets solvents "activated charcoal tube: 200/800" [26, 35–37, 44].

Solvent	Acetone	n-Hexane	MEK	Cyclohexane	Trichlorethylene	Toluene
Retention time (min)	6.2	7.7	8.3	9.4	10.9	15.3
Area peak	882337	3552515	20758	2107460	892254	2678766
Concentration (mg/l)	14.10	11.78	14.37	13.89	26.16	15.48

Table 5.
Retention time (min) concentration (mg/l) and surface area of peaks of the various solvents.

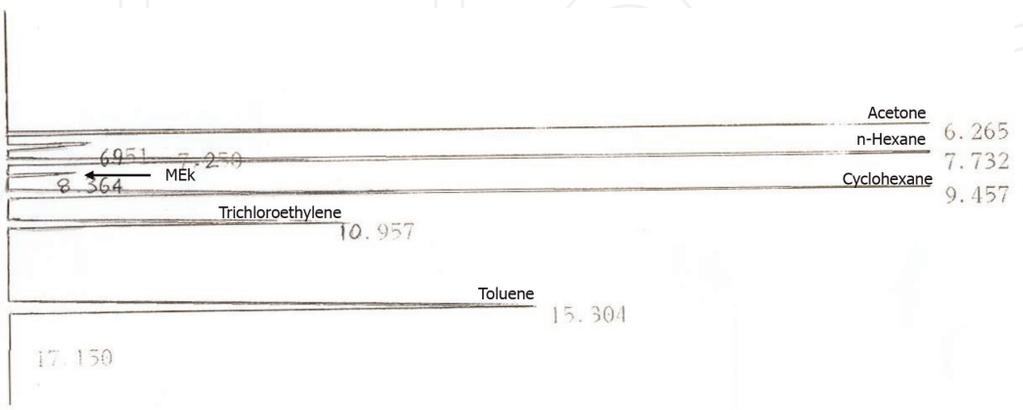


Figure 2.
Chromatogram of a standard injected in the same analysis conditions as those of the samples.

thickness = 0.25 μm). To optimize this method, different conditions were tested such as oven temperature, split/splitless injections, injected volume, and column type and length [37–39].

2.3.1.2 Dosing the metabolites of target solvents in urine

Depending on the nature of the metabolites of solvents, the following techniques were used for their quantification (**Figure 3** and **Table 6**) [37, 44–49]:

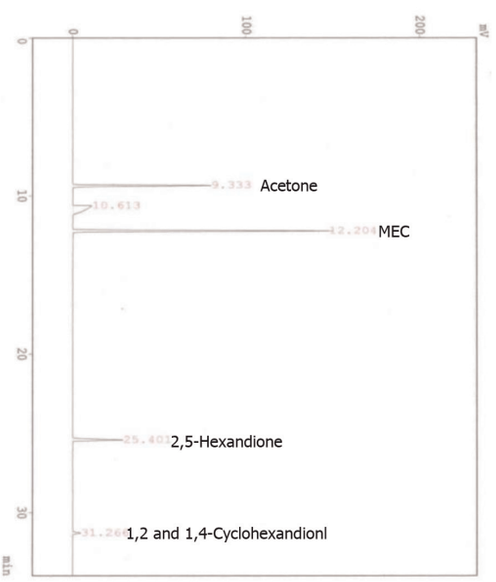
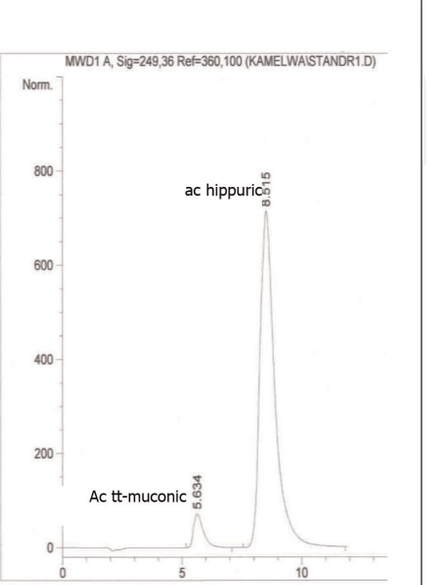
	GC-FID	HPLC
metabolite (Solvent)	**Acetone** (Acetone), **2,5-Hexanedione** (N-Hexane), **MEK** (MEK), **1,2 and 1,4Cyclohexandiol** (Cyclohexane)	**hippuric acid** (Toluene) **Trans, trans muconic acid** (Benzene)
chromatogram		

Figure 3.
Chromatograms of two standard injected under the same conditions as analytical samples.

	GC-FID			HPLC		
Metabolites	**Acetone**	**2,5-Hexanedione**	**MEK**	**1,2 and 1,4-Cyclohexandiol**	**Trans, trans-muconic acid**	**Hippuric acid**
Retention time (min)	9.333	12.204	25.401	31.266	5.6	8.5
Area peak	379899	762130	176371	29836	2062.5	31054.3
Concentration (mg/l)	3507.1	3614	957	174.4	13.5	1214

Table 6.
Retention time (min) concentration (mg/l) and peak area of the different metabolites.

- Either by GC-FID:
    - SHI MADZU® chromatograph GC-17A
    - Capillary column Hewlett-Packard® HP-1 (L = 60 m, inner diameter = 0.25 mm, film thickness = 1 μm)
- Or by HPLC:
    - Chromatograph agilent 1100 series
    - Column shim-pack CLC-ODS (n) 15 cm

As mentioned before, HPLC and GC conditions were optimized, and validation criteria (repeatability, detection limit, linearity, and recovery test) were evaluated.

2.4 Biometrological exposure limit values

In the absence of Tunisian exposure guideline values for the workplace air quality and biological samples [7, 8], we referred to the French, American, and/or German values. Then, we adopted the most severe among them as reference values (**Table 7**) [17, 28–31, 50, 51].

More specifically, the air concentrations were compared to threshold limit value-time-weighted average (TLV-TWA) for solvents.

For the biological exposure indices (BEI) related to metabolites (**Table 7**) [16, 34–36], they were as follows: acetone for acetone, 2,5-hexanedione for hexane, 1,2-cyclohexanediol for cyclohexane, methyl ethyl ketone for methyl ethyl ketone, hippuric acid for toluene, and trans, trans-muconic acid for benzene [32, 52, 53].

3. Results

3.1 Airborne solvent quantification

All conducted measurements in different companies showed that the exposure to solvents varies from one process to another and from one station to another [16]. Direct results of airborne concentration measurements of the solvents are published in our previous publication [16]. Average airborne concentrations of hexane are particularly high especially with overruns of the TLV in upper worker, sole maker, and finishing positions in all processes except for the artisanal type 2. For the other

Solvent	No. CAS[1]	la France (UE[2]) VME[6] ppm[8]	la France (UE[2]) VME[6] mg.m⁻³	USA (ACGIH[3]) TLV-TWA[7] ppm	USA (ACGIH[3]) TLV-TWA[7] mg.m⁻³	Germany (MAK[4]) ppm	Germany (MAK[4]) mg.m⁻³	Our study (Tunisia) Adopted VM ppm	Our study (Tunisia) Adopted VM mg.m⁻³
Acetone	67-64-1	500	1210	500	-	500	1200	**500**	**1200**
cyclohexane	110-82-7	200	700	300	-	200	700	**200**	**700**
n-Hexane	110-54-3	20	72	50	-	50	180	**20**	**72**
Methyl ethyl ketone (MEK, 2-butanone)	78-93-3	200	600	200	-	200	600	**200**	**600**
Toluene	108-88-3	50	192	50	-	50	190	**50**	**190**
trichlorethylene	79-01-6	75	405	50	-	-	-	**50**	**-**
Benzene	71-43-2	1	3.25	0.5	-	1	3.2	**0.5**	**1.6**

Biological Exposure Index (BEI) "Urine"	la France (EU) VGF[9] (1997)	USA (ACGIH) BEI[10]	Germany (DFG[5]) BAT[11]	Our study (Tunisia) IBE adopted
Acetone	100 mg/l	50 mg/l	80 mg/l	**50 mg/l**
1,2-cyclohexanediol	-	-	170 mg/g creat	**170 mg/g creat**
2,5 hexanedione	-	0.4 mg/l	-	**0.4 mg/l**
Methyl ethyl ketone	-	2 mg/l	5 mg/l	**2 mg/l**
hippuric acid	2500 mg/g creat	1600 mg/g creat	-	**1600 mg/g creat**
trichloroacetic acid	100 mg/g creat	15 mg/l (Proposal 2007)	**A**	**15 mg/l**
trans, trans-muconic	5 mg/l	0.5 mg/g creat	**B**	**0.5 mg/g creat**

(A) [Trichlorethylene] in air (ml/m³)	[Trichloroacetic acid] in urine (mg/l)
10	20
20	40
30	60
50	100

(B) [Benzene] in air (ml/m³)	[Trans, trans-muconic acid] in urine (mg/l)
0.3	-
0.6	1.6
0.9	-
1.0	**2.0**
2.0	3.0
4.0	5.0
6.0	7.0

[1]CAS, chemical abstract service; [2]EU, European Union; [3]ACGIH, American Conference of Governmental Industrial Hygienists; [4]MAK, maximum-Arbeitsplatz konzentration; [5]DFG, Deutsche Forchungs-Gemeinschaft; [6]VME, exposure average value calculated with respect to a reference period of 8 hours; [7]TLV-TWA, time-weighted average (weighted average values over 8 hours per day and 40 hours per week); [8]ppm, parts per million by volume of air; [9]VGF, value guide French; [10]EIB, biological exposure indices; [11]BAT, Bioloischer Arbeitsstoff-Toleranz-Wert (biological values tolerated in the workplace).

Table 7.
Values of airborne and biological exposure limits for solvents studied [9, 10, 13, 17, 25, 27, 28].

quantified solvents (acetone, cyclohexane, methyl ethyl ketone, and toluene), they were relatively high without exceeding the TLV.

3.2 Dosage of urinary metabolites

We limited ourselves to dosing urine samples collected during the first period: a stage where companies are on average activity (from 28 May to 28 July 2008).

3.2.1 Dosage of metabolites by HPLC

Table 8 summarizes the main data urinary dosages of two solvent metabolites: the hippuric acid and trans, trans-muconic acid that are the respective biomarkers

Process	Working post	Operator	n	Hippuric acid (mg/g creatinine)		Trans, trans-muconic acid (mg/g creatinine)	
				Range	Average	Range	Average
Industrial *"1 company"* 13 men and 9 women	Quilting	**Man**	4	124.3–222.3	159.1	0.8–3.5	1.7
	Upper worker	*Man*	2	80.8–242.2	161.5	0.7–1.6	1.2
		Women	5	33.9–352.5	190.9	0.9–4.4	2.4
		Total	7	33.9–352.5	182.5	0.7–4.4	2.1
	Sole maker	**Man**	5	57.0–359.7	192.7	0.2–6.0	3.1
	Finish	*Man*	2	67.7–138.0	102.8	1.7–1.9	1.8
		Women	3	71.5–381.7	194.7	1.5–5.5	2.8
		Total	5	67.7–381.7	158.0	1.5–5.5	2.4
	Serigraph	**Women**	1	—	180.3	—	1.6
Semi-industrial *"3 business"* 25 men and 8 women	Chopped off	**Man**	2	207.3–6768.1	3487.7	0.1–0.7	0.4
	Quilting	**Man**	1	—	749.3	—	0.0
	Upper worker	*Man*	9	380.4–9322.3	3112.7	00–03	0.1
		Women	3	25.5–5358.6	3523.9	00–02	0.1
		Total	12	25.5–9322.3	3215.5	0.0–0.3	0.1
	Sole maker	**Man**	11	546.7–7277.2	2349.4	0.0–0.4	0.1
	Finish	*Man*	2	2178.0–2609.5	2393.8	0.0–0.4	0.2
		Women	5	0.0–2823.9	1117.6	From 0.0 to 0.0	0.0
		Total	7	0.0–2823.9	1482.2	0.0–0.4	0.1
Artisanal *"6 companies"* 13 men	Upper worker	*Man*	4	295.8–1775.0	903.4	0.0–2.2	1.5
	Sole maker	*Man*	5	57.5–4582.7	1086.3	0.1–2.9	1.6
	Upper worker/sole maker	*Man*	4	440.2–4784.5	3292.5	0.0–0.2	0.1

Table 8.
Assays of urinary hippuric acid and trans, trans-muconic acid according to workstation.

of toluene and benzene. The parameters are the number of urine samples collected (n) per workstation and sex, the arithmetic mean of urinary concentrations of metabolites, and the range of concentrations.

The hippuric acid was particularly high with average exceeding the TLV for certain employees in the semi-industrial process for the majority of workstations, including the cutting. We noted particularly high values of the toluene in type 2 artisans, while the TLV was not exceeded in the industrial process.

The trans, trans-muconic acid was highlighted in the industrial process and artisanal type 1 with average ranging from 1.2 to 3.1 mg/g creatinine, far exceeding the TLV.

3.2.2 Dosage of metabolites by GC

Data on urinary dosage of metabolites of the four solvents, acetone, 2,5-hexandione, methyl ethyl ketone, and 1,2-cyclohexandiol, which are the respective biomarkers of acetone, hexane, cyclohexane, and MEK were not usable due to a technical problem in GC.

4. Comments and discussion

4.1 Reviews and bias

We had to suffer from some delay in achieving our airborne sampling and therefore an impact on the quality of our data because of different difficulties. In large part, it is due to the heaviness of administrative procedures to follow in Tunisia for the acquisition of scientific equipments. We have waited for over a year to have the air sampling pumps (May 2006, making contact with the supplier until June 2007, receipt of the order). Meanwhile, we adjusted the analytical analysis protocols for solvents and their metabolites. It required bibliographical research and repeated tests in the laboratory as it was not a directed technology transfer (North-South) [22, 39–43].

We were able to quantify the airborne samples with activated charcoal tubes after their storage at 4°C, and that was achieved within a short time. We did not have that opportunity for urine samples, and we had to freeze them since we were neither (and technicians) capable of performing these dosages nor owning sufficient material (one GC). This GC had also some technical problems, and we have not been able to use these results since conservation methods have not been respected. Only the results of the metabolites made by HPLC (hippuric acid and trans, trans-muconic acid) were analyzed.

4.2 Airborne sampling equipments

This material is of great interest to develop this type of action and toxicological metrology in the Sfax region. Indeed, this is the first time that there has been the acquisition of active sampling materials in the field of occupational health in Tunisia. Moreover, it is also the first opportunity on the establishment of a structured approach in occupational and environmental toxicology through GEET laboratory (previously known as 3E) in a new theme "impact of hazardous substances on environment and human health."

4.3 Biometrological measurements

For a dozen years, the use of solvents is undergoing a revolution, because of occupational risk prevention constraints but mostly because of regulatory

requirements for environmental protection. These regulatory changes led to changes in the nature of the applied solvents and how to use them [17, 29, 54]. Meanwhile the number of exposed workers is growing in Tunisia. This is confirmed on the international level (in France): the SUMER 2003 survey showed that the number of employees exposed to solvents has increased since 1994 from 12.2 to 14.7% mainly in the chemical industry [2].

Thus, risk assessment studies in various sectors using solvents were started, but the shoe manufacturing sector remained unexplored. This is the case of the study of Poirot and Hubert-Pelle [17] that evaluated exposures to solvents with airborne samples in various industrial activities but not in the manufacture of glue.

If these airborne sampling and biotoxicological analyses were made for the first time in the sector of footwear manufacturing in Sfax, they included a sample of companies from the three manufacturing processes (industrial, semi-industrial, and artisanal); this was preceded by a preliminary risk assessment along with job tasks examinations and an inventory of the handled products [5, 6]. This risk assessment could be improved due to the experience we have gained and with the best knowledge of the sector and the risk prioritization in it.

The results of airborne sampling have confirmed that the existing gaps between the different shoe companies and different workstations were generally those that were indirectly estimated by the workstations observations.

All the conducted sampling in the companies indicates that employees' exposure to organic solvents is quite variable depending on the performed job task.

The hippuric acid was highlighted in the urines of some employees with exceedances of the limit value; however, the TLV of toluene has not been exceeded in the companies. This could be explained by a dermal exposure, especially since we have not recorded the use of gloves by workers when they handle preparations used in shoe manufacturing (glues, thinners, strippers).

We recorded the presence of trans, trans-muconic acid in urine analyses with exceedances of the biological limit value set at 0.5 mg/g creatinine (**Table 7**) for some employees in industrial or artisanal shoe companies. In contrast, the inventory of the handled products in the processes did not show the presence of benzene or unleaded gasoline. So, this is due either to the contamination of the used solvents by impurities or an environmental contamination by car exhausts (unleaded gasoline 95) especially since the majority of the employees in these shoe companies use two-wheeled vehicles (bicycle or motorcycle).

On the other hand, the analyses of some samples of the products that are handled in the manufacturing of shoes are highly recommended. Furthermore, it also recommended to start an environmental study to check the air quality in the major thoroughfares in Sfax, a city known for its pollution, and to make urine sampling in order to explore the benzene metabolite for people who are exposed to car exhaust (such as traffic wardens, auto mechanics) and unexposed ones.

5. Conclusion

GC and HPLC methods have been adjusted, optimized, and effectively used for the determination of OS and their metabolites in airborne and urine samples of solvent manipulators. The exploitation of these indicators had necessitated the use of new techniques for occupational surveillance for the first time in the region. Thus, a process of occupational risk assessment via a biotoxicological and airborne monitoring for solvent exposures is now set.

This study allowed us to provide information on chronic exposure to solvents in the shoe industry and to establish an initial observation on solvent exposure profiles

in this sector. However, we know that exposure to solvents is not constant over time and varies according to the task performed and the utilized process. Therefore, the investigation on exposure needs not only the average exposure in comparison with TLV but also to identify the polluting phases in order to determine the short-term exposure.

In the footwear manufacturing sector, following the identification phase of the used solvents and the highlighting of overruns in airborne concentrations of some hazardous products, we plan to focus on the carcinogenic characteristic of certain preparations and especially their potential toxicity for reproduction, since we noted the increase of female presence in the shoe manufacturing sector and some cases of couple sterility.

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Conflict of interest

Authors have declared that no conflict of interest exists.

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