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Analytical survey of hydroquinone in skin lightening cosmetics available on the Belgian market

by

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Abstract

The objective of the current study was to check the conformity with the "Cosmetic" European Directive and derived Belgian legislation of imported skin lightening cosmetics, seized by the Customs' services, and imported as well as Belgian manufactured ones, sampled by the Food Inspection Service. Analyses were performed according to the high pressure liquid chromatography method, published in the Directive 95/32/EC and recently adapted in the own laboratory. The method involves one single isocratic run analyses of hydroquinone and the derived ethers.

Skin lightening cosmetics with hydroquinone concentrations exceeding the compulsory norm of 2 % are frequently available on the Belgian market. Analysis results gathered since 1985 evidence that >25 % of the

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preparations examined had a concentration which was significantly higher than 2 %, with maximal values as high as ~7 %. Only bleaching milks were well in compliance with the legislation; creams and gels, on the contrary, were often in infringement. The highest values were observed in 1998 and 1999; the majority of the Belgian manufacture was in accordance with the directive.

The outcome of the present study illustrates a general trend rather than a representative ratio of "illegal" products, since the sampling was mainly designed to intercept "suspect" preparations. Nevertheless, the authors are confident that the demand for these products is elevated and that a pragmatical control is the better tool to reduce the commercialization of such "illegal" preparations. Moreover, other non regulated skin lightening compounds are presently available on the market too.

Keywords

Hydroquinone, analytical survey, skin lightening cosmetics

Introduction

Topical administration of skin lightening products with hydroquinone (HY) is sometimes used to remove minor cutaneous pigmentation and this may be legitimately done by white as well as coloured people in preference to more noxious agents such as ammoniated mercury or the 4-Methoxyphenol (ME), 4-Ethoxyphenol (ET) and 4-Benzyloxyphenol (BE) ethers of HY (1, 2). It is well known that for some dermatological diseases, eg. hypermelanosis, HY-containing skin therapeutic preparations with concentrations exceeding 5 % are utilized as depigmenters.

Since HY interferes with melanin synthesis, it has long been recognized as a favourite compound in skin toning preparations (3). The precusor to melanin is tyrosine, which is converted to the dark pigment by tyrosinase-mediated oxidative polymerisation. Denton et al. (1) evidenced that HY can completely inhibit the enzymatic oxidation of tyrosine and, hence, prevent the formation of new melanin.

HY-containing creams and other cosmetic products, such as gels and lotions, are often applied to even out the skin colour on the facial

areas. It is also known, however, that certain ethnic groups apply these products on large parts of their body (2, 4) and that this practice can possibly aggravate adverse health outcomes, especially when often repeated.

Spencer (3) reported HY to be effective at a concentration of 1.5 – 2.0 % in a cosmetic cream, producing a temporary lightening of skin colour. Concentrations >5 % were liable to cause redness or burning. Skin sensitization to HY or its derived ethers and adverse effects such as patchy depigmentation have abundantly been reported in the literature (2, 4, 5, 6, 7, 8). HY is generally considered a less potent agent and safe from adverse reactions when used at low concentrations, whereas its ethers are ascribed severe and irregular depigmenting qualities (4), eventually inducing acute dermatitis development after application (9). In addition, it can not be excluded that some patients are sensitized by HY with cross-sensitization to ME (9, 10).

The importance of the trade of HY containing agents should not be underestimated. It is believed that approximately 25 million units of HY containing skin lighteners are commercialized annually in the European Community and the United States.

Compulsory legislation

The Belgian legislation on cosmetic products (Royal Decree of October 15, 1997) adheres strictly to the European directives; basically, the Council Directive 76/768/EC of the European Community is compulsory. It aims at harmless cosmetic compounds when used under normal and foreseeable conditions.

At the date of publication of the mentioned Council Directive the use of HY was already restricted to a maximal authorized concentration of 2 % in cosmetic products with obligatory labelling, warning against the use of HY to dye eyelashes and eyebrows.

The second Council Directive 82/368/EC specified its field of application: HY could only be used as a hair dye, other uses were forbidden.

However, following the first opinion of the Scientific Committee on Cosmetics (SCC), dated February 24, 1983, it was concluded that

"... In view of the hazard presented by other depigmenting agents, the Committee agrees to use Hydroquinone at concentrations not exceeding 2 % in cosmetic products for the depigmentation of localized melanotic areas, provided that precautions are fully indicated on the label ..."

On the basis of this opinion, the 5th Commission Directive 84/415/EC authorized the use of HY as a local skin lightening agent, only when the maximal concentration did not exceed 2 % in the cosmetic products and when appropriate warnings were put up on the product's packaging. The mandatory labellings are "Contains hydroquinone", "Avoid contact with the eyes", "Apply to small areas", "If irritation develops discontinue use" and "Do not use on children under the age of 12". In the 6th Commission Directive 85/391/EC the derived ethers ME, ET and BE were forbidden in cosmetic products.

The EC workgroup on the classification and labelling of dangerous substances ECBI/32/97 classified HY as Carcinogen Cat 3 and Mutagen Cat 3 (R 40), meaning that HY is a substance which causes concern owing to a possible mutagenic and carcinogenic effect. Moreover, evidence from appropriate studies was insufficient for a Cat 2 ranking (substances which should be regarded as mutagenic and carcinogenic for humans).

It was observed though that HY containing cosmetics with instructions for application that suggest brightening of the skin were plenteously available in shops of areas with large Asian and African immigrant groups. Hence, problems arising from unappropriate utilization remained a matter of concern, especially since the concentrations of HY and its derivatives were sometimes found to be as high as 10 %.

Several calls for a ban of HY in cosmetics due to elevated prevalence of ochronotic changes in users of HY containing skin lighteners led the SCC to evaluate most recent toxicological data, including genotoxicity *in vitro* and *in vivo*, results of NTP carcinogenicity bioassays (NTP TR 366, October 1989; NIH publication No-2821) as well as clinical data. The conclusion was as follows:

"... ~45 % (worst case) of Hydroquinone applied dose in humans, are absorbed but readily, within less than 12 minutes, degraded and excreted. For the use of topically administered bleaching agent, and under the premises of a 2 % Hydroquinone cream preparation, and following the acknowledged procedure, the safety margin is 1960. The present cosmetic use of Hydroquinone does not support the evidence

of a possible relation between human exposure and mutagenic risk. Carcinogenity studies on rats and mice have provided some evidence of tumor induction by Hydroquinone, but the results are insufficient to establish a correlation between human exposure and the consequent development of cancer. A number of publications dealing with cross sectional surveys and case reports have described ochronosis and leukomelanoderma resulting from the use of cream containing hydroquinone ... "

Due to the observed clinical side effects, the Scientific Committee on Cosmetics and Non Food Products (SCCNFP) stated the opinion (SCCNFP/0077/98)

"... that hydroquinone should not be used as a depigmenting agent in cosmetic products ..."

On the basis of this opinion a ban of HY as skin lightener in cosmetic products was proposed by the European Commission.

This disposition was adopted by the Committee for Adaptation to Technical Progress in the 24th Commission directive, 2000/6/EC. EU member states are asked to bring into force the laws, regulations and administrative provisions necessary to comply with the directive no later than June 30, 2000 and to take necessary measures to ensure that skin lightening cosmetic products containing HY will not be available to the end users (consumers) after January 1, 2001. Nevertheless, the use of HY as a hair dye remains authorized (SCCNFP/0078/98).

Enforcement control

One distinguishes two different types of supervision: 1) the control measures at the Customs and 2) the surveillance sampling programmed and organised by the national Food Inspection Service.

Any product considered by the law of January 24, 1977 beit food or other consumables such as cosmetics eg. which shows visual properties suggesting decay or toxicity can be seized according to procedures defined in the Royal Decree of February 9, 1981. Whenever a Custom officer presumes high levels of HY in the presented skin bleaching cosmetics the goods are seized and kept in custody till intervention of a Food Inspection Officer. The latter one either inspects the goods at the spot or subsamples for further chemical analysis in one of the recognized laboratories, eg. whenever cosmetics are concerned. Since goods are

generally cleared when an experienced Food Inspection Officer judges them well in agreement with the public health labelling norms, any sampling for subsequent laboratory control deliberately aims at intercepting "positive" cosmetic preparations. All parties which were regularly found to be in agreement with the compulsory directives are not sampled on a regular basis; moreover, listings with goods conform to the Belgian rules or, on the contrary, infringing them are regularly updated and handed to the Customs' Services. Interventions of the Food Inspection Officer are, therefore, restricted to doubtful cases and are not carried out on a routine basis.

When subsampling for subsequent analysis in the laboratory is carried out, the remaining goods are kept in custody till analysis' results are available. When results are negative, meaning that the HY concentrations are ≤ 2 %, goods can be cleared. On the contrary, when the results are positive (concentrations exceeding 2 %), goods are definitely seized and destroyed by incineration. Prior to destruction the Food Inspection Officer informs the Customs' Service of his arguments. Costs are mostly recouped on the supplier.

Import of "forbidden" cosmetics occurs very often by regular air travellers carrying 100 to 200 items (in one luggage bag eg.). Destruction costs of smaller amounts of positive samples, some 100 tubes eg., are generally carried by the Food Inspection Services.

In addition to the interventions at the Customs, the Food Inspection Services also programme surveillances of the retail trade in order to control suspect goods on a regular basis and to repress abuse. Sometimes surveillances are carried out by order of the European Commission or in view of prudence preparation. The programme on HY surveillance must be seen as surveillance and control on the living up to the rules.

Chemical analysis

Chromatographic analysis techniques are now widely used for the determination of HY in skin bleaching and lightening cosmetics. Generally, the procedure involves solvent extraction in combination with reversed phase high performance liquid chromatography (HPLC) and variable wavelength UV-VIS absorbance detection (11).

Although very few reports in literature deal with the simultaneous determination of HY and its ethers in the same matrix (12, 13), the

method published in the sixth Directive 95/32/EC of the European Commission related to methods of analysis for cosmetic products describes the determination of HY and its ethers ME, ET and BE in one single isocratic run and uses response factor calculation to obtain the concentrations. This latter method is applied in the laboratory for Analyses of Consumables and Cosmetics (Scientific Institute of Public Health, Brussels).

All chromatographic analyses were performed with an assembled HPLC and data analysis system, consisting of a dual headed reciprocating pump (Hewlett Packard 1050), an injector valve equipped with a 20 µL loop (Rheodyne), a variable wavelength UV-VIS absorbance detector (Hewlett-Packard 1050) and a personal computer (PC 1000 Dell, Optiplex G 166). The analytical column was a Bondapak Phenyl column (Waters; 10 µ, 300 x 3.9 mm I-D). The mobile phase was a tetrahydrofuran:water mixture (45:55, v:v) pumped at a flow rate of 1.0 mL min^{-1}. Both solvents were individually He-degassed from reservoirs with an in-line degasser (Hewlett-Packard). The UV detector was operated at 295 nm; all calculations were based on peak areas. Validation in view of quality assurance of the analytical procedure was done according to the ISO 5725 principles and reported by Borremans et al. (14)

Otherwise, an electroanalytical method for the simultaneous determination of hydroquinone and the derived ethers using a carbon paste electrode was developed by Wang (15). The method allows for preconcentration of the analytes at the electrode surface prior to voltametric determination.

A synopsis of marketed skin lightening agents in Belgium

The annual analysis programme of the Customs' and Food Inspection Services focuses on the occurrence of HY-containing cosmetics since 1985. In this discussion of the data set one should consider, however, that skin bleaching preparations were target sampled, meaning that the Customs' officers had strong arguments to suspect the goods to be positive. Therefore, the relative ratio of positive samples logically exceeds the fraction of positive compounds in a representative sample of available cosmetics on the Belgian market. In the present investigation we emphasize the major trends and patterns, rather than giving too much strenght to the absolute numbers of positive samples.

The median value of all HY-concentrations measured during the period 1985 - 1999 (N = 129) is roughly 2 % (Figure 1), corroborating that approximately one half of all inspected cosmetics exceeds the norm concentration set by the EC. Here we use median and quartile values rather than averages, since the data distribution is obviously non-parametric. The upper quartile (the top 25 % of all concentrations) ranges from 3 to 7 %, which is very significantly in excess of the norm.

The yearly distributions evidence that interquartile ranges consistently encompass the norm concentration with only one exception which is the year 1985 (Figure 1). The goods sampled in 1985 showed HY concentrations ranging from 3 to 5 %, with a median value of 5 %. Obviously, the latter goods were strongly suspect and this suspicion has been confirmed by laboratory analysis. All other distributions showed median values of 2 %, ranging from 2 to 3 %. Nevertheless, the upper quartiles were consistently higher than 2 % and, especially, the samples collected in 1998 and 1999 showed maximal values as high as 7 % and 5 %, respectively. Even when only very few highly concentrated compounds were discovered, their presentation in the "unofficial" trade circuits is regarded as a menacing sign.

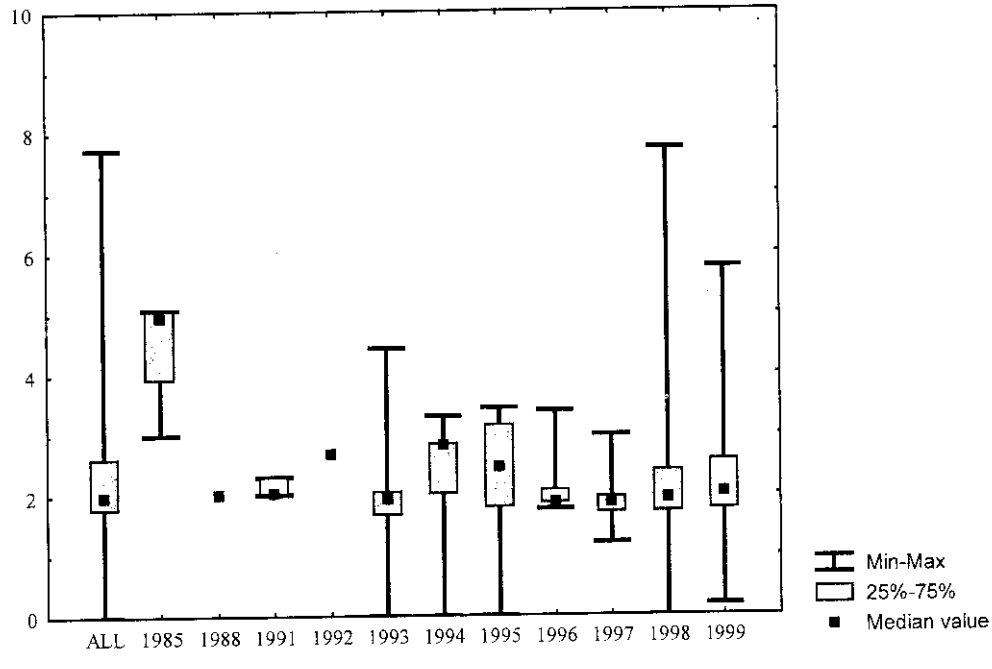

Fig. 1: Yearly distributions of measured hydroquinone concentrations in cosmetic samples from the Belgian market.

The majority of inspected goods were creams (N = 75); their median HY concentration amounted to 2.0 %, whereas the upper quartile ranged from 2.7 to 5.1 % (Figure 2). With one half of the samples exceeding the norm concentration, the cream distribution is very similar to the one of gels (N = 21). The median HY concentration in bleaching gels was 2.1 %, the upper quartile ranged from 3.7 to 7.7 % (Figure 2). The investigation covered also a smaller number of milks and other cosmetics (such as lotions and soaps). Bleaching milks were well in compliance with the compulsory norm with a median HY concentration of 1.9 % and a maximum of 2.1 %, respectively (Figure 2). Other cosmetics (N = 11), on the contrary, showed rather high variability like creams and gels. The median and maximal HY concentration amounted to 2.0 % and 5.1 %, respectively (Figure 2). The lotions and soaps were both sometimes positive and sometimes negative.

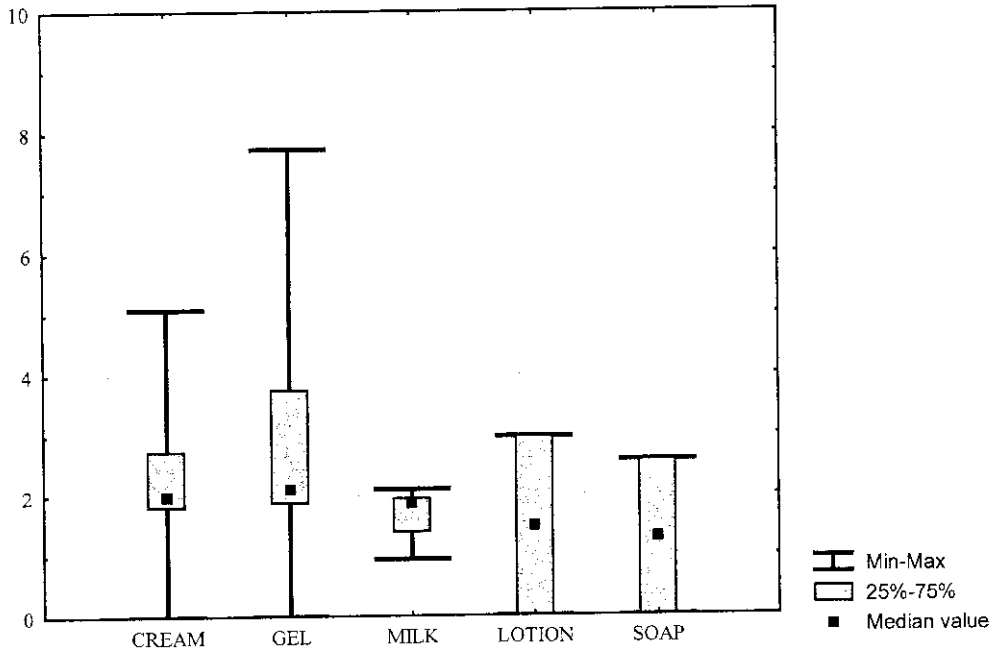

Fig. 2: Preparation-specific distribution of measured hydroquinone concentrations.

In addition to type-related differences of the analysed cosmetics, the study aimed also at revealing possible differences with respect to the country of origin. It must, however, be added here that the supplier country of most compounds, as it could be derived from the labels does not inherently refer to the country of production. In addition, numerous samples did not at all reveal a country of orgin. In the comparison one single

sample from Switserland, one single sample from Thailand and 4 South African samples were not taken into consideration. We identified 13 Belgian, 28 French, 19 British and 13 American preparations (Figure 3). In general, positive as well as negative samples were found with relatively similar distributions throughout. A majority of Belgian samples was in compliance with the Directive. The upper quartile of HY concentrations ranged from 2.2 to 4.9 %, with mainly gels exceeding the norm concentration. The French samples showed a similar distribution. The upper quartile ranged from 2.1 to 7.7 %, which is the highest concentration observed. Most of the positive French bleaching agents were creams; moreover, one lotion with an exceptionally high concentration (6.7 %) of the forbidden ME was also withdrawn from trade. British and American goods showed a completely similar pattern, with approximately 50 % of positive samples and upper quartiles ranging from 2.6 to 5.6 % and from 2.8 to 3.0 %, respectively.

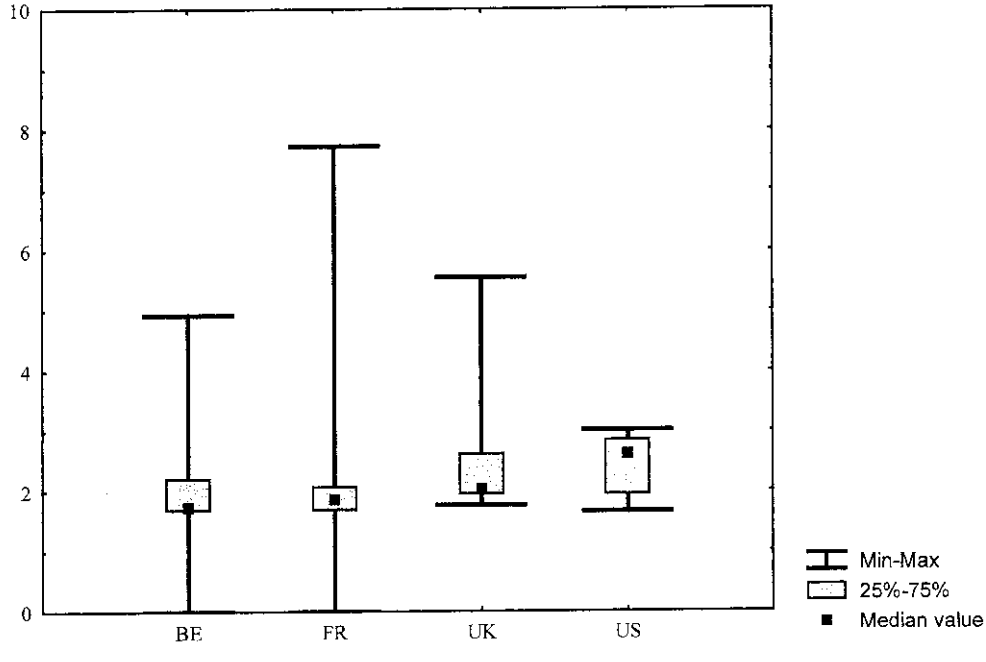

Fig. 3: Distributions of measured hydroquinone concentrations in cosmetics manufactured in Belgium, France, Great Brittain and the United States of America.

Conclusion

For over 10 years skin lighteners with instructions for application suggesting "healthy bright and lovely appearance" consistently contained very high HY concentrations. The small prints on the packaging only

exceptionally mentioned that the cosmetic product contained HY. Moreover, when the active constituent was named, this was done without stating its function. Undesirable health effects can, therefore, not be excluded.

During each of the sampling years the upper quartile of concentrations exceeded ~2.5 %, with maximal values of 7.7 % and 5.6 % being observed in 1998 and 1999. Few high values do not necessarily confirm a current occurrence of enhanced concentrations but should be considered as an alarming sign, suggesting that in many cases the legally accepted concentration of 2.0 % is inefficient and intentionnaly exceeded by "irresponsable" producers. In addition hereto, seizure of one single ME-containing preparation also corroborates the availability of illegal products on the Belgian market. The demand for such products has probably persisted or even increased. Pragmatic control and clearly labelled information are the better tools in view of reducing the utilisation of those harmful preparations.

The present investigation focussed on skin toning and bleaching cosmetics that are often used by dark people. It did not include other agents such as kojic acid, arbutine, azealic acid, ... which are also known to interfere with melanin synthesis. The latter compounds are generally used in luxurious and expensive cosmetics for skin care; the cosmetic regulations do not interdict their use.

Samenvatting

De bedoeling van deze studie is na te gaan in welke mate huidbleekmiddelen beantwoorden aan de Europese Directieve voor cosmetica en aan de afgeleide Belgische wetgeving. Het betreft hier geïmporteerde cosmetische verbindingen, die in beslag werden genomen door de Douane, evenals producten die in buiten- of binnenland werden vervaardigd en door de Algemene Eetwareninspectie werden bemonsterd. De analyses gebeurden met hoge drukvloeistofchromatografie, zoals beschreven in de Directieve 95/32/EC en recent aangepast in het eigen laboratorium. Er werd gebruik gemaakt van een isochratische methode voor de bepaling van hydrochinon en zijn ethers.

Huidbleekmiddelen waarvan de concentratie hoger is dan de vastgestelde norm van 2 % worden herhaaldelijk aangetroffen op de Belgische markt. Analyseresultaten vanaf 1985 tonen aan dat in meer dan 25 % van de gevallen de concentraties significant hoger zijn dan 2 %, met maxima van ~7 %. Alleen huidbleekmelken waren in overeenstemming met de wetgeving; crèmes en gels waren dikwijls in overtreding. De hoogste waarden werden vastgesteld in 1998 en in 1999. Hier moet aan toegevoegd dat een meerderheid van de Belgische producten in overeenstemming was met de Directieve.

Deze studie illustreert enkel een algemene trend. De cijfers mogen niet worden geïnterpreteerd als representatief voor de fractie aan "illegale" producten, omdat de bemonsteringen erop gericht waren "verdachte" producten te onderscheppen. De auteurs zijn evenwel van mening dat er veel vraag is naar dergelijke producten en dat een pragmatische controle het betere middel is om de verhandeling van dergelijke "illegale" bereidingen terug te dringen. Overigens zijn er ook andere huidbleekmiddelen beschikbaar en deze laatste zijn niet aan een regelgeving onderhevig.

Résumé

Le but de cette étude est de vérifier la conformité de produits cosmétiques d' éclaircissement de la peau, à la directive "Cosmétique" Européenne et à la législation Belge qui en dérive. Ces produits saisis par les Servives des Douanes à l' importation en Belgique, ou manufacturés en Belgique, sont prélevés par le Service d' Inspection Alimentaire. Les analyses sont effectuées par la méthode de chromatographie liquide à haute pression publiée dans la directive 95/32/CE et récemment adaptée dans notre laboratoire. L' hydroquinone et ses éthers sont analysés dans un seul parcours chromatographique isocratique.

Des cosmétiques éclaircissant la peau avec des concentrations d' hydroquinone supérieures à la limite légale de 2 % sont fréquemment disponibles sur le marché Belge. Les résultats d' analyse collectés depuis 1985 montrent que > 25 % des préparations examinées avaient une concentration significativement plus élevée que 2 % avec des valeurs maximales atteignant ~7 %. Seuls les laits éclaircissants étaient conformes à la législation; les crèmes et les gels, au contraire, étaient souvent en contravention. Les valeurs les plus élevées ont été observées en 1998 et 1999; la majorité des produits fabriqués en Belgique étaient en conformité avec la directive.

Les résultats de cette étude illustrent une tendance générale plûtot qu' une proportion représentative de produits "illégaux", puisque le prélèvement était principalement destiné à intercepter des échantillons "suspects". Néanmoins, les auteurs constatent que la demande pour ces produits est élevée et qu' un contrôle suffisant est le meilleur outil pour réduire la commercialisation de telles préparations illégales. Par ailleurs, d' autres composés éclaircissant la peau, non réglementés sont actuellement disponibles sur le marché.

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