Better compliance and better tolerance in relation to a well-conducted introduction to rub-in hand disinfection

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Summary: The aim of the study was to demonstrate that the introduction of rub-in hand disinfection (RHD) in hospital units, with the implementation of suitable equipment, drafting of specific protocols, and training users, improved compliance of hand disinfection and tolerance of user's hands. In four hospital units not previously using RHD an external investigator conducted two identical studies in order to measure the rate of compliance with, and the quality of, disinfection practices, [rate of adapted (i.e., appropriate) procedures, rate of correct (i.e., properly performed) procedures, rate of adapted and correct procedures carried out] and to assess the state of hands (clinical scores of dryness and irritation, measuring hydration with a corneometer). Between the two studies, the units were equipped with dispensers for RHD products and staff were trained. Compliance improved from 62.2 to 66.5%, quality was improved (rate of adapted procedures from 66.8% to 84.3%, \(P<10^{-6}\), rate of correct procedures from 11.1% to 28.9%, \(P<10^{-6}\), rate of adapted and correct procedures from 6.0 to 17.8%, \(P<10^{-8}\)). The tolerance was improved significantly (\(P<10^{-2}\)) for clinical dryness and irritation scores, although not significantly for measurements using a corneometer. This study shows the benefit of introducing RHD with a technical and educational accompaniment.

Keywords: Hand-disinfection; tolerance; compliance.

Introduction

Hand disinfection is considered one of the most important measures for preventing hospital-acquired infections.\(^1,2\) However its implementation remain incomplete due to resource difficulties and workload, with many variations between professional groups and clinical specialities.\(^3-8\)

Hand hygiene procedures recommended in France\(^9,10\) are either washing (simple, hygienic or surgical) or hand rubbing with aqueous alcohol solutions (hygienic or surgical rubbing). For each level of exposure risk (limited, intermediate or high) two adapted procedures are recommended (washing or rubbing). Despite these recommendations, hand disinfection is still often synonymous merely with washing; rub-in hand disinfection (RHD) has not been adopted on a large scale.
RHD was introduced into some hospitals 10 years ago. In many places, it was introduced progressively on the basis of published data,11–14 and to respond to difficulties with hand washing. Initially, RHD was reserved for emergencies, and only later as a regular procedure with specific protocols, which makes it impossible to evaluate its true benefit in these hospitals. In order to determine whether RHD resulted in greater compliance and improved state of hands, we therefore carried out a better prepared introduction in non-user care units.

The introduction of RHD in treatment units in this study was associated with a campaign for adequate equipment and promoting hand hygiene. Therefore the benefit measured is that of the complete programme.

**Materials and methods**

**Population**

The study was carried out in four hospital units not previously using RHD at the E. Herriot Hospital (University Hospital Centre) in Lyon: a rheumatology unit, a urology unit, a paediatric unit and a paediatric intensive care unit.

All members of staff of all professional categories were observed: nurses, nursing auxiliaries, ancillary staff, paediatric nursing auxiliaries, physiotherapists and doctors.

**Products**

The study was carried out using an antiseptic solution for hands already in use in Lyon: Sterillium® (mecetronium etisulfate, propanol-1 and propanol-2; Bode Chemie Gmbh and Co., Hamburg, Germany).

**Development of the study**

**Survey phase 1, before the introduction of RHD (18 November 1998 to 3 February 1999)**

This initial phase was carried out without making any change to usual hand washing methods in the units. It included a compliance study and an assessment of the state of hands.

**Introduction of RHD (4 February to 17 February 1999)**

Each of the four units was equipped to make the use of RHD instinctive. Dispensers for the hand wash agents were installed, close to strategic points wherever possible: in treatment rooms, food stores, medical offices. These areas were provided with incentive stickers.

An informative meeting was organized in each of the four units to answer questions from nursing and medical staff and to define conditions for using RHD based on local and national recommendations.9,10

**Survey phase 2, after introduction RHD (3 March to 8 April 1999)**

This phase began at least two weeks after introducing the new procedure in order to give the staff enough time to get used to the product. This phase was carried out by the same investigator in exactly the same way as the first phase.

**Observance study**

**Hand hygiene procedure definitions**

A procedure was classed as ‘adapted’ if it was appropriate for the clinical situation. It was classed as ‘correct’ if performed properly, irrespective of its appropriateness to the clinical situation.

**Data collection**

All observations were made by the same external investigator using identical methods for both periods. Each member of nursing staff was observed for 1.5 h and for a series of successive activities during each period. The data gathered for each act included: the type of activity, the immunocompetence of the patient concerned, the possible infection by the patient concerned, the type of hand hygiene procedure carried out (if any), its adapted and correct nature, and the type of error for an incorrect procedure. All data were recorded anonymously.

**Main judgement criteria**

**Rate (%) of compliance**

The rate of compliance for disinfecting hands was defined as the number of hand hygiene procedures carried out (washing or antisepsis) compared with the number of situations where this procedure was considered necessary.

**Secondary judgement criteria**

**Rate (%) of adapted procedures**

This rate enables the suitability of the chosen hand hygiene procedure to be assessed, i.e., relationship
of the microbiological efficiency of the procedure chosen to the level of risk incurred, in relation with local recommendations. This is defined as the number of adapted procedures compared to the number of procedures carried out.

Rate (%) of correct hand hygiene procedures
This rate gives the proportion of procedures performed correctly. A procedure is considered correct if it is carried out according to the protocol set and complies with the key points specified in Table I. The rate is defined as the number of correct procedures compared to the number of procedures carried out. Incorrect procedures were classed in one of three categories:

1. risk of infection – for errors which induced a risk of infection (e.g., insufficient contact time);
2. risk of causing cutaneous intolerance (e.g., excessively short rinsing);
3. double risk in cases of both the above errors.

Rate (%) of adapted and correct procedures carried out
This rate is the combination of the criteria used above for adapted and correct procedures. It is defined as the number of adapted and correct procedures carried out, compared with the number of procedures expected.

For each rate, a gross rate was calculated for the ‘before’ and ‘after’ periods, then specific rates for units, professional categories and levels of risk.

Tolerance study
This study was carried out using two different approaches: a clinical method and a para-clinical method.

Judgement criteria for the clinical method
Two judgement criteria were used, a dryness score and an irritation score.

These are validated scores previously used by our team\textsuperscript{15,16} and initially adapted from articles by Larson et al.\textsuperscript{17–19} The dryness score is calculated by adding points quantifying the dryness (Table II). The irritation score is calculated by adding points quantifying the irritation (Table III).

The clinical assessment of the cutaneous state of hands was carried out by the investigator at the same time as the observation, i.e., once for each period.

Judgement criterion for the para-clinical method
The judgement criterion used was the average value of 10 measurements of the hand’s cutaneous hydration. Cutaneous hydration was measured using a CM825\textsuperscript{®} corneometer (Courage and Khazala Electronic, Monte Carlo, France) which measures the skin’s electrical capacity, on a scale from 0 to 100. Values lower than 35 indicate very dry skin,
35–50 indicate dry skin and greater than 50 normally hydrated skin.

For the first period all measurements were made in January (the apparatus was not available at the beginning of the study). For the second period, measurements were taken at the same time as the clinical assessments. The measurements were taken using a probe strapped on to the back of the hand at least 5 min after washing or antisepsis.

Tolerance data were marked on a sheet with the subject’s name. Separate sheets were used for each period to avoid bias.

Analysis methods

Data were entered using Epi Info version 6 and the SPSS version 8 software. Qualitative judgement criteria were compared between the two periods (before and after) using Mantel Haenzel’s Chi-square test with a significance threshold of 5% (P < 0.05).

The before/after comparison of variables assessing tolerance was carried out using Student’s t-test for matched series.

Results

Observance

For the first period, 87 subjects were observed for a total of 105 h 45 min. There were 614 occurrences of patient contact, (i.e., 5.8/h) warranting hand hygiene. For the second period 77 subjects were observed for a total of 82 h 10 min. There were 421 occurrences (i.e., 5.1/h).

The gross rate of compliance was 62.2% during the first period and 66.5% during the second period (non-significant difference, in only unit 1 was there a significant difference (P = 0.03). No relationship was shown between the number of occurrences per hour and compliance. The overall results and the results for each unit are given in Table IV.

The rate of adapted procedures increased from 66.8% during the first period to 84.3% during the second period (P < 10^-5). The rate of correct procedures was 11.1% during the first period and 28.9% during the second (P < 10^-6). The quality of hand hygiene procedures improved significantly during the second period in all units except unit 1.

The rate of adapted and correct procedures increased from 6.0% during the first period to 17.8% during the second (P < 10^-8). This difference was also highly significant in all units except unit 1. Details are given in Table V.

Observance and level of risk

Analysis of compliance rates according to levels of risk showed an improvement for both intermediate and limited exposure levels of risk. This improvement was not significant but was greater for intermediate (58.2–69.3%) than for limited risk (63.4–65%); no high exposure risk activities were observed. Analysing the procedure according to the level of risk also showed improved compliance. This improvement was significant for both intermediate (70.7–92.3%, P < 10^-5) and for limited risk (65.7–82.5%, P < 10^-3).

Observance and professional categories

Nurses showed a significant improvement in compliance (60.8–68.4%, P < 0.05). Improvement was not statistically significant for nursing auxiliaries or

### Table IV

<table>
<thead>
<tr>
<th>Unit</th>
<th>Gross compliance according to units and periods</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before carried out/expected</td>
</tr>
<tr>
<td>1</td>
<td>30/57</td>
</tr>
<tr>
<td>2</td>
<td>86/122</td>
</tr>
<tr>
<td>3</td>
<td>118/177</td>
</tr>
<tr>
<td>4</td>
<td>148/258</td>
</tr>
<tr>
<td>Total</td>
<td>382/614</td>
</tr>
</tbody>
</table>

* Mantel Haenzel χ² test.

### Table V

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Before nb (%)</th>
<th>After nb (%)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedures carried out</td>
<td>382</td>
<td>280</td>
<td>&lt; 10^-5</td>
</tr>
<tr>
<td>Adapted procedures (66.8%)</td>
<td>255</td>
<td>236</td>
<td>&lt; 10^-6</td>
</tr>
<tr>
<td>Correct procedures (11.1%)</td>
<td>42</td>
<td>81</td>
<td>&lt; 10^-5</td>
</tr>
<tr>
<td>Expected procedures (614)</td>
<td>614</td>
<td>421</td>
<td>&lt; 10^-8</td>
</tr>
<tr>
<td>Adapted and correct procedures (6.0%)</td>
<td>37</td>
<td>75</td>
<td>&lt; 10^-8</td>
</tr>
</tbody>
</table>

* Mantel Haenzel χ² test.
paediatric auxiliaries. For doctors and ancillary staff rates of compliance were lower during the second period but this is based on a small number of observations for these two categories.

The rates of adapted procedures and correct procedures showed a significant improvement with nurses, paediatric auxiliaries and ancillary staff. For each rate the values measured for nurses were greater than for other professional groups.

**Procedures**

During the second period RHD was used in 43.0% of cases for limited risk and in 36.5% of cases for intermediate risk.

**Errors**

Simple washing was more correctly carried out during the second period: 36.2% vs. 15.0%, $P<10^{-4}$. The quality of antiseptic washes remained practically unchanged. There was a decrease in the number of errors associated with a tolerance risk (insufficient rinsing for example) but not a large reduction in the number of errors which could have led to the procedure’s inefficiency and therefore a risk of infection (contact time too short).

**Tolerance study**

For the clinical method, 86 subjects were seen during the first period and 80 during the second period. Seventy-seven were seen during both periods. For the para-clinical method 84 subjects were seen during the first period, 80 during the second period, and 76 during both periods.

**Development of clinical tolerance: dryness**

The average dryness score was 1.08 during the first period and 0.66 during the second period. The scores of individuals lost during the second period did not differ from the scores of others. There was an overall decrease in dryness of hands after RHD was introduced. This was significant in units 1 and 3 (Table VI). Lower dryness scores after RHD was introduced were found in all professional groups.

**Clinical tolerance: irritation**

The average irritation score was 0.85 during the first period and 0.24 during the second. The scores of individuals lost during the second period did not differ from the scores of others. Irritation scores were reduced significantly after RHD was introduced, particularly in units 3 and 4 (Table VII) and applied to all professional categories.

**Para-clinical tolerance**

Average cutaneous hydration was 36.0 in the first period and 38.9 in the second. The results for individuals lost in the second period did not differ from the results of other individuals. As shown in Table VIII, there was a non-significant improvement. Analysis of development of cutaneous hydration scores for hands accordingly rank showed lower irritation scores after RHD was introduced for nurses, paediatric auxiliaries and ancillary staff. Because of the low number of subjects according to rank, no statistical test was carried out.

Clinical dryness scores and corneometer measurements were significantly related (in linear regression $R^2=0.210$, $P<10^{-3}$). No significant relationship was found between the clinical irritation score and hydration measurements on the corneometer.

<table>
<thead>
<tr>
<th>Table VI</th>
<th>Development of dryness by unit and by period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit</td>
<td>Average score before*</td>
</tr>
<tr>
<td>1</td>
<td>0.90</td>
</tr>
<tr>
<td>2</td>
<td>1.10</td>
</tr>
<tr>
<td>3</td>
<td>1.07</td>
</tr>
<tr>
<td>4</td>
<td>1.13</td>
</tr>
<tr>
<td>Total</td>
<td>1.08</td>
</tr>
</tbody>
</table>

*For all subjects observed. †For the 77 subjects observed both before and after. ‡Student’s t-test for matched series.

<table>
<thead>
<tr>
<th>Table VII</th>
<th>Development of irritation by unit and by period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit</td>
<td>Average score before*</td>
</tr>
<tr>
<td>1</td>
<td>0.55</td>
</tr>
<tr>
<td>2</td>
<td>0.53</td>
</tr>
<tr>
<td>3</td>
<td>1.24</td>
</tr>
<tr>
<td>4</td>
<td>0.74</td>
</tr>
<tr>
<td>Total</td>
<td>0.85</td>
</tr>
</tbody>
</table>

*For all subjects observed. †For the 77 subjects observed both before and after. ‡Student’s t-test for matched series.
Discussion

Compliance with hand disinfection in our study was relatively high in comparison with others. However, it is comparable with the results of our study carried out in 1998 at the CHLS and those of other studies from outside France.

The compliance varied between units and was no better where risks were greater, contrary to other studies. The lowest rate of compliance was recorded in the intensive care unit and was accompanied by a greater workload in the first period but not in the second. Thus workload does not appear to be an explanatory factor.

Observance differed between professional categories and was lower for doctors and physiotherapists, as in other studies. These two groups were hardly affected by the campaign: only two doctors attended the informative meetings. The rate of adapted procedures as well as the rate of correct procedures collected in our study are similar to the rates given in the literature.

The introduction of RHD led to a greater number of procedures carried out and particularly to improved quality, associated with a greater cutaneous tolerance. This result is similar to studies already published which also show a greater effect, compared with a simple programme for promoting the hygiene of hands.

Improved compliance was significantly more pronounced in unit 1, which benefited from adapted equipment and complete information since all of the nursing staff were present at the informative meeting. This highlights the importance of preparing the introduction of RHD.

In the other units compliance was improved non-significantly (unit 3) or remained unchanged (units 2 and 4), but the quality of procedures carried out was significantly greater after the introduction of RHD, which is perhaps linked to the simpler nature of RHD compared to washing. The rate of adapted correct procedures carried out is a judgement criterion rarely used in the literature, but it gives a good overall picture of the practice of disinfecting hands. It tripled after the introduction of RHD (from 6.0 to 17.8%), demonstrating the value of the programme.

The tolerance analysis showed a clear improvement in the state of the hands of nursing staff in the second study period. This improvement was very significant with the method using clinical results, both for the type of dryness and the type of irritation. The difference in dates may explain this, but meteorological conditions showed no difference between the two periods. The improvement in the state of hands therefore seems due mainly to RHD, as demonstrated by others. The presence of additives in the solutions helps provide better protection for the state of hands. This improvement could also be explained by the improved quality of disinfection technique in the second period. The errors associated with a tolerance risk almost disappeared in the second period.

Although time savings were not measured in this study, it should be noted that simply washing hands requires approximately 1.5 min, excluding time to reach a sink, an antiseptic wash needs 2.5 min and RHD less than 1 min. Since RHD was used in almost 40% of cases during the second period, a considerable amount of time must have been saved, which is likely to favour better compliance.

Results obtained with the corneometer correlated well with those of the clinical dryness assessments and the two thus seem to measure the same characteristic. The corneometer appeared less discriminatory than the clinical assessment, perhaps because measurement is carried out on a single point, on the back of the hand. Dryness on the back of hands often only appears following dryness on nails and fingers. However, the corneometer was often better perceived than the clinical method, which the nursing staff considered subjective. Future studies might explore more discriminatory methods, such as measuring the loss of transepidermal water or increasing the number of points measured.

### Table VIII: Cutaneous hydration scores for hands according to units and according to periods

<table>
<thead>
<tr>
<th>Unit</th>
<th>Average before*</th>
<th>Average after*</th>
<th>Average difference†</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37.6</td>
<td>38.9</td>
<td>1.3</td>
<td>0.71 (ns)</td>
</tr>
<tr>
<td>2</td>
<td>35.2</td>
<td>28.3</td>
<td>-7.0</td>
<td>0.005</td>
</tr>
<tr>
<td>3</td>
<td>35.7</td>
<td>38.0</td>
<td>2.0</td>
<td>0.42 (ns)</td>
</tr>
<tr>
<td>4</td>
<td>36.2</td>
<td>44.2</td>
<td>8.0</td>
<td>0.08 (ns)</td>
</tr>
<tr>
<td>Total</td>
<td>36.0</td>
<td>38.9</td>
<td>2.9</td>
<td>0.3 (ns)</td>
</tr>
</tbody>
</table>

* For all subjects observed.
† For the 76 subjects observed both before and after.
‡ Student’s t-test for matched series.
Although alcohol-based products are suspected to be more irritant than soap, our work showed the opposite. However such a test was too short to provide a reliable measurement of the different irritant effects in chronic use.

In conclusion, our work has demonstrated a variety of benefits from the introduction of a well-tolerated hand disinfection programme using RHD. The study emphasizes the importance of making appropriate equipment available and the need to make particular efforts to include medical staff in educational efforts.

Acknowledgments

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Dermatological aspects of a successful introduction and continuation of alcohol-based hand rubs for hygienic hand disinfection

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KEYWORDS
Alcohol-based hand rubs; Occupational dermatitis; Irritant contact dermatitis; Detergents; Handwash

Summary With the new Centers for Disease Control and Prevention (CDC) guideline on hand hygiene, hospitals often introduce alcohol-based hand rubs for hand disinfection. Healthcare workers, however, may reject the new products because of skin irritation or other skin-related problems, which they experience after years of handwashing. In order to facilitate a successful introduction and continued use of alcohol-based hand rubs in hospitals, we have reviewed and summarized the major studies on the topic. Occupational hand dermatitis may occur in up to 30% of healthcare workers. It is mainly described as an irritant contact dermatitis caused by detergents. The diagnosis is usually clinical. Allergic reactions are very rare. After using an alcohol-based hand rub for the first time, healthcare workers may have a burning skin sensation that can be explained by pre-irritated skin. In this case the skin barrier has usually been impaired by frequent handwashing or occlusive gloves. This may result in a vicious circle whereby the healthcare worker increases the frequency of handwashing and reduces the frequency of hand disinfection. Prevention of irritant contact dermatitis is possible by selection of a low-irritating hand rub, which contains emollients, the correct use of the hand rub and a clear guideline when to disinfect and wash hands in the clinical setting. Common mistakes in the use of alcohol-based hand rubs are application to pre-irritated skin and washing hands before hand disinfection, which is, in general, not necessary, or after hand disinfection, which results in washing off the emollients. Clear preparation and guidance of healthcare workers before the introduction of alcohol-based hand rubs can help to enhance compliance in hand hygiene. The switch from handwash to alcohol-based hand rub will improve healthcare workers skin if mistakes are avoided and hand rinses are used correctly.

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Background to alcohol-based hand rinses (ABHRs)

Hand hygiene is currently undergoing a global renaissance. For decades antiseptic or plain soaps have been considered to be the first choice for hand decontamination in many countries, e.g. the United States and the United Kingdom. In many central European countries, however, ABHRs have been used at the same time. This is explained mainly by their faster antimicrobial activity, broader spectrum of antimicrobial activity and better skin tolerance. Their use has now been endorsed by the new Centers for Disease Control and Prevention (CDC) guideline on hand hygiene, which clearly favours ABHRs for hygienic hand disinfection. Many hospitals and their infection control teams now face the challenge of introducing a new type of hand antiseptic. Experiences with the introduction of ABHRs have been reported. In France, for example, both compliance and skin condition improved after introduction of an ABHR. In a US hospital, however, compliance increased, but the overall satisfaction with the hand rub was modest. This review highlights the most important dermatological aspects that should be considered when introducing ABHRs in a healthcare institution.

Quality of ABHRs

Most ABHRs for hygienic hand disinfection or surgical hand disinfection in Europe are classified as medicinal products. They are therefore subject to national or European drug laws. This has a major impact on the quality and documentation required for the hand rinse. Active ingredients must have a quality that is compatible with the European Pharmacopoeia. A minimum level of purity is thereby guaranteed. The purity of raw materials certainly has an impact on the local tolerance of a hand rinse.

 Frequencies of occupational hand dermatitis among healthcare workers (HCWs)

ABHRs are mainly used by HCWs. This occupation is a classical risk factor for hand dermatitis. The most extensive investigations concerning the epidemiology of hand dermatitis in the general population were performed in Sweden. Meding et al. reported a one year prevalence between 9.7 and 11.8% (with a tendency to decrease in the later years) and a point prevalence of 5.4%. In HCWs, a far higher point prevalence of hand dermatitis (17–30%) can be found. This is supported by a retrospective study of Smit and Coenraads, in which an overall incidence of 6.5 cases/1000 person-months in nurses and 1 case/1000 person-months in office employees was estimated. The consequences are serious because many employees lose their jobs due to hand dermatitis (occupational skin disease). In a population-based register study of occupational skin diseases in Northern Bavaria, Dickel et al. observed an annual incidence rate of 7.3 cases per 10 000 healthcare workers.

Causes of occupational hand dermatitis

In epidemiological studies it is very difficult to
determine the cause of hand dermatitis, as contact dermatitis is not a notifiable disorder. The most frequent cause of hand dermatitis in the general population seems to be irritant contact dermatitis (ICD, 35%), followed by atopic dermatitis (22%) and allergic contact dermatitis (19%). In HCWs the pathogenesis of a contact dermatitis is also most frequently an irritant dermatitis. Allergies are of secondary importance. Of the many topical preparations HCWs work with, disinfectants (like ABHRs) and detergents are the most frequent contact substances. The results of a questionnaire showed frequent skin contact with disinfectants (76%) and detergents (72%) in the workplace. Mostly, relevant allergies in HCW are due to sensitization against glove ingredients (Latex, rubber chemicals, starch glove powder) and disinfectant ingredients (glutaraldehyde, formaldehyde and glyoxal). With respect to these disinfectant ingredients an increase of the sensitization rate of HCWs compared with the general population is noticeable: glutaraldehyde (9.9% versus 2.6%), formaldehyde (3.6% versus 2.1%) and glyoxal (4.2% versus 1.4%). No allergies have been proven for the alcohol component of the hand disinfectants. However, many nurses complain about burning sensations after contact with ABHRs and assume an allergy to the product. As stated above, an allergy to ABHRs can therefore be discounted.

However, the potential for irritation caused by ABHR, has to be considered. In a detailed patch test study, it was found that a 60% n-propanol solution did not induce any irritation on healthy skin. Even on pre-irritated skin, the damage to the skin (evaluated by measurement of transepidermal water loss and skin surface capacitance) caused by a 60% n-propanol solution which is the concentration used in daily practice, was very low. For a 100% n-propanol solution, the irritation was much greater. It can be concluded that the alcohol part of ABHRs rarely provokes relevant irritation on intact skin and that for most procedures of daily hand hygiene, ABHRs should be preferred.

Clinical symptoms of occupational hand dermatitis

The reason for the burning sensation on contact with ABHRs is a pre-irritated skin. If the skin barrier is disrupted, e.g. by frequent wet work, alcohol may penetrate more easily into the epidermis. Even in the epidermis there are nerve receptors that are simulated by the alcohol, resulting in a burning sensation, but not in further irritation. The cause of the problem of the burning sensation is therefore the pre-irritated skin, leading to an impaired epidermal barrier and not the negligible irritation caused by the alcohol itself. A burning sensation after alcohol application may indicate that the skin barrier is seriously impaired.

Pathogenesis of occupational hand dermatitis

In HCWs, the predominant mechanisms of skin irritation are repeated exposure to moisture, work with occlusive gloves and contact with aggressive surface disinfections. Even water on its own can be an irritant. These risk activities often lead to a subclinically impaired skin barrier, before the first clinical irritation (often in the interdigital spaces) becomes apparent. Further aggravating factors are an atopic disposition, genetic predisposition and climatic conditions. The strongest influence on the manifestation of irritant skin changes is, by far, individual behaviour. When mild irritations (like handwashing) affect the skin frequently, the regenerating mechanism can no longer maintain a sufficient barrier. The skin barrier gets more and more disrupted and further irritation occurs more easily.

In daily routine, HCWs are exposed to both handwashing and disinfection with ABHR. If the epidermal barrier becomes disrupted and alcohol causes a burning sensation during use, this is often interpreted by the user as ‘aggressiveness’ of the ABHRs. As a logical consequence, the user reduces applications of ABHR and tries to compensate with increased handwashing. This leads, unfortunately, to more barrier disruption, which is for a while unnoticed, but will often lead to clinically relevant hand dermatitis. A vicious circle is initiated.

Diagnosis and treatment of occupational hand dermatitis

The diagnosis of ICD is predominantly clinical one. Diagnostic tests (like patch tests) are usually performed to exclude allergic contact dermatitis. Because most subjects suspect that an allergy to ABHR is responsible for their hand dermatitis, an allergic patch test is often performed. As the true explanation is usually not the ABHR but rather the
individual’s behaviour (e.g. frequent handwashing), these tests are usually negative. Irritant tests, like the epicutaneous patch test with sodium lauryl sulphate, are helpful in evaluating an individual skin susceptibility, but the value of these tests should not be overestimated, because the pathogenesis of ICD is based on the combination of individual predisposition with external irritation.43

When skin changes are apparent and the diagnosis is clear, early treatment is essential. In HCWs, ICD appears mostly in the interdigital spaces and on the dorsum of the hands. Rough and scaly skin is predominant with only minor inflammation. The main symptom (if any) is a burning sensation. This stage of the disorder is best treated by avoidance of the irritation and the application of lipid-rich tropical agents. When the inflammation gets worse, a short application of a corticosteroid-containing external agent is often required.44,45 If the ICD is not treated adequately, allergens may penetrate the disrupted barrier into inflamed tissue with numerous stimulated immunocompetent cells, causing a second problem: allergic contact dermatitis.46 At this stage, the skin often shows pronounced erythema and vesicles, and the predominant problem is itching. The best therapy at this stage is immunosuppressive topical external agents such as corticosteroids or tacrolimus. In the chronic stages, ICD and allergic contact dermatitis of the hands may have a similar clinical picture.

Prevention of occupational hand dermatitis

There are several measures possible to prevent the above course of events. The most effective is primary prevention,47 which can be separated into collective and individual measures. The development of low-irritating disinfectants (like ABHR) is a preventive measure and part of the creation of a safe occupational environment. The correct use of hand disinfections is important among the individual measures of prevention.48 In general, it is not necessary that irritants (e.g. handwashing) are avoided completely. In most cases a reduction of the duration of frequency of exposure is sufficient.49 Wherever possible replacement of incorrect, irritant behaviour (here handwashing) by less irritant measures (like use of ABHR) is recommended. This change in behaviour must be taught, as must the correct use of gloves and protective clothing. Regular teaching is one of the most important measures in the prevention of ICD.18,24,50 This should take place during induction, as well as at regular intervals during working practice. Knowledge about irritation and irritants, such as actual irritants in a given working environment, and the advantages of ABHRs over handwashing must be stressed. All possible individual means of prevention such as protection by gloves, clothes, barrier creams and correct skin cleaning should be considered.51 Practical illustrations such as the testing of cream applications with a fluorescence technique are very helpful.52,53

The use of a moisturizer in supporting the regeneration of the skin barrier is widely accepted even by affected individuals. It forms part of secondary prevention, because it is mostly introduced after the first skin changes are visible. This approach is supported by most dermatologists, but its efficacy is unconfirmed. Only a few studies with repeated irritation and subsequent application of a moisturizer have been undertaken.54 Usually, a slight improvement was noted at the treated areas, but the effect was not dramatic. Further studies, especially under daily working conditions, are needed.

Common mistakes in the use of ABHR

Unhealthy/irritated skin

Damaged skin is not always visible and may well be tolerated by the HCW if no alcohol is applied. Especially in situations where ABHR are introduced for the first time, it is crucial to make sure that the skin is healthy before the alcohol is applied. Otherwise there might be a burning sensation, erythema or fissures. The HCW might reject the ABHR due to symptoms that are the result of pre-existing skin disorders.

Handwash before hand disinfection

In general there is no need to wash before hygienic hand disinfection. Washing the hands will result in moist skin, which predisposes to toxic skin reactions. In addition washing removes the superficial sebum layer of the skin and thereby enhances skin irritation and dryness. For this reason ABHR should only be applied to dry hands.

Handwash after hand disinfection

Hands should not be washed immediately after hygienic hand disinfection. This will remove not only the superficial sebum layer of the skin, but in
addition the emollients that are included in many ABHR in order to improve the skin care after use.

Choice of ABHR

The ABHR should be a formulation with emollients. Lack of emollients may lead to dryness of the skin and may impair compliance. Subjective assessment of the emollient effect may reveal considerable differences. The hand rub should have only a minimal risk of skin irritation and sensitization. Finally user acceptability may be a key factor irrespective of other objective factors. User acceptability may be influenced by factors like smell, skin feeling after application and speed of drying. Gels should, in addition, be assessed for tackiness and build up.

How to use ABHR correctly

The right way to use ABHRs is summarized in Table II. As stated above, hand rubs should only be applied to dry and clean skin. A product should be rubbed into the skin until the skin is dry. This will take approximately 30 s. Hands should not be washed immediately after the hand disinfection, because it will remove the superficial skin sebum and the emollients of the hand rub. Between applications of hand rubs, hands should be washed only when they are visibly soiled. A mild, non-alkaline soap should be used. Water for a handwash should be cold. The duration of the handwash should be as long as necessary to remove visible contamination but at the same time as short as possible. Residual soap should be rinsed off completely. Brushes should not be used.

Skin care lotions and creams should be used between hand hygiene procedures, especially at the end of a shift. Older skin may require more intensive skin care. Hands should be dry before gloves are put on. Gloves should be worn only as long as necessary.

References


Table II Aspects of correct hand hygiene with ABHR

<table>
<thead>
<tr>
<th>Type of procedure</th>
<th>Aspect of use</th>
<th>Correct application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand disinfection</td>
<td>Type of alcohol-based hand rub</td>
<td>Hand rub with emollients, minimal risk of skin irritation and minimal risk of skin sensitization</td>
</tr>
<tr>
<td></td>
<td>Procedure for hand rub</td>
<td>Apply product to dry and clean skin. Rub the product into the skin until the skin is dry (approx. 30 s). No handwashing immediately after hand disinfection. Minimize number of handwashes between disinfections</td>
</tr>
<tr>
<td>Handwashing</td>
<td>Type of soap</td>
<td>Mild, non-alkaline</td>
</tr>
<tr>
<td></td>
<td>Procedure for handwash</td>
<td>Cold water. Minimize duration of handwashing. Do not use brushes. Rinse off residual soap. No handwash immediately before hand disinfection unless hands are visibly soiled</td>
</tr>
<tr>
<td>Skin care</td>
<td>General aspects</td>
<td>Use lotions or creams between hand hygiene procedures. Older skin may require more intensive skin care</td>
</tr>
<tr>
<td>Gloves</td>
<td>General aspects</td>
<td>Hands should be dry before gloves are put on (after handwashing or hand disinfection). Wear gloves only as necessary</td>
</tr>
</tbody>
</table>

Hands should only be washed when they are visibly soiled.
56. Kramer A, Bernig T, Kampf G. Clinical double-blind trial on
the dermal tolerance and user acceptability of six alcohol-based hand disinfectants for hygienic hand disinfection. 

*J Hosp Infect* 2002;51:114–120.


Dermal and pulmonary absorption of ethanol from alcohol-based hand rub

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SUMMARY

Background: Ethanol intoxication of healthcare workers (HCWs) using alcohol-based hand rubs (ABHRs) in the workplace is a potentially serious issue. This study quantified the level of ethanol absorption among HCWs after hygienic hand disinfection.

Methods: Eighty-six HCWs from Nancy University Hospital were tested before and after a 4-h shift. Participants used ABHR containing 70% ethanol. Levels of ethanol, acetaldehyde and acetate in blood and urine were determined using gas chromatography. A breathalyzer was used to measure the level of ethanol in expired air.

Results: Ethanol [mean concentration 0.076 (standard deviation 0.05) mg/L] was detected in the expired air of 28 HCWs 1–2 min post exposure. Ethanol, acetaldehyde and acetate were undetectable in blood after a 4-h shift, and urine tests were negative in all participants.

Conclusion: Ethanol exposure from ABHR, particularly inhalation of vapours, resulted in positive breathalyzer readings 1–2 min after exposure. Dermal absorption of ethanol was not detected. Pulmonary absorption was detected but was below toxic levels.

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Introduction

Alcohol-based hand rubs (ABHRs) are currently the first choice for hand hygiene in healthcare settings because they have better antimicrobial activity than antiseptic soaps,1,2 are effective, easy to use and improve compliance.3,4 Their use is recommended before and after patient contact, and for procedures such as intravenous cannulation, provided the hands are not visibly soiled.5 Most commercially available ABHRs contain 60–95% alcohol in the form of ethanol, propan-1-ol, propan-2-ol or a combination of these.6,7 A small amount of alcohol is absorbed from ABHRs and can be detected in the blood.8,9 As ethanol intoxication of healthcare workers (HCWs) at work is potentially serious, particularly for pregnant women and motorists, it is important to elucidate the effects of frequent use of ABHRs on blood levels. Most countries have legal blood alcohol levels for drivers of 0.0–0.8 mg/mL (a potentially fatal concentration).10 Estonia, Hungary, Latvia, the Czech Republic, Romania and Slovakia have zero tolerance regarding blood alcohol levels in drivers. Also, alcohol consumption varies with religion and culture.11 Muslim HCWs may be concerned about exposure to alcohol,12 producing a potential barrier to the use of ABHRs.
Absorbed alcohols diffuse widely. Ethanol is mainly metabolized in the liver, with smaller quantities found in kidney, muscle, lung, intestine and possibly brain. Ethanol is oxidized to acetaldehyde and then converted to acetate. This study measured ethanol absorption from ABHR in several categories of HCWs to determine if routine use during a 4-h shift under real-life conditions might cause toxicity. Levels of ethanol, acetaldehyde and acetate were measured in blood, urine and expired air.

Materials and methods

Participants were chosen at random. HCWs completed a questionnaire recording their position, age, gender, height, weight, alcohol consumption, use of medication, and medical and surgical history. Height and weight were used to calculate body mass index (kg/m²). HCWs on regular medication or with visible lesions on their hands were excluded, as were those with alcohol sensitivity or a history of alcohol or drug abuse. Ethical approval was obtained from the Committee for the Protection of Human Subjects 'Est III' (France) and the French Health Products Safety Agency. Participants signed an informed consent form after receiving detailed information about the study. Consent was obtained from all participants and the study was approved by the Committee for the Protection of Human Subjects ‘Est III’ (France) and the French Health Products Safety Agency. Participants were informed of the study’s purpose and that they could withdraw at any time. To ensure the anonymity of the participants, identifiers were removed from the data analysis. Consent was obtained from all participants and the study was approved by the Committee for the Protection of Human Subjects ‘Est III’ (France) and the French Health Products Safety Agency. After receiving detailed information about the study, all participants signed an informed consent form.

Exposure study

Ethanol exposure of 86 HCWs aged 18–50 years was assessed under normal working conditions at the University Hospital of Nancy, France. Participants applied 3 mL of ANIOSGEL 85 NPC (Laboratories Anios, Lille, France) to their hands and rubbed them together until dry (30 s), several times during a 4-h shift. Each participant started with a 100-mL bottle of ABHR of known weight. ANIOSGEL contains ethanol (700 mg/g or 755 mL/L), water, glycerine, acrylates/C10-30, alkyl acrylate cross-polymer, bisabolol, caprylic/capric triglycerides PEG-4, esters, PEG-8 caprylic/capric glycerides, aminomethylpropanol and methylpropanediol.

Ethylotest breathalyzer

The level of ethanol in expired air was measured using an electronic Ethylotest Alco-Sensor FST (Intoximeters, Inc., St. Louis, MO, USA), which can detect 0.00–2 mg/L (+/–0.01 mg/L). Measurements were taken before a 4-h work shift (pre-exposure) and 1–2 min after the shift.

Blood and urine collection

Blood and urine samples were collected before a 4-h shift (pre-exposure) and 5–10 min, after the last application of ABHR. The skin was disinfected with a non-alcoholic antiseptic. Blood was collected in a Vacutainer (Becton Dickinson, Franklin Lakes, NJ, USA), and urine was collected in a 60-mL bottle. Samples were stored for up to 2 h at 4 °C before analysis.

Analysis of ethanol, acetaldehyde and acetate concentrations

Levels of ethanol, acetaldehyde and acetate were measured with a gas chromatograph (GC 3900, Varian Analytical Instruments, Walnut Creek, CA, USA) equipped with an injector 1177 EFC 21 split/splitless, and a flame ionization detector with capillary column (CP-SIL 19CB; 25 m × 0.53 mm, 2 μm; Varian Analytical Instruments). The gas chromatograph was set with hydrogen at 25 mL/min and air at 300 mL/min. The nitrogen carrier gas flow was set at 5 mL/min. The temperatures at the injector and detector were set at 220 and 200 °C, respectively. In each case, calibration was performed using an internal standard method. Methanol was used as the internal standard. Samples were analysed using a modified Varian protocol, which involves direct injection of the biological specimen into the gas chromatograph with little pretreatment. Plasma or urine is mixed with the internal standard solution and injected in the gas chromatograph. Each sample was analysed in duplicate. Contamination of the gas chromatographic column with non-volatile material was prevented by using a glass liner in the injector as a precolumn. The glass liner (without glass wool) was replaced after approximately 50 injections.

The reagents used (ethanol 96%, methanol 99.5% and acetaldehyde 99.5%) were obtained from Merck (Darmstadt, Germany).

Preparation of biological samples

The standard sample solution was a mixture containing methanol and ethanol with the concentration ratio. Sealed blood sample tubes were centrifuged for 5 min at 800 g. Urine was centrifuged at 1000 g for 15 min at 4 °C. The samples were stored in closed microsample containers at −20 °C until analysis. One hundred microlitres of samples were taken and mixed with 100 μL of internal standard (methanol), and stored in a closed microsample container. Standard sample preparation was prepared by diluting 100 μL of ethanol with 100 μL of methanol.

A 1-μL syringe (Hamilton Microliter Syringes, Interchim, Hamilton, Bonaduz, Switzerland) was flushed several times to remove the air in the needle. 0.5 μL of sample was measured in the syringe and injected manually in the split injector of the gas chromatograph.

Data calculation

Results were obtained using Galaxie Version 1.9 SP1 (Varian Analytical Instruments). The peak heights were used to calculate the concentrations of ethanol and its metabolites in the samples. The concentration of ethanol in plasma is 1.17 times the concentration in the whole blood. The detection limit of ethanol and acetaldehyde was 0.1 mg/L. Peaks were identified for acetaldehyde, methanol and ethanol.

Statistical analysis

Data were analysed using Statistical Package for the Social Sciences Version 17 (SPSS Inc., Chicago, IL, USA).
Ten males and 76 females (mean age 40 years) participated in this study. Most participants had Fitzpatrick skin type II (69.8%), 15.1% had skin type III, 3.5% had skin type IV and 1.2% had skin type VI. Table I shows the demographic and physical data of the study participants.

The mean usage of ABHR was 27.5 [standard deviation (SD) 14.9] g per 4-h shift (range 1.2–59.84 g), representing approximately nine (SD 5) hygienic disinfections. Figure 1 shows ABHR usage for each subject during a 4-h shift. The amount of ABHR used varied with profession and workplace. Table II shows the mean usage of ABHR by type of HCW and breathalyser values.

Ethanol, acetaldehyde and acetate concentrations

Pre-exposure
Ethanol, acetaldehyde and acetate were undetectable in the blood and urine of 85 participants. Ethanol (0.39 mg/L) was detected in the blood of one radiology technician.

Post-exposure
Ethanol (0.22 mg/L) was detected in the blood of a senior nurse who had only used 7.9 g of ABHR during the 4-h shift. Acetaldehyde was detected in the blood of a laboratory technician, who turned out to have a history of liver disease and was therefore excluded from the study. All urine alcohol tests were negative.

Measurement of ethanol by breathalyser

Pre-exposure
Ethanol was not detected in the expired air of any of the participants.

Post-exposure
After a 4-h shift, the level of ethanol in expired air approximately 2 min after the last application of ABHR was 0 in 58 HCWs. In the remaining 28 HCWs, the mean level of ethanol was 0.076 (SD 0.05) mg/L (95% confidence interval 0.03–0.23).

Discussion
Hand disinfection is vital for the prevention of nosocomial infections, and ABHRs are routinely used for hand hygiene. However, extensive use of such products in healthcare settings could expose HCWs to potential risks. Previous studies have shown that some of the alcohol used for disinfection is absorbed, can be detected in the blood and may cause alcohol toxicity.13,14 Other studies have demonstrated a significant increase in alcohol blood levels after application of alcohol-containing preparations to the skin.15,16 In contrast, a recent investigation reported no significant transdermal absorption of ethanol or 1-isopropanol in 14 healthy volunteers within 1 h of application of hand disinfectant (containing ethanol, 1-propanol and skin-protecting additives) or the alcohols alone.17 The present study focused on real-life hand hygiene practices and use of ABHRs in the workplace by measuring transdermal and pulmonary absorption of ethanol. Gas chromatography associated with a flame ionizing detector is the most precise, reliable and rapid method for alcohol determination in a biological specimen. Plasma and urine were injected without pretreatment so the method was able to detect concentrations as low as 0.1 mg/L ethanol. The baseline values

Table I
Demographic and physical data of study participants

<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>86</td>
</tr>
<tr>
<td>Males</td>
<td>10</td>
</tr>
<tr>
<td>Females</td>
<td>76</td>
</tr>
<tr>
<td>Age (years)</td>
<td>40</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64 (11.7) 44–105</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.4 (7.8) 150–192</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.8 (1.8) 19.6–28.5</td>
</tr>
</tbody>
</table>

SD, standard deviation; CI, confidence interval.

Figure 1. Usage of alcohol-based hand rub (ABHR) by healthcare workers during a 4-h shift.
of ethanol, acetaldehyde and acetate indicated alcohol abstinence of subjects before the shift. After a 4-h shift, values were below the maximum physiological levels of ethanol and acetaldehyde. Thus, no significant transdermal absorption of ethanol had occurred despite several applications of ABHR, supporting the results of previous studies. It has been reported that 55–60% of inhaled alcohol vapours can be absorbed into the bloodstream as HCWs rarely use masks when applying ABHR. Pre-exposure breathalyzer tests registered zero in all participants, but a mean ethanol level of 0.076 (SD 0.05) mg/L was measured in the expired air of 28 HCWs (95% confidence interval 0.03–0.23 mg/L) 1–2 min post-exposure. Values returned to zero in all participants within 15 min. The threshold limit set by the Highway Code for drivers in France is 0.25 mg/L, and positive breathalyzer readings could result in sanctions for drivers.

This study has several limitations. The chosen exposure period was only 4 h, and surgical hand rub was not tested. The number of applications of ABHR varies markedly between HCWs depending on the nature of clinical activity, the hospital setting and compliance with hand hygiene programmes. Indeed, the US Centers for Disease Control and Prevention hand hygiene guidelines report that the compliance of HCWs with hand hygiene practices varies between 5% and 81%, with an overall average of 40%. In the present study, the mean amount of ABHR used during a 4-h shift was 27.5 g (i.e. approximately nine hand disinfections). This suggests exposure to alcohol every 26.6 min, which is a very short exposure period. Furthermore, ethanol absorption corresponded with exposure dose and time. Previous data have shown that the small amounts of ethanol absorbed are divided into two portions: one portion (2–5%) is excreted unmetabolized in urine, sweat and breath; and the remainder is metabolized quickly, eliminated rapidly and does not accumulate, making it difficult to detect ethanol and its metabolites in blood and urine.

Detection of acetaldehyde in the blood of a subject with liver disease could stimulate further research. HCWs suffering from liver disease or who are metabolically deficient could be at increased risk of toxicity. Another area for research is the consequences of long-term daily and frequent use of ABHR.

## Conclusion

The ABHR used by HCWs in routine work did not lead to the absorption of a detectable amount of ethanol. Dermal absorption was not detected. Values detected from pulmonary absorption were below the levels known to be toxic in humans. Therefore, the use of ABHR is safe for healthy HCWs.

### Conflict of interest statement

D. Ahmed-Lecheheb was supported by ANRT: National Association of Research and Technology and ANIOS Laboratories.

### Funding sources

This study was financed by the Department of the Environment and Public Health, Faculty of Medicine, Nancy University, France and University Hospital of Nancy, France.

### References


### Table II

Mean usage of alcohol-based hand rub (ABHR) during a 4-h shift by category of healthcare worker and breathalyzer reading

<table>
<thead>
<tr>
<th>Profession</th>
<th>N</th>
<th>Mean ABHR usage (g/4 h) ± SD [range]</th>
<th>Mean breathalyzer reading (mg/L) (SD) [range]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurses</td>
<td>39</td>
<td>30.5 (15.3) [4.7–59.8]</td>
<td>0.02 (0.03) [0–0.17]</td>
</tr>
<tr>
<td>Nurse assistants</td>
<td>11</td>
<td>30.2 (12.5) [8.7–50.3]</td>
<td>0.05 (0.07) [0–0.23]</td>
</tr>
<tr>
<td>Radiology technicians</td>
<td>11</td>
<td>28.6 (13.2) [15.7–55.8]</td>
<td>0.02 (0.06) [0–1.19]</td>
</tr>
<tr>
<td>Doctor</td>
<td>1</td>
<td>26.7</td>
<td>0</td>
</tr>
<tr>
<td>Clinical dieticians</td>
<td>2</td>
<td>25.1 (6.1) [20.8–29.4]</td>
<td>0</td>
</tr>
<tr>
<td>Hospital cleaners</td>
<td>15</td>
<td>24.5 (16.2) [7.5–59]</td>
<td>0.02 (0.04) [0–0.16]</td>
</tr>
<tr>
<td>Clinical research assistants</td>
<td>1</td>
<td>14.6</td>
<td>0</td>
</tr>
<tr>
<td>Laboratory technicians</td>
<td>4</td>
<td>12.5 (14.8) [1.2–34.1]</td>
<td>0</td>
</tr>
<tr>
<td>Social worker</td>
<td>1</td>
<td>11.5</td>
<td>0.06</td>
</tr>
<tr>
<td>Senior nurse</td>
<td>1</td>
<td>7.9</td>
<td>0</td>
</tr>
</tbody>
</table>

SD, standard deviation.
Original contribution

Does the clinical use of ethanol-based hand sanitizer elevate blood alcohol levels? A prospective study

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Abstract

**Background:** Ethanol-based hand sanitizers (EBHSs) are used in most health care facilities in the United States. Infection control personnel advocate the use of generous quantities of EBHS before and after contact with patients. Although it is assumed that little systemic absorption of ethanol occurs during EBHS use, many alcohols are absorbed to varying degrees via the transdermal route. Ethanol intoxication by employees in the medical workplace is a potentially serious finding, and it is of forensic and medical-legal importance to elucidate the effects of frequent use of EBHS upon serum blood ethanol levels (BELs). To investigate the effect of frequent use of EBHS upon serum blood ethanol concentrations, we prospectively studied 5 volunteers undergoing frequent application of EBHS.

**Methods:** Enrolled subjects applied 5 mL of the product (62% denatured ethyl alcohol manufactured by Kimberley-Clark, Roswell, GA) to both hands and rubbed until dry. This activity was repeated 50 times over 4 hours. Participants had their blood drawn before as well as after completing the study. Each participant was without alcohol exposure during the 12 hours preceding the study.

**Results:** Five volunteers were enrolled. All had an initial blood ethanol level of less than 5 mg/dL. All 5 participants completed the 4-hour study. There were no noted adverse reactions during the study. Blood ethanol level upon completion of the 50 applications of EBHS was less than 5 mg/dL in all 5 study participants.

**Conclusion:** The results of this study demonstrate that use of ethanol-based hand sanitizers, when frequently used in accordance with labeling, do not raise serum blood ethanol levels.

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1. Introduction

Ethanol-based hand sanitizers (EBHSs) are used in most health care facilities in the United States. Infection control personnel advocate the use of generous quantities of EBHS before and after contact with patients [1]. This translates to the use of these products 10 to 25 times per hour, depending
2. Methods

2.1. Study design

This was a prospective, nonblinded study. The institutional review board at our institution approved the study.

2.2. Study protocol

Participants were the investigators and associate investigators of the study. All are employees in the emergency department at the study institution. Enrolled subjects applied 5 mL of the product (62% denatured ethyl alcohol manufactured by Kimberley-Clark) to both hands and rubbed until dry. This activity was repeated 50 times over 4 hours. Participants had their blood drawn before as well as after completing the study. No laboratory tests were performed other than the ethanol levels. Prestudy blood ethanol levels were ordered to ensure a prestudy level of less than 5 mg/dL. All participants were adults between the ages of 18 and 50 years, without history of hepatic or renal disease. Each participant had no alcohol intake or exposure during the 12 hours preceding the study, including EBHS. Other exclusion criteria included allergy to EBHS or any of its ingredients, any rash on the extremities, and current use of disulfiram or any drug known to have disulfiram-like reactions with ethanol intake.

2.3. Data analysis

In this study, the independent variable was time in relation to frequent use of hand sanitizer. The dependent variable was blood ethanol concentration, measured as milligrams per deciliter. The null hypothesis was that frequent use of alcohol-based sanitizers does not raise blood alcohol levels. A paired t test was used for analysis. The expected blood ethanol level before the frequent use of alcohol-based sanitizer was 0 to 5 mg/dL, which is deemed undetectable by the assay used by our laboratory. This is equivalent to a mean ± SD of 2.5 ± 1.25 for those with undetectable blood ethanol levels. An increase to 5 mg/dL would be statistically significant (an effect size of 2.5/1.25 = 2 SD). The sample size was adjusted with 1000 iterations of a Monte Carlo simulation until the power was between 80% and 85% with a level of confidence of 95%. According to this method, 5 subjects acting as their own controls would be needed to detect a 2 SD effect size with a level of confidence of 95% and a power of 80%.

3. Results

A total of 5 volunteers were enrolled. All had an initial BEL of less than 5 mg/dL. All 5 participants completed the 4-hour study. There were no noted adverse reactions during the study. Blood ethanol level upon completion of the 50 applications of EBHS was less than 5 mg/dL in all 5 study participants.

4. Discussion

Ethanol is the most frequently abused intoxicant in the United States [3]. The proliferation of work-related drug testing programs, integration of EBHS into health care facilities, and the widespread abuse of ethanol make it imperative to define what, if any, contribution the use of ethanol-based hand sanitizers have on the BEL of users of such products. Medical review officers (MROs) may be asked to review an employee’s claim that he or she was not using ethanol, and the MRO must use the best available evidence to guide these important, life-altering decisions. The MRO involved in evaluating such reports relies on past case reports, knowledge of laboratory analytical techniques, and other scientific evidence to validate or negate claims of drug use in the workplace. We have previously reported a case report of a negative BEL after frequent use of EBHS [4]. Before that report, no human reports of serum ethanol levels after frequent clinical use of EBHS had been reported. This study, which demonstrates negative serum ethanol levels with extremely frequent use of EBHS, concludes that the contribution to BEL of EBHS is negligible and can be discounted by the involved reviewing authority in cases where cause of elevated BEL is unclear. Because of the heavy and consistent use of EBHS in this study, these results are likely to be reproducible in all clinical settings.

5. Limitations

This study tested the ability of EBHS to elevate BEL in healthy, adult males. Although the findings likely apply to other human populations, this cannot be proven from our data. Furthermore, we dealt only with EBHS being used as intended. This study does not rule out BEL elevation by EBHS that has been misused in some manner, such as through ingestion or application to mucous membranes. An important remaining question is whether EBHS may contribute to or cause disulfiram-alcohol reactions in
susceptible individuals. The finding of a negative BEL does not preclude the possibility that EBHS may cause such reactions. Topical application of products containing aldehyde-dehydrogenase inhibitors has been noted to cause such reactions in persons taking oral ethanol [5]. Because of the requirements set forth by the institutional review board, we were unable to study the effects of EBHS upon patients at risk for disulfiram-ethanol reactions. This is an important topic, worthy of future research.

6. Conclusion

The results of this study demonstrate that use of ethanol-based hand sanitizers, when frequently used in accordance with labeling, does not raise serum blood ethanol levels.

References

Holding Thermal Receipt Paper and Eating Food after Using Hand Sanitizer Results in High Serum Bioactive and Urine Total Levels of Bisphenol A (BPA)

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Abstract

Bisphenol A (BPA) is an endocrine disrupting environmental contaminant used in a wide variety of products, and BPA metabolites are found in almost everyone’s urine, suggesting widespread exposure from multiple sources. Regulatory agencies estimate that virtually all BPA exposure is from food and beverage packaging. However, free BPA is applied to the outer layer of thermal receipt paper present in very high (~20 mg BPA/g paper) quantities as a print developer. Not taken into account when considering thermal paper as a source of BPA exposure is that some commonly used hand sanitizers, as well as other skin care products, contain mixtures of dermal penetration enhancing chemicals that can increase by up to 100 fold the dermal absorption of lipophilic compounds such as BPA. We found that when men and women held thermal receipt paper immediately after using a hand sanitizer with penetration enhancing chemicals, significant free BPA was transferred to their hands and then to French fries that were eaten, and the combination of dermal and oral BPA absorption led to a rapid and dramatic average maximum increase (Cmax) in unconjugated (bioactive) BPA of ~7 ng/mL in serum and ~20 μg total BPA/g creatinine in urine within 90 min. The default method used by regulatory agencies to test for hazards posed by chemicals is intra-gastric gavage. For BPA this approach results in less than 1% of the administered dose being bioavailable in blood. It also ignores dermal absorption as well as sublingual absorption in the mouth that both bypass first-pass liver metabolism. The elevated levels of BPA that we observed due to holding thermal paper after using a product containing dermal penetration enhancing chemicals have been related to an increased risk for a wide range of developmental abnormalities as well as diseases in adults.

Introduction

Bisphenol A [BPA; bis(4-hydroxyphenyl)propane; CAS #80-05-7] is one of the highest volume chemicals in commerce with 15-billion pounds produced per year [1], and based on the presence of BPA metabolites in urine, it can be concluded that virtually everyone is exposed [2,3]. BPA has estrogenic and other endocrine disrupting activities [4,5]. BPA molecules are polymerized to make polycarbonate plastic used for food and beverage containers, epoxy resins used to line cans, and dental composites and sealants, but free (unpolymerized) BPA is also used as an additive (plasticizer), such as in polyvinyl chloride (PVC) products. Our interest is in the use of BPA in thermal paper, which is used for airline ticket, gas, ATM, cash register and other types of receipts (Figure 1). The print surface of thermal paper is coated with milligrams of free BPA per gram paper as a heat-activated print developer [6], and it appears that free BPA is readily transferred to other materials that the thermal paper contacts [7].

While small lipophilic compounds such as BPA (logP = 3.4; molecular weight 228 Da) can pass through skin [8,9], regulatory agencies have assumed that this route of human BPA exposure should not be significant in spite of the lack of data and acknowledged “significant uncertainties” around the issue of human exposure to BPA from thermal paper [10]. However, a factor that has not been considered in estimating transdermal exposure to BPA from thermal paper is that hand sanitizers are now commonly used, particularly in fast-food restaurants where people may handle thermal receipts before eating or ordering food. Hand sanitizer and other skin care products may also be used by cashiers while working. Exposure to BPA from thermal paper goes beyond just transdermal exposure and consumption of food that is picked up and eaten with a BPA-contaminated hand.
The transfer of a chemical directly from hand-to-mouth (mouthing behavior) has been proposed to be an important variable for estimating total chemical exposure in humans [11], particularly in young children [12].

The use of hand sanitizers and other skin-care products, including soaps, lotions and sunscreens, is significant because some contain mixtures of chemicals that are also used as dermal penetration enhancers to increase the transdermal delivery of drugs and chemicals that are suitable for transdermal delivery and are impacted by dermal penetration enhancers have a LogP > 1.5 and a molecular weight < 300 Da [9]. There are many factors that impact the ability of compounds to pass through skin in addition to molecular weight and lipophilicity, including differences arising from the location of skin on the body, gender and age [13]. Mixtures of dermal penetration enhancing chemicals can act synergistically to increase by up to 100 fold the dermal penetration of small lipophilic molecules such as estradiol [8,9], with which BPA shares physical-chemical and biological properties [4]. For example, Purell hand sanitizer (Gojo Industries), which we used in the current study, contains a number of dermal penetration enhancers, such as isopropyl myristate and propylene glycol, and is (63% w/w) ethanol. The use of hand sanitizers has increased in recent years and is now about a 200 million dollar a year industry just in the USA [14]. The impact of the use of personal care products such as moisturizing lotions that contain dermal penetration enhancing chemicals on exposure to environmental chemicals has been identified as a concern [15].

To assess the relevance of this research to real-world behavior, we conducted a preliminary observational study in fast-food restaurants, food courts and shopping malls in Columbia Missouri. Receipt contact time varied widely, but was sometimes substantial. In one restaurant, we found that receipt contact time ranged up to 65 sec for people purchasing food that was eaten in the restaurant; the 75th percentile for time holding the receipt was >12 sec, and the 90th percentile >32 sec. In a fast-food restaurant that is part of an international chain, take-out food was placed into a bag and the top of the bag was folded, then the thermal receipt was stapled to the top of the bag; the result was that the print surface of the receipt (coated with BPA) was grabbed when the bag was picked up. The contact time between the hand and thermal receipt was thus considerably longer than would be the case for food eaten in the restaurant. In a food court we observed that some fast-food restaurants had hand sanitizer dispensers available for use by customers next to the cash register, and customers were observed using the hand sanitizer before handling the thermal receipt. The estimate is that 50 million people eat in a fast-food establishment every day in the USA [16]. Finally, our experiments here are also relevant to occupational exposures, because we observed in a national chain big-box store that all cash registers had a hand sanitizer dispenser next to them for use by the cashiers.

Our objectives were to examine the impact of having dry hands vs. wet hands due to using a popular hand sanitizer that contains dermal penetration enhancing chemicals on extraction of BPA from the surface of thermal receipt paper coated with BPA. We also measured (using a LC/MS/MS assay) unconjugated, bioactive BPA (uBPA) and its conjugated metabolites, BPA-glucuronide (BPA-G) and BPA-monosulfate (BPA-S), in serum and urine in adult male and female subjects after holding a thermal receipt. To determine the proportion of thermal receipts that contained BPA, we examined receipt papers for the presence and amount of BPA. We also examined receipts for the most commonly used BPA replacement chemical, bisphenol S [bis(4-hydroxyphenyl)sulfone; BPS; CAS 80-09-1].

Methods

Ethics statement

The University of Missouri School of Medicine Institutional Review Board approved all procedures involving human subjects, and sample collection was conducted by licensed personnel in the Clinical Research Center (CRC) within the University of Missouri School of Medicine. Subjects were informed of the procedures, and provided written consent. The signed consent forms were retained. The University IRB approved the consent procedure.

Subjects

Participants for the different experiments in this study were recruited through a weekly University of Missouri campus-wide email newsletter. Candidates (men and women) were pre-screened by age, height, weight, and health status. Participants selected were 20–40 years old (average 27.0 yrs), and an attempt was made to select those with average height, weight and normal-range body-mass index. Participants selected were not taking any prescription or non-prescription medication other than oral contraceptives; the type of oral contraceptive used was recorded. To ensure that pregnant women were excluded from the study, all women were administered a pregnancy test when they arrived at the CRC.

For all studies participants were asked to refrain from touching thermal paper receipts, consuming food or beverages stored in polycarbonate or other types of plastic containers as well as canned food and beverages during the 48 hr prior to participating in the study, in order to reduce background BPA levels in body fluids as much as possible. The participants also filled out a questionnaire concerning their activities during the prior 48 hr (see Section S3 in File S1 for questionnaire).

For experiments in which there was hand contact with thermal receipt paper, subjects were required to wash their hands with soap and water, rinse thoroughly, and then dry using Kimwipes (Kimberly-Clark, Irving, TX). A number of soaps were screened for BPA content and/or chromatographic interference prior to the start of the study, and the soap chosen was Sofsoap “Aquarium series” (Colgate Palmolive Company, Manhattan, NY), which showed no detectable BPA or chromatographic interference with the assay of BPA. Standard brown laboratory paper towels were tested and found to contain BPA at around 6 µg/towel. Because of this, Kimwipes, which tested negative for BPA, were used throughout for drying hands. Water from faucets used in the CRC was tested and found to be below the limit of detection (LOD) for BPA content (detection limit was 10 pg/mL by HPLC).
with CoulArray detection based on C-18 extraction of 250 ml of water).

Sample analysis

Analysis of BPA in extracted samples occurred within an accredited facility (Veterinary Medicine Diagnostic Laboratory) within the College of Veterinary Medicine at the University of Missouri.

Reagents. Solvents (methanol, acetonitrile) and water were HPLC grade, and were obtained from Fisher Scientific. BPA, bisphenol S (BPS), and BPA monosulfate (BPA-S) were obtained from Sigma-Aldrich (St. Louis MO; purity >99%, 98% and 95% respectively). C18-BPA was obtained from Cambridge Isotope Laboratories Inc. (Andover, MA; purity 99%), and both BPA-G (purity 98%) and BPA D-glucuronide (BPA-DG; purity >99%) were provided by the National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC. Ethanol (200 proof) used for hand swipes was obtained from Decon Labs, Inc. (King of Prussia, PA).

Total receipt BPA and BPS content. Weighed samples of each receipt (3x3 cm) were incubated overnight in methanol at room temperature. The methanol extracts were diluted in methanol, typically to a final dilution of 1/10,000, and BPA content was analyzed by HPLC with CoulArray detection (see Section S1 in File S1 for details). We also analyzed the same receipt sample extracts for BPS using LC/MSMS (see Section S1 in File S1 for details).

BPA levels in Kimwipe hand swipes. Kimwipe swipes were incubated in methanol at room temperature overnight, and aliquots were taken from the methanol extract for analysis. BPA in the methanol extract was determined by HPLC with CoulArray detection.

BPA levels in French fries. French fries were incubated individually in methanol overnight. The fries were then removed, and the samples centrifuged briefly to separate any solid and/or oily matter, and a sample of the clear methanol extract was assayed. Equal volumes from the 10 extracts from the 10 French fries touched by each participant were pooled, and a single measurement was made for each participant. Quantitation was made by HPLC with CoulArray detection.

Serum sample collection and extraction. Multiple-point blood samples were collected via IV catheter into 10 mL syringes, and the syringes were emptied into the same uncoated vacuumer tubes (for details and catalog numbers of collection materials Section S1 in File S1). Single point blood samples were collected by venipuncture into uncoated glass vacutainer tubes (Becton Dickinson, Franklin Lakes, NJ). All blood samples were allowed to clot at room temperature for 15–30 min and then refrigerated until centrifugation at 4°C for 15 min. The serum was transferred with glass Pasteur pipets into 15 mL centrifuge tubes and then frozen at −20°C. Samples were extracted using C18 SPE as previously described [17]; see Section S1 in File S1. Procedural blanks were also run alongside the samples to monitor for reagent contamination or interference. Serum extracts were analyzed by LC/MSMS.

Urine sample collection and extraction. All urine samples were collected directly into Sameco polypropylene specimen cups (Fisher Scientific, Waltham, MA) and were immediately refrigerated (4°C for 2–5 hours) until they could be transferred to the research laboratory, at which point they were frozen at −20°C. The total BPA concentration (representing a combined measure of unconjugated and conjugated BPA) was measured by LC/MSMS (see Section S1 in File S1).

Assay of creatinine in urine. To calculate creatinine-corrected urine BPA concentrations, urine creatinine was measured using an ELISA kit (R&D Systems Inc., Minneapolis, MN), according to manufacturer’s instructions. Sensitivity of this assay is 0.02 mg/dL.

Field blanks. The possibility of BPA leaching from each piece of equipment used in the collection or processing of samples identified above was determined by passing BPA-free water through all collection equipment, which was then handled and assayed for BPA as described below for the actual samples. All equipment and sample handling was determined to not leach detectable BPA before any sample collections occurred.

Statistical methods and calculation of pharmacokinetic parameters

For both uBPA and BPA-G, the area under the concentration-time curve (AUC) up to the last measured serum concentration above the LOQ, i.e. AUC (0–90 min), was calculated by using the linear trapezoidal rule. The average AUC (0–90 min) (ng/mL) was calculated by dividing AUC (0–90 min ng/mL)/90 min. Time (Tmax) of maximal plasma BPA concentration (Cmax) was directly obtained from the raw data. Comparisons of men and women were conducted using the Mann-Whitney U test or ANOVA. Statistical significance was set at P<0.05, two-tailed test. All data are presented as mean±SEM.

Experiment 1: Measurement of BPA and BPS in 50 used thermal receipt papers

The objective of this experiment was to determine the amount of BPA and BPS in thermal receipt paper and to determine the proportion of receipts that contained BPA or BPS, which is the most commonly used BPA replacement chemical. Thermal paper sales receipts were obtained by purchasing items from 41 different vendors in Columbia, MO and from a further 9 vendors in Southern Missouri (50 receipts total). Weighed portions of each paper were extracted and assayed for BPA by HPLC with CoulArray detection and for BPS by LC/MSMS. After screening, an unused roll was obtained from a vendor from which a BPA-positive receipt had been identified. The BPA content of paper from this roll was confirmed prior to being used for testing with human subjects in Experiments 2, 3 and 4.

Experiment 2: BPA transferred to a hand with and without using hand sanitizer due to holding a thermal receipt for different lengths of time

The objective of this experiment was to determine the amount of BPA extracted by a hand from a standard piece of thermal receipt paper immediately after using Purell hand sanitizer (Experiment 2-A) or with dry hands (Experiment 2-B). Subjects in both experiments cleaned and dried their hands prior to the experiment and between each trial. For Experiment 2-A the subjects (2 men and one woman) each held the thermal paper for different lengths of time: 2, 15, 30, 45, 60 or 240 sec (in 6 separate trials for each subject). Both hands were wetted by applying three “squirts” of Purell to each hand, and the hands were then briefly rubbed together to distribute the hand sanitizer evenly across both palms and fingers, but the sanitizer was not allowed to dry prior to holding the receipt paper. In experiment 2-B the subjects (2 men and 2 women) held the receipt with dry hands for 60 or 240 sec (2 separate trials for each subject). In both experiments an 8 x 12 cm portion of thermal paper cut from an unused receipt roll that was obtained from a local merchant (previously identified as containing 27.2 mg BPA/g paper) was placed BPA-coated (print surface) side
down into the right hand. The hand was swiped 3 times each with
3 ethanol-soaked Kimwipes, and BPA was extracted from the
Kimwipes with methanol and measured by HPLC with CoulArray
detection.

Experiment 3: Serum and urine BPA in men and women
before and after transdermal and oral exposure to BPA
from thermal receipt paper after using hand sanitizer

The objective of this experiment was to measure the transfer of
BPA from thermal paper receipts to hands, and the amount of
BPA remaining on the surface of a hand 90-min later, after using
Purell hand sanitizer (as described in the prior experiment) in 5
male and 5 female subjects. In addition, we measured the amount
of BPA transferred from a BPA-contaminated hand to 10 French
fries, and measured blood and urine concentrations of uBPA,
BPA-G and BPA-S before and after ingestion of the French fries
and BPA absorption through skin. The design of the study is
shown in Figure 2.

The background level of BPA on the dominant hand was
determined when the subjects first arrived at the CRC. The
dominant hand was swiped 3 times with 3 separate Kimwipes
soaked with ethanol, from which we extracted BPA for analysis by
HPLC with CoulArray detection, and the hands were then
cleaned. The subjects' weight and height were determined, after
which they provided a baseline urine specimen, an IV port was
inserted into the cubital vein, and a baseline blood sample was
collected. Purell hand sanitizer was applied to the hands as
described in Experiment 2. An 8×12 cm piece of thermal paper
cut from an unused receipt roll (used in Experiment 2) was then
placed BPA-coated side down into each hand with the hands still
wet. The subjects held the receipt papers for 4 min in each hand.
The dominant arm of each subject was determined based on
whether the person was right or left handed, and in this
experiment the non-dominant hand remained contaminated with
BPA for the duration of the experiment. Blood was collected from
the cubital vein in the contaminated arm of one set of subjects
(N = 7) and from the cubital vein in the non-contaminated arm of
other subjects (N = 3). We note that the phlebotomist did not
handle the thermal paper for either Experiment 3 or Experiment
4. The study coordinator who did handle the paper wore gloves to
do so and did not touch the blood tubes of other equipment. A
separate person swiped the subjects’ hands after thermal paper
exposure and wore fresh gloves for each swipe session and
discarded them immediately afterwards.

French fries that had been purchased from a local fast food
restaurant and had been found to not contain detectable BPA
were briefly warmed in a toaster oven. Immediately after holding
the thermal receipts in each hand, the subjects picked up a French
fry in each hand, and held both fries for 10 sec. The fry held in the
dominant hand was placed into a labeled glass tube, and the fry
that was held in the non-dominant hand was eaten. A total of 10
French fries was handled by each hand and either placed in a test
tube or eaten using this same procedure. Approximately 4 min
elapsed between removal of the receipt paper from the hand and
consumption of the last French fry. Thus, it took about 8 min from
the time that the thermal receipt paper was first touched and
consumption of the last French fry.

After the last French fry was consumed, the subject’s dominant
hand was swiped with 3 ethanol-soaked Kimwipes to clean BPA
off the hand and for determination (by extracting BPA from the
Kimwipes) of the amount of BPA remaining on the hand
immediately after holding the 10 French fries that were placed
into test tubes. The non-dominant hand was not cleaned after
holding the receipt paper and eating French fries, and thus was a
continuing source of transdermal BPA exposure over the following
90-min period of blood collection.

Blood samples were collected from the cubital vein from the still
contaminated arm of 7 subjects, 4 males and 3 females, and from
the uncontaminated arm of 3 subjects, one male and 2 females.
The blood collected from the BPA-contaminated arm provided
direct information about BPA absorbed from the hand on which
BPA remained for 90 min, since the cubital vein is one of the
major veins draining the hand; this blood is not subject to first-pass
liver metabolism prior to going to the heart and being transported
in the arterial circulation to tissues. The blood collected from the
 uncontaminated arm provided information about BPA in the
systemic (mixed) circulation.

Blood was collected from the IV port before holding the thermal
paper (baseline) and at 15, 30, 60 and 90 min after consumption of
the last French fry. The non-dominant contaminated arm (from
which the French fries were eaten) was not allowed to touch
anything during the 90-min after holding the receipt paper and
then picking up the 10 French fries; this hand was swiped with 3
ethanol-soaked Kimwipes after the final 90-min blood collection at
the end of the study. After these swipes were obtained, both hands
were thoroughly cleaned and a second urine sample was collected.

Experiment 4: Serum and urine BPA in men and women
before and after transdermal exposure to BPA from
thermal receipt paper with dry hands

The objective of this study was to examine the amount of BPA
transferred to a clean dry hand and then present in serum and
urine without using hand sanitizer. In this study we examined 12
adult men and 12 adult women subjects. The subjects washed and
dried their hands and provided a baseline blood and urine sample
as described in Experiment 3. The non-dominant hand was
swiped 3 times each with 3 ethanol-soaked Kimwipes to obtain a
baseline measure of BPA on the hand prior to holding a thermal
receipt. After the hand was dry, subjects held an 8×12 cm piece of
thermal receipt paper (from the roll used in Experiment 1) with the
non-dominant dry hand for 4 min. Thirty minutes later a second
blood sample was collected from the contaminated arm, after
which the BPA was swiped from the contaminated hand with
ethanol-soaked Kimwipes as described previously. As above, the
contaminated hand was not allowed to touch anything during the
30-min period prior to the second blood collection. The hands
were washed, and a second urine sample was collected 60 min
after holding the receipt paper.

Results

Experiment 1: Measurement of BPA and BPS in thermal
receipt paper

Thermal receipts were collected at stores, bars and restaurants
in mid-Missouri. Of the 50 receipts, 22 (44%) contained high levels
of BPA (Table 1). High levels of the BPA replacement chemical
BPS were found in 26 (52%) of the receipts, and 2 receipts
contained an unidentified chemical as the print developer [18]; see
Section S2 in File S1 for individual values. These findings suggest
that BPS is now as commonly used as BPA as a developer in
thermal receipt paper. Note that these findings had been obtained
with purchases, while the receipt paper used in Experiments 2, 3
and 4 came from an unused roll of thermal paper that we
determine contained BPA as the developer.
Figure 2. Schematic diagram of the protocol for Experiment 3 in which thermal receipt paper containing BPA was held with a hand wet from using Purell hand sanitizer, after which the subjects picked up 10 French fries and ate them, resulting in both oral and transdermal routes of exposure. Of the 5 male and 5 female subjects, 7 subjects had serum collected from the cubital vein in the arm with a contaminated hand that contained the BPA from holding thermal paper. Three subjects had blood collected from the cubital vein in the unexposed arm that did not have BPA on the hand throughout the 90-min test period during which blood was collected. Urine samples were obtained before and at the end of the test period.

Table 1. BPA and BPS concentrations in 50 thermal paper receipt samples.

<table>
<thead>
<tr>
<th>Chemical in paper</th>
<th>mg/g receipt</th>
<th>mg/8 x 12 cm receipt</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPA-positive (44%)</td>
<td>19.6 ± 1.0</td>
<td>9.0 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>(11.5–26.3)</td>
<td>(6.1–11.3)</td>
</tr>
<tr>
<td>BPS-positive (52%)</td>
<td>23.5 ± 0.7</td>
<td>10.8 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>(15.2–30.1)</td>
<td>(7.1–13.2)</td>
</tr>
</tbody>
</table>

Two (4%) of 50 papers tested did not contain either BPA or BPS and did not show any estrogenic activity in a MCF-7 breast cancer cell proliferation assay (data not shown). Values are mean ± SEM, with the range of measured values given in parentheses. See Section S2 in File S1 for individual receipt data.
Experiment 2: BPA transferred to a hand with and without using hand sanitizer due to holding a thermal receipt for different lengths of time

The data shown in Figure 3-A reveal that after using Purell hand sanitizer with the hand still wet, the maximum amount of BPA swiped from the palm and fingers of the hand (581±19 μg BPA) occurred after holding a receipt for 45 sec. After holding a receipt for 2 sec, 40% (235±19 μg BPA) of maximum was recovered from the hand, and within 15 sec 58% (339±19 μg BPA) of maximum was recovered from the hand. The decrease in BPA swiped from the hand between 45 sec and 4 min to 73% of maximum (425±19 μg BPA) may have been due to absorption into skin occurring at a greater rate than transfer to the skin from the thermal receipt.

The data in Figure 3-B show that holding a thermal receipt with dry hands resulted in dramatically lower amounts of BPA being extracted from the receipt relative to the amounts extracted immediately after using hand sanitizer. The ratio of the extracted BPA swiped from the wet vs. dry hand was higher at 60 sec (ratio = 185) than at 240 sec (ratio = 51), reflecting the fact that while the amount of BPA swiped from a wet hand decreased between 60 and 240 sec, the levels increased over this time when the hand was dry, likely due to a reduced rate of absorption with dry relative to wet hands.

Experiment 3: Serum and urine BPA before and after transdermal and oral exposure to BPA from thermal receipt paper after using hand sanitizer

We measured the amount of BPA swiped from the dominant hand after using hand sanitizer, holding a receipt and then eating 10 French fries, which took 8 min. BPA levels were not significantly different for the 5 males (mean±SEM: 126±19 μg) and the 5 females (mean±SEM: 128±10 μg). These levels measured at about 8-min after first touching the thermal receipt paper were lower than levels measured at 45 sec and 4 min in Experiment 2 (Figure 3-A), which likely reflects rapid transdermal absorption of BPA due to the use of hand sanitizer as well as some of the BPA having been transferred to the French fries. Importantly, females transferred significantly more (58±19 μg) BPA from their dominant hand to the 10 French fries than males (15±3 μg; Mann-Whitney U; P<0.05), resulting in females having a significantly higher oral BPA dose than males between 4–8 min after applying the hand sanitizer.

Since the participants had been instructed to avoid known sources of BPA, such as canned products, and instructed not to touch thermal paper, 9 of the 10 subjects had undetectable BPA on their dominant hand prior to washing their hands when they first arrived at the Clinical Research Center; none of the subjects was a cashier. However, one female had 0.9 μg of BPA extracted from her hand upon arriving at the CRC, and she was also found to have a very high background concentration of serum uBPA (14.3 ng/mL) prior to holding the thermal receipt paper (subject #3; Figure 4-B). This was the only female subject who was menstruating and thus using products to control menstrual flow, and she also indicated use of hand and body lotion 7–9 times in the prior 48 hr, which was more than any other female or male subject (see Section S3 in File S1). However, even though female #3 (Figure 4-B) had very high background serum uBPA, she showed a dramatic 9.5 ng/mL increase relative to baseline in serum uBPA after holding the thermal receipt and eating 10 contaminated fries at the 15 min blood collection time (15 min after consuming the last French fry). The increase relative to baseline in serum uBPA for female #3 was thus virtually identical to the maximum increase (relative to baseline) found for the other 2 females who had low baseline serum uBPA levels and that were tested in the same way (blood was collected from the BPA contaminated arm; Figure 4-A; Table 1).

Experiment 3-A: Collection of blood from the cubital vein in the contaminated arm with BPA remaining on the hand throughout the 90-min test period

The data for female subject #3 are not included in the pharmacokinetic data (Table 2) calculated for the remaining 6 subjects that had blood collected from their contaminated arm but who had undetectable baseline levels of BPA on their hands when they first entered the CRC and also had very low baseline uBPA in serum (0.23±0.15 ng/mL; N=6). These 6 subjects showed a dramatic increase in serum uBPA after holding the thermal receipt...
and eating 10 contaminated fries. Females had a greater Cmax and maximum increase relative to baseline in serum uBPA and BPA-G than males after holding the thermal paper, while males reached peak levels of uBPA (Tmax) later than females. The average uBPA value, based on the area under the concentration-time curve [AUC (0–90 min)] did not differ between males and females, while for BPA-G, the AUC (0–90 min) was greater for females than males. The ratio of BPA-G/uBPA based on the average AUC (0–90 min) was very low (0.35 ± 0.12 for males and 1.82 ± 0.30 for females), consistent with routes of absorption of BPA (dermal and sublingual) that bypass first pass metabolism [19,20].

Only female #3 (Figure 4-A) showed a marked increase in serum BPA-S relative to baseline, revealing that while BPA-G is the major conjugated metabolite of BPA in most men and non-pregnant women, some individuals do form significant amounts of BPA-S. Urine total BPA (unconjugated and conjugated) increased dramatically between baseline and 90 min after handling thermal paper, although unlike the serum data, there was no difference between males and females (Table 2).

**Figure 4. Individual serum profiles of BPA, BPA-G and BPA-MS in men and women prior to (B = baseline levels) and after holding BPA-containing receipt paper for 4 min followed by picking up and eating 10 French fries over about 4 min with a BPA-contaminated hand.** The BPA then remained on the contaminated hand throughout the following 90-min period of blood collection (blood was collected between 15–90 min after eating the last French fry). Panel A: data for serum BPA collected from the contaminated arm with BPA remaining on the hand for 4 males and 2 females that had very low baseline serum uBPA. Panel B: serum BPA data collected from the contaminated arm from Female #3 who had a high baseline serum concentration of uBPA. Panel C: serum BPA data for one male and 2 females who had systemic blood collected from the uncontaminated arm.

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Experiment 3-B: Collection of blood from the cubital vein in the uncontaminated arm to measure BPA in mixed systemic blood throughout the 90-min test period

We also obtained data from 3 subjects who had the same procedures described above except that they had blood collected from the cubital vein in the opposite uncontaminated arm that did not have BPA remaining on the hand during the 90-min period of blood collection. The 3 subjects consisted of one male and 2 females (age 22.3 ± 0.9 yrs, BMI 26.0 ± 0.9). While the baseline serum uBPA levels were very low (Figure 4-C; Table 3), the average serum uBPA AUC (0–90 min) for the two female subjects (Table 3) was similar to the data from the other 7 subjects discussed in Experiment 3-A (Table 2). Even for the male subject with low serum uBPA after holding thermal receipt paper, BPA-G in serum increased between baseline and 90 min (Figure 4-C), and urine total BPA increased dramatically over the 90-min test, similar to the increase in total urine BPA in the women (Table 3). These findings show that high levels of uBPA could be detected in the systemic circulation of subjects after holding thermal receipt paper and eating 10 French fries. Levels of total BPA in urine at
Subjects. Male and female subjects held a single 8 x 12 cm piece of thermal paper BPA was swiped from the surface of the hand: for examinaed this (Figure 3-B). However, 30 min after holding the thermal receipt paper, since we had previously determined on the hands of any subject after washing and drying the hands holding the thermal paper with a dry hand. No BPA was detected unlike the prior experiment, no hand sanitizer was used prior to thermal receipt paper in the non-dominant hand for 4 min, but 26.9 thermal receipt paper with dry hands 2 before and after transdermal exposure to BPA from 5 subjects (Table 2). baseline or 90 min in these 3 subjects (Table 3) were similar to levels measured in the other 7 subjects (Table 2).

Experiment 4: Serum and urine BPA in men and women before and after transdermal exposure to BPA from thermal receipt paper with dry hands

We conducted this study with 12 male (age 27.7 ± 1.6 yrs, BMI 26.9 ± 0.9) and 12 female (age 25.0 ± 1.6 yrs, BMI 25.2 ± 1.5) subjects. Male and females subjects held a single 8 x 12 cm piece of thermal receipt paper in the non-dominant hand for 4 min, but unlike the prior experiment, no hand sanitizer was used prior to holding the thermal paper with a dry hand. No BPA was detected on the hands of any subject after washing and drying the hands prior to holding the thermal receipt paper. We did not determine the amount of BPA transferred to the hand immediately after holding the thermal receipt paper, since we had previously examinaed this (Figure 3-B). However, 30 min after holding the thermal paper BPA was swiped from the surface of the hand: for men (5.5 ± 1.7 µg g range: 0.8–22.5 µg range: 1.3–10.6 µg). There was no difference between males and females in the urine total BPA concentration at baseline or at 60 min, and there was also no difference between total urine BPA at baseline vs. 60 min for either males or females (Figure 5-A). There was a tendency (based on 2-tailed t-tests) for males to have higher serum uBPA at baseline (P = 0.08) and after 30 min (P = 0.06) relative to females (Figure 5-B). While there was no sex difference in conjugated BPA (cBPA), consisting of both BPA-G and BPA-S, at the baseline blood collection (Figure 5-C), at 30 min after holding the thermal receipt males had significantly higher serum conjugated BPA than females (ANOVA; P < 0.001).

Discussion

Our data provide the first evidence that the use of very large amounts of free BPA as a developer on the print surface of thermal paper (~20 mg BPA/g paper) could be an important factor in accounting for the high levels of bioactive serum uBPA and urine total excreted BPA reported previously in various human populations [21]. We conducted this study to mimic aspects of the behavior of people in a fast-food restaurant where we have observed people using hand sanitizer and handling a thermal receipt for variable periods of time prior to picking up and eating food with their hands. In Figure 3 we show that holding a receipt for 45 sec immediately after using a product with dermal penetration enhancing chemicals in the hand sanitizer that we used, and thus transdermal BPA absorption is very rapid due to the penetration enhancing chemicals. The data in Figure 3-A also suggest that a very large amount of BPA is transferred from thermal paper to a hand as a result of holding a thermal receipt for only a few seconds immediately after using a product with dermal penetration enhancing chemicals. The data in Figure 3-A also suggest that transdermal BPA absorption is very rapid due to the penetration enhancing chemicals in the hand sanitizer that we used, and thus

For these subjects blood was collected from the arm draining the hand that remained contaminated with BPA throughout the 90-min period of blood collection. Urine total BPA at baseline and at 90 min are presented as both actual concentration (ng/ml) and creatinine adjusted (ng/g creatinine) values. For the one female (Female 2; Figure 5-B) who had very high baseline serum uBPA (data not included in this table), the average serum AUC (0–90) values for uBPA and BPA-G were 6.05 and 4.49 ng/ml, respectively, and urine total BPA levels at baseline and at 90 min were 0.41 and 41.41 ng/ml, respectively.

For the one female (Female 3; Figure 5-B) who had very high baseline serum uBPA (data not included in this table), the average serum AUC (0–90) values for uBPA and BPA-G were 6.05 and 4.49 ng/ml, respectively, and urine total BPA levels at baseline and at 90 min were 0.41 and 41.41 ng/g creatinine, respectively.

doi:10.1371/journal.pone.0110509.t002

Discussion

Our data provide the first evidence that the use of very large amounts of free BPA as a developer on the print surface of thermal paper (~20 mg BPA/g paper) could be an important factor in accounting for the high levels of bioactive serum uBPA and urine total excreted BPA reported previously in various human populations [21]. We conducted this study to mimic aspects of the behavior of people in a fast-food restaurant where we have observed people using hand sanitizer and handling a thermal receipt for variable periods of time prior to picking up and eating food with their hands. In Figure 3 we show that holding a receipt for 45 sec immediately after using a product with dermal penetration enhancing chemicals resulted in the maximum amount of BPA that was swiped from the palm and fingers (581 µg BPA). After holding the receipt for 2 sec 40% of maximum was recovered from the hand, and within 15 sec 58% of maximum was recovered. Between 45 sec and 4 min, the amount of BPA recovered from the surface of the hand decreased, which may have been due to absorption into skin occurring at a greater rate than transfer to the skin from the thermal receipt. These findings show that a very large amount of BPA is transferred from thermal paper to a hand as a result of holding a thermal receipt for only a few seconds immediately after using a product with dermal penetration enhancing chemicals. The data in Figure 3-A also suggest that transdermal BPA absorption is very rapid due to the penetration enhancing chemicals in the hand sanitizer that we used, and thus

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Parameter</th>
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<th>Female</th>
<th>All</th>
</tr>
</thead>
<tbody>
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<td>Serum uBPA</td>
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<td>90 min (ng/ml)</td>
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<td>90 min (µg/g creatinine)</td>
<td>18.20±5.33</td>
<td>40.93±22.56</td>
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</table>

For these subjects blood was collected from the arm draining the hand that remained contaminated with BPA throughout the 90-min period of blood collection. Urine total BPA at baseline and at 90 min are presented as both actual concentration (ng/ml) and creatinine adjusted (µg BPA/g creatinine) values.

Unconjugated BPA (uBPA) and glucuronidated BPA (BPA-G) pharmacokinetic parameters for 4 male and 2 female subjects who held thermal receipt paper and ate French fries after using hand sanitizer (shown in Figure 5-A).

Table 2. Unconjugated BPA (uBPA) and glucuronidated BPA (BPA-G) pharmacokinetic parameters for 4 male and 2 female subjects who held thermal receipt paper and ate French fries after using hand sanitizer (shown in Figure 5-A).
measurement of BPA swiped from the surface of the hand likely underestimates the actual amount of free BPA transferred from the print surface of thermal paper. We note that since the thermal receipt paper is sold in rolls, the non-print surface has BPA transferred to it from the print surface (Figure 1). By swiping the two surfaces with ethanol on Kimwipes, the print surface was found to contain an 8.7-fold greater amount of BPA relative to the non-print surface of the thermal receipt paper roll used in these experiments (data not shown).

In both men and women there was a dramatic increase in serum uBPA after using hand sanitizer with dermal penetration enhancing chemicals and then holding thermal receipt paper and eating French fries with the BPA-contaminated hand (Figure 4-A and 4-B). While the sample size was small, our data suggest higher maximum serum levels (Cmax) for females and a greater maximum increase relative to baseline for both uBPA and BPA-G (the primary conjugated BPA metabolite) for females relative to males (Table 2). This finding was related to a greater transfer of BPA from the hand to the French fries and thus a greater oral dose (by about 4 fold) in females relative to males. However, we cannot rule out that the skin of females also allows greater transdermal transport of BPA relative to males due to sex differences in skin permeability [13]. In fact, our data are consistent with the hypothesis that a combination of both transdermal and buccal/sublingual absorption (Figure 2) resulted in the dramatic increase in both serum uBPA (Figure 4-A and 4-B) and total BPA excreted in urine (Table 2). The profile of serum uBPA suggests that females absorbed BPA more rapidly than

Table 3. Unconjugated BPA (uBPA) and glucuronidated BPA (BPA-G) pharmacokinetic parameters for one male and two female subjects who held thermal receipt paper and ate French fries after using hand sanitizer (shown in Figure 5-C).

<table>
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<th>Analyte</th>
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<tr>
<td>Serum uBPA</td>
<td>Baseline (ng/ml)</td>
<td>0.06</td>
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<td>Cmax (ng/ml)</td>
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<td>15.00–60.00</td>
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<td>Average AUC (0–90 min) (ng/ml)</td>
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<td>3.47±0.06</td>
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<td>Serum BPA-G</td>
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<td>Cmax (ng/ml)</td>
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<tr>
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<td>Average AUC (0–90 min) (ng/ml)</td>
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<td>Urine Total BPA</td>
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<td>Baseline (µg/g creatinine)</td>
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<td>90 min (ng/ml)</td>
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<td>90 min (µg/g creatinine)</td>
<td>27.35</td>
<td>14.11±1.16</td>
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For these subjects mixed systemic blood was collected from the uncontaminated arm over the 90 min after BPA exposure. Urine total BPA at baseline and at 90 min are presented as both actual concentration (ng/ml) and creatinine adjusted (µg/g creatinine) values.

doi:10.1371/journal.pone.0110509.t003

Figure 5. BPA in urine and serum of 12 men and 12 women who held thermal receipt paper with dry hands for 4 min, Panel A: the total concentration of BPA in urine (expressed relative to creatinine) at baseline and 60-min after holding the thermal receipt. Panel B: unconjugated BPA (uBPA) in serum at baseline and 30 min after holding the thermal receipt. Panel C: conjugated BPA (BPA-G and BPA-S) in serum at baseline and 30 min after holding the thermal receipt paper. * = significant difference between males and females (P<0.001).

doi:10.1371/journal.pone.0110509.g005
males (Figure 4-A), consistent with females having a shorter time to reach the maximum serum level (Tmax) of uBPA (Table 2). The later Tmax in men than in women is consistent with men having a thicker stratum corneum (the outermost layer of the epidermis) relative to women [22,23]. In addition to skin thickness, another possible explanation for the sex differences we observed (Table 2) would be a greater use of skin moisturizers in females than in males, which could impact both the transfer of BPA to the hand from the surface of thermal paper as well as transdermal absorption of BPA. Our finding that males tended to have higher serum uBPA and had significantly higher serum conjugated BPA than women at 30 min after holding a receipt with a dry hand (Figure 5-B and 5-C) requires further study, since the more rapid absorption of BPA found for women after using hand sanitizer (Figure 4-A and 4-B) would have been missed at the 30-min blood collection time.

For the 3 females that had blood collected from the cubital vein in the same arm with the BPA contaminated hand (Figure 4-A and 4-B; Table 2), the maximum increase in serum uBPA relative to baseline (≈10 ng/mL) was about two-times greater than the maximum increase found in the other two females whose blood was collected from the opposite uncontrolled arm (≈5 ng/mL; Table 3; Figure 4-C). This difference between blood collected from a vein draining the contaminated hand vs. blood from the opposite uncontaminated arm (reflecting uBPA in the systemic circulation) suggests that a substantial amount of uBPA in blood from the contaminated arm was due to the BPA that was transdermally absorbed before its mixing in the general circulation. Our data from the cubital vein draining the contaminated hand that had BPA remaining on it for 90 min thus support the hypothesis of a higher arterial than mixed venous blood BPA concentration during the dermal absorption phase in the framework of a physiologically based pharmacokinetic (PBPK) model [24]. The hypothesis that served as the basis for collecting blood from the same arm in which BPA was being absorbed is that a portion of the BPA contaminated blood would be transported from the contaminated hand through the cubital vein and then to the heart. Subsequently, the contaminated blood would enter the arterial circulation and be transported to the tissues in the body, including endocrine target tissues. This leads to the prediction that during the dermal absorption of BPA, the BPA concentration in arterial blood is likely more relevant to consider in terms of exposure than the BPA concentration in the mixed venous blood, because blood in a vein draining the contaminated hand is not subjected to clearance by enzymes in the liver prior to reaching endocrine target tissues in arterial blood.

When examining all of our data for serum unconjugated and conjugated BPA, we show significant inter-subject variability in the absorption and clearance of BPA (Figure 4), which was also previously found for the estrogenic drug used in oral contraceptives, ethinylestradiol [25]. A particular concern is that there are individuals who have limited capacity to excrete BPA or other estrogenic compounds; one population at risk is patients with early-stage or advanced kidney disease [26,27].

The default method of administration of chemicals to animals by regulatory agencies is by intra-gastric gavage, regardless of how the chemical is used or whether there are known non-oral routes of exposure [28]. It is thus not surprising that US and European regulatory agencies [29,30] have modeled human exposure to BPA based on results from intra-gastric gavage administration of BPA to animals, which results in direct transport of BPA to the liver via the mesenteric vessels and extensive first-pass metabolism (detoxification) in the liver (Figure 2); the result is less than 1% of the gavage administered dose being bioavailable in blood [19,31]. However, Gayrard et al. [19] found high absorption and bioavailability (~70%) of BPA following sublingual administration that was dramatically different than the much lower bioavailability (<1%) of BPA following gavage administration in a parallel experiment. These findings directly challenge predictions that it is not possible to find the high blood levels of biologically active uBPA that have actually been measured in numerous human biomonitoring studies [21,32] but are currently being rejected for use in risk assessments by the US-Food and Drug Administration (US-FDA) as not plausible [31].

In contrast to the extremely high ratio of BPA-G to uBPA (>100:1) predicted by gavage exposure studies due to rapid phase 2 metabolism in the liver, the average ratio of BPA-G to uBPA in our Experiment 3 was 0.84±0.33 based on the average AUC (0–90 min) for the 6 subjects with blood collected from the arm with the contaminated hand (Figure 5-A; Table 2); this ratio was also low for the subjects with systemic blood collected from the uncontaminated arm (Table 3). These findings indicate that the primary route of BPA exposure was not via gastrointestinal absorption after eating the BPA-contaminated French fries, since this ratio would be predicted to exceed 100:1 [31,33]. One reason may have been that, in addition to transdermal absorption, the BPA transferred to the French fries would have been on the surface of the fries and thus easily absorbed by the highly vascularized epithelium in the mouth [19].

In the present study we measured total BPA in urine to be able to relate our findings to a very large epidemiological literature showing BPA in urine to be correlated with abnormal development and diseases in children and adults [5,34]. The geometric mean for adults in the 95th percentile for total BPA in urine reported in NHANES 2003/4 was about 11 μg/g creatinine [2] and the range of values at the 95th percentile include values we measured here. Periodically, BPA levels exceeding those we found are reported in studies that measured BPA in urine [21], and it is possible that those assays are of people who had very recently been exposed to BPA in a manner similar to our experiment.

Our findings thus provide evidence regarding how some people could be found to have very high urine levels of BPA. Importantly, the amount of total BPA in urine was ~20 μg BPA/g creatinine (~20 ng/mL urine uncorrected for creatinine). This high level of urine total BPA collected 90 min after using hand sanitizer and holding a thermal receipt (Table 2 and Table 3) has been associated with a significant increase in the likelihood of developing cardiovascular disease and type 2 diabetes [35,36]. BPA levels in human urine have also been related to a wide range of other diseases in over 60 human epidemiological studies [5,34]. Published findings include: reproductive effects in women (polycystic ovary syndrome, altered ovarian response to hormones, reduced fertilization success, implantation failure, endometrial disorders, reduced embryo quality, miscarriage, premature delivery and breast cancer), reproductive effects in men (reduced libido, sperm quality, altered sex hormone concentrations and embryo quality), altered thyroid hormone concentrations, obesity, impaired liver function, impaired immune and kidney function, inflammation, and neurobehavioral deficits such as aggressiveness, hyperactivity and impaired learning [3,34]. The estimate of the costs per year of additional cases of just cardiovascular disease in the USA attributable to BPA is 1.5 billion dollars [37].

In a study that involved handling thermal receipts (without using hand sanitizer) continuously for 2 hr, which would be relevant for a cashier, there was a significant increase in urine total BPA relative to baseline [38]. This finding is consistent with prior data that cashiers have higher levels of BPA in urine than the general public [39]. Blood concentrations of BPA were not
determined in these studies, and they also did not take into account that perhaps 50% of the receipts handled may have contained BPS rather than BPA (Table 1). The results of these studies indicate that with repeated handling of thermal receipts in an occupational setting, even without the use of hand sanitizer, there is a significant increase in BPA exposure. Future studies involving handling of thermal paper need to include analysis of the thermal paper to determine if the developer used is BPA or some other chemical. Related to the issue of occupational exposure to BPA is our observation that at least one big-box store in Columbia, Missouri provides hand sanitizer dispensers for use by all cashiers, and our data suggest this can not only markedly increase transfer of BPA from the thermal paper to hands but also increase transdermal absorption of BPA.

Our findings that thermal receipt paper is a potential source of high exposure to BPA are supported by data showing that BPA readily leaches from thermal receipts and thus likely contaminates anything that a receipt contacts. Thus, environmental contamination caused by the use of unpolymerized (free) BPA in thermal paper is widespread [7]. The dermal penetration enhancing chemicals present in personal care products as well as hand sanitizers cause a breakdown of the dermal barrier leading to an increase in transdermal absorption [8,9]. While BPA was reported to be absorbed through pig and human skin in vitro [40], our data show after holding a receipt for 60 sec, there was 185-times more BPA transferred to a wet hand due to holding thermal receipt paper immediately after using hand sanitizer with penetration enhancing chemicals as opposed to when the hands were dry (Figure 3). The specific mixtures of chemicals used in products will impact transdermal exposure to environmental chemicals such as BPA [8,9], and additional research is needed to determine the degree to which alcohols and other chemicals impact exposures. This is important because when soap and water are not available, hand sanitizers are recommended to reduce infectious disease transmission [http://www.cdc.gov/handwashing/when-how-handwashing.html]. It is also important to determine the length of time after using skin-care products with dermal penetration enhancing chemicals that there is an impact on absorption of environmental contaminants.

The issue of assay performance is obviously very important and was examined using a round robin validation process in Europe for a number of chemicals, including BPA, which identified that some laboratories were able to accurately assay uBPA and other chemicals without contamination, while other laboratories were unable to assay uBPA or other chemicals accurately [41]. Importantly, our findings reported here are based on measurement of uBPA with a sensitive, validated, contamination-free LC/MSMS assay. Specifically, our laboratory is one of three in the U.S. that recently successfully completed a NIH-sponsored round-robin measuring uBPA in human serum [17]. In addition, in the present experiment, the time course of blood uBPA concentrations after a controlled BPA exposure in our university Clinical Research Center (Figure 4) is not consistent with any spurious contamination; this conclusion was also supported by the use of field blanks. It is thus clear that the prediction that any finding of uBPA in human serum must be due to sample contamination [31] is not valid, even though a few investigators report being unable to control BPA contamination in their assays [42,43]. Supporting our conclusion is a report from the CDC in which sources of contamination were identified and systematically eliminated during the successful development of assays for BPA and three other chemicals [44]. The issue of the potential for assay contamination is thus not unique to BPA and simply requires the use of standard assay procedures and appropriate controls that should be routinely employed.

Conclusions

Thermal paper requires a chemical in the surface coating as a print developer. The current preferred developers, BPA and BPS, have both been shown to have estrogenic activity [45,46]. This is leading to widespread exposure to both of these endocrine-disrupting chemicals [7,47], and BPS is more persistent in the environment relative to BPA and is thus an unacceptable replacement for BPA [18,48]. A recent EPA report examined 19 alternative chemicals, including BPS, that could potentially replace BPA as a developer in thermal paper and concluded that “No clearly safer alternatives to BPA were identified in this report; most alternatives have Moderate or High hazard designations for human health or aquatic toxicity endpoints” [18]. The report identified that “decision makers may wish to consider alternative printing systems”. Two of the papers screened for our current study employed a developer other than BPA or BPS that was not estrogenic in a MCF-7 human breast cancer cell proliferation assay (data not shown), but lack of estrogenic activity does not imply safety, as indicated in the EPA report.

Thermal paper is a major source of BPA contamination in recycled paper, and its use results in the widespread contamination of other products and the environment [49] due to the presence of large amounts of free, unpolymerized BPA in the surface coating of thermal paper (Figure 1). Further, our findings are consistent with other data reporting that BPA can be transferred from the surface of thermal paper to items it contacts. Because no safe alternatives to the use of BPA or its primary replacement chemical BPS in thermal paper have been identified, our findings provide support for the EPA’s recommendation that thermal paper should be replaced with other safer technologies [18].

Our study provides the first data that thermal paper may be a significant factor in accounting for high levels of bioactive BPA in human serum and total BPA in urine that have been associated with diseases that are increasing in frequency in human populations [21,34]. Our findings also suggest that the impact of the use of dermal penetration enhancing chemicals in skin care products on transdermal absorption of environmental contaminants should be taken into consideration in risk assessments and should be a priority for future research.

Supporting Information

File S1 Section S1: Sample handling, extraction and assay methods. Section S2: Table of individual BPA and BPS values for 50 thermal receipt papers. Section S3: List of questions asked each subject.

Author Contributions

Conceived and designed the experiments: FVS AMH JAT. Performed the experiments: AMH JAT CLM. Analyzed the data: JAT PLT RWS MRE FVS. Contributed reagents/materials/analysis tools: FVS. Contributed to the writing of the manuscript: FVS AMH CLM JAT SCN WWV PLT RWS.
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How irritant is alcohol?
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Summary

Background Alcohol-based hand rubs are used worldwide to prevent transmission of nosocomial pathogens.

Objectives To investigate skin irritation caused by alcohols alone and in combination with detergent washing.

Methods Single and repetitive patch testing with 60–100% alcohols [ethanol, 1-propanol, 2-propanol (synonyms: isopropyl alcohol, isopropanol)], a positive control [0–5% sodium lauryl sulphate (SLS)] and negative controls (empty chamber and water) were performed. Wash tests were performed with 80% ethanol and 0–5% SLS on the forearms with each agent alone and with both agents in a tandem design. Skin hydration, erythema and barrier disruption [measured as transepidermal water loss (TEWL)] were evaluated (always 15 volunteers).

Results We found no significant change in skin barrier or erythema induced by the alcohols in the patch tests, whereas skin hydration decreased significantly. Application of alcohols to previously irritated skin did not show a stronger skin barrier disruption than application of SLS alone. Wash tests demonstrated that alcohol application caused significantly less skin irritation than washing with a detergent (TEWL, P < 0.001; skin hydration, P < 0.05; erythema, P < 0.05). Even on previously irritated skin, ethanol did not enhance irritation. By contrast, a protective effect of ethanol used after skin washing was observed (TEWL, P < 0.05; skin hydration, P < 0.05; erythema, P < 0.05).

Conclusions Alcohol-based hand rubs cause less skin irritation than hand washing and are therefore preferred for hand hygiene from the dermatological point of view. An alcohol-based hand rub may even decrease rather than increase skin irritation after a hand wash due to a mechanical partial elimination of the detergent.

Millions of healthcare workers perform hand disinfection with alcohol-based hand rubs several times daily. Their efficacy for control of nosocomial infection led to widespread U.S. government endorsement. The assumption of poor skin toler- ance, however, remains a major reason for low compliance rates. ‘Hand hygiene’ may lead to irritation and hand eczema. The prevalence of eczematous hand lesions in medical staff remains between 20% and 40%. The nursing and related professions (employees in the healthcare system) have up to a six times increased risk for occupational dermatitis. Irritant contact dermatitis is frequently observed in these occupations and is widely accepted as unavoidable. Even a mild interdigital eczema can be an important sign for future hand eczema on which microbes can grow more easily. Irritant skin changes in healthcare employees are undoubtedly caused by frequent wet work and contact with detergents. Nevertheless, ‘hand hygiene’ procedures are often quoted as important pathogenic factors for the development of hand dermatitis.

When the irritant effect of alcohol on the skin has been evaluated, most authors found low toxicity. By contrast, many healthcare workers complain about unacceptable skin irritation caused by alcohol-based hand rubs. Even in the Guideline for Hand Hygiene in Healthcare Settings of the Centers for Disease Control, skin tolerability of alcohol-based hand rubs is stated as potentially problematic: ‘Although alcohols are among the safest antiseptics available, they can cause dryness and irritation’.

The assumed irritation due to alcohol-based hand antiseptics may hold up their wide use, especially in the U.S.A. This study, therefore, evaluates the irritant potencies of the relevant

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types of alcohols alone and in sequence with use of a detergent in a highly standardized test design (patch test) as well as in a more realistic standardized wash test.

Materials and methods

Study population and design
A total of 105 healthy volunteers without skin diseases (49 women and 56 men, age range 18–52 years, mean ± SD 32 ± 8.2) participated. Atopic individuals were excluded. Written informed consent was obtained, and the study was approved by the ethical committee of the University of California San Francisco (CA, U.S.A.) and the University of Marburg (Germany). The study was performed in a multicentre design in San Francisco, U.S.A., and Marburg, Germany. Subjects were instructed not to apply topical ‘leave-on’ products such as lotions or creams to the test sites for 1 week prior to study. Before the measurements began, the volunteers rested in the test room for acclimatization for at least 30 min.

Test procedure

Two different tests were performed: the repetitive occlusive patch test (Fig. 1) and the wash test.

Repetitive occlusive patch test

The repetitive occlusive patch test consists of two occlusive applications of substances on the same test area (tandem application), each lasting 24 h. Sixty microlitres of the test solution was pipetted in large Finn Chambers (Epitest, Helsinki, Finland; inner diameter 12 mm) and applied for 24 h on the back. After removal of the patch, the test area was marked and a further patch (with the same agent or with another agent) was subsequently applied on the same area for another 24 h. The removal of the second patch was performed at 48 h; evaluation was conducted before the first application (0 h) and after 72 h (hence, substance-nonspecific alterations of measurements due to occlusion could be minimized). Each group consisted of 15 volunteers, and an empty chamber and a distilled water chamber were used as controls. Alcohols (> 99% purity) were supplied by Bode Chemie GmbH & Co. KG (Hamburg, Germany); sodium lauryl sulphate (SLS, > 99% purity) was supplied by Sigma Chemicals (St Louis, MO, U.S.A. and Munich, Germany).

Part 1 consisted of repetitive applications of the same patch: ethanol, 1-propanol or 2-propanol (synonyms: isopropyl alcohol, isopropanol), each in the concentration of 60%, 70%, 80%, 90% and 100% (ethanol 99%).

Part 2 consisted of repetitive applications of alcohol patches (ethanol 80%, 1-propanol 60% and 2-propanol 70%, analogous to the concentrations used in commonly used alcohol-based hand rubs, followed by SLS 0.5% patches and vice versa. SLS 0.5% and an empty chamber served as controls.

Wash test

Procedure 1: SLS wash test. This standardized wash test was performed on the forearm: a foam roller (Lehnartz, Remscheid, Germany) was soaked with SLS 0.5% and moved 10 times within 1 min up and down on the volar forearm. Then, the roller was soaked again with test solution and the whole procedure was repeated for altogether five times. At the end, the forearm was rinsed with clear tap water and dried carefully with a paper towel. For each washing procedure 50 mL of test solution was used. In two groups (see below) tap water was used instead of SLS.

Procedure 2: disinfection test. For simulation of hand disinfection with an alcohol-based hand rub, the procedure was basically identical to the SLS wash test, except that alcohol was allowed to air dry on the skin between each treatment.

Procedure 3: combination of hand washing and disinfection. In this procedure the forearm was washed and dried first and disinfected thereafter. Therefore, a surgical hand disinfection was mimicked.

The described procedures were performed twice daily for 7 days with evaluation on day 0 (baseline: before the first procedure), on day 8 and after 2 days of skin recovery on day 10. In each test group, a comparison between two different procedures (each of them on one forearm) was performed by a randomized assignment of a procedure to one forearm.

The following groups were tested: (i) ethanol 80% alone (procedure 2) vs. SLS 0.5% alone (procedure 1); (ii) ethanol 80% alone (procedure 2) vs. SLS 0.5% followed by ethanol 80% (procedure 3); (iii) SLS 0.5% (procedure 1) alone vs. SLS 0.5% followed by ethanol 80% (procedure 3); (iv) SLS 0.5% (procedure 1) followed by tap water (procedure 1) vs. SLS 0.5% followed by ethanol 80% (procedure 3) after 2 days of skin recovery.
0.5% followed by ethanol 80% (procedure 3); and (v) ethanol 80% alone (procedure 2) vs. tap water alone (procedure 1).

**Biometrics**

Bioengineering measurements of transepidermal water loss (TEWL), skin hydration and erythema were performed. TEWL was evaluated with a Tewameter TM210 (Courage & Khazaka, Cologne, Germany; Acaderm, Menlo Park, CA, U.S.A.). During the TEWL measurements, the probe was hand held by use of an insulating glove until a stable TEWL value was established (~1 min). Air convection was prevented by reducing movements and talking in the test room. Temperature and humidity were recorded (20–22 °C, 40–55% relative humidity). The results were evaluated according to the guidelines for TEWL measurement by the Standardization Group of the European Society of Contact Dermatitis. Each TEWL test value consisted of the mean of two single measurements.

Skin hydration was evaluated with a Corneometer CM 920 (Courage & Khazaka; Acaderm); each test value was attained by taking the mean of five single measurements. Erythema was measured with a Chromameter CR 300 (Minolta, Osaka, Japan); during measurement the light in the test room was dimmed, and each test value was attained by taking the mean of five single measurements.

**Subjective sensations**

After the washing procedure each volunteer estimated his/her subjective sensations of dryness, itching and burning on a visual analogue scale ranging from 0 to 10. The full length of the scale was defined as the subjective maximum sensation; each participant marked the degree of his/her individual sensation on the scale. We measured the length between 0 and the marked point for each sensation.

**Statistics**

Statistical analysis was performed using SPSS software version 11.5 (SPSS, Chicago, IL, U.S.A.). The results of the bioengineering measurements were calculated regarding their symmetrical distribution with the Kolmogorov–Smirnov test. Because they showed a symmetrical distribution, the values are shown as mean ± SD. Differences between the bioengineering values of each test procedure were calculated regarding significance by means of the paired, two-sided Student’s t-test. Statistical significance was accepted when \( P \leq 0.05 \).

**Results**

**Patch tests**

**Alcohols alone**

We noticed a significantly decreased skin hydration induced by alcohols compared with the empty chamber and the water chamber (Fig. 2). This decrease tended to be stronger with ethanol and 1-propanol than with 2-propanol. Remarkably, decreased hydration seemed less pronounced at higher alcohol concentrations. No significant change from the negative controls was seen regarding erythema (chromameter values) and skin barrier (TEWL values) at all patches (data not shown).

**Alcohols and sodium lauryl sulphate**

When SLS 0.5% was applied in a tandem test design with the alcohols or controls, no significant change was found for skin hydration (\( \Delta \) skin hydration = difference between SLS + alcohol and SLS + empty chamber) for any sequence. A different picture was observed for TEWL and erythema. The highest \( \Delta \)TEWL and \( \Delta \)erythema were found with a tandem application of SLS (Table 1). A single SLS application followed by an empty chamber (control) significantly increased TEWL. Replacement of the empty chamber with any of the three alcohols revealed a similar \( \Delta \)TEWL. When SLS was applied in the second patch after a preceding empty chamber (control) or a preceding patch with any of the three alcohols, \( \Delta \)TEWL was also in a similar range.

**Wash tests**

**Ethanol 80% vs. sodium lauryl sulphate 0.5%**

As shown in Table 2, there was a significant increase of barrier disruption, a lower skin hydration and a greater erythema at the forearm washed with the detergent compared with the disinfected forearm at the end of the treatment period (day 8). Although a stabilization of the skin physiology was seen 2 days later, the SLS-treated side was still more affected.

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washing, all skin physiological parameters were significantly
increased by water barrier disruption, decreased skin hydration and increased erythema) than disinfection alone. This effect was also apparent on day 10 but with diminished values (Fig. 3b). Subjective sensations were stronger on the SLS-treated side.

**Ethanol 80% vs. sodium lauryl sulphate 0.5% followed by ethanol 80%**

The combination of washing and disinfection caused significantly greater impairment of all evaluated physiological skin parameters (increased barrier disruption, decreased skin hydration and increased erythema) than disinfection alone. This effect was also apparent on day 10 but with diminished values (Fig. 3b). Subjective sensations were stronger on the SLS/ethanol side, especially regarding dryness and itching.

**Sodium lauryl sulphate (SLS) 0.5% vs. SLS 0.5% followed by ethanol 80%**

The skin physiology evaluated by water barrier disruption, skin hydration and erythema was clearly affected by washing with SLS. When the skin was disinfected with ethanol after washing, all skin physiological parameters were significantly less influenced by the combination than by the washing procedure alone. Therefore, the skin was less irritated by washing and disinfection compared with washing alone (Fig. 3c). By contrast, there were moderate subjective sensations, especially on the SLS/ethanol side, regarding burning and dryness.

**Sodium lauryl sulphate (SLS) 0.5% followed by water vs. SLS 0.5% followed by ethanol 80%**

Both procedures led to comparable skin physiology changes. A tendency towards a pronounced decrease of skin hydration was seen with the combination of SLS with ethanol but this did not reach the level of significance. However, there were no significant differences between both forearms at 8 or 10 days (Table 2). Although there were only moderate subjective sensations, the number of burning sensations at the SLS/ethanol side was higher.

**Ethanol 80% vs. water**

Forearm disinfection with ethanol led to similar changes in skin physiology as did washing with water alone. There was a

| Table 1 | Changes in transepidermal water loss (TEWL), skin hydration and erythema (mean ± SD) after tandem application of various hand hygiene agents in a repetitive occlusive patch test design |
|--------------------------------------------------|---------------------------------|----------------|----------------|
| **Type of treatment** | **ΔTEWL** | **ΔSkin hydration** | **ΔErythema** |
| SLS 0.5% followed by empty chamber (control) | 23.0 ± 8.6 | -5.6 ± 9.0 | 5.2 ± 2.3 |
| SLS 0.5% followed by SLS 0.5% | 40.9 ± 12.5** | -1.6 ± 10.7 | 7.4 ± 3.2* |
| Empty chamber followed by SLS 0.5% | 18.2 ± 8.9* | -0.4 ± 10.1 | 3.6 ± 6.3** |
| Empty chamber followed by SLS 0.5% (control) | 16.2 ± 9.3 | -3.2 ± 15.8 | 4.9 ± 2.1 |
| Ethanol 80% followed by SLS 0.5% | 17.3 ± 11.1 | -3.6 ± 7.8 | 3.1 ± 2.2 |
| 1-propanol 60% followed by SLS 0.5% | 15.1 ± 7.5 | -4.4 ± 10.1 | 3.6 ± 2.6 |
| 2-propanol 70% followed by SLS 0.5% | 14.3 ± 8.5 | -0.1 ± 11.8 | 2.8 ± 1.9** |

SLS, sodium lauryl sulphate. The difference between side A and side B is significant at *P < 0.05 or **P < 0.001.

| Table 2 | Changes in transepidermal water loss (TEWL), skin hydration and erythema (mean ± SD) after tandem wash tests with hand hygiene agents; procedures were performed on the forearms (side A and side B), and Δ-values (difference from basal values on day 0) are shown |
|--------------------------------------------------|---------------------------------|----------------|----------------|
| **Substance/procedure** | **ΔTEWL** | **ΔSkin hydration** | **ΔErythema** |
| Side A Ethanol 80% | 3.9 ± 4.0** | 1.5 ± 1.1** | -6.8 ± 5.8 | -3.2 ± 6.1 | 0.6 ± 0.6* | 0.4 ± 0.4* |
| Side B SLS 0.5% | 9.7 ± 5.6** | 6.1 ± 2.1** | -10.1 ± 6.1* | -5.8 ± 7.2 | 1.8 ± 1.6* | 0.9 ± 1.1* |
| Side A Ethanol 80% | 2.4 ± 1.0** | 1.1 ± 3.4** | -7.7 ± 3.5* | -3.5 ± 3.6* | 0.6 ± 0.3* | 0.1 ± 0.4 |
| Side B SLS 0.5% followed by ethanol 80% | 8.0 ± 4.0** | 4.1 ± 2.0** | -11.7 ± 5.2* | -6.4 ± 6.1* | 1.0 ± 0.5* | 0.4 ± 0.5 |
| Side A SLS 0.5% | 9.9 ± 5.1* | 6.8 ± 3.4* | -10.6 ± 4.6* | -5.9 ± 5.6* | 2.1 ± 1.2** | 1.0 ± 0.9* |
| Side B SLS 0.5% followed by ethanol 80% | 6.9 ± 3.3* | 4.7 ± 2.3* | -6.6 ± 5.8* | -2.8 ± 6.3* | 1.2 ± 0.9** | 0.5 ± 0.6* |
| Side A SLS 0.5% followed by water | 7.9 ± 9.1 | 4.9 ± 5.8 | -7.2 ± 6.3 | -5.4 ± 5.1 | 1.7 ± 1.5 | 0.3 ± 0.5 |
| Side B SLS 0.5% followed by ethanol 80% | 8.6 ± 6.4 | 5.2 ± 4.3 | -9.6 ± 5.8 | -4.5 ± 5.7 | 1.6 ± 1.4 | 0.6 ± 0.6 |
| Side A Ethanol 80% | 1.6 ± 2.1 | 0.6 ± 1.3 | -3.5 ± 8.2 | -1.9 ± 8.5 | 0.1 ± 0.6 | -0.2 ± 0.9 |
| Side B Water | 1.5 ± 2.0 | 1.2 ± 1.7 | -1.1 ± 7.5 | -0.1 ± 9.7 | 0.2 ± 0.8 | -0.2 ± 1.5 |

SLS, sodium lauryl sulphate. The difference between side A and side B is significant at *P < 0.05 or **P < 0.001.
tendency on day 8 and 10 towards a pronounced decrease of skin hydration caused by ethanol, but these changes were not significant. At day 10 (3 days after completion of the washing) the values were nearly normal. Subjective sensations were not different between the two sides.

**Discussion**

Ethanol, 1-propanol and 2-propanol lead to only minor skin barrier changes (comparable with those with water or the empty chamber) and no changes in erythema independent of the concentration tested. This is a first indication that these substances are not important irritants when the contact duration is limited, and supports previous findings.14,15 In contrast, detergents can (depending on their type and concentration) induce relevant barrier disruption and inflammation even after a single patch test.22 A decrease of skin hydration can also be observed after the application of alcohols even in the occlusive patch test design, with the strongest decrease with 1-propanol, followed by ethanol; the smallest decrease was observed with 2-propanol. With a single 24-h application, decreased skin hydration was not detected (data not shown). There is a tendency towards a greater decrease of skin hydration perceivable at the lower concentrations of ethanol and 1-propanol. These differences are small; we currently have no explanation for this phenomenon. However, our results demonstrate the ability of epicutaneously applied alcoholic substances to reduce skin hydration, as described earlier.23–26 It was not possible to induce detectable irritation (barrier disruption or erythema).

Fig 3. Bioengineering changes (mean ± SD) caused by wash procedure with (a) ethanol 80% vs. sodium lauryl sulphate (SLS) 0.5%, (b) ethanol 80% vs. SLS 0.5% followed by ethanol 80%, or (c) SLS 0.5% vs. SLS 0.5% followed by ethanol 80%. Differences between both procedures were significant at *P < 0.05 or **P < 0.001, with SLS inducing a stronger irritation (a), SLS/ethanol inducing a stronger irritation (b) and SLS alone inducing a stronger irritation (c).
feature of ethanol. We did not detect an increase in erythema, in accordance with results from studies in which no or only minor irritant potency is described after application of an alcohol-based hand rub,13–16,17–22 which can be further reduced by addition of emollients.33,34 In our model skin hydration was moderately reduced by ethanol treatment, slightly more than by tap water. By contrast to ethanol, the detergent SLS induced a much stronger barrier disruption and a pronounced skin hydration decrease, despite the fact that the concentration of the detergent was low (0.5%), which was emphasized by the moderate increase of erythema. In our view ethanol has only a low irritancy which is clinically relevant only regarding its potential for reducing skin hydration.

The most interesting question remains the ability of alcohol-based hand rubs to induce skin damage when applied on previously irritated skin as described previously.15 The hands of healthcare workers are often previously irritated because of wet work and the occlusive milieu of gloves.3,5 Because alcohol-based hand rubs are sometimes used after hand washing (classic procedure of surgical hand antisepsis), the combination of washing with a detergent and disinfection may be a crucial point in occupationally induced hand dermatitis.

First, we investigated the influence of a repetitive tandem application on skin physiology with patch tests. Consequently, ethanol, 1-propanol and 2-propanol were applied before or after an SLS patch. Remarkably, no increase of irritation was induced when the alcohol (regardless of which) was applied after the SLS patch. This demonstrates that the detergent-induced skin irritation, detected by barrier disruption, decrease of skin hydration and increase of erythema, was not exacerbated by these alcohols. Even after the combined application, skin hydration was not different from that following use of the detergent alone. When the application order was reversed (first an alcohol patch then the SLS patch), the degree of irritation remained the same. Hence, no alcohol impaired the skin physiology such that the following detergent induced a greater irritation. In this feature, all three types of alcohols are different from several other (including physical) irritants, which enhanced skin reaction induced by a detergent in a tandem patch test design as shown previously.35–38 We confirmed the finding of Kappes et al., who demonstrated that 1-propanol did not enhance the cumulative skin irritation when used after SLS,39 and we can furthermore extend their results to 2-propanol and ethanol.

The relevant question remains, however, if the detergent-induced irritation can be exacerbated by a subsequent application of ethanol. Surprisingly, all skin physiological parameters evaluated were less impaired by the combination of SLS with ethanol compared with SLS alone. This suggests that application of ethanol after hand washing may reduce irritant skin changes caused by washing. Similar results were shown in a short test protocol by Pedersen et al.40 They used commercial products in an intensive repetitive application test over 2 days and also detected diminished irritation induced by the combination of washing and disinfection compared with washing alone. It was uncertain whether this protective effect was due to different amounts of detergents applied, or to the glycerol which was added to the disinfection solution.40 In our study, we demonstrated that the combination of SLS washing with subsequent ethanol treatment induced similar skin irritation as the combination of SLS washing with subsequent water treatment. Hence, the protective effect is most likely to be caused by a washout of detergent molecules which are on and in the stratum corneum and which may lead to a prolonged skin irritation.41 This washout can be achieved with similar results by ethanol or water treatment. The important finding of this study is that alcohols used in hand rubs did not induce further skin irritation. Contrarily, disinfection may even reduce irritation caused by detergents, which might be an important element in the concept of early prevention.42

Why do so many healthcare employees believe that alcohol-based hand rinses are strong irritants and that these substances lead to hand dermatitis? One reason is the fact that alcoholic solutions induce burning sensations (sensory irritation) at previously irritated skin. This was observed by our volunteers especially in the groups in which SLS treatment was followed by ethanol. In these groups, irritation was induced by SLS and the subsequently applied ethanol could possibly penetrate more easily to sensory nerve endings. However, despite the fact that the application caused sensory discomfort, the physiology of the skin was not altered. Healthcare employees, however, will blame the alcohol-based product for this discomfort and not the underlying disturbed barrier function.12,43 The consequences are obvious: the probably harmless disinfection procedure will be neglected and increasingly replaced by further hand washing. This does not lead to immediate discomfort, but will exacerbate the skin condition in a vicious circle.44 Burning after the use of alcohol-based hand rubs should probably be recognized as a sign for an already disturbed skin barrier and for an impending hand dermatitis. Chew and Maibach summarize the extensive recent literature on irritation that may be beyond this mechanism.45 Based on our results, the influence of longer and exaggerated (20 times every day) use of alcohols and different aspects of tandem effects, as well as the effect on individuals with an increased risk of hand dermatitis (e.g. atopic individuals) should be investigated in detail.

Our study is of relevance for all medical staff, because it demonstrates the good skin compatibility of three alcohols frequently used in alcohol-based hand rubs and underlines the known problematic skin compatibility of detergents and hand washing. Promotion and education (most effectively during clinical training) may individually be necessary to encourage the use of alcohol-based hand rubs.15,42,46 Moreover, the visibly improved skin condition after the regular use of alcoholic hand disinfection may encourage healthcare employees to change their behaviour.2,15,34,37,38

The advantages of alcohol-based hand disinfection compared with hand washing regarding its bactericidal efficacy are obvious. Because there is evidence that hand washing before disinfection may decrease rather than increase bactericidal efficacy of the combined procedure, reduction of hand washing
may be recommended not only from the skin physiological point of view but also for hygienic reasons. We do not wish to overgeneralize the results and understand the difficulties of extrapolating from 100 volunteers to millions of users. Yet the data provided by these highly controlled observations offer the foundation for epidemiological investigations and further investigations such as methods of decreasing sensory irritation.

Acknowledgments

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References

INNOCUITÉ DES PHA

RAPPORT AFSSAPS
05 JANVIER 2010
Relatif à l’innocuité des produits hydro-alcooliques (PHA) à base d’éthanol utilisés pour la désinfection des mains à peau saine par le grand public dans le cadre de l’épidémie de la grippe A (H1N1)

Fait suite à l’Avis du 28 Septembre 2009
CONTEXTE

- Pandémie grippale : virus A H1 N1
- Recommandations Ministère de la santé
  - Hygiène des mains par lavage eau + savon
  - Hygiène des mains par friction hydro-alcoolique
- Réflexion menée par AFSSAPS pour le grand public (en particulier femme enceinte et enfant)
• Des désinfectants pour les mains
• Produits biocides de type 1
• 2 formes recommandées : solutions et gels
• Exclues : lingettes et mousses désinfectantes
• PHA largement diffusées depuis 10 ans
Dangers liés à l’éthanol

- Dangers reconnus dans les boissons alcoolisées
- Fondées sur études épidémiologiques chez l’homme lors d’ingestion.
- ABSENCE DE DONNEES pertinentes par voie inhalée ou cutanée, même lors des expositions professionnelles (AFSSET, 2009, à paraître)
Exposition par voies cutanée et inhalée lors de l’utilisation des PHA

- Recommandations de la SFHH : définition du volume nécessaire :
  habituellement  1,5 à 3 ml
- Etudes de la littérature : 1,2 à 4 ml
- Voie cutanée :
  › Étude Brown (2007), mesure lors d’utilisation intensive
    De faibles quantités éthanol peuvent être absorbées (haleine)
  › Étude Kramer (2007): étude sur 3 PHA en teneur différente : 79,2% des échantillons en dessous de la limite de détection (0,5 à 2,3% d’éthanol est absorbé).
Rappel : seuil d’alcoolémie toléré au volant est de 0.5 g / litre

Conditions maximales expérimentales, non réalistes pour le grand public sauf mésusage

Notion éthanolémie endogène (de 0 à 35.2 mg/l) : jus de pomme par exemple
Etude par Kinnula (2009), pédiatrie Finlande:

- 82 enfants, 3.5 à 7 ans, résultats en dessous du seuil de détection pour les 2 groupes test (dose de PHA 1.5 et 3 ml)
- Questionnaire montre que 74% utilisent PHA (eau + savon si mains visuellement sales) et 13% se lavent les mains à eau + savon avant la friction avec PHA
Exposition par inhalation

- **Etude (rapport AFSSET 2009, à paraître)**
  - milieu professionnel, local peu ventilé
  - 2 frictions par IDE (3ml sur 1 mn) avec produit à 80% éthanol, puis 60% éthanol
  - Valeurs atmosphériques mesurées : pic et valeur de base de 30mg/m³ = pollution ambiante pour utilisation régulière PHA
  - Ethanolémie très faible : 1.28 mg/l
Tolérance aux PHA

- PHA à base d’alcool mieux tolérés chez les professionnels de santé
- Dessèchement cutané possible à forte concentration ➙ agent hydratant associé
- Si peau humide ➙ risque d’irritation (SFHH); efficacité moindre
- Risque allergique très faible (OMS, 2009)
- Pas d’étude sur peau abîmée mais non conseillé avant restauration de la barrière cutanée
Précautions d’emploi des produits hydro-alcooliques

- Prévenir le risque de projection oculaire chez l’enfant
- Prévenir le risque d’ingestion (proscrire les produits à base d’arômes), fabrication à partir d’alcool dénaturé
Chez les professionnels, éthanolémie induite par exposition intensive aux SHA extrêmement faible voire quasi nulle.

Pas de risque sanitaire supplémentaire identifié par l’AFSSAPS, dans des conditions normales d’utilisation chez l’homme

Pas de nécessité de poursuivre une évaluation spécifique du risque chez la femme enceinte et l’enfant

Utilisation des PHA sur peau saine++ et sèche
Récommandations grand public

- Référence : avis de l’Afssaps du 28/09/09
- Mains à peau saine, épidémie grippe A
- 2 procédures applicables
  - Lavage des mains eau et savon
  - Produits hydro-alcooliques
    - en seconde intention, sur des mains non souillées
    - en l’absence de point d’eau
    - en environnements collectifs
    - en conditions normales d’utilisation
L'évolution des techniques d’hygiène des mains, grâce à la mise à disposition des produits hydro-alcooliques (PHA), a joué un rôle déterminant dans l’amélioration de l’observance de l’hygiène des mains. Si ces produits sont plus efficaces et mieux tolérés que les savons antiseptiques, ils sont également plus simples d’utilisation et plus accessibles (disponibilité au lit du patient/résident, disponibilité en flacon individuel, ne nécessitant pas d’installation de point d’eau, ...) [1].

Toutefois, les rumeurs et les attaques récurrentes dont certaines relayées par les médias sur les risques sanitaires que représenteraient l’exposition chronique c’est à dire régulière aux PHA instillent de la méfiance, de la suspicion ... et entraînent naturellement des questionnements de la part de soignants quant à l’innocuité de ces produits qu’on leur demande d’utiliser de manière pluriquotidienne dans le cadre de leur activité professionnelle.

Toutes ces allégations génèrent des doutes et sont probablement un frein à l’utilisation des PHA par les professionnels de santé. Cet état de fait est d’autant plus délétère que l’hygiène des mains par friction avec un PHA est un des piliers majeurs de la stratégie de prévention des infections associées aux soins.

L’objectif de ce document est donc de répondre de manière factuelle et argumentée aux questions récurrentes posées sur les PHA afin d’éclairer les personnels de santé.

Pour argumenter les réponses, différentes sources d’informations valides ont été exploitées :
- Revue de la littérature scientifique
- Consultation de rapports :
  - Innocuité des produits hydro-alcooliques à base d’éthanol utilisés par le grand public dans le cadre de l’épidémie de la grippe A(H1N1). Agence nationale de sécurité des médicaments et des produits de santé (AFSSAPS), 2011
  - Evaluation des risques de l’éthanol en milieu professionnel. Agence nationale de sécurité sanitaire alimentation, environnement, travail (ANSES), 2010
- Interrogation de différentes structures :
  - du centre antipoison de Strasbourg,
de l’Institut national de recherche et de sécurité pour la prévention des accidents du travail et des maladies professionnelles (INRS),
• du Centre international de recherches sur le cancer (CIRC).

La présentation des résultats est réalisée comme suit : l’argumentaire est développé après chacune des interrogations exprimées de manière récurrente.

Résultat

L’EXPOSITION CHRONIQUE (=REGULIERE) AUX PHA CONSTITUE-T-ELLE UN RISQUE POUR LA SANTE DES PROFESSIONNELS DE SANTÉ?

1.1. L’ABSORBTION CUTANEE ET INHALATOIRE DE L’ALCOOL CONTENU DANS LES PHA REPRESENTE-T-ELLE UN RISQUE POUR LA SANTE DES PROFESSIONNELS DE LA SANTE DANS LES CONDITIONS NORMALES D’UTILISATION, NOTAMMENT CHEZ LES PERSONNES FRAGILES (femme enceinte ou en contact avec des nouveau-nés) ?

L’absorption percutanée ou respiratoire des PHA a fait l’objet de plusieurs travaux. Extrêmement faible, l’absorption n’atteint dans aucune étude un seuil préoccupant et les auteurs sont souvent obligés de faire appel à des techniques plus sensibles que les dosages de routine pour doser les produits absorbés [2]. L’absorption par voie cutanée ou inhalée de l’éthanol, survenant lors des frictions des mains de manière «intensive» avec des PHA (1 application toutes les 20 minutes pendant 6 heures), est extrêmement faible, voire quasi nulle. Quel que soit la voie d’exposition (cutanée ou inhalée), les concentrations observées se situent dans l’intervalle de variation des valeurs d’éthanolémie endogène (= que le corps fabrique naturellement). Il n’y a pas de contre-indication à l’utilisation des PHA par la femme enceinte ou un professionnel s’occupant de nouveau-nés. La réalisation des frictions à distance du nouveau-né peuvent être proposées pour ne pas perturber la mobilisation des compétences olfactives du nouveau-né lors des mises au sein.

➔ Sur la base des données disponibles, l’Afssaps en 2011 n’a pas pu identifier un risque sanitaire supplémentaire cancérigène, reprotoxique ou neurotoxique, consécutif à l’exposition à l’éthanol contenu dans les produits hydro-alcooliques, dans les conditions normales d’utilisation chez l’homme et quel que soit la voie d’absorption (cutanée ou inhalée) [3].

1.2. L’EXPOSITION CHRONIQUE AUX PHA AUGMENTE-T-ELLE LE RISQUE D’HÉPATITE CHEZ LES PROFESSIONNELS DE SANTE ?

En 2010, le RFCLIN avait sollicité l’Institut national de recherche et de sécurité pour la prévention des accidents du travail et des maladies professionnelles (INRS) et le centre antipoison de Strasbourg concernant la toxicité prétendue des PHA. Cette sollicitation était motivée par une rumeur qui circulait en Franche-Comté d’un cas d’hépatite attribuée à une intoxication avec les PHA.
Si un tel événement avait été confirmé, ce cas aurait été documenté, rapporté dans la littérature et signalé dans le cadre du dispositif national de pharmacovigilance. Or, le centre antipoison de Strasbourg n’en avait pas connaissance et aucune alerte AFSSAPS n’avait été publiée.

A la suite de notre sollicitation, l’INRS avait formulé la réponse suivante le 14 avril 2010 : « Les études effectuées pour réaliser l’évaluation des risques en milieu de travail (dont la problématique des PHA) ont montré que l’exposition cutanée et inhalatoire liée à cette activité n’augmente pas de façon significative l’éthanolémie endogène physiologique des sujets. Il nous paraît donc peu probable qu’une telle exposition puisse à elle seule provoquer une hépatite. Nous attirons bien sûr votre attention sur le fait que ces solutés ou gels ne sont pas tous à base d’éthanol et qu’il s’agit souvent de préparations ou mélanges. De plus, les professions de soins peuvent être sujettes à des hépatites autres que toxiques (viraux notamment). »

Au final, il n’est pas possible que l’exposition aux PHA soit à l’origine d’une hépatite alcoolique dans les conditions normales d’utilisation de ces produits.

1.3. L’UTILISATION DE PHA PAR DES PERSONNES, Dont DES PERSONNELS DE SANTE, AYANT DES ADDICTIONS À L’ALCOOL ANCIENNES OU EN COURS NE LEUR EST-ELLE PAS PREJUDICIALE ?

Il n’y a pas de contre-indication formelle à l’utilisation de PHA par ces populations. En revanche, dans ces circonstances, un échange avec le médecin du travail est à encourager pour privilégier le PHA le moins odorant et le moins incommodant. Dans les services d’addictologie accueillant des patients en cure de désintoxication, cette même réflexion devrait être menée au cas par cas.

1.4. QU’EN EST-IL DE LA TOLERANCE CUTANEE AUX PHA CHEZ LES PROFESSIONNELS DE SANTE ?

Le recours fréquent au lavage des mains est un facteur important d’irritation cutanée. Différents travaux ont prouvé que l’utilisation de PHA améliorait autant la sécheresse cutanée mesurée objectivement que la sensation subjective de sécheresse ou d’irritation [4, 5].

Les PHA sont destinés à être utilisés sur peaux saines. De manière générale, les PHA sont bien tolérés sauf dans les cas suivants :

- application sur peau abîmée : dans ce cas, une sensation de brûlure immédiate peut être constatée,
- application sur une peau humide : elle peut augmenter l’irritation. Si un lavage des mains est requis, il est impératif d’attendre complet avant de procéder à l’application d’un PHA.
  Remarque : pour les personnels ayant un antécédent d’allergie aux parfums → privilégier des PHA sans parfum [3].

Dans le guide de la SF2H publié en 2009, il est rappelé qu’en France, on observe une évolution de la composition des PHA qui sont fabriqués de plus en plus souvent à base d’éthanol moins irritant que le propanol ou l’isopropanol [2]. Les auteurs rappellent également que la tolérance cutanée est surtout bien corrélée à la teneur en glycérine, agent protecteur le plus répandu [2,
et que l’association systématique dans ces produits d’un agent hydratant ou de glycérine, limite l’irritation due à l’éthanol [3].

→ Au final, de nombreux rapports confirment que les formulations des PHA sont bien tolérées et souvent associées à une meilleure acceptabilité et une meilleure tolérance cutanée que les autres produits utilisés pour l’antisepsie des mains [7].

1.5. QUEL EST LE RISQUE D’ALLERGIE LIE AUX PHA ?

Pour ce qui concerne le risque d’allergie lié aux PHA, les travaux plaident pour un risque extrêmement faible. Cependant, les personnes ayant un antécédent allergique aux parfums devraient privilégier des PHA sans parfum, parfum dont le risque allergénique est connu. Les PHA avec parfum ne sont normalement plus disponibles sur le marché.

Dans tous les cas, cela doit être discuté avec le service de santé au travail. Il n’est pas rare que des professionnels rapportent une notion d’intolérance ou d’allergie mais après observation des pratiques, cela relève souvent d’une mauvaise utilisation et notamment la réalisation de friction hydro-alcoolique sur des mains humides. Un accompagnement et une formation permettent dans ce contexte de redéfinir les conditions d’utilisation correctes des PHA.

→ Au final, le risque d’allergie aux PHA est rare. Il est donc important de demander aux soignants de rapporter au médecin du travail tout signe évocateur d’irritation et/ou d’intolérance. Ce signalement permettra de documenter l’événement en lien avec un service de dermatologie et d’adapter la conduite à tenir au cas par cas. Dans la majorité des cas, corriger une pratique non conforme (utilisation sur mains humides) permet de maîtriser le désordre.

1.6. LES PHA SERAIENT DANGEREUX POUR LA SANTÉ, CAR ILS FAVORISERAIENT L’ABSORPTION PAR LA PEAU DE BISPÉNOL A, UN PERTURBATEUR ENDOCRINIEN NOCIF, QU’EN EST-IL ?

En 2015, Les résultats de l’étude expérimentale d’Hormann et al. ont été largement relayés et parfois déformés dans les medias grand public, lançant une polémique. L’objectif de cette étude était de monter un éventuel effet des PHA sur l’absorption du bisphenol A, l’hypothèse étant que les PHA la favoriseraient [8].

Le Dr Pierre PARNEIX, président de la société française d’hygiène hospitalière, a répondu à cette allégation en 2015 : « Les nombreux articles publiés sur cette étude laissent penser que les PHA contiendraient du bisphénol A, un perturbateur endocrinien, or pas du tout. En réalité, les chercheurs ont demandé dans ce cas précis aux volontaires de mettre une grosse dose de gel antibactérien sur leurs mains sans exercer de friction, puis leur ont collé un ticket de caisse dessus et observé si du bisphénol A (contenu dans ces bouts de papier) pénétrait dans la peau au bout de quatre minutes.

Expérimentalement, cette étude n’a pas vraiment de sens, d’une part parce que les mains mouillées à l’eau favorisent également l’absorption de bisphénol A et d’autre part car on ne met jamais une quantité aussi élevée de solution hydro-alcoolique sur les mains et enfin, parce que
personne ne tient un ticket de caisse les mains mouillées ou recouvertes de solution hydro-alcoolique pendant quatre minutes.

**Le danger, c’est le bispéhénol, pas le gel antibactérien.**

D’ailleurs, la France a interdit l’utilisation du bispéhénol dans les emballages des produits alimentaires et de nombreuses grandes enseignes ont éliminé ce composé de leurs tickets de caisse suite à l’action menée par la ministre de l’Écologie.

En créant une alerte autour d’un produit et en le détournant complètement de son usage normal, l’étude est contraire aux bonnes pratiques d’utilisation des solutions hydro-alcooliques.

*Ce gel est en effet devenu une technique de référence en établissement de santé. Grâce à son utilisation dans les services, on augmente le taux d’observance et on baisse le taux d’infections, notamment les infections nosocomiales comme le staphylocoque doré. C’est aujourd’hui un élément crucial pour assurer des soins de qualité. »*


2. **EST-IL POSSIBLE DE COMMANDER DES PRODUITS POUR L’HYGIENE DES MAINS INNOVANTS, COMME, PAR EXEMPLE, CEUX À BASE VÉGÉTALE ET SANS ALCOOL ?**

Il est fortement recommandé pour le choix des produits d’hygiène des mains pour le traitement hygiénique des mains par friction de n’accepter que des produits répondant à certaines normes (NF EN 1040, NF EN 1275, NF EN 1500 +/- EN 14476) [2].

Les normes d’activité exigées des produits sont reprises sur le guide de la SF2H de 2009 et sont mentionnées sur la fiche technique des produits. Les établissements doivent donc être vigilants à ces critères d’éligibilité des produits lors de leur achat.

3. **AU REGARD DU CRITÈRE H3-INFLAMMABLE DE L’ÉTHANOL NOTAMMENT, QUELLE EST LA FILIÈRE DE PRISE EN CHARGE DE FLACONNAGES DE PHA SELON QU’ILS CONTIENNENT DES RESTES, RÉSIDUS DE PRODUIT OU N’AYANT PAS FAIT L’OBJET D’UN RINÇAGE SÉCURISÉ ?**

Les flacons ne doivent pas être rincés. Les flacons vides ou contenant un volume faible sont éliminés dans la filière des déchets assimilables aux ordures ménagères (DAOM). En revanche, si les flacons sont encore remplis, ils doivent suivre la filière des déchets chimiques.

d’une cigarette par exemple. Aucun incendie n’a eu lieu dans les aires de stockage, ni à cause de l’électricité statique.

⇒ Même si les PHA sont inflammables, le risque d’incendie lié à ces produits est très faible. Il est cependant important de les mettre à l’écart de toute flamme ou source de chaleur ou d’étincelles [10,11].

4. QUELS SONT L’INTÉRÊT ET LA PERTINENCE DE L’INDICATEUR ICSHA, S’AGISSANT D’UN MARQUEUR INDIRECT QUI PEUT REFLÉTER L’APPROPRIATION DE CETTE TECHNIQUE DE DÉSINFECTION DES MAINS PAR LES PROFESSIONNELS DE SANTÉ MAIS PAS NÉCESSAIREMENT ?

L’ICSHA est un indicateur défini au niveau national dont la publication est opposable aux établissements de santé. Le programme national d’actions de prévention des infections associées aux soins (Propias) 2015 indique la mise en place d’un indicateur de consommation dans les 2 autres secteurs de l’offre de soins (secteur médico-social et soins de ville) [12].

La pertinence de cet indicateur est cependant souvent discutée, en particulier parce qu’il est un marqueur indirect de la mise en œuvre effective de l’hygiène des mains dans les établissements de santé. Comme le rappelle la SF2H dans le guide « Recommandations pour l’hygiène des mains, juin 2009 », d’autres indicateurs complémentaires peuvent être développés au sein des établissements : suivi de l’observance des prérequis à l’hygiène des mains (mesure de l’absence de port de bijou, ongles courts, absence de vernis...), la réévaluation de protocoles, des audits de pratiques ...

Il appartient à chaque établissement de créer ses propres indicateurs de suivi complémentaires. Le croisement des informations permet ainsi d’avoir une appréciation la plus complète et fidèle possible du niveau de respect des bonnes pratiques d’hygiène des mains et une lisibilité sur les pistes et actions d’amélioration à privilégier.

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