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Is skin irritancy of the hand wash products solely related to their pH?

SUMMARY

Background: It is undeniable that diligent and effective hand hygiene will assist in reducing the spread of potentially harmful pathogens. There are many active ingredients to select from including but not limited to alcohols, parachlorometa-xylenol (PCMX), 2,4-dichlorophénoxyphénol (Triclosan) and even new hydrogen peroxide mixtures. To be credible, each product with its designated active ingredient must demonstrate antimicrobial activity according to the local regulatory requirements in order to make such claims.

Often, the mix and levels of the active ingredients in competing products are identical. So manufacturers have resorted to differentiation of their respective products through fragrance, packaging format, price and most notably the 'skin friendly' profile, which is determined based on an estimated frequency of hand decontamination by healthcare professionals. It is also often implied by manufacturers that the pH of the product must be neutral (~6 to 7) to be considered mild and non-irritating to skin over prolonged use. This study was designed to dispel this long-held notion through a scientific examination of the effects of pH of a given solution on skin.

Methods: Five formulations were tested for their dermal irritation. Ten healthy subjects (Laboratory IDEA-France) were tested to validate the innocuousness of hand cleansing lotions whose pH had been adjusted to 3 or 10, using strong and weak acids and bases.

Results: Formulations tested herein at pH of 3 or 10 were found to be non-irritating.

Conclusions: This study shows that pH cannot be considered as the sole criterion in determining the irritancy of handwash formulations.

INTRODUCTION

Many cosmetic and hygiene products have an acidic pH (alpha hydroxy-acid-based creams for instance) or an alkaline pH (soaps for example). Is this enough to consider them as potentially irritant to the skin? Or, are there other factors that contribute to the skin irritation of these products?

The circumstances surrounding the development of dermatitis are complex but do not involve any immunological mechanism.[1] The level of skin irritation is generally linked to numerous factors such as the chemical structure of components (acids, alkali, oxidants, reductors, solvents, chelators, surfactant, etc.), their concentration, the contact time, the skin area, the skin's integrity, the environmental conditions (temperature, hygrometry) and so forth.

The typical symptomatology is represented by the appearance of a local inflammatory reaction (vasodilatation of micro-blood vessels with redness, œdema, pain and itching), which might evolve, in extreme cases, towards skin necrosis.[1]

The purpose of this study was to demonstrate that an acidic or alkaline pH in itself does not mean that a given preparation will be irritating to the skin.

IRRITATION/ CORROSION THEORY

To better understand the skin irritation or corrosion's process, we need to take into account the following criteria:

- The mechanism of the chemical reaction.
- Activation energy required by these reactions.
- Influence of the aggressive chemical's electron balance.

For the skin to be damaged, a contact between the xenobiotic and the organism is required.[2]

During the chemical reaction, corrosives and irritants exchange electrons with the skin components (lipids, sugars, amino acids, enzymes, mineral salts). This concept is called 'donor-acceptor electron exchange' where the chemical and the skin components can alternatively play the role of electron donor or acceptor. This exchange involves six types of aggressive chemical reactions: acidic, alkaline, oxidation, reduction, chelation (calcium or magnesium) and solvatation.[2]

Ions for acido-alkaline reactions, electrons for oxido-reduction reactions, or parts of molecules (addition-substitution) are exchanged between the aggressive chemical and the skin components.[2]

In this study, corrosive and irritant substances such as acids and alkali will be developed by using the concept of pK or dissociation constant or, in other words, the real skin corrosion/irritation potential brought by acids or alkali.

pH (in log) is the relative measure of the activity of hydrogen ions H^+ in a given solution:

$$pH = -\log [H^+]$$

Thus, pH 2 means that the concentration in H^+ ions is 10^{-2}.

The pK, or dissociation constant, represents the capacity of a chemical to dissociate in water to liberate H^+ ions, in the case of acids, or OH^- ions in the case of alkali.

For an acid, for which the dissociation constant is K_a, the reaction with water will be:

$$HA + H_2O \rightarrow A^- + H_3O^+$$

$$\Longrightarrow Ka = \frac{[A^-] \bullet [H_3O^+]}{[AH]}$$

$$\text{and} \quad pKa = -\log Ka$$

As can be seen from the above equations, the stronger the acid, the lower the pK_a.

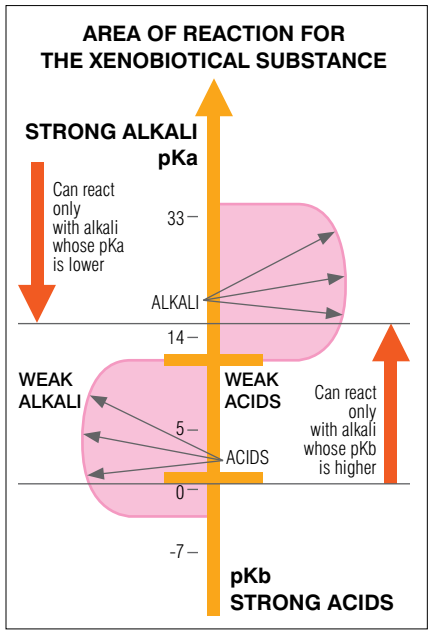
It can also be demonstrated in the same way that the stronger the alkali, the higher the pK_b.

Strong acids have a pK_a inferior to 0 and strong alkalis have a pK_b superior to 14 since they dissociate completely in water while weak acids and alkali are only partially dissociated.

The concept of pK explains why the pH cannot really be taken into consideration to evaluate the irritation or corrosive potential of a preparation. At a given pH, the quantity of liberated H^+ or OH^- ions may be important (the preparation will be irritant or corrosive) or not (depending on the concentration and/or the contact time, the preparation might be slightly irritant or perfectly well tolerated) [3,4].

The following figure shows the possible reaction between acids and alkali[3].

Figure 1. Acid-alkali reactions



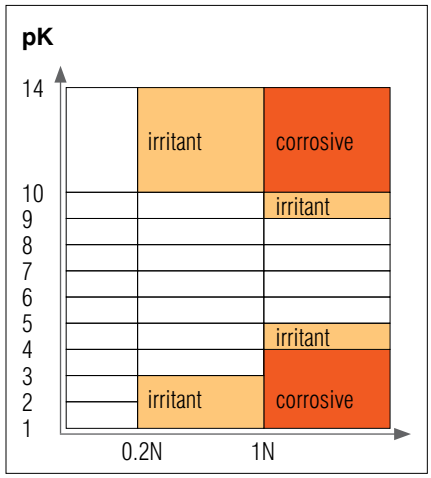
Based on Figure 1, it is easier to understand that a given acid AH is going to react with the alkali B, which has a higher energy value and, if it is sufficiently concentrated, it will also react with all alkali situated between B and A; A being the conjugate base of the acid AH. Of course, this principle also applies to alkali.

The irritant or corrosive potential of an acidic or alkaline preparation may be predicatively evaluated taking into account the pK and the concentration of the components responsible for the pH; the contact time is also a factor which determines the kinetic and the intensity of the dermatological reaction.

Studies on the eye proved that an acidic or an alkaline solution at a concentration inferior to 0.2N has absolutely no corrosive or even irritant action on the eyes.[5]

The following figure[6] shows that an acidic or a basic solution with a pK ≤3 or > 10, but at a low concentration (0.2 to 1N), will be irritant only.

Figure 2. pK and concentration correlation with irritation and corrosion



At concentration ≥ 1N, the solution will be irritant for intermediate pK (4 to 5 or 9 to 10).

And, for pK 5 to 9 and whatever its concentration, the solution will have no effect on eyes.

To illustrate this notion even better, we should remember that certain foodstuffs, such as sodas, lemon juice and vinegar have a pH between 2 and 3. These foodstuffs are obviously in frequent contact with the mouth and mucous membranes.

MATERIALS & METHODS/ CLINICAL STUDIES

It has been shown, by the means of a study involving 10 healthy subjects (Laboratory IDEA – France), to validate the innocuousness of hand cleansing lotions whose pH have been adjusted to 3 or 10 using, respectively, one weak acid (lactic acid), one strong acid (hydrochloric acid), one weak base (sodium carbonate) and one strong base (sodium hydroxide) whose respective pK are given in Tables 1 and 2. The formulation of the hand cleansing lotion is described in Table 3.

This is an *in vivo* 48h single patch-test method. In this test, a dose of 0.02 ml of test-product, pre-diluted at 2% in distilled water, was applied on the skin of one arm and maintained in contact for 48 hours with a semi-occlusive plaster, in order to maxi-

Table 1. The chemical structure of acids used in this study

ACIDS	CHEMICAL STRUCTURES	pK_a
Lactic acid	$CH_3 - CH(OH) - COOH$	3.08
Hydrochloric acid	HCl	< -2.00

Table 2. The chemical structure of alkalis used in this study

ALKALI	CHEMICAL STRUCTURES	pK_b
Sodium carbonate	$CH_3 - CH(OH) - COOH$	6.00 10.33
Sodium hydroxide	NaOH	> 14.00

Table 3. The formulation of the hand cleansing lotion

INGREDIENTS (INCI)	% (w/w)
AQUA	Qsp 100.00
TRIDECETH-10	7.00
PEG-33 CASTOR OIL	3.00
CAPRYLGLUCOSIDE 2.00	
PEG-200 HYDROGENATED GLYCERYL PALMATE (and) PEG-7 GLYCERYL COCOATE	2.00
ACID or ALKALI	To make up to pH 3 or 10

mize the potential effects. In all cases, the concentration of acid or base really in contact with the skin was about 0.05 to 0.11N. Obtained diluted solutions of test-products had a pH of 3.00 +/- 0.05 or 10.00 +/- 0.05.

Ten healthy female and male subjects (with normal skin) were 18 to 65 years old and did not suffer from any dermatological disease.

The clinical score measurement, 30 minutes after the plaster removal, took into account the redness, oedema and blistering. Depending on the intensity of the skin reaction, the score ranges from 0 to 4. The sum of the scores, divided by the number of subjects, defines the Medium Irritation Index (M.I.)[7], which allows us to classify the test-products according to the table 4.

RESULTS

In-vivo test results showed that there is no irritation for any of the samples. Table 5 shows that all samples have medium irritation index of zero, which classifies them as non-irritant.

Table 4. Medium Irritation Index Classification

M.I.I. ≤ 0.20	Non irritant
0.20 < M.I.I. ≤ 0.50	Slightly irritant
0.50 < M.I.I. ≤ 2.00	Moderately irritant
2.00 < M.I.I. ≤ 3.00	Very irritant
M.I.I. > 3.00	Extremely irritant

Table 5. Summary of irritation test results for test solutions

PRODUCTS	A.I.I.	RESULTS
Formulation pH 3 (lactic acid)	0.00	Non irritant
Formulation pH 3 (hydrochloric acid)	0.00	Non irritant
Formulation pH 10 (sodium carbonate)	0.00	Non irritant
Formulation pH 10 (sodium hydroxide)	0.00	Non irritant

CONCLUSIONS

The perception for product safety is that if the pH of a product is not neutral, it will be an irritant and/or corrosive. In this study, it was shown that this perception is not true. The formulations at pH of 3 and 10 were non-irritating in these experiments.

Thus, for weak acids and alkali, as well as for diluted strong acids and bases (< 0,2N), the quantity of H^+ or OH^- free ions will still be too low to react with the epidermal amino acids and provoke the production of irritation inducers. The pH must not be the only criteria used to predict the potentially irritant character of a cosmetic preparation; lots of ingredients (surfactants, preservatives, perfumes…) have an intrinsic irritating power independent of their pH. Their chemical structure, as well as their concentration, must be taken into account during the formulation process and during the toxicological investigations, which are run before launching the products on the market. ●

LITERATURE CITED

1. F. Testud *« Pathologie toxique en milieu du travail»*. Edition Alexandre Lacassagne, 1993.
2. F. Burgher, J. Blomet, L. Mathieu *« Le risque chimique et la santé au travail»*. Edition Prévor Valmondois, 1996.
3. J.L. Antoine, J.L. Contreras, D.J. Van Neste *« Dermatosen in beruf und umwelt »* Band 1989, 37, 3, 96-100.
4. Nangia, P.H. Andersen, B. Berner and I. Maibach *« High dissociation constants (pKa) of basic permeants are associated with in vivo skin irritation in man »*. Contact Dermatitis. 1996, 34, 237-242.
5. Reim M, Schmidt-Martens FW, Horster B, Scheidhauer E. *«Morphologische und biochemische befunde bei experimentellen verätzungen mit alkali»*. Ber Dtsch Ophtalmol Ges 77; 749-759, 1980.
6. F. Burgher, L. Mathieu, J. Blomet *« Fiches de Données de Sécurité – Prévention du risque chimique – Outil pratique d'interprétation »*. Edition AFNOR, 2004.
7. Docteur Pascale DENIS-KANDEL, Protocole n° 1.01 48H 05/04, Evaluation de la tolérance cutanée d'un produit cosmétique après application unique sous pansement occlusif pendant 48 heures, (sous contrôle médical), 1er décembre 2005.