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Dermatologic reactions to disinfectant use during the COVID-19 pandemic

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Abstract Infection preventive practice of using disinfectants against SARS-CoV-2 has become the new normal due to the COVID-19 pandemic. Although disinfectants may not be applied directly to the human body, it remains at high risk of exposure including close skin contact on disinfected surfaces or during handling. This dermal contact, on a regular basis, can induce hazardous skin reactions like irritation, inflammation, and burning in severe conditions. Disinfectants are germicide chemicals that can penetrate the skin and create skin reactions that are usually regarded as irritant and allergic contact dermatitis. More importantly, disinfectants can react with skin components (proteins and lipids) to facilitate their skin penetration and disrupt the skin barrier function. Whereas the antimicrobial actions of disinfectants are well understood, much less is known regarding their dermatologic reactions, including but not limited to irritation and hypersensitivity. We reviewed the skin reactions created by those disinfectants against SARS-CoV-2 approved by the European Chemical Agency and the US Environmental Protection Agency.

Introduction

The emergence of a novel coronavirus (SARS-CoV-2) at the end of 2019 was declared as a global pandemic by the World Health Organization (WHO) on March 11, 2020.[1] The alarming situation has triggered the practice of preventive actions that include the use of various disinfectants to sanitize the environment and to reduce the spread of infections. Owing to unawareness and inadequate experience in handling disinfectants among the public, this may cause an inappropriate use of disinfectants, which can create untoward events. Our skin is, thus, at risk of exposure to disinfectants, especially during handling, storage, and application. Even though direct contact with disinfectants may not be often established, the risk of skin contact to the chemical residuals on disinfected surfaces remains high, especially when disinfectant use has become a routine practice.

Disinfectants are small and moderately lipophilic molecules (molecular weight <500 Da and log P ~1 to 4), which can penetrate the skin to induce a direct skin reaction. Skin reactions to various disinfectants can be wide, ranging from inflammation, lichenification, to discoloration, and even necrosis. Disinfectants are germicidal by definition and can react with epidermal keratin filaments and lipids, similar to reactions created by many antimicrobials to the lipid membrane and protein structure of microorganisms. These actions can facilitate skin penetration of chemicals into the deeper skin layers to aggravate any adverse reactions.

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Most disinfectants can be regarded as potential skin irritants and/or sensitizers (allergens), including those indicated for human hygiene, such as alcohols and peroxygen compounds.[2] In response to external stimuli such as disinfectants, the skin immune system can react by secreting a range of pro-inflammatory mediators, including cytokines and chemokines, especially from keratinocytes, T cells, and dermal fibroblasts.[3,4] They can create irritant (ICD) or allergic contact dermatitis (ACD).[5] ICD is a nonspecific inflammatory response triggered by innate immune system due to toxic effects on the skin cells.[5] While ACD is considered a delayed hypersensitivity response, where skin inflammation is mediated by antigen-specific T cells (adaptive immunity). The inflammation is not directly caused by the chemicals but rather the response of T cells to the haptenized protein.[5]

We have provided a comprehensive summary of dermatologic reactions due to the exposure of disinfectants. The data on percutaneous penetration and interactions with skin components in facilitating skin penetration are also highlighted. We have included only the disinfectants commonly found in consumer products from the lists of disinfectants approved by (1) the European Chemical Agency[6] and (2) the US Environmental Protection Agency[7] for use against SARS-CoV-2, where these disinfectants have demonstrated efficacy against a harder-to-kill virus or another type of human coronavirus similar to SARS-CoV-2.

Classification of disinfectants

Table 1 shows the list of disinfectants commonly found in consumer products based on the various chemical classes and their examples and have included adverse reactions associated with the use of disinfectants and their skin penetration ability in Tables 2 and 3.

Alcohols

WHO recommends the use of alcohols, namely, ethanol (80%v/v) and isopropanol (75%v/v) in handrubs.[8] Percutaneous penetration of both alcohols is generally low even with extensive use.[9–11] They may create both ICD and ACD.[8,12] This could be related to the solvent effect on skin components (Table 2) or preirritated skin with disrupted skin barrier.[13] Because isopropanol is more irritating than ethanol,[14] emollients, such as glycerol or propylene glycol, may be added to hand preparations.[15–17] Allergic reactions, including contact urticarial, have been reported.[18–20] The triggers may be due to impurities, aldehyde metabolites, or fragrances in the product.[19,21]

Table 1 Classification of disinfectants and related examples

Classification	Examples
Alcohols	Ethanol, isopropanol
Aldehydes	Glutaraldehyde
Bases	*Oxides/hydroxides*
	Calcium dihydroxide, calcium hydroxide, calcium magnesium oxide, calcium magnesium tetrahydroxide, calcium oxide
	Carbonates
	Sodium carbonate, sodium carbonate peroxyhydrate, ammonium bicarbonate, ammonium carbonate
Biguanides	Polyhexamethylene biguanide hydrochloride (polyhexanide)
Chlorine and chlorine compounds	Chlorine dioxide, hydrochloric acid, hypochlorous acid, sodium chlorite, sodium hypochlorite, sodium dichloro-S-triazinetrione (sodium dichloroisocyanurate)
Glycols	Triethylene glycol, 1,2-hexanediol
Iodophors	Polyvinylpyrrolidone iodine
Metal ions	Silver ions, copper ions (copper sulfate pentahydrate)
Organic acids	*α-Hydroxy acids*
	Citric acid, glycolic acid, lactic acid
	Fatty acids
	Caprylic acid (octanoic acid), pelargonic acid (nonanoic acid)
Peroxygen compounds	Hydrogen peroxide, peroxyacetic acid (peracetic acid), potassium peroxymonosulfate
Phenolic compounds	Ortho-phenylphenol, ortho-benzyl-para-chlorophenol, thymol, chlorocresol
Surfactants	*Anionic surfactants*
	Dodecylbenzenesulfonic acid
	Cationic surfactants/quaternary ammonium compounds
	Old generation: benzalkonium chloride (alkyl dimethyl benzyl ammonium chloride), benzethonium chloride
	New generation: dialkyl dimethyl ammonium halide/carbonate (didecyl dimethyl ammonium chloride/carbonate, octyl decyl dimethyl ammonium chloride, dioctyl dimethyl ammonium bromide, didecyl dimethyl ammonium bicarbonate), dimethyl ethylbenzyl ammonium chloride
Thiazoles	Methylchloroisothiazolinone, methylisothiazolinone

Table 2 Skin irritation, sensitization, and significant skin manifestations of disinfectants

Classification	Examples	Skin irritation	Skin sensitization	Skin manifestations	Effect on skin components
Alcohols	Ethanol	Yes[8,12,14]	No[18–20]	Dryness, itchiness, burning (at high concentrations)	• Stratum corneum (SC) lipid solubilization, fluidization, and extraction[111–115] • SC protein denaturation[112,116]
	Isopropanol	Yes[8,12,14]	No[18–20]		
Aldehydes	Glutaraldehyde	Yes[24,25]	Yes[24,25]	Yellow-brown discoloration	• Crosslinking with protein (discoloration)[27]
Biguanides	Polyhexamethylene biguanide hydrochloride (polyhexanide)	No[34]	Yes[29,34]	Edema, redness, flaking with papules	n.a.
Chlorine and chlorine compounds	Sodium hypochlorite	Yes[38,39]	No[40]	Burning sensation, pain, redness, edema, blisters, tissue necrosis	• SC protein and lipid oxidation[117–119]
Glycols	Triethylene glycol	No[120]	No[120]	n.a.	n.a.
	1,2-Hexanediol	No[121,122]	No[122]	n.a.	• SC lipid fluidization and disordering[121–123]
Iodophors	Polyvinylpyrrolidone iodine	No[44–49]	No[124]	Burns with blisters and tissue necrosis (associated with wounds)	n.a.
Metal ions	Silver ions	No[58]	No[58]	Brown-black discoloration	• Photoreduction on keratin protein (discoloration)[59,60]
α-Hydroxy acids	Citric acid	No[61,125]	No[61,125]	Peeling, burning, skin thickening, reversible photosensitivity, contact urticaria, reduced melanin deposition	• Disruption of tight junction and adhesion of keratinocytes[126] • Inhibition of tyrosinase activities of melanocytes[74]
	Glycolic acid	Yes[61,125]	No[61,125]		
	Lactic acid	Yes[61,125]	No[61,125]		
Fatty acids	Caprylic acid (octanoic acid)	Yes[127–129]	No[127–129]	n.a.	n.a.
	Pelargonic acid (nonanoic acid)	Yes[127–129]	No[127–129]	Skin thickening	• Epidermal cell apoptosis, reduction of keratinocyte proliferation, and Langerhans cells[127,129,130] • SC lipid disordering[131] • Surfactant action on keratin protein and cell membranes[127]
Peroxygen compounds	Hydrogen peroxide	Yes[75,78–80]	No[75,78–80]	Blanching, vacuolar eruption, erythema, edema, peeling, burns (at high concentrations)	• Hemoglobin oxidation, oxygen-induced vasoconstriction[76,132] • SC protein and lipid oxidation, lipid solubilization
	Peroxyacetic acid (peracetic acid)	Yes[82]	No[82]	Burning sensation, itchiness	n.a.
Phenolic compounds	Ortho-phenylphenol	Yes[133]	No[133]	Leucoderma	• Inhibition of tyrosinase activities of melanocytes[134]
	Thymol	No[135]	No[135]	n.a.	• SC lipid fluidization[136,137] • SC protein denaturation and lipid plasticization[138]
	Chlorocresol	Yes[139,140]	No [a,139,140]	Urticaria[141,142]	Protein denaturation and lipid plasticization[138]
Anionic surfactants	Dodecylbenzenesulfonic acid	Yes[143]	No[143]	Roughness, erythema	• SC protein denaturation and lipid solubilization[144,145]
Cationic surfactants	Benzalkonium chloride (alkyl dimethyl benzyl ammonium chloride)	Yes[146,147]	No [a,146,147]	Inflammation	• SC lipid solubilization (cholesterols)[97,148] • SC protein denaturation[149]
	Benzethonium chloride	Yes[150]	No [a,150]		
	Didecyl dimethyl ammonium chloride	Yes[101–105]	Yes[101–105]	Urticaria, swelling, erythema, itchiness	• SC lipid solubilization (cholesterols)[151]

n.a., not available/unknown.

[a] Potential due to increased cases.

Table 3 Molecular weight, log *P*, and skin penetration of disinfectants

Classification	Examples	Molecular weight (Da)	Log *P*[a]	Skin penetration
Alcohols	Ethanol	46.1	−0.16	Yes (low)[9,10]
	Isopropanol	60.1	0.25	
Aldehydes	Glutaraldehyde	100.1	−0.27	Yes (low)[22,23]
Biguanides	Polyhexamethylene biguanide hydrochloride (polyhexanide)	Variable (average: 1415.0)	−2.39[34]	Yes (low)[28]
Chlorine and chlorine compounds	Sodium hypochlorite	74.4	0.32	Yes (very low)[38]
	Chlorine dioxide	67.5	0.26	No[42]
Glycols	Triethylene glycol	150.2	−1.30	No[152]
	1,2-Hexanediol	118.2	0.62	
Iodophors	Polyvinylpyrrolidone iodine	365.0	1.36 (iodine)	Yes[43]
Metal ions	Silver ions	107.9	−0.73	Yes (low)[56]
α-Hydroxy acids	Citric acid	192.1	−1.32	Yes[61–64]
	Glycolic acid	76.1	−1.04	
	Lactic acid	90.1	−0.47	
Fatty acids	Caprylic acid (octanoic acid)	144.2	2.70	Yes[128]
	Pelargonic acid (nonanoic acid)	158.2	3.14	Yes[128]
Peroxygen compounds	Hydrogen peroxide	34.0	−0.45	n.a.
	Peroxyacetic acid (peracetic acid)	76.1	−0.30	n.a.
Phenolic compounds	Ortho-phenylphenol	170.2	3.32	Yes[84,85,153–156]
	Thymol	150.2	3.43	Yes (very low)[138]
	Chlorocresol	142.6	2.79	Yes (very low)[138]
Anionic surfactants	Dodecylbenzenesulfonic acid	326.5	6.56	No[92]
Cationic surfactants	Benzalkonium chloride (alkyl dimethyl benzyl ammonium chloride)	Variable (C10: 311.9; C12: 340.0; C14: 368.1; C16: 396.1)	C10: 1.74; C12: 2.63; C14: 3.52; C16: 4.41	Yes[99]
	Didecyl dimethyl ammonium chloride	362	4.01	Yes[100]

n.a., not available/unknown.

[a] Calculated using MarvinSketch program (ChemAxon Ltd., Hungary) unless otherwise specified.

Aldehydes

Glutaraldehyde does not readily penetrate the skin (10% glutaraldehyde: up to ~14%; 0.75% and 7.5% glutaraldehyde: ~0.2%)[22,23]; however, it is irritating and can cause necrosis at higher concentrations (20%).[24,25] ACD frequently occurs due to occupational (1% to 2%) and experimental (1% to 10%) exposures.[24] This involves a Th2-dominant cytokine expression profile with a higher interleukin-4 (IL-4) over Th1-associated interferon-γ (IFN-γ).[26] Yellow-brown skin discoloration has the tanning effect from glutaraldehyde cross-linking of proteinaceous components such as keratin and collagen that alters the protein structure, thus creating yellow-brown discoloration.[27]

Biguanides

The dermal absorption of polyhexamethylene biguanide hydrochloride (PHMB) or polyhexanide is low (4%).[28] ACD is rare (0.5%) with application of 0.4% to 0.5% PHMB, and even at 5% PHMB, the reporting remains insignificant (0.8%).[29] Despite this, ACD is continually reported in recent years and has partial cross-reactivity with other biguanides such as chlorhexidine and polyaminopropylbiguanide.[30–33] PHMB is recognized as a moderate-to-strong skin sensitizer at concentrations above 1.2%.[34] Anaphylaxis rarely occurs and may be related to wound treatment involving damaged skin.[35–37]

Chlorine and chlorine compounds

The percutaneous penetration for hypochlorites is low and is attributed to its high reactivity, oxidizing, and alkalinity properties when in contact with proteinaceous materials.[38] Hypochlorites are nonirritating when diluted (0.1%) but are skin irritants at 5% to 10%.[38,39] Heat release from an exothermic reaction with water may worsen the reactions.[40] Other skin manifestations, such as burning sensation, pain, redness, edema, blisters, and necrosis, are known.[40] Beyond 10%, hypochlorites are corrosive and can cause chemical burns.

Chlorine dioxide (ClO_2) is a highly reactive and unstable chlorine compound. The oxidizing effect on the skin may be similar to hypochlorites but milder even at very high

concentrations considering the rapid degradation.[41] Even though chlorine gas produced can be irritating to the skin, the effect is insignificant, because no dermal uptake occurs with intact human skin.[42]

Iodophors

Iodophors or polyvinylpyrrolidone (povidone, PVP) iodines (PVP-I) is nonstaining, being relatively less toxic and irritating, compared with iodine. Topical absorption seems to be time dependent.[43] ICD (usually 10% PVP-I) sometimes occurs with chemical burns, pain, blistering lesions, and tissue necrosis.[44–49] Such burns, however, are often observed in damaged skin and/or wounds with prolonged exposure.[48,50,51] These side effects are associated with the wet condition during application and the continuous release of free iodine (I_2) that act as weak oxidants such as iodine cations (H_2OI^+).[48] ACD and anaphylactic reactions are seldom reported and mainly may be due to other ingredients such as alcohols and PVP,[52–55] which can induce IgE-mediated allergic reactions.[52]

Metal ions

Percutaneous absorption of silver and its nanoparticle forms is usually low in both intact and damaged skin (<4%), because its ionized form does not penetrate the skin readily.[56,57] ACD is known to occur due to the other ingredients.[58] Local skin discoloration (brown-black) is occasionally observed and be seen more frequently with topical application to wounds.[59,60] This is not true argyria (blue-grayish discoloration), which is more long-lasting and common after chronic exposure through inhalation or oral ingestion.[59]

α-Hydroxy acids

α-Hydroxy acids (AHAs), including citric acid (CA), glycolic acid (GA), and lactic acid (LA), can penetrate the skin, but the dermal absorption is dependent on pH, concentration, and time.[61–64] Burning, dermatitis, skin peeling, itching, and moderate sunburns are frequently reported at a concentration ≤10% or a pH ≥3.5.[65] This can be related to the expression of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and IL-1α.[66] An increased epidermal and dermal thickness is common at higher concentrations (CA and GA: 20% to 40%; LA: 12%).[67–70] AHA may also induce reversible skin photosensitivity and contact urticaria.[61,71,72] CA and GA (≥3%) can induce apoptosis of keratinocytes that enhances photodamage to the skin.[73] AHA may also decrease melanin deposition in the skin *in vivo*.[69,74] AHA at lower concentrations has none of these effects and is highly useful in dermatologic practice.

Peroxygen compounds

Dermal penetration of hydrogen peroxide (H_2O_2) remains unknown due to the rapid degradation into oxygen and water, especially when in contact with organic materials.[75] A transient skin blanching, usually benign, is often detected.[76] In addition, vacuolar eruption due to oxygen bubble formation in the skin (gas embolism) is a unique clinical manifestation from an exposure of up to 35% H_2O_2.[77] H_2O_2 is usually nonirritating at a low concentration (≤10%) despite being a strong oxidizing antiseptic.[75,78–80] At 35%, H_2O_2 can cause reversible erythema and edema but irreversible skin desquamation. With a concentration of more than 50%, chemical burns are usually noticed. Prolonged exposure may produce the same reactions at a lower concentration.

Skin irritation, erythema, scaling, and roughness may occur with repeated application of 0.1% to 0.2% of peracetic acid (PA).[81] Acute skin irritation has been observed at 0.5% to 3%.[82] A regular spray, using 0.2% to 0.5% PA during the SARS outbreak in 2002 to 2003 created multiple health hazards, including skin irritation, burning, and itching, lasting up to 5 hours.[83] The cause may be due to the excellent lipid solubility of PA and its strong oxidative disruption on the skin lipids and keratin protein.

Phenolic compounds

Phenol and its derivative, especially ortho-phenylphenol (OPP) or biphenyl-2-ol and ortho-benzyl-para-chlorophenol (OBPCP), have excellent skin-penetrating power.[84,85] Skin reactions can develop with short contact. ACD related to OPP and OBPCP may occur even at low concentrations (0.1%).[86–88] Chemical burns and digital tip gangrene have occurred after persistent exposure to 0.5% halogenated phenol; the actual causative compound was not stated.[89] Depigmentation or leukoderma is another clinical concern when applying OPP and OBPCP (1%),[90,91] although the depigmentation is reversible but with the repigmentation process taking upward to a year or more.

Surfactants

Anionic surfactants

Sodium dodecylbenzenesulfonate does not readily penetrate the skin, but penetration may happen due to prolonged contact.[92] Repeated application (1%) can result in moderate to severe erythema and skin roughness.[92–96]

Cationic surfactants (quaternary ammonium compounds)

Benzalkonium chloride (BAC) can penetrate the skin and induce skin irritation and inflammation at low concentrations (0.1%).[97,98] ACD is rare.[99] Newer generations of quaternary ammonium compounds (QAC), dialkyl QAC, such as didecyl dimethyl ammonium chloride (DDAC), have poor cutaneous *in vitro*.[100] ACD has been reported at very low concentrations (0.01%), and immediate hypersensitivity is possible.[101–105] Urticaria, swelling, erythema, and itchiness can be found at higher concentrations (1% to 10%).[104,106] DDAC may

produce mixed hypersensitivity that induces both IgE- and T-cell-mediated responses.[107–109] DDAC can be a skin irritant and sensitizer, probably stronger than BAC.

Safety preventive measures

Although the use of disinfectants is inevitable, it is crucial to consider the following points to minimize or avoid any potential dermatologic reactions:

- Damaged skin is prone to adverse reactions from a direct absorption of disinfectants, and extra care should be given to avoid contact with disinfectants.
- While multiple disinfectants may be used together or formulated as a single product to achieve synergistic effects, an enhanced adverse effect is expected.
- Whenever dermatitis is known, disinfectants that are weak or nonirritants and sensitizers should be prioritized. Patch testing may be considered. It is important to avoid using disinfectants from a similar class that is known to be allergic to the users in consideration of a potential cross-reactivity.
- It is necessary to use protective garments during handling to avoid direct contact from spillage. Even with regular use of protective attires, unnoticeable punctures in the gloves on multiple uses and the handling of disinfected surfaces can expose users to contamination. Possible interactions of disinfectants with protective garments may occur; for example, glutaraldehyde at 2% to 3.4% may penetrate latex gloves after 45 min, and thus butyl rubber and nitrile rubber gloves are recommended.[110]
- Emphasis is given only on the dermatologic reactions in this review, but the exposure through other manners such as ocular route and inhalation is often significant and most probably toxic. For instance, chlorine compounds are known to emit chlorine gas during preparation and application. The exposure to the eyes is thus high and toxic.

Conclusions

The dermatologic events are usually, but not always, related to prolonged exposure and contact with concentrated disinfectants. Many dermatologic adverse events remain unreported. Some skin reactions, especially sensitization, can develop for compounds currently known to be a nonirritant or sensitizer.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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