Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHAPTER

22

Antiseptic drugs and disinfectants with special scrutiny of COVID-19 pandemic related side effects

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This year's chapter about the side effects of antiseptic drugs and disinfectants is quantitatively dominated by data regarding the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which caused the Coronavirus Disease 2019 (COVID-19) pandemic. Recent reviews showed that several disinfectants are efficacious against SARS-CoV-2 including commonly used alcohol-based products (60–80% vol) as well as the WHO recommended formulations for hand sanitizer (Jing et al., 2020 [R]; Rai, Ashok, & Akondi, 2020 [R]) (Table 1, Fig. 1). The pandemic led to so far unseen levels of exposure to disinfectants and associated side effects (Table 2) (Atolani et al., 2020 [r]; Goh, Ming, & Wong, 2021 [R]; Patruno, Fabbrocini, Stingeni, & Napolitano, 2020 [r]; Tan & Oh, 2020 [r]). For example, human spaying with various disinfectants using so-called disinfection tunnels or walkthrough sanitation gates has occurred in several countries, while being condemned by international and national health organizations (Mallhi et al., 2020 [r]; Gray & Van Niekerk, 2020 [S]). Some authors have postulated that the pandemic might lead to a second pandemic—a pandemic of dermatitis (Bhatia et al., 2020) [r]. The demand for disinfectants led so far that alcohol was declared as an "essential good" in some countries and alcohol of various sources was diverted for being used as disinfectant, even if quality standards had to be temporarily lowered, e.g., allowing fuel- and technical-grade alcohol containing more impurities than normally tolerated in disinfectants (Neufeld et al., 2020 [r]; Opatz, Senn-Bilfinger, & Richert, 2020 [r]). It was even suggested that spirits such as vodka might be used for disinfection purposes, if no other products were to be available, as alcohol solutions down to 30% vol might still inactive SARS-CoV-2 (Neufeld et al., 2020) [r].

While the effectiveness of hand sanitation is one of the first examples of evidence-based medicine (Opatz et al., 2020) [r], the COVID-19 situation was unfortunately exacerbated by non-evidence based suggestions and off-label product use. Most prominently, the former US president Donald Trump stated in a widely quoted press briefing: "And then I see the disinfectant, where it knocks it out in a minute. One minute. And is there a way we can do something like that, by injection inside or almost a cleaning. Because you see it gets in the lungs and it does a tremendous number on the lungs. So it would be interesting to check that. So, that, you're going to have to use medical doctors with. But it sounds—it sounds interesting to me." (The White House, 2020) [S].

Following that calls to US poison control centers spiked by 20% and disinfectant makers warned against injecting or ingesting cleaning products (Kuehn, 2020 [A]; Reihani et al., 2021 [r]). While there is no systematic evidence available on the side effects of intravenous disinfectant use, a review of the available limited literature suggests significant toxic outcomes including death (Shah & Leung, 2020) [R]. In a survey of 502 adults in the United States in May 2020, 39% engaged in non-recommended high-risk practices with the intent of preventing SARS-CoV-2 transmission, including washing food products with bleach, applying household cleaning or disinfectant products to bare skin, and intentionally inhaling or ingesting the products. Respondents who engaged in these high

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TABLE 1 Activity of antimicrobial ingredients against enveloped viruses such as coronaviruses summarized by experts from the American Contact Dermatitis Society.

Ingredient	Virucidal activity against enveloped viruses[a]	Allergenicity[b]
Chloroxylenol	High	+
Ethanol	High	−
Povidone iodine	High	+/−
Sodium hypochlorite (bleach) (0.21%)	High	−
Triclosan/triclocarban	High	+/−
Benzalkonium chloride	Moderate	+
Chlorhexidine digluconate	Moderate	+
Benzethonium chloride	Low	−
Phenolic compounds	Low	−
Quaternary ammonium compounds	Low	−

[a]*High virucidal activity: <1 min; moderate virucidal activity: 1–30 min; low virucidal activity: >30 min.*
[b]*The + symbol indicates that the ingredient is found in the American Contact Dermatitis Society core patch testing panels, +/− indicates scattered reports of contact allergy and the − symbol indicates that allergenicity is rare.*
Reprinted from Rundle, C. W., Presley, C. L., Militello, M., Barber, C., Powell, D. L., Jacob, S. E. et al. (2020). Hand hygiene during COVID-19: recommendations from the American Contact Dermatitis Society. Journal of the American Academy of Dermatology, 83(6), 1730–1737. https://doi.org/10.1016/j.jaad.2020.07.057. [S], Copyright 2020, with permission from Elsevier.

risk practices frequently reported adverse effects such as respiratory, skin or eye irritation (Gharpure et al., 2020) [c].

Similarly, in Iran social media accounts and some news agencies circulated false stories of curing COVID-19 by drinking high-proof alcohol, poisoning over 2000 due to inadvertent consumption of methanol with bleach (Reihani et al., 2021 [r]; Chick, 2020 [r]; Dindarloo et al., 2020 [C]). Similar methanol poisonings occurred in Azerbaijan and Turkey as consumers tried to protect themselves against the virus by drinking illegally sold alcohol, but methanol poisoning also occurred in the United States in connection of methanol-containing hand disinfectants (Neufeld et al., 2020) [r]. An opinion poll from Russia revealed that 69% of Russians believed that alcohol consumption helps to protect against COVID-19 leading the WHO to publish counterstatements that alcohol ingestion does not destroy SARS-CoV-2 but actually facilitates infection (Neufeld et al., 2020) [r].

Currently, it is too early to fully evaluate the ongoing pandemic's impact regarding adverse effects of antiseptic drugs and disinfectants. Most of the studies reviewed below, were initial reports or anecdotes regarding the first COVID-19 wave in spring 2020. For example, observational studies comparing the incidences of adverse effects between the full year of 2020 and previous years are not yet available but expected to be reviewed in the next editions of SEDA. Some researchers proposed that non-intended effects of the excessive use of disinfectants might also lead to an increase in antimicrobial resistance as well as toxic impacts on the environment (Mahmood et al., 2020 [MC]; Nabi et al., 2020 [r]), but it is much too early to detect such effects as well.

ALL COMMONLY USED ANTISEPTICS AND DISINFECTANTS [*SEDA-37, 273; SEDA-40, 289*]

Skin

According to the experience from Wuhan, China where 42 000 health workers from all over China gathered to care for the large number of COVID-19 patients, commonly seen adverse reactions after using disinfectants include allergic and irritant contact dermatitis. The commonly used skin disinfectants were 75% ethanol and iodophor (probably povidone-iodine). The authors did not provide any quantitative data, however (Long et al., 2020) [c]. In a single center cross-sectional study in April–May 2020 of staff at a university hospital in Ireland, 223 (83%) of 270 participants reported symptoms of irritant contact dermatitis; nearly all reported an increase in frequency of hand washing (Kiely et al., 2021) [c]. Exaggerated hand washing with detergents/disinfectants can impair the hydrolipid mantle of the skin surface and may also be responsible for irritation and even the development of contact dermatitis (Darlenski & Tsankov, 2020) [r]. In an observational study of 6273 children in Denmark following COVID-19 reopening of schools introducing increased hygiene measures, the frequency of hand hygiene was associated with increases in the incidence of irritant contact dermatitis. The relative risk for handwashing >10 times/day was 2.23 (1.96–2.54 95% CI), while for using alcohol-based hand sanitizer

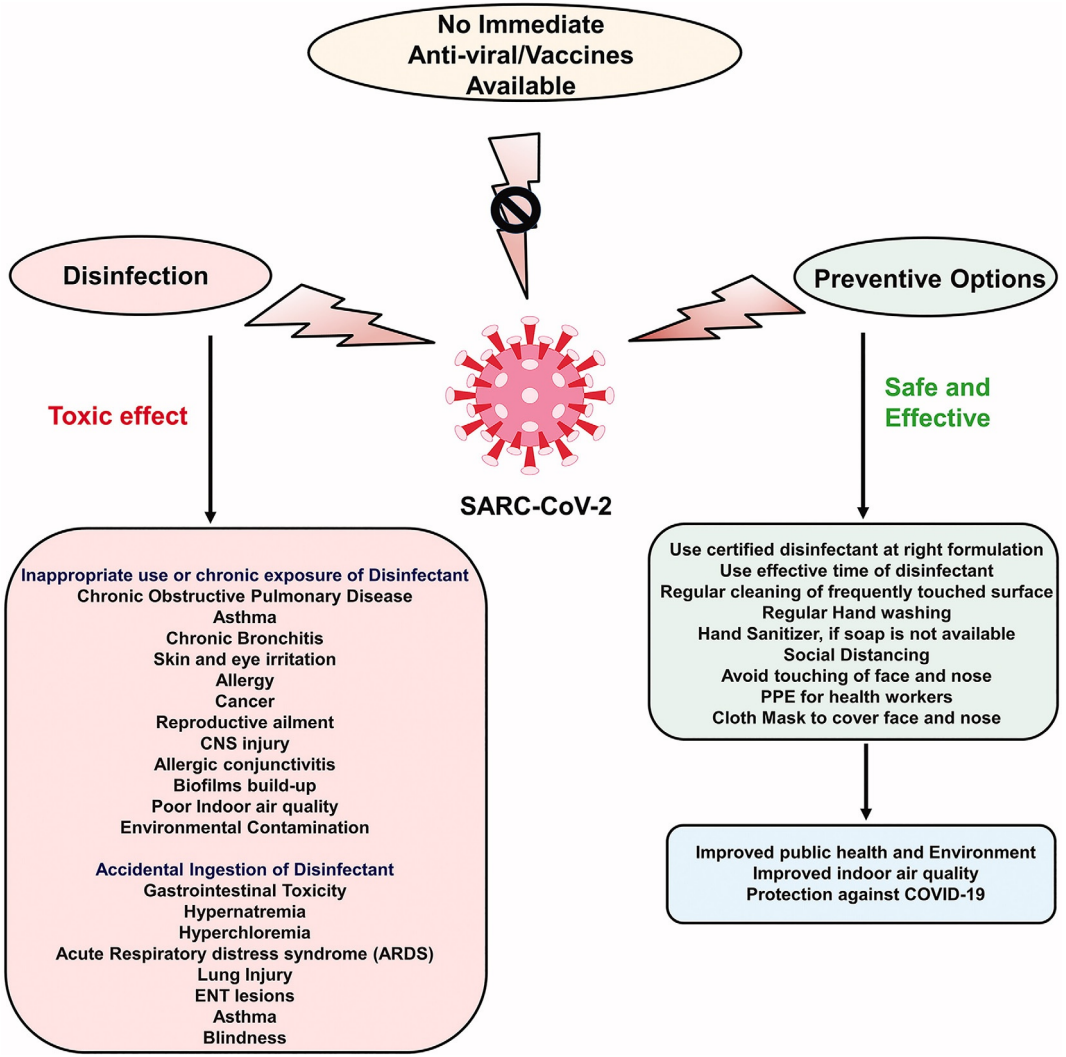

FIG. 1 Schematic representation providing an overview of adverse effect of improper use of disinfectants and safe alternatives against COVID-19 infection. Reprinted from Rai, N. K., Ashok, A., & Akondi, B. R. (2020). Consequences of chemical impact of disinfectants: safe preventive measures against COVID-19. Critical Reviews in Toxicology, 50(6), 513–520. https://doi.org/10.1080/10408444.2020.1790499. [R], Copyright 2020, with permission from Taylor & Francis Ltd., available on http://www.tandfonline.com.

TABLE 2 COVID-19 related side effects of antiseptic drugs and disinfectants.

Product type	Agent	Affected organs and systems	References
Bleach + vinegar	Sodium hypochlorite	Respiratory	Kuehn, 2020 [A]
Polypropylene surgical mask	Formaldehyde-releaser	Immunologic	Aerts et al., 2020 [A]
Disinfectants	Ethanol adulterated with methanol	Drug misuse, drug overdose, drug contamination/adulteration	Reihani, Ghassemi, Mazer-Amirshahi, Aljohani, & Pourmand, 2021 [r]; Neufeld, Lachenmeier, Ferreira-Borges, & Rehm, 2020 [r]; Aschenbrenner, 2020 [r]
Walkthrough sanitation gates/disinfection tunnels[a]	Several (alcohol, bleach, etc.)	Respiratory, skin, eye, immunologic, gastrointestinal	Gray & Van Niekerk, 2020 [S]; Mallhi, Khan, Alotaibi, & Alzarea, 2020 [r]
Hand disinfectants	Alcohols and other agents	Skin, immunologic, eye	Darlenski & Tsankov, 2020 [r]; Borch et al., 2020 [C]; Bhatia et al., 2020 [r]; Goh, Ming, & Wong, 2021 [R]; Araghi, Tabary, Gheisari, Abdollahimajd, & Dadkhahfar, 2020 [R]; Shetty, Jayadev, et al., 2020 [r]
Hand disinfectants	Insufficient amount of active ingredients	Drug formulations, drug adulteration	Aschenbrenner, 2020 [r]
Disinfectants	All types	Drug overdose (poisoning)	Babic, Turk, & Macan, 2020 [c]; Dindarloo et al., 2020 [C]; Chang et al., 2020 [MC]; Gharpure et al., 2020 [c]
Home-made disinfectants	Alcohols and other compounds	Drug formulations (ineffective), drug overdose (poisining in children)	Hakimi & Armstrong, 2020 [MC]
Excessively used hand sanitizers	Alcohols	Interactions (increase in antimicrobial resistance)	Mahmood et al., 2020 [MC]

[a]*Note: this is not an evidence-based measure to prevent SARS-CoV-2 infection.*

>7 times/day it was 1.20 (1.02–1.41 95% CI). The authors recommend that some of the hand washing should be replaced with the use of hand sanitizer (Borch et al., 2020) [C]. A similar conclusion of preferring alcohol-based hand rubs instead of frequent handwashing with soap and water was suggested in a review about the risk factors of hand dermatitis during the COVID-19 pandemic (Araghi et al., 2020) [R]. Suggestions for skin-care to avoid side effects from use of disinfectants and other protective equipment in health-care workers were reviewed (Yan et al., 2020) [E].

Drug overdose

During January–March 2020, poison centers in the United States received 45550 exposure calls related to cleaners (28158) and disinfectants (17392), representing overall increases of 20.4% and 16.4% from January to March 2019 (37822) and January–March 2018 (39122). Exposures among children aged less than 5 years represented a large percentage in the 3-month study period for each year (40–47%) (Chang et al., 2020) [MC]. The exposures in children may be partially attributable to home-produced hand disinfectants that were improperly stored in beverage bottles (Hakimi & Armstrong, 2020) [MC]. An exposure modelling study also determined 3-year-old children as the age group with highest exposure, especially in scenarios of contact with disinfected surfaces (Li, Sangion, & Li, 2020) [E]. Cases of exposure to disinfectants reported to the Croatian poison control center doubled in the first half of 2020 (41 vs 21 cases in 2019), and exposure to sanitizers increased about nine times (46 vs 5 cases in 2019). In 2020, the most common ingredients involved in poisoning incidents were hypochlorite/glutaraldehyde in disinfectants, and ethanol/isopropanol in sanitizers (Babic et al., 2020) [c]. All of these studies associated the increase in 2020 with COVID-19. In a cross-sectional study in Iran, 42% out of 1090 participants during the COVID-19 outbreak experienced at least one adverse effect on their hands, feet, eyes, respiratory or gastrointestinal systems after sequential uses of disinfectants, while 1.7% of participants had to obtain medical help following ingestion of disinfectants (Dindarloo et al., 2020) [C]. In a similar study of 502 participants in the United States 25% reported at least one adverse effect that they believed had resulted from using cleaners or disinfectants including nose or sinus irritation (11%), skin irritation (8%), eye irritation (8%), dizziness, light-headedness, or headache (8%), upset stomach or nausea (6%), or breathing problems (6%) (Gharpure et al., 2020) [c].

ALCOHOLS [SEDA-7, 266; SEDA-12, 202; SEDA-15, 250; SEDA-19, 235]

Although several alcohols have been shown to be effective antimicrobials, ethanol (ethyl alcohol, alcohol), isopropanol (isopropyl alcohol, propan-2-ol) and n-propanol (propan-1-ol, in particular in Europe) are the most widely used. Alcohols exhibit rapid broad-spectrum antimicrobial activity against vegetative bacteria (including mycobacteria), viruses, and fungi but are not sporicidal (McDonnell & Russell, 1999) [R].

Drug formulations

The American Contact Dermatitis Society published recommendations for hand hygiene during COVID-19. With respect to hand dermatitis, alcohol-based hand sanitizers with moisturizers were suggested as they have the least sensitizing and irritancy potential compared to soaps and synthetic detergents (Rundle et al., 2020) [S]. The antiviral efficacy of ethanol was found to be better than the one of 1-propanol or 2-propanol (Verbund für Angewandte Hygiene, 2021) [S].

Drug overdose

In the past, it was shown that topical uses of alcohols as disinfectants (e.g. in the form of hand disinfectants) may only lead to very low—if any—blood concentrations either by skin penetrations, especially through lacerated skin, or by inhalatory exposure, but generally below thresholds of toxicity (Lachenmeier, 2008) [R]. The exception has been the use in children, specifically preterm babies, where percutaneous toxicity may occur (Lachenmeier, 2008 [R]; Reybrouck, 1983 [R]; Reybrouck, 1988 [R]; Reybrouck, 1991 [R]). However, a curious COVID-19 event has been reported by a Mumbai alcohol treatment center in which excessive hand sanitizing zeal caused an alcohol-disulfiram reaction (Chick, 2020) [r]. The 43-year-old male patient using 250 mg disulfiram per day for the past 3 years being abstinent to alcohol reported to the hospital emergency department with what appeared to be an allergic reaction. He had rubbed his hands with sanitizer several times for several minutes following the rules in place due to the COVID-19 pandemic. Examination revealed erythema on the chest and face without mucosal swelling. The diagnosis was moderate disulfiram ethanol reaction. The symptoms settled following chlorpheniramine in an injectable form with vitamin C (De Sousa, 2020) [A]. Experimental follow-up research to this case report provided strong evidence that the alcohol amounts sufficient to cause a disulfiram reaction are inhaled when hand sanitizers are used in confined spaces, while absorption from the skin alone does not occur in pharmacologically significant quantities (Brewer & Streel, 2020) [c]. A case of a preschool-aged girl was described. The child was found unresponsive at home next to an open ethanol-based hand sanitizer bottle. She became dizzy after ingesting an unknown amount, fell and hit her head. Her blood alcohol level was elevated at 273 mg/dL. She was discharged after 48 h recovery at hospital (Chang et al., 2020) [MC].

Skin

The most commonly reported skin reactions with the use of alcohol-based hand sanitizers are irritant contact dermatitis and allergic contact dermatitis, which are sometimes difficult to distinguish due to overlap and similarities of symptoms (Jing et al., 2020) [R]. A systematic review of studies (2000–2019) regarding the irritation potential of alcohol-based disinfectants found a low irritation potential of *n*-propanol alone. However, recent studies provide evidence for significant barrier damage effects of 60% *n*-propanol. Nevertheless, the authors judged this risk to be lower than for frequent handwashing with detergents (Tasar, Wiegand, & Elsner, 2021) [R]. Reactions to topical alcohols could be stronger in patients with aldehyde dehydrogenase deficiency (Löffler, Kampf, Lachenmeier, Diepgen, & John, 2012) [r] as well as in those under treatment with aldehyde dehydrogenase inhibitors (see case report in "Drug Overdose"). While detailed genetic epidemiologic research into this association is lacking so far, the increased alcoholic disinfectant use during COVID-19 might potentially lead to such an opportunity.

Eye

A case of a 26-year-old woman was described who reported having episodic redness, irritation and burning sensation the past few weeks in both her eyes, which sometimes occurred 6–7 times a day. There was a mild conjunctival congestion, but no discharge or lid edema, neither any drop in vision or photophobia. There was no obvious infection, so that the effects were associated to the patients' use of a hand sanitizer spray, which she sprayed almost hourly due to the COVID-19 pandemic (Shetty, Jayadev, et al., 2020) [r].

ALDEHYDES *[SED-15, 1439, 1513; SEDA-31, 409; SEDA-32, 437; SEDA-33, 479; SEDA-34, 377; SEDA-36, 339; SEDA-37, 273; SEDA-38, 211; SEDA-39, 209; SEDA-40, 289; SEDA-41, 251; SEDA-42, 247]*

Considering all disinfectants, aldehydes have a special status as they have the ability to pose occupational hazards even at very low concentrations in air (Lachenmeier, 2014 [R]; Lachenmeier, 2015 [R];

Lachenmeier, 2016 [R]; Lachenmeier, 2017 [R]; Lachenmeier, 2018 [R]; Lachenmeier, 2019 [R]; Lachenmeier, 2020 [R]).

Formaldehyde

Immunologic

Data from a multicenter prospective study in Spain, which included 18 hospitals, showed that from 4088 patch tested patients, 70 tested positive for formaldehyde releasers (1.7%). This incidence was judged as being low despite the wide-spread use of formaldehyde-releasing chemicals in Spain (Sanz-Sanchez et al., 2020) [MC]. A case of occupational allergic contact dermatitis caused by formaldehyde and 2-bromo-2-nitropropane-1,3-diol (bronopol) contained in a polypropylene surgical mask was described. A 38-year-old woman with a history of allergic contact dermatitis from formaldehyde developed a relapse after starting to work at a COVID-19 ward as auxiliary nurse following prolonged use of a particular polypropylene surgical mask, mimicking a flare-up of rosacea. The manufacturer of the mask revealed that it might contain trace impurities of formaldehyde and bronopol, a formaldehyde-releasing chemical. To avoid similar cases, specifically during the massively increased use of face masks during the COVID-19 pandemic, the authors suggest that contact sensitizers in facial masks should be labelled to allow selection of safer alternatives (Aerts et al., 2020) [A].

Hematologic

A case of methemoglobinemia following excessive occupational exposure to formaldehyde contained in hair-treatment products was presented. The 52-year-old female worked as hairdresser and prepared an unusual number of treatments during a 14-day period, followed by the patient's collapse at home. The ambulance service noted the patient being hypotensive and her skin being grey. On arrival at the hospital, the patient appeared cyanotic with SpO_2 of 88% despite receiving high-flow oxygen. On inserting an arterial line, the intensive care registrar noted chocolate brown-coloured blood. The blood gas analysis showed a raised methemoglobin level of 65%. The methemoglobinemia was treated by a 1 mg/kg dose of intravenous methylene blue and the patient fully recovered within 3 days. While the aetiology in this case remains undetermined due to co-exposure with various volatile components in the products, the methemoglobinemia was most plausibly explained by the occupational formaldehyde exposure (de Vere, Moores, Dhadwal, & Karra, 2020) [A], as some early experiments in the 1950s demonstrated that formaldehyde may greatly increase the oxygen affinity of haemoglobin (Guthe, 1954) [E]. The case may also offer a mechanistic explanation for previous cases of fatal poisonings in connection with formaldehyde-containing hair-straightening products (Monakhova et al., 2013) [E].

Mouth and teeth

A small occupational cohort study of 69 men with exposure to formaldehyde in woodwork industry compared to 69 matched controls was examined for periodontal disease using various diagnostic tests. Despite similar oral health status and oral hygiene levels in both groups, the condition of periodontal tissues in the exposed woodworkers was statistically significantly worse than in the controls. The prevalence of inflammation in periodontal tissues was also higher in middle and older age groups with prolonged exposure (Tokar, Batig, Ostafiichuk, Ishkov, & Sheremet, 2020) [c].

GUANIDINES

Chlorhexidine *[SED-15, 714; SEDA-31, 410; SEDA-32, 439; SEDA-33, 480; SEDA-34, 378; SEDA-36, 340; SEDA-37, 273; SEDA-38, 212; SEDA-39, 210; SEDA-40, 290; SEDA-41, 252; SEDA-42, 248]*

Skin

A prospective observational study compared patients with central venous catheter who had undergone antisepsis maintenance using either 0.05% chlorhexidine swabs ($n=372$) or 1% chlorhexidine swabs ($n=344$). The number of patients complaining of insertion site tenderness were 4 for 0.05% and 12 for 1% swabs. The risk ratio was 3.244 (95% CI: 1.056–9.963) (Kikuchi et al., 2020) [c].

Immunologic

In an analysis of data from a local laboratory in the UK (2018–2019), out of 109 requests for specific-IgE antibodies to chlorhexidine, seven patients (6.4%) were found positive. Retrospective analysis of 25 positive drug tests out of 186 tests performed at a hospital in the UK identified 2 patients (8%) with confirmed allergy to chlorhexidine. The first patient (47-year-old male) had anaphylaxis during angioplasty. The second patient (33-year-old female) developed significant hypotension on induction of anaesthesia during replacement of ureteric stent (Avison et al., 2020) [r].

Polyhexamethylene guanidine [SEDA-36, 341; SEDA-37, 273; SEDA-38, 213; SEDA-39, 211; SEDA-40, 292; SEDA-41, 253; SEDA-42, 249]

Polyhexamethylene guanidine (PHMG) has been used as an antiseptic, especially for the suppression of hospital

infection in the Russian Federation and as a disinfectant for sterilization of household humidifiers in Korea (Lachenmeier, 2014 [R]; Lachenmeier, 2015 [R]; Lachenmeier, 2016 [R]; Lachenmeier, 2017 [R]; Lachenmeier, 2018 [R]; Lachenmeier, 2019 [R]; Lachenmeier, 2020) [R]).

Respiratory

Further evidence was gathered on the association of the disinfectant PHMG with lung disease (see (Lachenmeier, 2014 [R]; Lachenmeier, 2015 [R]; Lachenmeier, 2016 [R]; Lachenmeier, 2017 [R]; Lachenmeier, 2018 [R]; Lachenmeier, 2020 [R]) for description of cases). Based on transcriptome analysis of lung tissues from 5 children with humidifier disinfectant lung injury (HDLI) and 5 controls, *NOTCH1* pathways were identified as the possible main fibrogenetic mechanism of HDLI in children following exposure to PHMG (Lee et al., 2020) [E]. The plausibility for adverse effects of PHMG on human tissues was further strengthened in several experimental *in vivo* and *in vitro* studies regarding induction of irreversible fibrosis at low-dose PHMG aerosol exposure in mice (Zhu et al., 2020) [E], toxic effects on the respiratory system with a no observable adverse effect level (NOAEL) below 1 mg/m^3 in rats (Lee & Seo, 2020) [E], toxic effects on the respiratory systems and toxic effects on the offspring in pregnant rats (Lee et al., 2021) [E].

Polyhexamethylene Biguanidine [SEDA-36, 341; SEDA-37, 273; *SEDA-38, 213; SEDA-39, 211*]

Polyhexamethylene biguanidine (PHMB, polyhexanide) is used for wound antisepsis. A recent risk-benefit analysis suggested the use of PHMB justified considering effectiveness and tolerability of the agent (Kramer, Eberlein, Müller, Dissemond, & Assadian, 2019) [R].

Skin

A case of tissue degeneration associated with PHMB was described in a 72-year-old patient. Within 6 days of PHMB application on an abscess, the wound regressed showing damage to granulation tissue, fascia, and epithelializing edges (Sams-Dodd & Sams-Dodd, 2020) [A].

BENZALKONIUM COMPOUNDS *[SED-15, 421; SEDA-32, 440; SEDA-33, 481; SEDA-34, 379; SEDA-36, 341; SEDA-37, 273; SEDA-38, 213; SEDA-39, 212; SEDA-40, 292; SEDA-41, 253; SEDA-42, 249]*

Sensory systems

It is believed that eye drops containing benzalkonium chloride as preservative may contribute to ocular surface disease (see also (Lachenmeier, 2014 [R]; Lachenmeier, 2015 [R]; Lachenmeier, 2016 [R]; Lachenmeier, 2017 [R]; Lachenmeier, 2018 [R]; Lachenmeier, 2020 [R])). Using an *ex vivo* eye irritation model based on excised rabbit corneas, benzalkonium chloride (0.2%) treated corneas showed increased epithelial lesions (Dutescu, Uthoff, Panfil, & Schrage, 2020) [E]. Based on *in vitro* research in rat liver mitochondria and yeast cells, the major causative factors underlying the adverse effects of benzalkonium chloride may be mitochondrial dysfunctions (Rogov et al., 2020) [E].

Respiratory

The toxicity of respiratory exposure to benzalkonium chloride was evaluated in rats for 2 weeks in accordance with OECD GLP test guidelines. Adverse effects in the nasal cavity and the lungs were detected with a no observed adverse effect levels of less than 0.8 mg/m^3 (Choi et al., 2020) [E].

TRICLOCARBAN *[SEDA-13, 206]*

Triclocarban (trichlorocarbanilide, TCC) has been used as an alternative to hexachlorophene, but its antibacterial efficacy is rather limited (Reybrouck, 1989) [R] and its use has been mostly phased out.

Teratogenicity

Maternal exposure of triclocarban in a rat model leads to transfer to the offspring, both trans-placentally and via lactation. The early-life exposure may interfere with lipid metabolism as increased fat-pad weights and hepatic triglycerides were observed (Enright et al., 2017) [E]. In another study in rats, in utero and lactational exposure to triclocarban was found to affect the offspring, as observed through an increase in pre-implantation loss potentially related to altered progesterone biosynthesis (Costa et al., 2020) [E].

HALOGENS

Sodium hypochlorite *[SED-15, 3157; SEDA-28, 262; SEDA-34, 380; SEDA-36, 342; SEDA-37, 273; SEDA-38, 214; SEDA-39, 213; SEDA-40, 293; SEDA-41, 255; SEDA-42, 250]*

Teeth

Sodium hypochlorite is used to irrigate root canals in dentistry and can cause many adverse reactions (Lachenmeier, 2014 [R]; Lachenmeier, 2015 [R]; Lachenmeier, 2016 [R]; Lachenmeier, 2017 [R]; Lachenmeier, 2018 [R]; Lachenmeier, 2019 [R]; Lachenmeier, 2020 [R]). The occurrence of hypochlorite injuries during endodontic

treatment, typically leading to localized or widespread tissue necrosis, is relatively rare but key to the successful treatment is an early identification of the condition (Shetty, Al-Bayati, et al., 2020) [R]. The appropriate management of such accidents was reviewed (Kanagasingam & Blum, 2020) [R]. Low-level laser therapy was suggested as adjunctive treatment in a case of a 39-year-old woman with a chemically induced ulcer caused by a sodium hypochlorite accident (Yamamoto-Silva et al., 2019) [A].

Drug overdose

Nearly, two-thirds of calls to US poison control centers regarding exposures to cleaning products and disinfectants involved bleach exposure. A case of a woman who soaked her groceries for cleaning in bleach, vinegar and hot water mixed together was described. After developing difficulty breathing, coughing and wheezing, the patient received oxygen and bronchodilators at an emergency department (Kuehn, 2020 [A]; Chang et al., 2020 [MC]).

Polyvinylpyrrolidone (povidone)-iodine *[SED-15, 1896; SEDA-31, 411; SEDA-32, 440; SEDA-33, 485; SEDA-34, 380; SEDA-36, 342; SEDA-37, 273; SEDA-38, 215; SEDA-39, 213; SEDA-40, 293; SEDA-42, 250]*

The safety of topically applied povidone-iodine for nasal and oral decontamination to reduce nosocomial spread of SARS-CoV-2 has been reviewed. The authors suggest that povidone-iodine can be safely used in the nose at concentrations up to 1.25% and in the mouth at concentrations up to 2.5% for up to 5 months (Frank, Capriotti, Brown, & Tessema, 2020) [R].

Endocrine

Four cases of hypothyroidism due to iodine overload in children with kidney failure (3.5-year-old boy, 2-week-old boy, 8-month-old girl, 5-month-old boy) receiving peritoneal dialysis were described. In each child the sole source of iodine exposure was povidone-iodine-impregnated gauze in the sterile transfer set cap associated with peritoneal dialysis (Mannemuddhu, Morgans, Pekkucuksen, Warady, & Shoemaker, 2020) [A].

Immunologic

A case of anaphylaxis in a 55-year-old woman was described who received an intravenous infusion containing paracetamol with povidone as excipient. The authors stressed the potential of excipients to cause severe allergy (Preuss, Goddard, Clarke, Platt, & Sadleir, 2020) [A].

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