Verbund für Angewandte Hygiene e.V.
Desinfektionsmittel-Kommission

As a biocidal active substance, ethanol is indispensable for hygienic hand disinfection*

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Abstract

Ethanol was first mentioned in the specialist literature in 1888 for antiseptic treatment of the hands. Since then ethanol, like 2-propanol and 1-propanol, has been used as an active substance in hand disinfectants in many countries around the world, mainly as the sole active ingredient in a concentration between 60% and 95%. Since 1977 the World Health Organization (WHO) has maintained a list of indispensable drugs (WHO Model List of Essential Medicines), last updated in 2019. On that list ethanol (70%, denatured) appears under Antiseptics (15.1. Antiseptics) and under alcohol-based hand disinfectants (80% v/v; 15.2. Disinfectants). Ethanol is featured on the core list of basic care active substances which, as a minimum, should be available.

The efficacy of ethanol against bacteria, yeasts and enveloped viruses is comparable with that of 1-propanol and 2-propanol. However, an extensive evaluation of the literature on the efficacy of these three alcohols against non-enveloped viruses revealed that ethanol is more effective than the two propanols against various adenoviruses, poliovirus, human enterovirus, echoviruses and different coxsackieviruses. Thanks to that superior efficacy against non-enveloped viruses, ethanol was chosen as the reference active substance (positive control) for determination of the efficacy of hand disinfectants against viruses on artificially contaminated hands in prEN 17430.

The amounts of ethanol absorbed through hand disinfection are below the toxicologically relevant concentrations. Therefore, when used as directed, ethanol-based hand disinfectants continue to be considered safe.

In summary, because of its superior efficacy against selected clinically relevant non-enveloped viruses ethanol is indispensable as a biocidal active substance for hygienic hand disinfection.

Ethanol for hand disinfectionn

Ethanol was first mentioned in the specialist literature in 1888 for antiseptic treatment of the hands [1]. Since then ethanol, like 2-propanol and 1-propanol, has been used as an active substance in hand disinfectants in many countries

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around the world, mainly as the sole active ingredient in a concentration between 60% and 95%, and occasionally with the addition of a non-volatile active substance such as e.g. chlorhexidine digluconate (CHG) [2].

Antimicrobial efficacy of ethanol compared to 1-propanol and 2-propanol

Bactericidal activity

The spectrum of action against bacteria is investigated in suspension tests (EN 13727). When used in a correspondingly highly concentration, all three alcohols demonstrate sufficiently good bactericidal activity (at least 5 $\log_{10}$ reduction) within 30 s [2–4].

Compared to the reference method, sufficiently good activity is also achieved by all three alcohols under everyday practice conditions (EN 1500; hygienic hand disinfection) if the active substance concentration is sufficiently high. When ethanol is used as the sole active substance, a concentration from 80% (w/w) is suitable for meeting the efficacy requirements in 30 s [2-4].

Yeasticidal and fungicidal activity

In concentrations between 70% and 83% ethanol demonstrates a broad spectrum of activity within 30 s against yeasts and dermatophytes [5–11]. Good activity against yeasts has also been reported for 1-propanol and commercially available propanol-based preparations [12–14].

Efficacy against enveloped viruses

The spectrum of action against enveloped viruses is investigated in suspension tests (EN 14476) in which the active substance solution is diluted to 80% with the addition of the organic challenge and the viral suspension, so that a solution of 99.8% ethanol contains 80% ethanol in the efficacy tests. When used in an adequately high concentration, all three alcohols demonstrate sufficiently good efficacy against several enveloped viruses (SARS-CoV-1, SARS-CoV-2, MERS coronavirus, influenza A virus, influenza B virus, HIV, HBV, HCV, vaccinia virus, togavirus, Newcastle disease virus, type 1 and 2 herpes simplex viruses, Ebola virus, Zika virus and respiratory syncytial virus [RSV]) within 30 s (at least 4 $\log_{10}$ reduction of viral infectivity) [2–4, 15].

Efficacy against non-enveloped viruses

The same method (EN 14476) is used to investigate efficacy against non-enveloped viruses in suspension tests. This shows a differentiated overall picture of the efficacy of these three alcohols (Table 1).

Noroviruses are of great clinical significance. Overall, ethanol and 1-propanol are more effective than 2-propanol against the murine norovirus. The majority of the various adenoviruses are inactivated by ethanol; knowledge about propanols is very limited. 2-propanol is insufficiently effective against poliovirus, human enterovirus and various coxsackieviruses, while sufficient inactivation with ethanol has been reported in some cases. Echovirus can be inactivated by ethanol in a markedly lower concentration compared with 2-propanol. Ethanol efficacy against different viruses such as HAV, rhinovirus and polyomavirus, is limited, while mixtures of 1-propanol and 2-propanol (40% plus 40% or 10% plus 20%) were ineffective against polyomavirus SV 40 [16]; no data could be found on the efficacy of 1-propanol or 2-propanol against HAV and rhinoviruses.

One way to improve the efficacy of ethanol is to add acids, so that formulations based on 45%, 55%, 69.4% and 73.5% ethanol (w/w) can be rendered sufficiently effective against type 1 poliovirus within 30 s or 1 min [17, 26, 39, 40]. Ethanol efficacy against polyomavirus SV 40 can also be markedly enhanced by adding acids [26, 40]. No comparable findings are available for 2-propanol or 1-propanol.

Ethanol-based preparations (72.4%. 86% or 89.5% active substance content) demonstrate good efficacy against noroviruses also under everyday use conditions in accordance with prEN 17430 within 30 s [41]. So far, no data are available on the propanol preparations.

Unique feature: efficacy against certain non-enveloped viruses

Overall, ethanol has a superior inactivating effect on various non-enveloped viruses compared to propanols. Therefore, if the hands are contaminated with selected non-enveloped viruses neither 2-propanol nor 1-propanol lends itself as a suitable biocidal active substance for hygienic hand disinfection. Thanks to that superior efficacy against non-enveloped viruses, ethanol was chosen in a concentration of 70% as the reference active substance (positive control) for determination of the efficacy of hand disinfectants against viruses on artificially contaminated hands in prEN 17430 [42].

Ethanol is an essential medicine for the WHO

In its guidelines on hand hygiene in health care, the World Health Organization (WHO) considers ethanol, in addition to 2-propanol, to be in principle a suitable active substance for hand disinfection [43]. For countries with limited financial resources a simple formulation with 80% (v/v) ethanol was recommended in 2009 as an inexpensive alternative to the commercially available preparations, since this can be produced locally [43]. Since 1977 the WHO has maintained a list of indispensable drugs (WHO Model List of Essential Medicines), last updated in 2019. On that list ethanol (70%, denatured) appears under Antiseptics (15.1. Antiseptics) and under alcohol-based hand disinfectants (80% v/v; 15.2. Disinfectants). Ethanol is featured on the core list of basic care active substances which, as a minimum, should be available [44].

Safety of using ethanol-based hand disinfectants

When assessing the safety of ethanol-based hand disinfectants, it is important that evaluation be based on the application of ethanol to the intact skin as directed. Ethanol has been shown to have a carcinogenic effect only following oral intake (absorption of 90% of ingested ethanol) [45]. The transdermal and inhalational absorption of ethanol following application to intact skin is outlined below.

Dermal and pulmonary absorption in hand disinfection

Earlier studies have already demonstrated that ethanol is rarely able to enter the body through the skin [46–49]. That finding is corroborated by more recent studies [50–52]. Using more sensitive detection methods, a systematic investigation of 20 subjects was carried out to determine how much ethanol could be detected in the blood after application of various hygienic or surgical hand disinfectants [53]. Three commercially available hand rubs were tested to that effect: a solution with 95% eth-

Table 1: Overview of the efficacy of solutions based on ethanol, 2-propanol and 1-propanol from suspension tests against various non-enveloped viruses; sufficient efficacy (≥ 4 log_{10} reduction or up to the test's detection limit, with details of the contact time required; insufficient efficacy with details of the contact time shown in italics against grey background; *w/w; **v/v; ***unclear whether w/w or v/v.

Species	Virus type	Ethanol	2-propanol	1-propanol	References
Rotavirus	Wa	85%* / 30 s			[5]
Murine norovirus (MNV)	Type 1	70% - 90%** / 30 s	*50%** / 30 s*	50% - 90%*** / 30 s	[17-23]
		70% - 90%** / 1 min	*60%** / 30 s*		
			60%*** / 1 min		
			*70%** / 30 s*		
			70%** / 5 min		
			80%** / 30 s		
			*90%** / 30 s*		
			90%** / 1 min		
Adenovirus	Type 5	40% - 95%* / 30 s			[17-19, 24]
	Type 2	50%*** / 10 min	50%*** / 10 min		[5, 25-27]
		55%* / 2 min			
		70%*** / 30 s			
		85%* / 2 min			
	Type 7	79% - 83%** / 60 s			[28]
	Type 8	*70%*** / 2 min*	*70%*** / 2 min*		[28, 29]
		*79% - 83%** / 60*			
	Type 19	*70%*** / 2 min*	*70%*** / 2 min*		[29]
	Type 37	*70%*** / 2 min*	*70%*** / 2 min*		[29]
Poliovirus	Type 1	*70%* / 3 min*	*70%** / 10 min*		[17-19, 24, 25, 30]
		73,5% / 30 s - 5 min*	*95%** / 10 min*		
		73,5%* / 10 min	*100% / 10 min*		
		80% / 2 - 5 min*			
		85,7% / 1 - 10 min*			
		95%* / 30 s			
		100% / 1 - 10 min			
Coxsackievirus	B5	79% - 95%** / 1 min			[28, 31]
	B1	79% - 95%** / 10 min	*95%*** / 10 min*		[25, 28]
	B2		*70% - 90%*** / 1 h*		[32]
	B3		*70% - 90%*** / 1 h*		[32]
	A7	*79% - 95%** / 10 min*			[28]
Echovirus	Typ 11	95%** / 20 s - 1 min			[33, 34]
	Typ 6	50%*** / 10 min	90%*** / 10 min		[25]
Human enterovirus	Typ 71	70% - 85%** / 10 min	*70%** / 10 min*		[35]
		95%** / 10 min	*95%** / 10 min*		
			100% / 10 min		
Hepatitis A virus (HAV)	HM175/24a	*80% - 95%* / 2 min*			[36]
Rhinovirus	Type 2	*80%*** / 3 - 60 min*			[37]
Polyomavirus	SV 40	*78,2%* / 10 min*			[38]

anol, a gel with 85% ethanol as well as a solution with 55% ethanol and 10% 1- propanol (all as w/w).

Application conditions for hygienic hand disinfection

In total, 20 applications of 4 ml hand rub each were performed within 30 min. As expected, application of the 95% ethanol hand rub led to the highest ethanol concentration in the blood (median of 20.95 mg/l after 30 min), followed by the 85% ethanol preparation (median of 11.45 mg/l after 30 min) and that with 55% ethanol (median of 6.9 mg/l after 30 min).

Application conditions for surgical hand disinfection

In this part of the study 10 applications were performed within 80 min. For each application 5 × 4 ml product was applied to the hands and forearms and rubbed in each case for 3 min. Here, the highest ethanol blood concentration was identified for the 85% ethanol-based gel (median of 30.1 mg/l after 30 min), followed by the 95% ethanol (median of 17.5 mg/l after 30 min) and the 55% ethanol (median of 81.5 mg/l after 20 min) preparations.

Assessment of safety based on the actual application

Conduct of 20 hygienic hand disinfection cycles within 30 min is rare in clinical practice. Furthermore, in this study 4 ml hand rub was used for each application, whereas the volume used in clinical practice is often 3 ml or less [54]. Likewise, conduct of 10 surgical hand disinfection cycles with 20 ml each for 3 min each within 80 min is rarely encountered in clinical practice. If the application cycle used in the study were to be implemented in clinical practice, in the 5 min interval between two surgical hand disinfection cycles the sterile protective clothing would have to be donned, the surgical procedure carried out and the surgical protective clothing doffed. Likewise, an application volume of 20 ml is somewhat too high since an exposure time of 1.5 min is currently recommended for many hand disinfectants, unlike the 3 min normally recommended up to 2005. Overall, it is therefore expected that in clinical practice the blood ethanol concentration after application of ethanol-based hand disinfectants will be lower than in the study. It is therefore important to evaluate these data in relation to the actual exposure [55]. A study of 34 staff members who had abstained from alcohol revealed that following an average of 32 hand disinfection cycles with an 80% ethanol-based preparation, the mean ethanol value (urine) was 1.7 mg/l; without alcohol abstinence the mean urine value was 110.4 mg/l [56]. Table 2 gives an overview of the ethanol concentration detected in the blood in relation to exposure.

The European Chemicals Agency (ECHA) summarized ethanol assessment as follows: Under the actual application conditions between 1% and 2% ethanol is absorbed through the skin [45]. 21% of the applied ethanol was absorbed through porcine skin with occlusion (max. value) versus 1% in non-occlusion [60]. Half of the ethanol evaporated from the skin in around 12 s [45].

Role of the respiratory tract in absorption and release of ethanol

In hand disinfection most of the ethanol is absorbed via the respiratory tract [62], while transdermal absorption tends to be low [48, 51]. Of the inhaled ethanol between 55% and 60% is absorbed and can thus be detected in the blood [63]. The highest ethanol concentration in the air following hygienic hand disinfection occurs after around 20–30 s (13–14 mg/l) [64]. 20 s after completion of hand disinfection that value will have dropped again to 0 [63]. The highest ethanol concentration in the air following surgical hand disinfection is identified after around 80 s (18–20 mg/l) [64]. The mean ethanol metabolization rate is 150 mg/l within one hour, corresponding to 0.15‰/h [65]. But it may also be 230 mg/l per hour [66]. Hence, on average 12.5 mg ethanol per litre is metabolized within 5 min.

Some of the absorbed ethanol is also released again via the respiratory tract. After 20 persons had performed a to-

Table 2: Ethanol concentrations in the blood in relation to exposure

Exposure	Persons	Ethanol blood concentration	Reference
Natural ethanol production by intestinal bacteria	1557	Mean value: 1.1 mg/l Median: 0.4 mg/l Max. value: 35 mg/l	[57]
No exposure to ethanol	26 children	Mean value: 0,32 mg/l	[58]
50 applications of 5 ml hand disinfectant rub (62% ethanol) in 4 h	5	< 0,5 mg/l	[59]
50 applications of 4 ml hand disinfectant rub (95% ethanol, w/w) in 30 min	20	Median: 20,95 mg/l Upper 95% CI: 21,34 mg/l	[53]
25 applications of 5 ml hand disinfectant rub (62% ethanol) in 2 h	1	< 5 mg/l	[60]
110 applications of 20 ml hand disinfectant rub (85% ethanol, w/w) in 30 min	20	Median: 30,1 mg/l Upper 95% CI: 32,11 mg/l	[53]
A glass of beer with around 12 g ethanol	Unknown	150 - 250 mg/l	[61]

tal of 30 hand disinfection cycles (70% ethanol) with 1.2–1.5 ml each within 1 hour, ethanol was detectable in the breath of six of these persons in concentrations between 0.001% and 0.0025%. The detection method used in this Australian study was very sensitive; accordingly, for example, the local police in Melbourne would not have been able to detect ethanol in this concentration in the breath. After 13 min at the latest, the values had dropped again to 0 [67]. Similar findings have been reported from New Zealand where 10 anaesthetists applied a 70% ethanol-based gel for 4 h according to the 5 moments of hand hygiene principle and the ethanol content of the breath was measured at the beginning of the work shift and then subsequently at 15 min intervals. Ethanol was detectable in the breath of six of the 10 anaesthetists when hand disinfection had been performed no earlier than the previous 2 min. The highest value measured was 0.64‰ [68].

Ethanol can also be unknowingly ingested in foodstuffs. For example, fruit juices can contain up to 3 g ethanol per litre [69], and apple juice may even have 1 g ethanol per 500 ml. Assuming an absorption rate of 90%, drinking half a litre apple juice can give rise to a blood ethanol concentration of 0.17‰ in a man with a body weight of 75 kg or of 0.25‰ ethanol in a woman with a body weight of 60 kg [70].

Summary assessment

In summary, based on all the data presented here it can be stated that ethanol compared to 1-propanol and 2-propanol is endowed with superior efficacy against selected clinically relevant viruses and that the amounts of ethanol absorbed during hand disinfection are below the toxicologically relevant concentrations and hence, when used as directed, ethanol-based hand disinfectants can be considered safe [71–73].

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