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by [Wahlberg JE](#)

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Erythema-inducing effects of solvents following epicutaneous administration to man — Studied by laser Doppler flowmetry

by Jan E Wahlberg, MD¹

WAHLBERG JE. Erythema-inducing effects of solvents following epicutaneous administration to man — Studied by laser Doppler flowmetry. *Scand J Work Environ Health* 10 (1984) 159–162. Skin exposure to solvents can cause erythema, edema, scaling, and, eventually, irritant contact dermatitis. The irritant potential of chemicals is usually assessed by visual scoring, but in recent years a more objective measuring technique, laser Doppler flowmetry (LDF), has been introduced for the assessment of erythema. The method is noninvasive and allows continuous recording. In the present study 11 solvents were applied for 5 min or less to the volar forearms of a man and the kinetics of the response is shown. For seven solvents (dimethyl sulfoxide, trichloroethylene, n-hexane, carbon tetrachloride, toluene, 1,1,1-trichloroethane, 1,1,2-trichloroethane) an increase was found over the pretreatment values, whereas four solvents (methyl ethyl ketone, ethanol, propylene glycol, distilled water) did not influence blood flow. The findings are discussed in relation to the macroscopic picture (whitening and erythema) and in relation to previous studies of the edema-inducing effects of the same solvents on man and experimental animals. It is concluded that LDF is well worth trying in cases of marginal irritancy and for predictive testing, since it seems to be more sensitive and reliable than the naked eye.

Key terms: irritant contact dermatitis, new objective method, predictive testing, whitening.

Skin exposure to solvents in industry is one of the common causes of irritant contact dermatitis (1, 2, 6, 7). Their defatting capacity is also claimed to impair the barrier function of the skin and thereby facilitate the penetration of other irritants and allergens and chemicals with inherent systemic toxicity, eg, metals and pesticides.

It has been shown that an inverse correlation exists between the boiling point of a solvent and its primary irritant effect (4). Assessment of the irritant potential of chemicals is usually undertaken through examination of the exposed skin sites and with the use of different scores for the degree of erythema, edema, scaling, pupules, etc. However, the subjectivity of the traditional visual scoring system has been criticized (16), and more objective methods are desirable. In recent years laser Doppler flowmetry has been applied for quantitative assessments of the erythema (8, 13, 15), and skinfold thickness measurements have been used for the edema (12). In previous studies (14, 15) nine solvents were applied topically to human, rabbit, and guinea-pig skin, and the resulting edema (ie, fluid accumulation) was assessed by skinfold thickness measurements with a caliper.

The aim of the present study was to assess the erythematous response of the same solvents objectively and quantitatively when applied topically to human skin and to compare the findings with previous results (14, 15).

Materials and methods

Solvents

Carbon tetrachloride (analytical grade), n-hexane (analytical grade), methyl ethyl ketone (analytical grade), toluene (analytical grade), trichloroethylene (extra pure) and 1,2-propylene glycol (all E Merck, Darmstadt, Federal Republic of Germany), dimethyl sulfoxide (DMSO), 1,1,1-trichloroethane (analytical grade), 1,1,2-trichloroethane (pure) (Fluka AG, Buchs SG, Switzerland), ethanol, and distilled water were the solvents tested.

Trafuril[®] (CIBA) was used as a positive control (15).

Laser Doppler flowmetry

The apparatus (Periflux[®], Perimed, Stockholm, Sweden) and the measuring technique have been described in detail in previous studies with sodium lauryl sulfate (8) and alkaline solutions (13).

Administration

The solvents (neat) were applied to the volar forearms of a healthy man in the following two ways:

¹ Department of Occupational Dermatology, National Board of Occupational Safety and Health, and Karolinska Hospital, Stockholm, Sweden.

Reprint requests to: Dr JE Wahlberg, Department of Occupational Dermatology, Karolinska sjukhuset, S-104 01 Stockholm, Sweden.

Figure 1. Blood flow values (BFV) after 5-min exposure in excess to dimethyl sulfoxide (— · — · —), trichloroethylene (— · — · —), n-hexane and carbon tetrachloride (— — —), toluene (— · — · —), and 1,1,1-trichloroethane and 1,1,2-trichloroethane (— — —). Four solvents (methyl ethyl ketone, propylene glycol, ethanol, and water) did not influence blood flow. Pretreatment BFVs are depicted to the left of the arrow.

Figure 2. Blood flow values after 1 (— · — · —), 3 (— · — · —), and 5 (— — —) min of exposure to trichloroethylene in excess.

Figure 3. Blood flow values after 1 (— · — · —), 3 (— · — · —), and 5 (— — —) min of exposure to 0.1 ml of dimethyl sulfoxide; 0.1 ml of the other 10 solvents did not influence blood flow.

1. A glass ring with an inner diameter of 20 mm (11) was fastened with rubber bands. The solvents were administered *in excess* (1.5 ml) so that the entire test site (3.1 cm²) was covered. No occlusion was used. After 5 min the remaining solvents were removed with cotton and the test sites dabbed dry. The recording started 6 min after the application. For trichloroethylene exposure, times of 1 and 3 min were also used.

2. Solvent (0.1 ml) was pipetted onto the skin and was allowed to spread freely and evaporate. After 5 min the test sites were dabbed with cotton. The measuring probe was attached, and the recording started 6 min after the application. For DMSO exposure, times of 1 and 3 min were also used.

Visual scoring

All sites were examined for erythema, whitening, edema, scaling, etc.

Results

Laser Doppler flowmetry

The output signal from the laser Doppler flowmeter is expressed in relative and dimensionless blood flow values (BFV) (8).

Excess administration: 1.5 ml on 3.1 cm². Exposure for 5 min caused an immediate increase in blood flow after the first method of administration for seven solvents (DMSO, trichloroethylene, n-hexane, carbon tetrachloride, toluene, 1,1,1-trichloroethane, and 1,1,2-trichloroethane) when compared to the pretreatment flow values (figure 1). Carbon tetrachloride and n-hexane yielded identical curves, as did 1,1,1- and 1,1,2-trichloroethane, and therefore only one solvent from each group is shown in figure 1. For n-hexane a gradual increase to maximum at 15 min was observed, while for the other solvents the maximums were reached as early as 6–10 min after the administration.

Four solvents (methyl ethyl ketone, ethanol, propylene glycol, and water) did not influence blood flow.

For six of the seven solvents causing an increased blood flow, the pretreatment values were reached within 60 min, while the blood flow in sites exposed to DMSO remained the same for more than 24 h.

For trichloroethylene shorter exposure times of 1 and 3 min also caused an increase in blood flow (figure 2). The pretreatment values were reached within 20–30 min.

Administration of 0.1 ml. DMSO (exposure times 3 and 5 min) caused a clear response (figure 3) after the administration of 0.1 ml, while the other 10 solvents

did not influence blood flow, probably due to evaporation.

Macroscopic picture

Exposure in excess (1.5 ml on 3.1 cm²) for 5 min gave rise to whitening and erythema. Spontaneous transient whitening was observed for methyl ethyl ketone, ethanol, 1,1,2-trichloroethane, and carbon tetrachloride. A marked and persisting erythema was observed for DMSO and trichloroethylene, and transient erythema for toluene. Trichloroethylene for 1 and 3 min caused transient whitening and then erythema. A slight and transient erythema appeared after 10–20 min of exposure to 1,1,1-trichloroethane, carbon tetrachloride, and n-hexane.

With the exception of DMSO, exposure to 0.1 ml of the solvents caused no erythema. When the test sites were gently *rubbed* with gauze after 10 s of exposure, whitening was observed for eight solvents, the only exceptions being DMSO and propylene glycol.

Subjective sensations

Stinging and/or burning was noticed after exposure to n-hexane, 1,1,2-trichloroethane, trichloroethylene, DMSO, and toluene, and to a less marked extent to 1,1,1-trichloroethane.

Discussion

Laser Doppler flowmetry is a newly introduced technique for measuring tissue blood flow (9, 10). The method is noninvasive and allows continuous recording. In dermatology it has been applied, for among other purposes, for the assessment of erythema in skin irritancy reactions (8, 15), for the assessment of erythema after the topical administration of nicotines (3), and also for the assessment of Raynaud's phenomenon (5) and other conditions involving impaired peripheral circulation.

The method seems to be more sensitive and reliable than the naked eye for the assessment of skin irritancy reactions (8, 15). An oil used in industry and claimed to have caused rashes on exposed workers was found to cause a gradual increase in blood flow recorded with the flowmeter, but no visible erythema (13).

As demonstrated in figures 1 and 2, seven solvents administered in excess caused increased blood flow with varying kinetics of the response, while the visible erythema was much harder to quantify. DMSO, trichloroethylene, and toluene gave rise to a marked erythema, and three other solvents to slight and transient erythema. The naked eye failed to detect the increased blood flow recorded with the flowmeter for 1,1,2-trichloroethane.

The whitening of the skin after exposure to solvents is a well known feature, but it has seldom been

Table 1. Ranking of erythema- and edema-inducing effects of solvents after topical administration to man and experimental animals. (Ranked in order of potency, 1 being the most potent, 6 the least)

Solvent	Erythema Laser Doppler flowmetry (figure 1)	Edema Skinfold thickness measurements (14, 15)	
		Rabbit	Guinea pig
Trichloroethylene	1	1	1
Dimethyl sulfoxide	2	Not tested	Not tested
n-Hexane	3	4	5
Carbon tetrachloride	3	2	4
Toluene	4	1	2
1,1,1-Trichloroethane	5	2	4
1,1,2-Trichloroethane	5	1	3
Ethanol	—	6	6
Propylene glycol	—	5	6
Methyl ethyl ketone	—	3	6

described in the literature (1). The observed whitening did not correspond to a decrease in blood flow, and this finding supports the view that it reflects changes in structure and the removal of skin lipids rather than vasoconstriction.

The interrelationship between erythema and edema is somewhat unclear, but in most cases the erythema is supposed to be the initial event.

Some findings from previous studies on solvents (14, 15) are reviewed in table 1, where they are ranked on the basis of edema-inducing effects after repeated, open exposures. This mode of application did not induce edema in human skin, and it was assumed that the solvents evaporated (14). For guinea pigs, trichloroethylene was found to be the most potent edema-inducing solvent and was then ranked first; then came toluene (ranked second), etc.

A comparison (table 1) of the erythema-inducing effect in man after one exposure (figure 1) and the edema-inducing effect in animals after 10 exposures shows that trichloroethylene is a potent inducer of both erythema and edema. On the other hand, for toluene and 1,1,2-trichloroethane, the edema-inducing effect seems to dominate.

The purpose of this report was to introduce a new method of assessment, and the findings cannot be generalized. However, in a forthcoming paper, the variation with age, sex, site, exposure time, concentration, etc, will be elaborated.

It is concluded that laser Doppler flowmetry is well worth trying for cutting fluids, detergents, acids, and for other cases where exposure to irritants is suspected or claimed, and for predictive testing (skin cleansing agents, medicaments, cosmetics, etc). The exposure time, mode of administration (single, repeated) and concentration of the test substance can be varied. This measuring technique is not claimed to replace the traditional visual scoring. However, in cases of marginal irritancy, or where the test sites look normal to the naked eye, it can furnish additional information.

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