Allergic contact dermatitis in childhood - a review and meta-analysis

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The prevalence of allergic contact dermatitis in children is underestimated. In the first years of life it is often confused with other types of dermatitis, such as atopic eczema. In fact, contact sensitisation may be found in 13.3 - 24.5% of randomly selected children; moreover, 56.5% - 94.4% of the positive test results are clinically relevant. There are convincing data that sensitisation to common contact allergens may occur already in the first months of life, and that contact allergy is more common among children under 3 years than in older children and adults. A meta-analysis of 23 epidemiological studies comprising altogether 2794 randomly selected children and 5705 children with suspicion of contact dermatitis has shown that sensitisation appears most commonly to nickel (8.3% of random children and 19.2% of children with dermatitis), thimerosal (2.1% and 14.0% respectively), cobalt (1.9% and 13.5%), fragrances (1.7% and 11.8%), chromium (1.5% and 12.4%), Kathon CG (1.4% and 21.0%), lanolin (0.7% and 12.1%) and balsam of Peru (0.5% and 10.8%). This suggests that patch testing should be included into the diagnostic routine in children with dermatitis.

Key words: children, allergic contact dermatitis, contact allergy, prevalence, contact allergens, patch tests, meta-analysis.

Results of a first study on the frequency of contact allergy in children were published in 1961 by Brigitte Langer [21]: Among 25 children with dermatitis she found 15 with positive patch tests. Shortly afterwards, in a study of 583 children without skin diseases, Kreissl and Wiedermann found that lowest rate of positive patch tests was among the youngest [19]. At that time, a paper was also published by Marcussen, who regarded all positive patch tests in young children as an unspecific irritation [26]. Since then, the belief about rarity of contact allergy in children was repeated by many authors [15, 16, 38, 44]. Even in 1981, the idea that contact allergy could develop already in childhood was still regarded by some as misleading [16]. However, results from more recent studies suggest that prevalence of contact allergy and contact dermatitis in childhood is underestimated and that hypersensitivity to common allergens may emerge already in the first months of life [3, 22, 28, 36]. Much misunderstanding in this field is due to differences in definitions, selection of study groups and methods used. The aim of this article was to consolidate and clarify knowledge on this topic.

Methods of literature search and inclusion criteria

The literature for this review was selected with the use of bibliographic databases (all years of Medline and Current Contents up to June 2001). Combinations of keywords were used related to childhood, patch tests, contact sensitization and contact allergy. Furthermore, reference lists of those articles were also analysed. Altogether 127 scientific articles were found, of which 54 were selected for this review. These were papers of special relevance to historical development of the debate, or those best illustrating changes in views and definitions. Additionally, meta-analyses were carried out of data on the prevalence of contact hypersensitivity in the general population of children. Inclusion criteria for meta-analyses were as follows:

- Study population defined as a representative sample, random sample or a group of healthy children,
- study subjects aged up to 18 years,
- studies of more than 50 subjects each,
- results published after 1980.

Seven studies met the above criteria [3, 5, 6, 11, 29, 47, 55]. Data on the hypersensitivity to individual allergens from the original studies were extracted and pooled, and the total prevalence rates were calculated with 95% confidence interval (95%CI). The results were restricted only to allergens that were analysed in at least 3 studies, which were carried out in at least 2 countries, and when the total number of tested children exceeded 1500.

A further meta-analysis comprised studies on the frequency of contact sensitization among children with dermatitis. Besides the 3 above-mentioned inclusion criteria, a further one was that the study populations were defined as children with eczema. 16 studies have met these criteria [2, 4, 8, 14, 18, 20, 35, 36, 39, 40, 42, 45, 48, 49, 52, 53]. Regarding the question of contact sensitization among children with atopic dermatitis, an appropriate meta-analysis could not be completed, as only 3 suitable studies were published after 1980 [13, 30, 32]. Altogether they comprised only 381 children.

The relationship between contact allergy and age

The popular view about the allegedly low prevalence of contact allergy among children, besides the previously mentioned historical publications, is also supported by a more recent study: Among 251 French patients with dermatitis, positive patch tests were recorded in 31% of children and 66% of adults [15]. Observations from many other studies suggest, however, the opposite. In another French study, the highest prevalence of contact allergy (88%) was found in the age group from 1 to 3 years, as compared to 58.9% among those older than 3 years [42]. Among German children, Pevny *et al.* found the highest frequency and relevance of positive patch tests in those aged from 3 to 8 years [34]. Perhaps most convincing are the results of a study of 1729 Austrian patients by Wantke *et al.*[53]. Their results illustrating the frequent appearance of contact allergies in children are quoted in Table 1.

Tab. 1. Most relevant contact allergens and frequency of sensitization in various age groups. Compilation of data from Wantke *et al.* [53].

Age group	Women	Men
0 - 7 y. o.	Thimerosal (37.5%)	Ethylmercuric chloride (28.1%)
	Nickel (27.5%)	Thimerosal (25.0%)
8 - 14 y. o.	Nickel (28.7%)	Thimerosal (30.9%)
	Thimerosal (26.6%)	Ethylmercuric chloride (14.7%)
20 - 50 y. o.	Thimerosal (25.3%)	Thimerosal (21.1%)
	Nickel (25.2%)	Ethylmercuric chloride (13.7%)
> 70 y. o.	Nickel (12.6%)	Nickel (11.2%)
	Balsam of Peru (9.7%)	Balsam of Peru (6.7%)

Contact allergy in the general population of children

The prevalence of contact hypersensitivity in the general population of children is estimated at 13.3 - 24.5% [3, 5]. Table 2 shows meta-analysis of data on the frequency of hypersensitivity among normal children. Nickel is the most frequent sensitizer in this group with sensitivity rate of 8.3%, followed by thimerosal, neomycin, cobalt and fragrances. Studies included in this analysis were carried out in Europe or the USA, therefore, the results are representative mainly for Caucasian children. Even though meta-analyses allow for better founded conclusions about the general population than single studies, one must bear in mind that the figures are compromised by methodological differences between the studies included. Additionally, depending on the availability of data, some countries are over-represented in the analyses, whereas others are not represented at all. However, until proper international multicentre studies will be carried out, we are left with results of single studies or preferably meta-analyses.

Tab. 2. Meta-analysis of published data on the prevalence of contact sensitization in the general population of children.

Allergen	Number of children:		Frequency (95% CI)	Data sources
	tested	positive		
Nickel	2794	232	8.3 (7.3 - 9.3)%	[3, 5, 6, 11, 29, 47, 55]
Thimerosal	2107	44	2.1 (1.5 - 2.7)%	[3, 5, 29, 55]
Neomycin	2694	54	2.0 (1.5 - 2.5)%	[3, 5, 11, 29, 47, 55]
Cobalt	2317	44	1.9 (1.3 - 2.4)%	[3, 5, 6, 11, 29]
Fragrance Mix	1793	31	1.7 (1.1 - 2.3)%	[3, 5, 29]
Chromium	2794	43	1.5 (1.1 - 2.0)%	[3, 5, 6, 11, 29, 47, 55]
Kathon CG	1655	24	1.4 (0.9 - 2.0)%	[5, 11, 29]
PTBPF	2531	28	1.1 (0.7 - 1.5)%	[3, 5, 11, 29, 55]
Colophony	1969	19	1.0 (0.5 - 1.4)%	[5, 11, 29, 55]
Lanolin	2531	18	0.7 (0.4 - 1.0)%	[3, 5, 11, 29, 55]
Carba Mix	2107	13	0.6 (0.3 - 0.9)%	[3, 5, 29, 55]
Balsam of Peru	2531	14	0.5 (0.3 - 0.8)%	[3, 5, 11, 29, 55]
Quaternium	1969	8	0.4 (0.1 - 0.7)%	[5, 11, 29, 55]
Black rubber Mix	2531	7	0.3 (0.1 - 0.5)%	[3, 5, 11, 29, 55]
Formaldehyde	1545	5	0.3 (0.0 - 0.6)%	[5, 29, 55]
PPD	1545	4	0.3 (0.0 - 0.5)%	[5, 29, 55]
Chinolone Mix	2217	6	0.3 (0.0 - 0.5)%	[3, 5, 11, 29]
Epoxy resin	1969	4	0.2 (0.0 - 0.4)%	[5, 11, 29, 55]
MBT	1545	3	0.2 (0.0 - 0.4)%	[5, 29, 55]
Mercapto Mix	2531	3	0.1 (0.0 - 0.2)%	[3, 5, 11, 29, 55]
Thiuram Mix	1969	3	0.1 (0.0 - 0.3)%	[5, 11, 29, 55]
Ethylenediamine	1969	3	0.1 (0.0 - 0.3)%	[5, 11, 29, 55]
Paraben Mix	1655	1	0.1 (0.0 - 0.2)%	[5, 11, 29]

95% CI = 95% confidence interval, PTBPF = para-tert-butylphenylformaldehyde resin, MBT = mercaptobenzothiazole, PPD = para-phenylenediamine.

Contact allergy among children with dermatitis

According to the literature, the frequency of contact hypersensitivity among children with various forms of eczema is estimated at 23.8 - 71% [20, 34]. Children below 3rd year are probably at highest risk. In a French study, 66% of 337 children with eczema aged 1 - 15 years were patch test-positive, most frequently to nickel and other metals, fragrances and rubber additives [42]. Hypersensitivity was most frequent among children below 3 years (88%), as compared to 58.9% of children above this age [42]. Also in an Italian group of 670 children, the highest frequency was found in those between 0.5 - 3 years [24]. Table 3 summarises results of 16 studies of children with suspected contact dermatitis.

Tab. 3. Meta-analysis of published data on the frequency of contact hypersensitivity among children with suspected contact dermatitis.

Allergen	Number of children:		Frequency (95% CI)	Data sources
	tested	positive		
Kathon CG	2004	420	21.0 (19.2 - 22.7)%	[4, 8, 18, 20, 40, 42]
Nickel	4903	940	19.2 (18.1 - 20.3)%	[2, 4, 14, 18, 20, 35, 36, 39, 40, 42, 45, 48, 49, 52, 53]
Mercuric ammonium chloride	2919	426	14.6 (13.3 - 15.9)%	[2, 4, 14, 18, 39, 53]
Thimerosal	3886	544	14.0 (12.9 - 15.1)%	[2, 4, 14, 18, 36, 39, 40, 42, 48, 49, 53]
Cobalt	4392	593	13.5 (12.5 - 14.5)%	[2, 4, 14, 18, 20, 35, 36, 39, 40, 42, 45, 48, 49]
Chromium	4288	534	12.4 (11.5 - 13.4)%	[2, 4, 14, 18, 20, 35, 36, 39, 40, 42, 45, 49, 52]
Lanolin	3555	431	12.1 (11.0 - 13.2)%	[2, 4, 14, 20, 36, 39, 40, 42, 48, 49, 52]
Fragrance Mix	4245	402	11.8 (10.8 - 12.8)%	[2, 4, 14, 18, 20, 36, 39, 40, 42, 45, 48, 49]
Balsam of Peru	4120	444	10.8 (9.8 - 11.7)%	[2, 4, 14, 18, 20, 35, 36, 39, 40, 42, 45, 49]
Colophony	4328	420	9.7 (8.8 - 10.6)%	[2, 4, 14, 20, 35, 36, 39, 40, 42, 45, 48, 49, 52]
Formaldehyde	4473	421	9.4 (8.6 - 10.3)%	[2, 4, 8, 14, 18, 20, 35, 36, 39, 40, 42, 49, 52]
Neomycin	4478	75	1.7 (1.3 - 2.0)%	[2, 14, 18, 20, 35, 36, 39, 40, 42, 45, 48, 49, 52, 53]
Mercapto Mix	3203	48	1.5 (1.1 - 1.9)%	[2, 14, 18, 20, 36, 39, 40, 42, 48, 49]
PPD	3545	53	1.5 (1.1 - 1.9)%	[2, 14, 18, 39, 40, 42, 45, 48]
MBT	2138	33	1.5 (1.0 - 2.1)%	[2, 18, 36, 40, 42, 45, 49]
PTBPF	2401	36	1.5 (1.0 - 2.0)%	[14, 18, 20, 39, 40, 42, 48]
Wood tars	1990	29	1.5 (0.9 - 2.0)%	[2, 20, 35, 39, 52]
Thiuram Mix	2986	34	1.1 (0.8 - 1.5)%	[2, 14, 18, 20, 39,40, 42, 48]
Black rubber Mix	2909	29	1.0 (0.6 - 1.4)%	[2, 14, 18, 20, 39, 40, 48, 49, 52]
Carba Mix	1941	16	0.8 (0.4 - 1.2)%	[2, 20, 36, 39, 40]
Ethylenediamine	2866	20	0.7 (0.4 - 1.0)%	[2, 14, 18, 20, 36, 39, 42, 52]
Turpentine	1716	12	0.7 (0.3 - 1.1)%	[20, 39, 45]
Paraben Mix	3152	14	0.4 (0.2 - 0.7)%	[2, 8, 14, 20, 39, 42]
Epoxy resins	2012	8	0.4 (0.1 - 0.7)%	[2, 20, 39, 42]
Benzocaine	1780	6	0.3 (0.1 - 0.6)%	[2, 18, 42, 45]
Quaternium 15	2124	4	0.2 (0.0 - 0.4)%	[2, 8, 18, 20, 42, 49]

95% CI = 95% confidence interval, PTBPF = para-tert-butylphenylformaldehyde resin, MBT = mercaptobenzothiazole, PPD = para-phenylenediamine.

Atopy, atopic eczema and contact allergy

The relationship between atopy and contact dermatitis remains unclear. The most popular hypothesis of the 1970's war that the presence of atopy would prevent contact sensitization. This view was supported by results from both laboratory [12, 27] and clinicoepidemiologic studies of that times [1, 43]. Nowadays, the picture is not so consistent anymore. On the one hand, Rees *et al.* [37] suggested that patients with subclinical or mild atopic dermatitis (AD) are less prone to develop contact hypersensitivity. Uehara and Sawai [50] could confirm this observation, however, only in the most severe AD cases. On the other

hand, there are also indications that AD could pose a risk factor for contact sensitization [46]. Recent epidemiologic studies also provide us with conclusions differing from the previous ones. Among 670 Italian children with contact allergy, there was a high incidence (77%) of atopic diathesis [24]. Pambor *et al.* found in eastern Germany positive patch tests in 24.8% of children with AD as compared to 18.4% among non-atopics [32]. Also in Norway, contact sensitization is found more frequently among atopic children (28.8%) that among non-atopics (17.9%) [11]. In France, 43% of 137 children with AD were found with contact sensitization, mostly to metals, fragrances, balsam of Peru, lanolin, neomycin and emollients [13]. Some authors have pointed on the risk of iatrogenic sensitization to external therapeutics (especially antiseptics and antibiotics) among children with AD [20, 33]. Also in adult life atopics develop occupational contact dermatitis more frequently than non-atopics [17]. However, Lisi and Simonetti carried out repeated patch tests in 61 children and concluded that atopic eczema does not constitute a risk factor for contact allergy, regardless the impaired barrier function of the skin [23]. Facing the above contradictions, further studies are needed to clarify the relationship between atopy and contact sensitization.

Most important contact allergens in childhood

Similar to adults, children most frequently become sensitized to ubiquitous allergens, such as nickel, antiseptics, fragrances, balsam of Peru, and lanolin. The sensitization rates to these and other allergens are shown in Tables 2 and 3. Interestingly, there are 3 haptens that seem to sensitize less frequently children with eczema than healthy ones: neomycin (1.7% versus 2.0%), Carba mix (0.6% versus 0.8%) and quaternium (0.2% versus 0.4%). Besides the fact that meta-analyses could have been affected by differences between populations studied in the original articles, these results might also indicate a lower clinical relevance of sensitization to these haptens. In contrast to the above, there are large differences in sensitization rates to thimerosal (2.1% among healthy and 14.0% among eczema children). Thimerosal is organic mercury preservative broadly used in vaccines. Many authors have pointed on the possible role of vaccines in the development of thimerosal sensitization [9, 31, 33, 51], though thimerosal-containing vaccines are still in use. Patrizi *et al.* reported on 5 children with AD aged 7 - 28 months, in whom administration of thimerosal-containing vaccines led to aggravation of eczema. In all these children patch tests with thimerosal gave positive results [33]. Another preservative - Kathon CG - shows major difference in sensitization rates between healthy children (1.4%) and those with dermatitis (21.0%). Children with foot dermatitis most frequently develop contact allergy to rubber additives, chromate and external therapeutics [7, 41, 54]. Depending on the clinical picture, Kuiters *et al.* attribute the clinical relevance to the following contact allergens: spices and neomycin in perioral dermatitis, and nickel, colophony, hydroquinone and external therapeutics in facial dermatitis [20].

Patch testing of children

In a historical study, Marcussen proposed that allergen concentrations for patch testing of children should be lower than for adults, e.g. 1% nickel sulfate instead of 5% [25]. This view was supported by Röckl *et al.* [38] who pointed on higher susceptibility of the infantile skin to unspecific irritants. Also Hjorth found the routine patch test concentrations too high for children and proposed to repeat each positive test with 50% of the initial allergen concentration [16]. Recently most authors speak, however, in favour of testing children with the same concentrations as adults. Veien *et al.* [52] did not encounter any interpretation difficulties in their study of 158 children patch tested with the standard tray. Also Pevny *et al.* recommended testing children with the same allergen concentrations as adults [34]. Among clinicoepidemiologic studies published during the last 10 years, 9 contained sufficient information about the concentration of the allergen and the vehicle used [3, 4, 11, 14, 18, 32, 42, 48, 53]. In general, the tests were done with allergen concentrations recommended for adults [10]. Among few exceptions were: nickel sulfate concentration of 1% (instead of 5%) applied by Sevila *et al.* [48], and the 0.5%-concentration of PPD (instead of 1%) in further 3 studies [3, 14, 18].

Roul *et al.* proposed for children a "shortened" version of the European Standard, which consists of 17 allergens (Tab. 4) [42]. Twelve of the proposed allergens were confirmed as frequent sensitizers by meta-analyses presented here. The selection of the remaining allergens is questionable, as the hypersensitivity rates to Paraben Mix and ethylenediamine are below 1% (Tab. 3). Instead, Kathon CG (sensitivity rate 21.0%), cobalt (13.5%), neomycin (1.7%), Mercapto Mix, PPD und wood tars (each 1.5%) are missing on Roul's list. Exactly as in case of adults, each positive patch tests results must undergo a scrutiny regarding it's clinical relevance [11, 42]. The clinical relevance of positive patch tests in children was estimated between 56.5% [48] and 94.4% [14]. Interestingly, Goncalo *et al.* [14] found among children aged up to 5 years a higher rate of relevant results (94.4%) than among older children (68.3% for those aged 6-10, and 77.5% for aged 11-14 y. o.).

Tab. 4. The "shortened" European Standard for children below 6 years proposed by Roul *et al.* [42].

Potassium dichromate 0.5%
Neomycin sulfate 20%
Thiuram Mix 1%
Formaldehyde 1%
Colophony 20%
Balsam of Peru 25%
Lanolin 30%
Paraben Mix 15%
para-tert-butylphenylformaldehyde resin (PTBPF) 1%
Fragrance Mix 8%
Nickel sulfate 5%
Mercaptobenzothiazole 2%
Thimerosal 0.1%
Tixocortol pivalate 1%
Budesonide 0.1%
Fusidic acid 2%
Ethylenediamine 1%
Petrolatum (Control)

Conclusions

- In randomly selected populations of children positive patch tests are found in 13.3 - 24.5%; at least half of them are clinically relevant.
- Contact hypersensitivity is more frequent among children below 3 years than among older children and adults.
- Children become sensitized to ubiquitous allergens, such as metals (especially nickel), preservatives (thimerosal, Kathon CG), fragrances, balsam of Peru and lanolin.
- Patch testing should be more used in the routine diagnostics of children with eczema.

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