Revised Minimal Baseline Series of the International Contact Dermatitis Group (ICDRG): Evidence Based Approach

Ali Alikhan MD1*, Lily S. Cheng BS2*, Iris Ale MD3, Klaus E. Andersen MD DMSc4, Magnus Bruze MD5, Hee Chul Eun MD PhD6, Chee Leok Goh MD7, An Goossens R. Pharm, PhD8, Jean-Marie Lachapelle MD PhD9, John McFadden FRCP10, Rosemary Nixon MBBS MPH11, Denis Sasseville MD12, Howard I. Maibach MD13

1Mayo Clinic, Department of Dermatology, Rochester, Minnesota
2University of California at Davis, School of Medicine, Sacramento, California
3Department of Dermatology, Republic University of Uruguay, Montevideo, Uruguay
4Department of Dermatology and Allergy Centre, Odense University Hospital, University of Southern Denmark, Odense, Denmark
5Department of Occupational and Environmental Dermatology, Skåne University Hospital Malmö, Lund University Malmö, Sweden
6Department of Dermatology, Seoul National University College of Medicine, Seoul, Korea
7National Skin Center, Singapore
8Contact Allergy Unit, Department of Dermatology, University Hospital K.U. Leuven, Leuven, Belgium
9Catholic University of Louvain, Brussels, Belgium
10St. John’s Institute of Dermatology, St. Thomas’ Hospital, London, England
11Occupational Dermatology Research and Education Center, Skin and Cancer Foundation Victoria, Melbourne, Australia
12McGill University Health Centre, Division of Dermatology, Montreal, Canada
13University of California at San Francisco, School of Medicine, Department of Dermatology, San Francisco, California

*Dr. Ali Alikhan and Ms. Lily Cheng are guest scientists to the ICDRG

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University of California, San Francisco
Department of Dermatology
110 Surge Bldg.
90 Medical Center Way
San Francisco, CA 94143-0989

Tel: 415 476 2468
Fax: 415 753 5304
Email: maibachh@derm.ucsf.edu; alialikhan1@yahoo.com; lscheng@ucdavis.edu

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ICDRG members: Iris Ale, Klaus E. Andersen, Magnus Bruze, Thomas L. Diepgen, Peter Elsner, Hee Chul Eun, Chee Leok Goh, An Goossens, Hemangi Jerajani, Jean-Marie Lachapelle, Howard I. Maibach, Kayoko Matsunaga, John McFadden, Rosemary Nixon, and Denis Sasseville
Abstract

The first ICDRG minimal baseline series was devised in 1997. In an effort to update this series, ICDRG members utilized an evidence based approach to expand the current minimal baseline series. In addition to the original 20 allergens of the 1997 series, we propose an additional 12 allergens. Additionally, we discuss important allergens which did not make our revised series, such as black rubber mix and mixed dialkyl thioureas. Finally, we discuss important principles in allergic contact dermatitis – namely, mindfulness of occult allergens, determination of clinical relevance, and occupational exposures.
Introduction

The first commonly used standard allergen series was proposed by Paul Bonnevie in 1939.¹ Today, many countries have groups dedicated to allergic contact dermatitis and patch testing, and several utilize their own standard allergen series.² This, however, makes the process of international collaboration difficult. As a means to develop international comparative data, the International Contact Dermatitis Group (ICDRG) created a standard series in 1997.³ The panel includes only 20 allergens, less than most national panels. We feel that it is time to expand this international panel to include allergens already employed in the panels of individual countries. We have attempted to provide the evidence and our reasoning.

Methods

To find national standard allergen panel components and concentrations, a literature search was performed by querying PubMed for articles containing the key words “patch testing”, “contact dermatitis” and/or the names of countries and contact dermatitis groups.² To supplement and corroborate information gathered in the search, representatives from 24 contact dermatitis groups were asked via e-mail to provide information on the standard allergen panels of their respective groups. Standard allergen panel components and concentrations were found for 15 countries. Two countries, Poland and Sweden, use the current 20 allergen panel of the ICDRG.

After the information was gathered, standard series allergens from 15 countries (as well as the current ICDRG series) were compiled - a member of the ICDRG (H.I.M.) and another physician (A.A.) examined the data and suggested (based on personal experience and the current literature) which allergens might be included in an updated expanded ICDRG minimal baseline series, which should not be included, and which warranted further discussion amongst members
of the ICDRG. Their recommendations were shared with the remaining ICDRG members for their input, suggestions and vote.

Results

We compiled the results and propose a new minimal baseline series for the ICDRG (Table I). Of the twenty previous allergens found in the first ICDRG panel, all remain in the current panel. Twelve new allergens are also included based on voting, discussions, and literature survey.

Comments relating to specific allergens included in the panel

1) 2-mercaptobenzothiazole (2%, petrolatum) and Mercapto mix

2-mercaptobenzothiazole, a common rubber additive, utilized for decades, continues to be a significant clinical problem. On these same grounds, mercapto mix is also included.

2) Para-phenylenediamine (4-phenylenediamine) (1%, petrolatum)

This is a major hair dye allergen. When there is a clinical suspicion of hair dye contact dermatitis, the hair dye battery and the patient’s dyes are indicated, as 4-phenylenediamine is not the only allergen. The question of clinically relevant active sensitization has been raised in Germany and thus 4-phenylenediamine has been removed from their baseline series. We believe clinical relevance outweighs the risk of active sensitization.

3) 4-tert-butylphenol formaldehyde resin (1%, petrolatum)
It is a newer allergen and a useful screen for consumer exposure (i.e. glues), but, in our experience, is often negative in occupational exposure. For occupation exposure, the worker’s own resin(s) should be added.

4) Formaldehyde (2%, aqueous)
Recent data suggests that 1% concentration misses clinically relevant patients – 2% is now preferred to 1%.

5) Tosylamide/formaldehyde resin (10%, petrolatum)
Though alternatives with lower sensitization potential are available, this is still ubiquitously used. It continues to be the major, but not only, nail polish allergen.

6) Fragrance mix I (8%, petrolatum)
Detailed studies indicate that approximately 50% of positive reactions are not reproducible (when individual components are applied), and may be irritant in nature. Positive tests should, therefore, be followed by subsequent testing with individual components of the mix so patients do not unnecessarily avoid fragrances.

7) Fragrance mix II (14%, petrolatum)
Preliminary data indicates that about 65% of positive reactions are reproducible when individual components are applied. We suggest for practical purposes (see above) that positive tests be followed by subsequent testing with individual components of the mix.
8) **Carba mix (3%, petrolatum)**

When patch test is positive, the patient should then receive subsequent testing with individual components of the mix due to large percentage of false positives.\(^\text{15}\)

9) **Chlormethyl/methylisothiazolinone (Kathon CG) (0.02%, aqueous)**

The 0.02% (200 ppm) concentration is preferred as the 0.01% (100 ppm) concentration, previously the gold standard,\(^\text{16}\) misses clinically relevant cases.\(^\text{17-21}\)

10) **Colophonium (colophony) (20%, petrolatum)**

While some cases are of obvious clinical relevance (i.e. adhesive tape), it is often difficult to trace the clinical relevance of a positive test. Some colophony esters do not cross react.\(^\text{22}\)

Additionally, colophony sensitivity may be a marker of fragrance sensitivity.\(^\text{23}\)

11) **Compositae mix (5%, petrolatum) and Sesquiterpene lactone mix (0.1%, petrolatum)**

Worldwide experience with both remains limited and it is likely that further studies will clarify contents, chemical purity, and clinical relevance.\(^\text{24-26}\) Of note, there are different compositae mixes, some of which are not easily available or not completely standardized.

12) **Diazolidinylurea (2%, petrolatum), Imidazolidinyl urea (2%, aqueous), and Quaternium-15 (2%, petrolatum)**

Some patients with positive patch tests appear to tolerate use depending on concentration in final product. The complex chemistry and clinical relevance of the so-called formaldehyde releasers
has been extensively reviewed by De Groot. Some, but not all, members recommend that if one is patch test positive, all should be avoided.

13) **Budesonide (0.01%, petrolatum), Tixocortol-21-pivalate (0.1%, petrolatum), and Hydrocortisone-17-butyrate (1%, petrolatum)**

These are excellent markers of corticoid sensitivity/ACD. “Use” testing (also known as provocative use testing or repeat open application testing) is valuable in establishing clinical relevance.34, 35

14) **Epoxy resin (1%, petrolatum)**

This is a useful screener but it is often necessary, especially in occupational exposure, to test with a patient’s appropriately diluted specific epoxy resin.36

15) **Lanolin alcohol (30%, petrolatum)**

It is a common cause of false positives due to Excited Skin Syndrome,37 and re-testing positives to rule out this phenomenon is helpful. “Use” testing to ascertain clinical relevance is also important to avoid falsely labeling patients as allergic to this ubiquitous material.

16) **Hydroyisohexyl-3-cyclohexene carboxaldehyde (Lyral) (5%, petrolatum)**

This new fragrance chemical is not used worldwide and may not be appropriate for certain countries. Nonetheless, it was voted in unanimously by our members.

17) **Neomycin sulfate (20%, petrolatum)**
The frequency of positives relates to local usage.

18) Nickel sulfate (5%, petrolatum)

This remains a worldwide clinical problem – when patch testing is negative, consider testing with a nickel-containing coin.

19) N-isopropyl-N-phenyl-4-phenylenediamine (IPPD) (0.1%, petrolatum)

A rubber chemical, the clinical relevance is often related to industrial rubber exposure. It is part of the black rubber mix, and less often positive than the mix itself.

20) Thiuram mix (1%, petrolatum)

This rubber accelerator mixture remains widely used, and subsequent testing of individual components of the mix is clinically indicated for those with positive patch testing.

21) Methylisothiazolinone (0.01%, aqueous)

This isomer is present in Cl+Me-isothiazolinone (Kathon CG), which contains both isomers. When tested alone the concentration is increased to 0.01%. Products typically contain much higher concentrations (up to 100 ppm) of this isomer compared to the combination (Kathon CG).

22) Paraben mix (16%, petrolatum)

It is a rare clinical allergen except in leg ulcers. Since greater than 50% of positives are not reproducible (irritant in nature), subsequent testing with individual components of the mix for
those with positive tests is recommended before recommending avoidance of this ubiquitous preservative.38

23) Potassium dichromate (0.5%, petrolatum)
It remains a highly clinically relevant allergen in cement workers and in those who wear leather gloves and shoes. Retesting to rule out Excited Skin Syndrome may be clinically indicated as this is a marginal irritant.

24) Myroxylon pereirae (Balsam of Peru) (25%, petrolatum)
This is a marker of fragrance delayed hypersensitivity but of often uncertain clinical relevance. Its usefulness will probably be determined in the next 5-10 years as there is additional experience with testing individual fragrance chemicals (i.e. flavor and fragrance series). Greater clinical confidence can be obtained when the fragrance mixes and their individual components are positive.

25) Methyldibromoglutaronitrile (0.3%, petrolatum)
Its use has greatly declined secondary to European legislation. It is likely it will be removed from the next baseline ICDRG series secondary to decreased use in consumer products.

26) Cobalt chloride (1%, petrolatum)
Determining clinical relevance is generally difficult. It typically represents co-sensitization with nickel sulfate. The cobalt spot test may help clarify clinical significance of patch test positivity.39
Comments relating to specific allergens NOT included in the panel

1) Bacitracin
This allergen was excluded from the series as it is presumably more of an American, rather than an international, problem.

2) Mixed dialkyl thioureas
This was excluded from the standard series in a close, non-unanimous vote. It may be found in a wristband or ankle/knee brace. Testing to a piece of the offending agent will often result in a positive test, though using the allergen as a back-up may be necessary.40

3) Ethylenediamine dihydrochloride
It was excluded from the series because one brand of corticosteroid that contained it as a stabilizer no longer has it, although generic preparations may still contain it.

4) 2-bromo-2-nitropropane-1,3-diol (Bronopol)
This was excluded from the standard series due to minimal usage and difficulty ascertaining clinical relevance. A minority of members thought it should be retained.

5) Black rubber mix
This very old allergen is a mixture of para-phenylenediamine-like chemicals that are present in rubber products (e.g. tires). Its frequency is low worldwide and thus it was excluded from the series. The decision to exclude this from the series was a close vote.
General Discussion

1% Rule

Early on, Niels Hjorth and the ICDRG clearly believed frequency was important in developing a routine series, and the general approximate cut-off was 1% positives in an eczema population in a massive screening. Many of the allergens in our recommended series are common worldwide and used everywhere. There are, however, important exceptions: occult allergens, clinical relevance, and incomplete knowledge of international burden.

Occult Allergens

Detailed history may not pick up covert/occult allergens (e.g. parabens, preservatives, corticosteroids). These may belong in a baseline series if they are rare but widely used (e.g. parabens, corticosteroids, preservatives).

Clinical Relevance and Usefulness of Patch Results

Diagnosing allergy is largely a clinical judgment as hard data is unavailable – we must constantly look for clinical relevance as patch test data is not, in itself, sufficient. We refer to algorithms for this purpose. Furthermore, it is important to demonstrate exposure for clinical relevance. We rule out Excited Skin Syndrome via repeat testing, false positives via “use” testing, and cross reactivity via detailed history and understanding of allergen chemistry. Details about Repeat open application testing (ROAT) or “use” testing may be found in Patch Testing and Prick Testing: A Practical Guide.

International Burden
We realize that we do not know much about allergy in all parts of the globe – patterns in Africa, South America, and much of Asia are largely unknown.

**Occupational Contact Dermatitis**

This should be examined with special series (e.g. baker’s series). We should not use special series on all patients, but those with specific exposures. Special series are detailed in *Patch Testing and Prick Testing: A Practical Guide*.47

**Conclusion**

This is an attempt to utilize evidence based criteria in defining the minimal baseline series of the ICDRG. However, the criteria remain relatively soft. Much remains to be done before this can be considered an evidence based success.
References


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Table I: Updated 2011 Minimal Baseline Series of the ICDRG

<table>
<thead>
<tr>
<th>Selected Allergens with Concentrations</th>
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<tbody>
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<tr>
<td>Epoxy resin – 1%*</td>
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<td>Formaldehyde (formalin) – 2%**</td>
</tr>
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<td>Fragrance mix I – 8%*</td>
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<td>Hydrocortisone-17-butyrate – 1%</td>
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<td>Hydroyisohexyl-3-cyclohexene carboxaldehyde (Lyral) – 5%</td>
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* represents allergens which were also part of the previous minimal baseline series from 1997; ** represents allergens which were also part of the previous minimal baseline series but have new concentrations in the 2011 updated minimal baseline series.