Chair: Kristiina Aalto-Korte
Occupational Medicine
Finnish Institute of Occupational Health
Helsinki, Finland
+358 30 474 2292
e-mail: kristiina.aalto-korte@ttl.fi

27 November 2018

Proposal for Harmonised Classification and Labelling of 3-aminomethyl-3,5,5-trimethycyclohexylamine (isophorone diamine; IPD, CAS number 2855-13-2)

The European Environmental and Contact Dermatitis Research Group (EECDRG) is a scientific group founded in 1984 and focussing on various aspects of contact dermatitis, with 21 members from 13 countries.

We want to express our support to the German proposition to give 3-aminomethyl-3,5,5-trimethycyclohexylamine (isophorone diamine; IPD, CAS number 2855-13-2) the harmonised classification as a skin sensitiser in Category 1A. The proposition was solely based on experimental animal data. We also want to point out that, in the dermatological literature, isophorone diamine is an established skin sensitiser that for decades has routinely been used in the diagnosis of allergic contact dermatitis related to exposure to epoxy products. A simple Medline search 'isophorone diamine allergy' produced 20 references from a period 1979-2016. Of these we present 15 that deal with contact allergy to isophoronediamine below.

on behalf of the EECDRG,

Kristiina Aalto-Korte, EECDRG Chair

1. Contact Dermatitis. 2016 Feb;74(2):83-93. doi: 10.1111/cod.12491.
Sensitization to reactive diluents and hardeners in epoxy resin systems. IVDK data 2002-2011. Part I: reaction frequencies.
Geier J(1), Lessmann H(1), Hillen U(2), Skudlik C(3), Jappe U(4)(5)(6).
Author information:
(1)Information Network of Departments of Dermatology, University of Göttingen, 37075, Göttingen, Germany.
(2)Department of Dermatology, University of Essen, 45122, Essen, Germany.
(3)Department of Dermatology, Environmental Medicine, and Health Theory, University of Osnabrück, 49069, Osnabrück, Germany.
(4)Department of Dermatology, University of Heidelberg, 69115, Heidelberg, Germany.
(5)Department of Dermatology, University of Lübeck, 23538, Lübeck, Germany.
(6)Division of Clinical and Molecular Allergology, Research Centre Borstel, Airway Research Centre North, Member of the German Centre for Lung Research, 23845, Borstel, Germany.
BACKGROUND: Epoxy resin systems (ERSs), consisting of resins, reactive diluents, and hardeners, are indispensable in many branches of industry. In order to develop less sensitizing ERS formulations, knowledge of the sensitizing properties of single components is mandatory.
OBJECTIVES: To analyse the frequency of sensitization in the patients concerned, as one integral part of a research project on the sensitizing potency of epoxy resin compounds (FP-0324).
METHODS: A retrospective analysis of data from the Information Network of Departments of Dermatology (IVDK), 2002-2011, and a comparison of reaction frequencies with (surrogate) exposure data, were performed.
RESULTS: Almost half of the patients sensitized to epoxy resin were additionally sensitized to reactive diluents or hardeners. Among the reactive diluents, 1,6-hexanediol diglycidyl ether was the most frequent allergen, followed by 1,4-butanediol diglycidyl ether, phenyl glycidyl ether, and p-tert-butylphenyl glycidyl ether. Among the hardeners, m-xylylene diamine (MXDA) and isophorone diamine (IPDA) were the most frequent allergens. According to the calculated exposure-related frequency of sensitization, MXDA seems to be a far more important sensitizer than IPDA. Up to 60% of the patients sensitized to hardeners and 15-20% of those sensitized to reactive diluents do not react to epoxy resin.
CONCLUSIONS: In cases of suspected contact allergy to an ERS, a complete epoxy resin series must be patch tested from the start.

2. Contact Dermatitis. 2015 Dec;73(6):336-42. doi: 10.1111/cod.12445.
Occupational allergic contact dermatitis caused by epoxy chemicals: occupations, sensitizing products, and diagnosis.
Aalto-Korte K(1), Pesonen M(1), Suuronen K(1).
Author information:
(1)Occupational Medicine, Finnish Institute of Occupational Health (FIOH), 00250, Helsinki, Finland.
BACKGROUND: Epoxy products are among the most common causes of occupational
allergic contact dermatitis. Diglycidyl ether of bisphenol A resin (DGEBA-R) is the most important sensitizer in epoxy systems.
OBJECTIVES: To describe patients with occupational allergic contact dermatitis

caused by epoxy products.
METHODS: Patients with allergic reactions to epoxy chemicals were chosen from test files (January 1991 to June 2014). Only patients with occupational contact allergy to some component of epoxy resin systems were included. We analysed patch test results, occupation, symptoms, and exposure data.
RESULTS: We found a total of 209 cases with occupational contact allergy to epoxy chemicals. The largest occupational groups were painters (n = 41), floor layers (n = 19), electrical industry workers (n = 19), tile setters (n = 16), and aircraft industry workers (n = 15). A total of 82% of the patients reacted to DGEBA-R. Diagnosis of the DGEBA-R-negative patients required testing with m-xylylenediamine, N,N'-tetraglycidyl-4,4'-methylenedianiline, 1,4-butanediol diglycidyl ether, 2,4,6-tris-(dimethylaminomethyl)phenol, diglycidyl ether of bisphenol F resin, N,N'-diglycidyl-4-glycidyloxyaniline, isophoronediamine, 4,4'-diaminodiphenylmethane, diethylenetriamine, and cresyl glycidyl ether. The hands/upper extremities were most commonly affected (69%), but facial symptoms were also frequent (60%).
CONCLUSIONS: Allergic contact dermatitis caused by to epoxy products cannot always be diagnosed by the use of commercial test substances. Workplace products need to be tested.

3. Contact Dermatitis. 2014 Sep;71(3):145-53. doi: 10.1111/cod.12280.
Contact allergy to epoxy hardeners.
Aalto-Korte K(1), Suuronen K, Kuuliala O, Henriks-Eckerman ML, Jolanki R.
Author information:
(1)Occupational Medicine, Finnish Institute of Occupational Health (FIOH), 00250, Helsinki, Finland.
BACKGROUND: Diglycidylether of bisphenol A resin is the most important sensitizer in epoxy systems, but a minority of patients develop concomitant or solitary contact allergy to epoxy hardeners. At the Finnish Institute of Occupational Health, several in-house test substances of epoxy hardeners have been tested in a special epoxy compound patch test series.
OBJECTIVES: To analyse the frequency and clinical relevance of allergic reactions to different epoxy hardeners.
METHODS: Test files (January 1991 to March 2013) were screened for contact allergy to different epoxy hardeners, and the clinical records of patients with allergic reactions were analysed for occupation, concomitant allergic reactions, and exposure.
RESULTS: The most commonly positive epoxy hardeners were m-xylylenediamine (n =
24), 2,4,6-tris-(dimethylaminomethyl)phenol (tris-DMP; n = 14), isophorone-diamine (n = 12), and diethylenetriamine (n = 9). Trimethylhexamethylenediamine (n = 7), tetraethylenepentamine (n = 4), and triethylenetetramine (n = 2) elicited some reactions, although most patients were found to have no specific exposure. Allergic reactions to hexamethylenetetramine, dimethylaminopropylamine and ethylenediamine dihydrochloride were not related to epoxy products.
CONCLUSIONS: Tris-DMP is an important sensitizer in epoxy hardeners, and should be included in the patch test series of epoxy chemicals.

4. Contact Dermatitis. 2010 Jan;62(1):55. doi: 10.1111/j.1600-0536.2009.01652.x.

Contact allergy to epoxy resins--a 10-year study.
Canelas MM(1), Gonçalo M, Figueiredo A.
Author information:
(1)Serviço de Dermatologia, Hospitais da Universidade de Coimbra, Praceta Mota Pinto, 3000-075 Coimbra, Portugal. mariamiguelcanelas@gmail.com
No abstract
(4 patients with contact allergy to IPDA among 24 patients with an allergic reaction to bisphenol A diglycidylether epoxy resin.)

5. Immunopharmacol Immunotoxicol. 2010 Sep;32(3):528-9. doi: 10.3109/08923970903468839.
Airborne allergy to isophoronediamine and epoxy resin.
Foti C(1), Bonamonte D, Antelmi A, Nettis E, Cassano N, Vena GA, Angelini G.
Author information:
(1)Dermatology Clinic, Department of Internal Medicine, Immunology and Infectious Diseases, University of Bari-Policlinico, Piazza Giulio Cesare 11, 70124 Bari, Italy. c.foti@dermatologia.uniba.it
No abstract. Case report.

6. Contact Dermatitis. 2004 Nov-Dec;51(5-6):263-72.
An attempt to improve diagnostics of contact allergy due to epoxy resin systems. First results of the multicentre study EPOX 2002.
Geier J(1), Lessmann H, Hillen U, Jappe U, Dickel H, Koch P, Frosch PJ, Schnuch A, Uter W.
Author information:
(1)Information Network of Departments of Dermatology (IVDK), University of Göttingen, 37075 Göttingen, Germany. jgeier@ivdk.org
Epoxy resin systems (ERSs) are a frequent cause of occupational allergic contact dermatitis. Sensitization occurs not only to the resins, but also to hardeners and reactive diluents. However, only a fraction of the ERS components currently in use are available for patch testing. With the multicentre study EPOX 2002, we attempted to improve diagnostics in this field by patch testing with components currently used in ERSs. During the first study period (October 2002 to July 2003), in addition to commercially available ERS patch test substances, 16 study substances (1 resin, 9 hardeners and 6 reactive diluents) were patch tested in 70 patients with suspected contact allergy due to ERSs and 22 patients with a prior positive patch test reaction to epoxy resin (ER) in the standard series. Most frequently, allergic reactions to ER based on diglycidyl ether of bisphenol A and F were observed (55.2% and 43.7%, respectively). Agreement between positive reactions to both resins, which can be explained by immunological cross-sensitization and/or coexposure, was substantial [Cohen's kappa 0.65 (95% CI: 0.49-0.80)]. Among the reactive diluents, 1,6-hexanediol diglycidyl ether (1,6-HDDGE) and 1,4-butanediol diglycidyl ether (1,4-BDDGE) were the most frequent allergens, with 19.5% and 18.4% positive reactions, respectively. Although agreement between positive reactions to 1,6-HDDGE and 1,4-BDDGE was even
better than with the 2 resins, the sample size is considered too small to decide reliably whether 1,6-HDDGE alone could serve as a marker allergen for both. Allergic reactions to p-tert-butylphenyl glycidyl ether and to phenyl glycidyl ether (PGE) occurred in 11.5% of the patients tested, with only moderate

agreement. All patients positive to cresyl glycidyl ether (6.8%) also reacted to PGE. Of the hardeners tested, m-xylylene diamine was the most frequent allergen (13.8%), followed by isophorone diamine (5.7%). No reactions were observed to several substances, the test concentration of which may have been too low and will be increased in the future.

7. Australas J Dermatol. 2000 Nov;41(4):222-4.
Occupational epoxy resin allergic contact dermatitis.
Rademaker M(1).
Author information:
(1)Department of Dermatology, Health Waikato, Hamilton, New Zealand. rademaker@xtra.co.nz
Sixteen cases of occupational contact dermatitis to epoxy resins were seen over a 5-year period. All were men. Six cases worked in the construction industry, two worked as painters, two as engineers, two as car windscreen repairers, and one each worked in a timber yard, a car yard, on a farm and as a cane-furniture salesman. Most presented with rashes on their faces (56%), hands (50%) or arms (37%). Two patients were allergic to the reactive diluent phenyl glycidyl ether, and one was allergic to the epoxy hardener isophorone diamine. The rest were allergic to the epoxy resin itself. Outcome in this series was poor because most continued to be exposed to epoxy resins in their workplace environment.

8. Contact Dermatitis. 2000 Aug;43(2):110.
Spill-induced sensitization to isophoronediamine.
Kelterer D(1), Bauer A, Elsner P.
Author information:
(1)Department of Dermatology, Friedrich Schiller University of Jena, Germany.
No abstract
(Case report: a bricklayer had contact allergy to IPDA and no other compound. IPDA was present in a glue hardener.)

9. Contact Dermatitis. 1998 Jul;39(1):46-7.
Occupational allergic contact dermatitis from isophoronediamine (IPDA) in operative-clothing manufacture.
Tarvainen K(1), Jolanki R, Henriks Eckerman ML, Estlander T.
Author information:
(1)North Karelia Central Hospital, Dermatological Department, Joensuu, Finland.
No abstract
(Case report: a worker in lamination machine, allergic reactions to epoxy resin, IPDA, own resin and hardener.)

10. Int J Dermatol. 1996 Dec;35(12):852-6.
Occupational allergic contact dermatitis caused by 2,4,6-tris-(dimethylaminomethyl)phenol, and review of sensitizing epoxy resin hardeners.
Kanerva L(1), Estlander T, Jolanki R.
Author information:
(1)Section of Dermatology, Finnish Institute of Occupational Health, Helsinki, Finland.

BACKGROUND: Epoxy resin compounds (ERC) include a large number of sensitizing
chemicals such as epoxy resins (ER), hardeners (curing agents), and reactive diluents. Allergic contact dermatitis (ACD) caused by ERCS is often occupational.
MATERIALS AND METHODS: We report a patient, sensitized to a hardener of a two-component epoxy paint. Three conventional patch test sessions were performed to diagnose the causative chemical. We also review the literature on sensitizing epoxy-resin hardeners.
RESULTS: A 47-year-old nonatopic woman developed dermatitis from a two-component
epoxy paint. Patch testing with epoxy resin was negative, but 2,4,6-tris(dimethylaminomethyl)phenol (tris-DMP), used in the paint hardener, induced an allergic patch test reaction. We also review briefly other epoxy hardeners that have caused allergic dermatitis, including: (1) aliphatic polyamines, e.g., ethylenediamine, diethylenetriamine, triethylenetetramine, 3-dimethylaminopropylamine, and trimethylhexamethylenediamine; (2) cycloaliphatic polyamines, e.g., isophoronediamine and
3,3'-dimethyl-4,4-diaminodicyclohexylmethane; (3) aromatic amines, such as 4,4'-diaminodiphenylmethane, m-phenylene diamine, and 1,3-xylylene diamine; (4) dicyanodiamide; (5) triglycidyl isocyanurate, an epoxy compound that may be used as an epoxy-resin hardener; and (6) additives in epoxy accelerators, such as hexavalent chromate.
CONCLUSIONS: No one chemical can be used to screen for sensitization to the many different epoxy hardeners. Extensive patch testing may be required to reveal the hardener that has caused the allergy. The hardener,
2,4,6-tris-(dimethylaminomethyl)phenol (tris-DMP), is a new sensitizer. To verify ACD caused by tris-DMP, patch-testing at 1% in petrolatum is suggested.

11. Contact Dermatitis. 1995 Apr;32(4):239.
Occupational airborne allergic contact dermatitis due to
3-amino-methyl-3,5,5-trimethylcyclohexylamine.
Patussi V(1), Kokelj F, Buttazzi P.
Author information:
(1)SPISAL, ULSS 12, Conegliano (TV), Italy.
No abstract
(case report: a floorcoater had only IPDA contact allergy. IPDA was present in the epoxy hardener that he had used.)

12. Contact Dermatitis. 1993 Nov;29(5):281-2.
Occupational airborne allergic contact dermatitis in parquet layers.
Lodi A(1), Mancini LL, Pozzi M, Chiarelli G, Crosti C.
Author information:
(1)Department of Dermatology, University of Milan, San Paolo Hospital, Italy.
No abstract
(Case report: a parquet layer with contact allergy to epoxy resin and IPDA. His epoxy hardener contained IPDA)

13. Contact Dermatitis. 1992 Jul;27(1):52-3.
Contact sensitization due to isophoronediamine.
Guerra L(1), Vincenzi C, Bardazzi F, Tosti A.

Author information:
(1)Department of Dermatology, University of Bologna, Italy.
No abstract
(Case report: 3 cases with allergic reactions to IPDA; a varnisher, a mechanic in car factory and an non-occupational case with established exposure to IPDA in a glue hardener. In other two cases the exposure remained unclear)

14. Contact Dermatitis. 1984 Mar;10(3):146-50.
Hand dermatoses and contact allergic reactions in construction workers exposed to
epoxy resins.
van Putten PB, Coenraads PJ, Nater JP.
In 23/135 (18%) workers exposed to epoxy resins, a work-related dermatosis on the hands and/or forearms had been present during the past 3 years. In 9 persons, the occupational dermatosis was still present at the time of investigation. In all workers, patch tests were performed with epoxy resin, isophoronediamine, triethylenetetramine and xylenediamine. Positive patch tests were observed in 27 of the 135 exposed workers (20%) 13 of whom had never previously experienced skin problems. Epoxy resin accounted for the majority of the positive reactions. There was no relation between a history of atopy and the development of contact allergy. Only half of all workers had received any safety instructions. The wearing of gloves (mostly cotton), intended to protect the skin, had an adverse effect.

15. Contact Dermatitis. 1979 Mar;5(2):120-1.
Contact allergy to the epoxy hardener isophoronediamine (IPD).
Dahlquist I, Fregert S.
No abstract
(Case report: 2 epoxy workers, both allergic to IPDA and epoxy resin.)