

New Contact Allergens: 2008 to 2015

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Every year, new contact allergens, chemicals reported to have caused contact allergy/ACD for the first time, are described in literature. In the journals *Contact Dermatitis* and *Dermatitis*, 172 such compounds were identified in the period 2008–2015, 119 of which induced ACD. These are presented with the following data: name, synonyms, Chemical Abstracts Service (CAS) number, patch test data, function or class, causative product, number of patients, occupation (in case of occupational ACD), additional clinical data (if applicable), and references. Approximately one third of the new allergens were ingredients of cosmetics, followed by drugs causing occupational ACD (18%), chemicals in rubber, plastics, and paints (9%), drugs causing a drug eruption (9%), as well as chemicals used in laboratories inducing occupational ACD (8%). In 40%, the dermatitis was occupationally acquired. Fifty-three other chemicals causing contact allergy as indicated by positive patch test reactions only are shown without specifics.

Every year, new contact allergens, chemicals reported to have caused contact allergy/allergic contact dermatitis (ACD) for the first time, are described in literature. The relevant literature for the past 7 years is reviewed in this article.

MATERIALS AND METHODS

All articles in the journals *Contact Dermatitis* and *Dermatitis* published in the period March 2008 through June 2015 were screened for new allergens: chemicals, which have caused contact allergy, reported for the first time. This was assumed to be the case, when they were not mentioned in the book *Patch Testing*,¹ in which the literature on test concentrations and vehicles of contact allergens has been implemented up to February 2008. The compounds identified as “new contact allergens” were divided into the following 2 groups: (1) chemicals, which have caused ACD, usually described in the form of case reports with both clinical and patch test data and (2) compounds for which only positive patch test reactions were mentioned, without clinical data of ACD. For the chemicals of group 1, in which category cases of drug eruptions with a positive patch test (systemic dermatitis, strictly speaking not ACD) were included, the following data were collected and are presented here: name, synonyms, CAS (Chemical Abstracts Service, <http://www.cas.org>) number, patch test data (test concentration, vehicle, number of negative controls, sometimes a test advice), function or class of chemical, product causing ACD in which the allergen was present, number of allergic patients

described, occupation (in case of occupational ACD), and sometimes additional clinical data, for example, contact urticaria, airborne ACD, (fixed) drug eruption with positive patch test, cross-reactions, and coreactions. Chemicals identified as belonging to group 2 are only tabulated here without additional data. Such new allergens may be found especially in patch test studies of new test materials in unselected or selected groups of patients. Cross-reacting chemicals and chemicals inducing positive patch test reactions, indicated by the authors as being relevant but without providing specifics, were also included in this group. For most chemicals, only 1 or 2 articles describing ACD were encountered. A full literature review of all allergens was not aimed.

RESULTS

In the 7-year period under review, 119 new contact allergens causing ACD were identified in the literature reviewed (Table 1). Most were ingredients of cosmetics ($n = 39$, Table 2), followed by drugs causing occupational ACD ($n = 21$), chemicals in rubber, plastics, and paints ($n = 11$), drugs causing a drug eruption ($n = 11$), chemicals used in laboratories inducing occupational ACD ($n = 9$), as well as topical drugs ($n = 8$). In 48 of 119 new allergens (40%), the dermatitis was occupationally acquired and was often (26/40, 65%) clinical of the airborne type. In 15 (58%) of these 26 cases, it concerned health care workers who were sensitized to drugs by breaking or crushing tablets. Fifty-three chemicals causing contact allergy as indicated by positive patch test reactions only (group 2, see Materials and Methods) were identified and are shown in Table 3.

DISCUSSION

In the period under review, on average, 17 new contact allergens causing ACD were described per year. Approximately one third comprises ingredients of cosmetics. Their functions are mostly described¹²⁷ as “skin-conditioning agents,” which may include

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TABLE 1. Chemicals Causing Allergic Contact Dermatitis/Systemic Dermatitis for the First Time in the Period 2008–2015

Name of Chemical	Synonym(s)	CAS Number	Test Concentration, Vehicle, Controls, and Reference	Other Information (Function, Chemical Group, Product Group, No. Allergic Patients, Product Implicated, Other Data)	
Acetamidocaproic acid*	Acexamic acid, 6-acetylaminocaproic acid	57-08-9	5% and 10% pet, 10 controls were negative ²	Topical drug used to prevent scars, 1 patient	
Acetochlor		34256-82-1	0.01% acetone, 10 controls were negative ³	Herbicide, 1 patient sensitized from repeated accidental occupational contact, erythema multiforme-like allergic contact dermatitis	
Alprazolam		28981-97-7	Crushed tablet 10% and 30% pet, 21 controls were negative, the pure chemical was not tested ⁴	Benzodiazepine drug; 2 health care workers with occupational airborne ACD from crushing tablets; in 1 patient, the reaction was a cross-reaction to tetrazepam	
Ambroxol hydrochloride		23828-92-4	Commercial drug 0.05%–10% pet, no controls performed ⁵	Anesthetic drug used for respiratory diseases; 1 patient with photosensitive eruption of the face, neck, and hands; positive patch tests, at lower concentrations aggravated by ultraviolet (UV)-B but not UV-A; eosinophilia	
4-Amino-2-hydroxytoluene*	5-Amino-o-cresol; 4-amino-2-hydroxy-1-methylbenzene	2835-95-2	1% pet, no controls performed ⁶	Color coupler in oxidative hair dyes, 1 patient with ACD from semipermanent hair dye, also reactions to <i>p</i> -phenylenediamine and other para-compounds	
<i>Argania spinosa</i> kernel oil	Argan oil	223747-87-3	Pure and 10% pet, 10 controls were negative, ⁷ pure, 8 controls were negative ⁸	Vegetable oil used for therapeutic purposes and in cosmetics, 1 patient with ACD of the scalp from using pure argan oil on psoriasis, ⁷ 1 patient with worsening of existing ACD by pure oil ⁸	
Aripiprazole		129722-12-9	Crushed tablet 30% pet, no controls mentioned, the pure chemical was not tested ⁴	Antipsychotic drug, a nurse with occupational allergic airborne contact dermatitis from crushing tablets, she also reacted to many other drugs	
Ascorbyl tetraisopalmitate*		183476-82-6	20% liquid paraffin, 20 controls were negative, ⁹ 0.05% in ? no controls mentioned ¹⁰	Antioxidant, skin-conditioning agent, and emollient in cosmetics and topical pharmaceuticals; 1 patient with ACD from a product to treat atopic dermatitis ¹⁰ and another reacting to an antiaging cream ⁹	
Baclofen		11134-47-0	Crushed tablet 30% pet, no controls mentioned, the pure chemical was not tested ⁴	Spasmolytic drug, a nurse with occupational airborne ACD from crushing tablets, she also reacted to many other drugs	
2(3 <i>H</i>)-Benzothiazolone		934-34-9	0.1% and 1% pet, no controls mentioned ¹¹	Corrosion inhibitor; 2 patients with foot dermatitis reacting to 2(3 <i>H</i>)-benzothiazolone (1 weak positive); in one, the chemical was identified in the shoes worn	

<i>Betula alba</i> bark extract*	84012-15-7	10% in jojoba oil, no controls mentioned, ¹² jojoba oil itself was negative	Botanical product used as fragrance ingredient and skin-conditioning agent in cosmetics; 1 patient, reacting to a medical skin care product
Biosaccharide gum-4*	905593-86-4	Glycofilm 1.5 P, an aqueous solution containing biosaccharide gum-4 (% unknown) and phenoxyethanol 1.5%; 10 controls were negative ¹³	Skin-conditioning agent (hydrating, protecting) in cosmetics, 1 patient reacting to an antiwrinkle cream
Bisoprolol	66722-44-9	crushed tablet 10% pet, 6 controls were negative, the pure chemical was not tested ⁴	β-Blocker; a pharmacy assistant with occupational airborne ACD from crushing tablets, who also reacted to many other drugs
4-(Bromomethyl)benzoic acid	6332-88-8	0.01%–0.1%–1% pet, ¹⁴ 0.1% wt/wt pet, ¹⁵ 10 controls were negative to 1% pet ¹⁴ and 0.1% pet ¹⁵	Chemical used in a laboratory, 2 patients with occupational airborne ACD, 1 also reacted to other bromide compounds: <i>N</i> -bromosuccinimide and 4-carboxybenzyl(triphenyl)phosphonium bromide ¹⁵
<i>N</i> -Bromosuccinimide	128-08-5	0.1% wt/wt pet, 10 controls were negative ¹⁵	Chemical used in a laboratory, 1 patient with occupational airborne ACD, also reactions to other bromide compounds: 4-(bromomethyl)benzoic acid and 4-carboxybenzyl(triphenyl)phosphonium bromide
Buprenorphine	52485-79-7	0.001%–0.002% pet, ¹⁶ commercial injection preparation 0.3 mg/mL in water, ^{16,17} 0.3 mg/mL in pet, ¹⁸ 10% aqua, ¹⁹ no controls mentioned ^{18,19}	Semisynthetic opioid analgesic in transdermal delivery system; 1 patient ¹⁶ ; 5 patients ¹⁷ ; 3 patients ¹⁹ ; 1 patient, in whom a systemic allergic reaction with severe dermatitis at the patch test site and influenza-like symptoms developed after oral tramadol; this was attributed to cross-sensitivity ¹⁸ ; 1 similar case ²⁰ ; 3 patients, no cross-reactivity ²¹ ; contact allergy sometimes diagnosed per exclusionem by a positive reaction to the transdermal patch and a negative reaction to the patch without buprenorphine ^{17,21}
Butyl cyanoacrylate	6606-65-1	10% pet, no controls mentioned ²²	Tissue adhesive; 2 patients, also reacting to ethyl and octyl cyanoacrylate
Calocephalin		0.1% alc, no controls performed because of limited supply of the test material ²³	Sesquiterpene lactone of the guaianolide type present in cushion bush (<i>Leucophyta brownii</i> , Compositae); 1 patient with occupational ACD; many patients allergic to Compositae plants react to calocephalin, probably from cross-reactivity to other sesquiterpene lactones

(Continued on next page)

TABLE 1. (Continued)

Name of Chemical	Synonym(s)	CAS Number	Test Concentration, Vehicle, Controls, and Reference	Other Information (Function, Chemical Group, Product Group, No. Allergic Patients, Product Implicated, Other Data)	
Capryldiethanolamine	Octyldiethanolamine; octylimino-bis-ethanol	15520-05-5	0.1%–2% pet, 20 controls were negative to 2% pet ²⁴	Corrosion inhibitor in metalworking fluids; 2 patients, 1 metalworker and a machinist, with occupational ACD; 1 also reacted to monoethanolamine, diethanolamine and methyldiethanolamine	
Capryloyl salicylic acid*		78418-01-6	1% alc, no controls performed because of lack of test material ²⁵	Skin conditioner in cosmetic products, 2 patients reacting to day and night cream	
Capsaicin*		404-86-4	0.5% pet, 30 controls were negative ²⁶	Chemical in chili peppers; 1 patient with occupational, partly airborne, ACD from spice mixtures in potato chips factory	
4-Carboxybenzyl(tri-phenyl) phosphonium bromide		17814-85-6	0.1% wt/wt pet, 10 controls were negative ¹⁵	Chemical used in a laboratory, 1 patient with occupational airborne ACD; also reactions to other bromide compounds: 4-(bromomethyl)benzoic acid and <i>N</i> -bromosuccinimide	
Carvedilol		72956-09-3	10% pet, 10 controls were negative ²⁷	β -Blocker; 1 patient, working in the pharmaceutical industry, with occupational airborne ACD	
Ceteareth-2*		68439-49-6 (generic)	20% pet, no controls mentioned ²⁸	Surfactant/emulsifier in cosmetics; 1 patient, ACD from deodorant; also reactions ceteareth-3, to lauryl alcohol and the ceteareth constituents cetyl alcohol, stearyl alcohol, and cetearyl alcohol, but not to higher ceteareths (–20, –25, –30)	
Ceteareth-3*		68439-49-6 (generic)	20% pet, no controls mentioned ²⁸	See under ceteareth-2	
Cetearyl glucoside*		246159-33-1	5% pet, 109 controls were negative ²⁹	Skin conditioning agent and emulsifier in cosmetics; 4 patients; in 3 also reactions to coco-glucoside, decyl glucoside, and lauryl glucoside; not indicated which glucoside was the primary sensitizer	
(<i>R</i>)-3-(2-Chloro-1-hydroxyethyl)-phenol			1%–5%–10% pet, no controls mentioned ³⁰	Precursor in the production of phenylephrine; 1 patient, a chemical worker with occupational ACD	

6-Chloropyridazin-3-amine	5469-69-2	0.5% alc, no controls mentioned ³¹	Chemical investigated for pharmaceutical properties; 1 chemist with occupational ACD, who also reacted to 6,8-dibromimidazo[1,2-a]pyrazine and ethyl 6-chloro-imidazo [1,2-b]pyridazine-2-carboxylate
Chromate(1-), (3-hydroxy-4-(2-(1-hydroxy-8-sulfo-2-naphthalenyl) diazenyl)-1-naphthalenesulfonate(4-))-sodium (1:1)	70942-15-3	1% pet, no controls mentioned ³²	Color; 1 patient reacting to surgical suture material; neither the structural formula, nor the CAS number, nor the molecular formula shown in the article correspond to the chemical known as acid blue 158 (CAS 6370-08-7)
Cobalt 2-ethylhexanoate	13586-82-8	1.3% pet, 24 controls were negative ³³	Accelerator in polyester resin; 1 patient, a boat-builder, with occupational ACD; also reactions to cobalt chloride, cobalt naphthenate, and nickel sulfate
C30-38 Olefin/isopropyl maleate/MA copolymer*	75535-27-2	5% and 10% pet, ^{34,35} 30 controls were negative to 10% pet ³⁵	Surfactant and viscosity-increasing agent, 2 patients reacting to sunscreens, ³⁴ 4 patients reacting to the same sunscreens ³⁵
(2-Cyano-1-methylethyl)-dodecylethylsulphonium tetrafluoroborate(1-)	72140-65-9	5% and 10% pet, 2 controls were negative ³⁶	Catalyst in dental impression material, 1 patient with allergic contact stomatitis
Cyclobenzaprine	6202-23-9	0.2%, 1%, and 2% pet; no controls mentioned, but report is reliable ³⁷	Muscle relaxing agent, 1 patient reacting to a topical pain medication
Desloratadine	100643-71-8	1% pet, 7 controls were negative, 10% pet causes irritant reactions ³⁸	Oral antihistamine, 1 patient with generalized eruption after oral desloratadine and a positive patch test
6,8-Dibromimidazo [1,2-a]pyrazine	63744-22-9	1%, 0.1%, and 0.01% alc, 20 controls were negative to the lowest concentration ³¹	Chemical investigated for pharmaceutical properties; 1 chemist with occupational contact allergy, who also reacted to 6-chloropyridazin-3-amine and ethyl 6-chloro-imidazo [1,2-b]pyridazine-2-carboxylate
Didecylmonium chloride*	7173-51-5	0.1% and 0.01% pet, the 0.1% concentration is irritant but may be necessary to detect sensitization ³⁹	Quaternary ammonium compound used for surface disinfection, 1 geriatric nurse with airborne occupational ACD, contact urticaria ⁴⁰
Didecylmethylpoly(oxyethyl) ammonium propionate	94667-33-1	5% pet, 10 controls were negative ⁴¹	Quaternary ammonium compound used for disinfecting medical devices, 1 dental assistant with occupational ACD, contact urticaria ⁴²

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TABLE 1. (Continued)

Name of Chemical	Synonym(s)	CAS Number	Test Concentration, Vehicle, Controls, and Reference		Other Information (Function, Chemical Group, Product Group, No. Allergic Patients, Product Implicated, Other Data)	
bis-Diglycerol poly-acyladipate-2*		82249-33-0	16% pet, 10 controls were negative ⁴³ ; 50% pet ⁴⁴ ; advice was given to test also its ingredient 12-hydroxystearic acid ⁴⁵		Emollient, ointment base, lanolin substitute; 1 patient reacting to a lipstick ⁴³ ; 1 patient allergic to a lip balm, in whom the reaction may have been caused by 12-hydroxystearic acid, a component of bis-diglycerol poly-acyladipate-2 ⁴⁴	
Dimethyl fumarate		624-49-7	0.01% wt/wt pet ⁴⁶ ; 0.1% pet ⁴⁷⁻⁴⁹ ; 0.1% sometimes results in too strong reactions, but identifies additional cases of sensitization ⁴⁷ ; test advice: 0.1% pet ^{48,49}		Antipsoriatic agent, antimould, and antibacterial agent used in furniture textiles, shoes, and clothes; >1000 people in Europe have been sensitized by dimethyl fumarate in Chinese furniture ^{50,51} and to a far lesser degree by shoes ^{47,52} and clothing ⁵³ ; contact urticaria ^{47,54} ; acute irritant contact dermatitis ⁴⁷ ; review articles ^{48,49}	
Dimethyl sulfate		77-78-1	0.1%-1% pet, 2 controls were negative to 0.1%, ⁵⁵ 1% may give false-positive results		Strongly methylating chemical used for organic syntheses, 1 patient working in a chemical/pharmaceutical company with occupational ACD from accidental contact with the pure chemical	
Dipentaerythritol fatty acid ester		208126-52-7	1% pet, 5 controls were negative ⁵⁶		Fatty acid ester used as emollient in cosmetics, 1 patient with pigmented contact cheilitis from a lipstick	
Diphenyl isodecyl phosphate	Isodecyl diphenyl phosphate	29761-21-5	0.05%-2.5% pet, no controls performed ⁵⁷		Chemical in polyvinyl gloves; 1 patient; contact allergy not proven (according to the authors), positive on D4 only, retesting not possible	
Dipyridamole		58-32-2	Crushed tablet 30% pet, 20 controls were negative, ⁵⁸ the pure chemical was not tested		Drug used in the secondary prophylaxis of cerebral infarction, 1 patient, drug eruption with positive patch test	
Distearyl phthalic acid amide*	Benzoic acid, 2-[(diocta-decylamino)carbonyl]; distearylphthalamic acid	87787-81-3	0.1% and 1% pet, 5 controls were negative ⁵⁹		Emulsifier in cosmetics and pharmaceutical preparations, 1 patient reacting to a shampoo	
Ditrimethylolpropane triethylhexanoate*		533926-00-0	Pure, 4 controls were negative ⁶⁰		Binder, dispersing agent, and emollient in cosmetics; 1 patient reacting to a lipstick	
Enalapril		75847-73-3	Crushed tablet 10% pet, 3 controls were negative, the pure chemical was not tested ⁴		Angiotensin-converting enzyme (ACE) inhibitor, a pharmacy assistant with occupational airborne ACD from crushing tablets, she also reacted to many other drugs	

Esomeprazole	119141-88-7	30% pet, no controls performed, ⁴ the pure chemical was not tested	Proton pump inhibitor, a nurse with occupational airborne ACD from crushing tablets, she also reacted to many other drugs
3-O-Ethyl-L-ascorbic acid*	86404-04-8	0.05%-5% pet, 3 controls were negative ⁶¹	Skin-conditioning and skin-lightening agent; 1 patient, reacting to a skin-lightening lotion
Ethyl 6-chloro-imidazo [1,2-b]pyridazine- 2-carboxylate	64067-99-8	0.5% alc, no controls mentioned ³¹	Chemical investigated for pharmaceutical properties; 1 chemist with occupational contact allergy, who also reacted to 6-chloropyridazin-3-amine and 6,8-dibromimidazo[1,2-a]pyrazine
Etoricoxib	202409-33-4	10% pet, no controls mentioned ⁶²	nonsteroidal anti-inflammatory drug, 1 patient with fixed drug eruption with positive patch test only on the previous fixed drug lesion
Fructooligosaccharides*	308066-66-2	10% aqua, 30 controls were negative ⁶³	Skin-conditioning agent and humectant in cosmetics, artificial sweeteners in food; 1 patient reacting to a skin cream
Glucan oligosaccharide	9074-78-6	1% and 5% aqua; 35 controls were negative to 5%, 1 had a doubtful reaction ⁶⁴	Skin-conditioning agent, 1 patient reacting to a skin lotion
Glycerol caprylate*	26402-26-6	1% and 5% pet, 3 controls were negative to 5% pet ⁶⁵	Emollient, emulsifier; 1 patient reacting to a facial cream
HC Blue no. 7*	83732-72-3	1% pet; of 54 controls, 49 were negative and 5 had an irritant reaction ⁶⁶	Hair dye precursor, 1 patient reacting to a hair dye
<i>Helichrysum italicum</i> , flowering tops, lipophilic fraction* Hesperidin methyl chalcone*	6-Methoxy-2-methyl-amino- 3-aminopyridine; 6-methoxy- N2-methyl-pyridine-2,3-diamine dihydrochloride Helydol	90045-56-0 3% pet, 10 controls were negative ⁶⁷ 024292-52-2 1% and 3% aqua, 13 controls were negative to 3% aqua ⁶⁸ 4035-89-6 Desmodur N3200 2.5%-5% pet, 5 controls were negative to 2% pet ⁶⁹	Botanical, skin-conditioning agent in cosmetics; 1 patient reacting to a moisturizing cream Antioxidant, 1 patient reacting to a cosmetic cream Aliphatic polyisocyanate used in hardeners of 2-component polyurethane paints, 1 case of occupational ACD in a packer working in a paint factory
Hexamethylene 1,6-diisocyanate biuret	Desmodur N3200	3779-63-3 Desmodur 3390BA and 3300 0.05%-5% pet, 9 controls were negative to Desmodur N3390BA 1% and 2% pet ⁶⁹	Aliphatic polyisocyanate used in hardeners of 2-component polyurethane paints, occupational ACD in a painter and in an office worker in a paint factory
Hexamethylene 1,6-diisocyanate isocyanurate	Desmodur N3390BA; Desmodur N3300	Desmodur N3900 0.5%-5% pet, 20 controls were negative ⁶⁹	Aliphatic polyisocyanate used in hardeners of 2-component polyurethane paints, occupational ACD in a laboratory worker in a paint factory

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TABLE 1. (Continued)

Name of Chemical	Synonym(s)	CAS Number	Test Concentration, Vehicle, Controls, and Reference		Other Information (Function, Chemical Group, Product Group, No. Allergic Patients, Product Implicated, Other Data)	
Hexyldecanol*		2425-77-6	10% pet, 3 controls were negative ⁷⁰		Emollient in cosmetics and pharmaceutical preparations, 1 patient reacting to an over-the-counter pharmaceutical	
2-Hydroxy-1-(4-(2-hydroxyethoxy)phenyl)-2-methyl-1-propanone	Irgacure 2959; 4-(2-hydroxyethoxy)-phenyl-(2-hydroxy-2-methyl-propyl)ketone (name used by authors, unknown)	106797-53-9	1% pet, 20 controls were negative ⁷¹		Photoinitiator for acrylate polymerization; 1 patient reacting to this chemical and several (meth)acrylates in a transcutaneous electrical nerve stimulator, the name used by the authors (second synonym) could not be found in chemical databases	
Iodoacetone		624-75-9	0.001% pet, 5 controls were negative ⁷²		Chemical used in the synthesis of new drugs, occupational ACD in a chemistry student	
Iomeprol		78649-41-9	1%-2%-5% aqua; 5 controls were negative to 5% aqua ⁷³		Radiological contrast medium, 1 patient with occupational ACD	
Ioversol		87771-40-2	Optiray 300 undiluted, no controls mentioned, ⁷⁴ the pure chemical was not tested		Radiological contrast medium, 1 patient with fixed drug eruption with positive patch test to the commercial product, cross-reactions to commercial products containing iohexol and iopamidol	
Isononyl isononanoate*		59219-71-5	1%-20% alc, 20 controls were negative to 5% alc ⁷⁵		Skin conditioner, emollient in cosmetics; 1 patient reacting to a lipstick (applied to the eyelids), who also reacted to trioleyl phosphate	
Levocetirizine	(-)-Cetirizine	130018-77-8	Crushed tablet 10% and 20% pet, no controls mentioned ⁷⁶		Antihistamine; 1 patient, fixed drug eruption with positive patch test	
Lisinopril		76547-98-3	10% pet, 3 controls were negative, the pure chemical was not tested ⁴		ACE inhibitor; a pharmacy assistant with occupational airborne ACD from crushing tablets, who also reacted to many other drugs	
Lorazepam		846-49-1	Crushed tablet, 30% pet, 20 controls were negative, ⁴ the pure chemical was not tested ^{4,77}		Benzodiazepine drug; 5 patients, of which 4 nurses, with occupational (airborne) ACD from crushing tablets; also, in some, reactions to other drugs including tetrazepam, and cross-reactions to bromazepam and clonazepam	
Lormetazepam		848-75-9	Crushed tablet, 10% pet; 20 controls were negative; the pure chemical was not tested ⁴		Benzodiazepine drug; a pharmacy assistant with occupational airborne ACD from crushing tablets, who also reacted to many other drugs	
<i>Magnolia officinalis</i> bark extract*			0.5% pet, 10 controls were negative ⁷⁸		Antimicrobial and skin-conditioning agent in cosmetics, 1 patient reacting to an antiaging cream	

<i>Melia azadirachta</i> seed oil*	Neem oil, margosa oil	8002-65-1	Pure, ^{79,80} no controls mentioned, ⁷⁹ 5 controls were negative ⁸⁰	Vegetable oil, used as skin conditioner (occlusive) in cosmetics and for various therapeutic purposes, 2 patients sensitized by neem oil used to treat a boil and alopecia
Menthoxypropanediol*		87061-04-9	2%-5% pet, 5 controls were negative to 5% ⁸¹	Synthetic derivative of menthol used in cosmetics for masking, refreshing, and as flavor and fragrance; 1 patient reacting to a (medicinal) lip balm
7-Methoxycoumarin	Herniarin	531-59-9	1% pet, the test concentration is not irritant ⁸²	Main coumarin in German chamomile, 3 patients allergic to German chamomile and 7-methoxycoumarin; 1 had contact with weeds, the second used chamomile tea as eyewash for her dog, and the third was a nurse who brewed chamomile tea for and treated patients with herbal ointments
Methyl hydroxystearate*	Methyl 12-hydroxy-stearate	141-23-1	1% pet, 7 controls were negative ⁸³	Synthetic wax used as an aid in the processing of rubbers, also used in cosmetics and specialty inks, 1 patient reacting to a rubber respirator
Methylphenidate		113-45-1	0.5%-20% pet ⁸⁴ ; in a previous study, 20% pet was established to be nonirritant	Psychostimulant for attention-deficit/hyperactivity disorder, 1 patient reacting to a transdermal drug-delivery system
Methyl-2-pyrrolidone <i>N</i> - + poly DL-lactic-co-glycolic acid		872-50-4 and 34346-01-5	Undiluted, 5 controls were negative ⁸⁵	Drug delivery system for subcutaneous injections of gonadotropin-releasing hormone agonist; 1 patient, drug eruption with positive patch test
Misoprostol		59122-46-2	1% pet, no controls mentioned ⁸⁶	Synthetic analog of prostaglandin E1 used for the prevention and treatment of gastric ulcers; 1 patient who reacted to a vaginal tablet for the induction of abortion with a lichenoid eruption, who had a positive patch test
Mono(2-ethylhexyl) maleate		7423-42-9	1% pet, 21 controls were negative ⁸⁷	Component of di-(<i>n</i> -octyl)-tin-bis(2-ethylhexyl maleate), a stabilizer in polyvinyl chloride gloves, 3 patients reacting to gloves and their ingredients di-(<i>n</i> -octyl)-tin-bis(2-ethylhexyl maleate) and mono(2-ethylhexyl) maleate
Naloxone		465-65-6	400 µg/mL from crushed tablet (?), no controls mentioned, ⁸⁸ commercial drug solution 0.04 mg/mL, 4 controls were negative ⁸⁹	Specific opioid-receptor antagonist, 1 chemist in a pharmaceutical company with occupational ACD, ⁸⁸ positive patch tests may also be cross-reactions from oxycodone contact allergy ⁸⁹

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TABLE 1. (Continued)

Name of Chemical	Synonym(s)	CAS Number	Test Concentration, Vehicle, Controls, and Reference	Other Information (Function, Chemical Group, Product Group, No. Allergic Patients, Product Implicated, Other Data)	
Naphazoline hydrochloride		835-31-4	1% pet, 20 controls were negative ⁹⁰		Peripheral alpha-2 adrenergic receptor agonist, vasoconstrictor, used in over-the-counter antiseptics and eye drops; 1 patient reacting to an antiseptic
(Z)-N-9-Octadecenylpropane-1,3-diamine	N-Oleyl-1,3-propylene diamine	7173-62-8	0.5% pet, no controls performed ⁹¹		Hardener in epoxy resin system, 1 concrete repair worker with (partly airborne) occupational ACD
Octyl cyanoacrylate	Ocrylate	6701-17-3	10% pet, no controls mentioned ²²		Tissue adhesive, 2 patients, also reacting to ethyl and butyl cyanoacrylate
Octyldodecyl xyloside*		423772-95-6	6% pet, 20 controls were negative ⁹²		Emulsifier; 1 patient reacting to a cosmetic serum; the test substance was a mixture of octyldodecanol 60%, octyldodecyl xyloside 20%, and polyethylene glycol (PEG)-30 dipolyhydroxystearate 20%; contact allergen identified per exclusionem
Olanzapine		132539-06-1	1% pet, ⁹³ 1% and 5% pet, ⁹⁴ 10 controls were negative ^{93,94}		Antipsychotic drug, 1 patient working in a pharmaceutical company ⁹³ and a pharmacist with occupational (airborne) ACD ⁹⁴
Oxybutinin		9633-20-5	Crushed tablet 30% pet, no controls mentioned, the pure chemical was not tested ⁴		Anticholinergic drug; 1 patient, nurse; occupational allergic airborne contact dermatitis from crushing tablets; also reactions to many other drugs
Oxycodone		76-42-6	Crushed 10, 40, 80 mg tablets, 10 mg/mL liquid; no controls mentioned ⁸⁸ ; commercial drug solution 10 mg/mL, 1% and 10% in water; 3 controls were negative ⁸⁹		Semisynthetic opioid analgesic medication, 3 patients with occupational (airborne in 1 or 2) ACD, ⁸⁸ 1 patient with drug eruption to oxycodone and positive patch test to oxycodone and many other drugs ⁸⁹
Pantoprazole		102625-70-7	5% and 10% pet; 10 controls were negative ⁹⁵ ; commercial tablet 20 mg, 15% and 30% pet; 10 controls were negative ⁹⁶		Proton pump inhibitor; 1 patient with occupational airborne ACD; 1 patient with drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis reacting to multiple drugs used, including pantoprazole; possibly cross-reactions to omeprazole, lansoprazole, esomeprazole, and rabeprazole
PEG-7 oleate*	PEG-7 monooleate	9004-96-0	Pure, 8 controls were negative ⁹⁶		Emulsifier, occupational ACD from a massage oil in a physiotherapist

Pentyl 6-deoxy-L-monopyranoside Perindopril	Pentyl rhamnoside; alkyl rhamnoside-C5	494844-0	1% aqua, 5 controls were negative ⁹⁷	Cosurfactant for microemulsions, 1 patient reacting to a moisturizing cream
		82834-16-0	Crushed tablet 10% pet, 3 controls were negative, the pure chemical was not tested ⁴	ACE inhibitor; a pharmacy assistant with occupational allergic airborne contact dermatitis from crushing tablets, who also reacted to many other drugs
Phenylethyl resorcinol*		85-27-8	0.1% and 1% pet, 2 controls were negative ⁹⁸	Skin-lightening agent, antioxidant, 1 patient reacting to a skin-lightening essence
Phenytol		57-41-0	5% and 10% pet, 50 controls were negative ⁹⁹	Antiepileptic drug; positive patch test in a patient with DRESS from carbamazepine, reactivated by phenytoin
Phytantriol*	3,7,11,15-Tetramethyl-1,2,3-hexadecanetriol	74563-64-7	0.02%-0.2%-0.5% pet, ¹⁰⁰ no controls performed, but report is reliable	Surfactant, humectant, and penetration enhancer in cosmetics; 1 patient reacting to a facial cream
Phytonadione epoxide*	Vitamin K1 oxide, vitamin K1 epoxide	25486-55-9	1% pet, no controls performed because of lack of test material ¹⁰¹	Astringent, skin protectant; 2, possibly 3 patients reacting to a cosmetic cream aiming at preventing purpura, teleangiectasia and hyperpigmentation after laser and radiation therapy
Polyester-8*	Polycrylene	862993-96-2	3% pet, 20 controls were negative to 1% and 3% pet ¹⁰²	Photostabilizer used in sunscreens, 1 patient reacting to a moisturizer sunscreen
Polyglyceryl-10 laurate*		34406-66-1	0.05%-1% aqua, 7 controls were negative ¹⁰³	Nonionic surfactant used in cosmetics; 1 patient reacting to an "essential gel" (cosmetic), probable cross-reactivity to polyglyceryl-4 laurate and polyglyceryl-6 laurate
Polyhexamethylene-guanidine hydrochloride		57028-96-3	Dilution series, lowest concentration 0.0003% in ???, 8 controls were negative to 0.0003% ¹⁰⁴	Cationic antimicrobial biocide, 1 patient with occupational ACD from a nonalcoholic hand rub
Polyolefin ester			0.003%-10% pet, 20 controls were negative to 0.1% ¹⁰⁵	One patient with occupational ACD from a lubricant grease; exact chemical identity unknown, possibly polyisobutene succinic ester
Polysilicone-15*	Parsol SLX	207574-1	10% pet, no controls mentioned ¹⁰⁶	Ultraviolet B sunscreen agent, 2 patients reacting to a lip care stick
Probenazole	3-Allyloxy-1,2-benzisothiazole 1,1-dioxide	27605-76-1	0.01%-1% pet; 20 controls were negative ¹⁰⁷ ; test advice, 0.01% pet	Agricultural chemical with antifungal properties, 3 patients with occupational ACD, testing with 1% pet may result in patch test sensitization
Quinine chlorhydrate	Quinine hydrochloride dihydrate	6119-47-7	30% pet, no controls mentioned ¹⁰⁸	Flavoring agent in tonic water, 1 patient with fixed drug eruption from drinking tonic water
Retapamulin		224452-66-8	Retapamulin ointment undiluted, no controls mentioned ^{109,110}	Semisynthetic pleuromutilin antibiotic for topical use, 1 ¹⁰⁹ and 3 ¹¹⁰ patients reacting to retapamulin ointment, active ingredient not tested, the ointment base was composed of white petrolatum only

(Continued on next page)

TABLE 1. (Continued)

Name of Chemical	Synonym(s)	CAS Number	Test Concentration, Vehicle, Controls, and Reference	Other Information (Function, Chemical Group, Product Group, No. Allergic Patients, Product Implicated, Other Data)	
Sevoflurane		28523-86-6	Repeated open application test with liquid sevoflurane ^{111,112} ; 3 controls had a negative repeated open application test ^{111,112} ; because of the volatility, patch tests may be false negative	Anesthetic for general anesthesia, a recovery room nurse with occupational airborne ACD, ¹¹¹ 2 cases of systemic occupational ACD in surgeons ^{112,113}	
Sodium chondroitin sulfate*		9007-28-7	1% pet, 50 controls were negative ¹¹⁴	Antistatic, hair conditioner, skin conditioner, and emollient in cosmetics; 1 patient reacting to a cosmetic cream	
Sodium cocoamphopropionate*		93820-52-1	1% aqua, 20 controls were negative ¹¹⁵	Amphoteric surfactant used in soaps, shampoos, and conditioners; 2 patients with occupationally aggravated ACD from liquid disinfectant soap	
Sotalol hydrochloride		959-24-0	Crushed tablet 10% pet, 3 controls were negative, the pure chemical was not tested ⁴	β-Blocker; a pharmacy assistant with occupational airborne ACD dermatitis from crushing tablets, who also reacted to many other drugs	
Tetrahydromagnolol*	5,5'-Dipropylbiphenyl-2,2'-diol	20601-85-8	0.5% pet, 4 controls were negative ¹¹⁶	Skin-lightening agent, 1 patient reacting to a cream and an essence	
Tinosorb M			10% pet, ¹¹⁷ the sunscreen methylene bis-benzotriazolyl tetramethylbutylphenol was not tested	Tinosorb M consists of 40%-55% methylene bis-benzo-triazolyl tetramethylbutylphenol, 6%-10% decyl glucoside, 0.2%-0.6% propylene glycol, 0.1%-0.5% xanthan gum in water ¹¹⁸ ; it is suggested that the allergen is usually not the active ingredient methylene bis-benzotriazolyl tetramethylbutyl-phenol (synonym: bisotrizole, CAS 103597-45-1), but decyl glucoside ^{117,118} ; xanthan gum may also cause allergic reactions ¹¹⁹ ; the literature is reviewed in de Groot et al ¹¹⁸	
Topiramate		97240-79-4	Crushed tablet, 30% pet, 17 controls were negative, the pure chemical was not tested ⁹⁹	Anticonvulsant, 1 patient with DRESS from topiramate with a positive patch test	
Trazodone hydrochloride		25332-39-2	Crushed tablet 30% pet, 12 controls were negative, the pure chemical was not tested ⁴	Antidepressant drug; a nurse with airborne ACD from crushing tablets, who also reacted to benzodiazepines	
Tricetareth-4 phosphate*		86338-11-6	0.5%-5% pet, 25 controls were negative to 2% pet ¹²⁰	Emulsifier, surfactant, wetting agent in cosmetics; 1 patient reacting to a body lotion	

Triethyleneglycol bis(2-ethylhexanoate)	94-28-0	0.03%-5% wt/wt alc 96%, 10 controls were negative ¹²¹	Plasticizer, 1 patient with ACD from spectacle frame
Trifluoroacetic acid	76-05-1	1% aqua, 5 controls were negative, but transient burning may be noticed ¹²² 0.005%-5% pet, 20 controls were negative to 0.016% and 0.005% ¹²³	Reagent used in organic synthesis, 1 laboratory technician with occupational airborne ACD Intermediate in the production of the drug flutamide, 1 pharmaceutical worker with occupational ACD
<i>N</i> -(3-Trifluoromethyl-4-nitrophenyl)phthalimide	3305-68-8	0.5% and 1% pet, 20 controls were negative to 1% pet ⁷⁵	Plasticizer, skin-conditioning, and occlusive agent in lipsticks and other cosmetics; 1 patient reacting to a lipstick; also contact allergy to isononyl isononanoate
Trioleyl phosphate*	101-01-9	1.35% pet, the test concentration is not irritant ¹²⁴	Accelerator in rubber, a surgeon and a nurse with occupational ACD from triphenylguanidine in rubber gloves, also reactions to diphenylguanidine
Valiya narayana thailam ayurvedic oil		Undiluted, 10 controls were negative ¹²⁵	Ayurvedic oil used for aromatherapy, base oil with material from 48 plants, 1 patient
Xanthan gum	11138-66-2	1% and 10% aqua, no controls mentioned ¹¹⁹	Thickener, enhancer of the viscosity and hydrating, emulsifying, gel-forming and skin-conditioning agent in cosmetic products and pharmaceuticals; 1 patient reacting to a sunscreen cream containing Tinosorb M (see there)
Zolpidem	82626-48-0	Crushed tablet, 30% pet, 19 controls were negative, ⁴ the pure chemical was not tested, ^{4,77} 10% pet, 10 controls were negative ²⁷	Imidazopyridine sedative hypnotic drug; a nurse with occupational airborne ACD from crushing tablets ⁴ ; a patient, working in the pharmaceutical industry with occupational airborne ACD ²⁷ ; 3 nurses with occupational sensitization to zolpidem and tetrazepam ⁷⁷

*This chemical is monographed in the *Ingredient Database of the Personal Care Council* (previously *CTFA: Cosmetic, Toiletry and Fragrance Association*), available at <http://online.personalcarecouncil.org/isp/Home.jsp> (subscription required).

alc indicates alcohol; aqua, water; pet, petrolatum; wt, weight.

“protecting,” “hydrating,” “humectant,” and “emollient.” The second category consists of emulsifiers and surfactants. Very few new contact allergens in the classic cosmetic categories causing allergic cosmetic dermatitis were identified: fragrances 2 (menthoxypropanediol and *Betula alba* bark extract, which are not classic fragrances but also have other functions), antimicrobials/preservatives 0, antioxidants 3 (ascorbyl tetraisopalmitate, hesperidin methyl chalcone, phenylethyl resorcinol, not classic antioxidants, also other functions), and hair dyes 2 (4-amino-2-hydroxytoluene, HC blue no. 7). There were 6 botanical extracts, but no essential oils were found to be new contact allergens. The second category of new contact allergens (21 chemicals, 18%) comprised drugs causing occupational ACD in health care workers and employees in the pharmaceutical industry. Seven of these were found as allergens in 1 individual only, a pharmacy assistant,⁴ and 4 in 1 other patient, a nurse,⁴ who both used to break/crush tablets. One of them had 8 positive patch test reactions (many +++), the other one had 10 reactions, which might indicate that false-positive reactions cannot be excluded. In addition, no controls were performed with 4 of the drugs and only 3 negative controls were reported with 3 drugs. Finally, in all cases, patch tests were performed with commercial crushed tablets, not the pure drug chemicals. Forty percent of all new allergens were found in an occupational setting. In this same period, 53 chemicals causing contact allergy as indicated by positive patch test reactions only were identified.

It may be concluded that although many new chemicals enter our environment every year, the number causing contact allergy/ACD—or better, the number reported to cause contact allergy/ACD—is low. This might partly be explained by modern and stringent premarketing safety testing (although the current methylisothiazolinone contact allergy epidemic may cast some doubt on that), but difficulties in identifying new allergens in the clinical setting may also play a role: components of products unknown, difficulties in obtaining suspected chemicals for testing, difficulties with establishing adequate test parameters, and patients unwilling to be (re)tested. In addition, dermatologists may not

TABLE 3. Chemicals That Have Caused Contact Allergy (as Shown by Positive Patch Tests Only) for the First Time in the Period 2008–2015*

Aluminum hydroxide
Aluminum lactate
Aluminum phosphate
4-Amino- <i>m</i> -cresol
2-Amino-3-hydroxypyridine
Beryllium sulfate tetrahydrate
Betamethasone
Betamethasone sodium phosphate
Bromazepam
Clotiazepam
Dexlansoprazole
<i>N,N'</i> -Diacetyl- <i>p</i> -phenylenediamine
2,4-Diaminophenoxyethanol hydrochloride
Diethyldithiocarbamyl-benzothiazole sulfide
Diethyleneglycol diglycidyl ether
Diethyl fumarate
Diethyl maleate
Dimethyl maleate
Dimethylthiocarbamyl-benzothiazole sulfide
Disodium tetrachloropalladate
Flumoxonide
Flunisolide
Geraniol, air oxidized
1-Hydroxyethyl-4,5-diaminopyrazole sulfate
<i>N,N'</i> -bis(2-Hydroxyethyl)- <i>p</i> -phenylenediamine
Hydroxyethyl- <i>p</i> -phenylenediamine sulfate
Iohexol
Iopamidol
Limonene-1-hydroperoxide
Limonene-2-hydroperoxide
Limonene, oxidized
Linalool, oxidized
Linalyl acetate, oxidized
Mazipredone
<i>p</i> -Methylaminophenol
Methyl- <i>N,N</i> -diethyldithiocarbamate
Methyl- <i>N,N</i> -dimethyldithiocarbamate
2-Methylmercaptobenzothiazole
Methylprednisolone hemisuccinate
2-Methylresorcinol
PEG-25 PABA
Polyglyceryl-4 laurate
Polyglyceryl-6 laurate
Polypropyleneglycol diglycidyl ether
Potassium alum dodecahydrate
Prednisolone hemisuccinate
Prednisolone 21-pivalate
Prednisolone <i>m</i> -sulfobenzoate sodium
Propanetriol glycidyl ether
Rabeprazole
Rhodium
Ropivacaine
TEA-salicylate

*More information on these chemicals can be found in De Groot.¹²⁶

TABLE 2. New Contact Allergens 2008–2015: Classes and Products

Class/Product	New Allergens, n (%)
Ingredients of cosmetics	39 (33)
Drugs causing occupational ACD (eg, in health care workers and employees of the pharmaceutical industry)	21 (18)
Oral/intravenous drugs causing drug eruptions	11 (9)
Chemicals in rubber, plastics, and paints	11 (9)
Compounds causing occupational ACD in chemical laboratories	9 (8)
Topical drugs, including transdermal delivery systems and excipients	8 (7)
Antimicrobials	4 (3)
Others	16 (13)

have investigated contact allergy to new allergens adequately or, if detected, have not reported their findings.

This study has various weaknesses. First of all, the search for new contact allergens was largely restricted to the journals *Contact Dermatitis* and *Dermatitis*. Although it feels safe to assume that the large majority of new contact allergens are described in these journals, it is equally safe to assume that new contact allergens have been missed, because they were reported in journals not surveyed. Secondly, chemicals were classified as new contact allergens, when they are not mentioned in *Patch Testing*.¹ However, I am aware that some allergens described before 2008 are not included in the book, because I missed them. This means that it cannot be excluded that an occasional chemical presented here as new allergen has in fact been reported before 2008. Thirdly, this review does not provide a full literature review for all chemicals (although most new allergens have been described in 1 publication only).

In conclusion, in the period 2008-2015, 119 new contact allergens causing ACD were identified in the literature reviewed, an average of (only) 17 per year. Approximately one third were cosmetic ingredients; other important categories were drugs, causing either occupational ACD in health care workers and employees in the pharmaceutical industry or systemic dermatitis based on type 4 hypersensitivity in patients taking them, and chemicals causing occupational contact dermatitis in chemists and other laboratory workers. An additional 53 chemicals causing contact allergy as indicated by positive patch test reactions only (without clinical data on ACD) were identified.

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