Received: 28 June 2022 | Accepted: 30 June 2022

DOI: 10.1111/cod.14181

REVIEW

CONTACT DERMATITIS WILEY

Preservatives in non-cosmetic products: Increasing human exposure requires action for protection of health

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Abstract

The widespread use of skin sensitizing preservatives is well-known. Contact allergy to preservatives is often caused by their presence in cosmetic products. Preservative use in non-cosmetic products is less well-known. We have reviewed European Union (EU) legislations on classification and labelling, biocides and cosmetics, concerning conditions for use of the most used sensitizing preservatives (including formaldehyde-releasing substances, isothiazolinones and parabens). We have analysed temporal trends in their use in non-cosmetic products (tonnes, number of products, concentrations), based on annual reports to the Swedish Products Register 1995–2018; and we discuss implications for stakeholders. Major changes over time are that the use of most of the preservatives has increased by tonnes and/or by number of products, and that several use concentrations have declined following harmonized classification as a skin sensitizer with low concentration limits for this classification. We conclude that the massive increase in use of preservatives is alarming, and that urgent action is needed for protection of health. Their use in non-cosmetic products is broad, increasing and often undisclosed. In the EU, legislations concerning chemicals can provide relevant restrictions to reduce their use and associated health risks, monitored by efficient surveillance. Prevention would be benefited by better coordination between legislations.

KEYWORDS
biocide, exposure, formaldehyde releaser, isothiazolinone, legislation, prevention, skin sensitization, temporal trend

1 | INTRODUCTION

The widespread use of preservatives and other biocides is well-known. Many preservatives are potent skin sensitizers; contact allergy to preservatives is often caused by skin exposure to cosmetic products containing them.[1] Among other health effects investigated for biocides are skin irritation, respiratory sensitization, respiratory irritation and CMR effects (carcinogenicity, mutagenicity or toxicity for reproduction).[2] Among the many biocides, some substances cause some of these effects and are classified accordingly.[3] It is also known that biocides may have negative effects on the environment, including selection for antimicrobial resistance; effects on biodiversity and ecosystems have been proposed.[4,5]

The word *Biocide* has a broad concept, which includes preservatives, but with definitions varying in different legislative instruments within and outside the European Union (EU), while *preservative* is used

for products that prevent (hinder) microbial growth. Preservatives and other biocides include various chemicals (acids, alcohols, antioxidants, etc.), various mode of action (e.g., algicide, bactericide, fungicide) and various purposes of use (e.g., antimicrobial for treatment, disinfection of surfaces, preservation of the product). The same substance may have many uses; examples are formaldehyde, glutaral (glutaraldehyde) and isothiazolinones. In this article we use the word preservative in relation to use in cosmetic products and according to the Biocidal Products Regulation (BPR); other uses are mentioned or specified. Currently, 365 individual active biocidal substances are listed in the BPR, and 62 of them are listed for use in products during storage (PT6).[6]

A general criterion for inclusion in the European baseline series[7] for patch testing (a routine, diagnostic clinical investigation to determine whether an individual has contact allergy to a chemical substance) is that at least 0.5%–1.0% of routinely patch tested patients have contact allergy to the substance. Currently, 10 preservatives are used in the comprehensive European baseline series, while around 50 biocidal substances used as a preservative, fungicide, disinfectant and/or algicide are commercially available as patch test preparations.[8] Numerous other biocides have been identified as human skin sensitizers but are seldom used for patch testing.[9–11]

Knowledge about the prevalence and temporal changes of contact allergy to preservatives and other biocides is largely based on monitoring contact allergy in dermatitis patients by diagnostic patch testing.[12–18] Other sources of information are population-based epidemiological studies, workplace studies, selected patient groups and case reports. It should be acknowledged, however, that there is considerable variation in access to dermatology and clinical patch testing services between and within countries.

Around 12% of patch tested dermatitis patients in Denmark was sensitized to at least one of the most frequently used preservatives in 2013, and the prevalence had increased in the previous decades.[13] The increasing trend was reported by other studies in Europe[12,19] and in North America.[15,20] The increase was related to use of methylchloroisothiazolinone/methylisothiazolinone (MCI/MI, CMIT/MIT), methylchloroisothiazolinone (MI, MIT) and methyldibromo glutaronitrile (MDBGN, DBDCB), then followed by decrease in many EU countries owing to restrictions introduced concerning their use in cosmetics.[16,19,21] Differences in prevalence rates or trends between countries or regions may be explained by commercially available patch test preparations used, accessibility to patch testing, use of certain substances and to differing cosmetics legislations, for example, formaldehyde and formaldehyde releasers,[22] methyldibromo glutaronitrile (MDBGN, DBDCB),[14,18] and iodopropynyl butylcarbamate (IPBC).[21]

Common sources of skin exposure and sensitization to preservatives and other biocides are consumer products including cosmetic products, detergents, paints and occupational exposure to chemical products (mixtures) and other products. Specific knowledge about occupational exposure and skin sensitization is, to large extent, based on compilations of patch test results by occupational groups in dermatology clinic databases, workplace studies and case reports.[23–27] Sensitization to isothiazolinones in painters has drawn much attention.[28–30]

Avoidance of skin exposure and contact dermatitis by sensitized individuals requires them knowing they are sensitized and ability to identify presence of the responsible substance. Identification may be relatively simple for cosmetic products and detergents with ingredient labelling, but extremely difficult for other products due to the lack of mandatory ingredient labelling. Knowledge on presence of preservatives is largely based on ingredient label information on cosmetic products and detergents[31,32] while knowledge about actual use concentrations is scarce outside industry. Results from chemical analyses of a few substances in cosmetic products, detergents and paints have been published.[29,33–36] Data in the Danish Products Register (PROBAS) on preservatives[37] and on isothiazolinones,[26] and a review of isothiazolinone use and legislation have contributed with additional information.[35]

Attempts to reduce risks and to prevent skin sensitization and allergic contact dermatitis to preservatives have been made, but action by industry and regulators has often been slow and limited. Examples are the well-known, severe and widespread epidemics of allergic contact dermatitis caused by MCI/MI, MI and MDBGN (DBDCB).[12,13]

In the present study we (1) review key elements of the EU regulatory framework concerning conditions for use and mandatory ingredient information on skin sensitizing preservatives; (2) analyse temporal trends in use of well-known skin sensitizing preservatives in non-cosmetic products; and (3) discuss implications for workers and consumers, dermatology and dermatitis patients, industry and regulators.

2 | REGULATORY FRAMEWORK AND EXAMPLES

The conditions for use of hazardous chemicals, the health risks they possess to consumers, workers and the environment and prevention of skin sensitization, vary between geographical regions and individual countries. Numerous EU legislations address the conditions affecting exposure of consumers and workers to chemicals, for example, legislations on chemicals, cosmetics and work conditions. Some of these legislations have had a major impact on the prevention of skin sensitization and subsequent allergic contact dermatitis.

We selected the most studied and well-known skin sensitizing preservatives for this article, namely those included in the European, North American and/or international baseline series for patch testing,[8] and a few additional, closely related sensitizing substances. Formaldehyde and 6 formaldehyde-releasing preservatives, 7 isothiazolinones, 5 parabens and 4 miscellaneous preservatives are discussed (Table 1).

We have compiled data on legally binding limits for use and other provisions of the selected skin sensitizing preservatives in non-cosmetic and cosmetic products in the EU (Tables 1, S1 and S2). We have also compiled data to assess current use, temporal trends and use concentrations in Sweden (Figures 1 and 2). Several years may pass between the initial alert of a serious health effect from a substance, evaluation and recommendation by risk assessors, a decision

TABLE 1 Skin sensitizing substances in the study, EU legislations and legally binding conditions for use according to the CLP, the BPR and the Cosmetics Regulation

Substance: INCI name; chemical name; abbreviation (CAS no.)	CLP[a], envir. (E), or health (H) hazard; Skin Sens. (conc. limit) (year)	BPR, main groups and product types (PT) for which use is approved[b]	Cosmetics Regulation, max. use conc. (year)
Formaldehyde and formaldehyde releasers			
2-Bromo-2-nitropropane-1,3-diol; Bronopol (52-51-7)	E, H	Disinfect. (PT2); Preserv. (PT6,9,11,12); Other (PT22)	0.1% (1986)
DMDM hydantoin; 1,3-bis (hydroxymethyl)-5,5-dimethylimidazolidine-2,4-dione (6440-58-0)	–	Preserv. (PT6,13)	0.6% (1986)
Diazolidinyl urea; 1-[1,3-bis (hydroxymethyl)-2,5-dioxoimidazolidin-4-yl]-1,3-bis (hydroxymethyl)urea (78491-02-8)	–	–	0.5% (1986)
Formaldehyde (50-00-0)	E; H; Skin Sens. 1, 0.2% (1996)	Disinfect. (PT2,3); Other (PT22)	– Prohibited (2019)
Imidazolidinyl urea; *N*,*N*″-methylenebis [*N*′-[3-(hydroxymethyl)-2,5-dioxoimidazolidin-4-yl]urea] (39236-46-9)	–	–	0.6% (1986)
Quaternium-15; bethenamine 3-chloroallylochloride (4080-31-3)	–	Preserv. (PT6,12,13)	– Delisted (2019)
Quaternium-15 *cis* isomer; *cis*-1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride (51229-78-8)[c]	E, H; Skin Sens. 1, 1% (2009)	Preserv. (PT6,13)	– Prohibited (2019)
Isothiazolinones			
Benzisothiazolinone; 1,2-benzisothiazol-3(2H)-one; BIT (2634-33-5)	E, H; Skin Sens. 1, 0.05% (1998)	Disinfect. (PT2); Preserv. (PT6,9,10,11,12,13)	–
Dichlorooctylisothiazolinone; 4,5-dichloro-2-octyl-2H-isothiazol-3-one; DCOIT (64359-81-5)[c]	E, H; Skin Sens. 1A, 0.0015% (2020)	Preserv. (PT7,8,9,10,11); Other (PT21)	–
Methylchloroisothiazolinone; 5-chloro-2-methyl-2*H*-isothiazol-3-one; 5-chloro-2-methyl-1,2-thiazol-3(2*H*)-one; MCI (CMIT or CIT) (26172-55-4)	–	Preserv. (PT6) (under assessment)	Rinse-off 0.0015% (in MCI/MI 3:1) (2014)
Methylchloroisothiazolinone (and) methylisothiazolinone; reaction mass of 5-chloro-2-methyl-1,2-thiazol-3(2*H*)-one and 2-methyl-1,2-thiazol-3(2*H*)-one (3:1); MCI/MI (CMIT/MIT) (55965-84-9)	E, H; Skin Sens. 1A, 0.0015% (2004)	Disinfect. (PT2,4); Preserv. (PT6,11,12,13)	Rinse-off 0.0015%; not with MI (2014)
Methylisothiazolinone; 2-methyl-2*H*-isothiazol-3-one; MI (MIT) (2682-20-4)	E, H; Skin Sens. 1A, 0.0015% (2018)	Preserv. (PT6,11,12,13)	Rinse-off 0.0015%; not with MCI/MI (2017)
Octylisothiazolinone; 2-octyl-2*H*-isothiazol-3-one; octhilinone (ISO); OIT (26530-20-1)	E, H; Skin Sens. 1, 0.0015% (2020)	Preserv. (PT6,7,8,9,10,11,13)	–
Methylbenzisothiazolinone; 2-methyl-1,2-benzothiazol-3(2*H*)-one; MBIT (2527-66-4)[c]	E, H; Skin Sens. 1A, 0.0015% (2020)	Preserv. (PT6)	–
Parabens (hydroxybenzoates)			
Butylparaben; butyl 4-hydroxybenzoate (94-26-8)[d]	–	–	0.14% or 0.8%[d] (2014)

(Continues)

TABLE 1 (Continued)

Substance: INCI name; chemical name; abbreviation (CAS no.)	CLP[a], envir. (E), or health (H) hazard; Skin Sens. (conc. limit) (year)	BPR, main groups and product types (PT) for which use is approved[b]	Cosmetics Regulation, max. use conc. (year)
Isobutylparaben; isobutyl 4-hydroxybenzoate (4247-02-3)[c,d]	–	–	– Prohibited (2014)
Ethylparaben; ethyl 4-hydroxybenzoate (120-47-8)[d]	–	–	0.4% or 0.8%[d] (1986)
Methylparaben; methyl 4-hydroxybenzoate (99-76-3)[d]	–	–	0.4% or 0.8%[d] (1986)
Propylparaben; propyl 4-hydroxybenzoate (94-13-3)[d]	–	–	0.14% or 0.8%[d] (2014)
Miscellaneous substances			
Glutaral; glutaraldehyde (111-30-8)	E, H; Skin Sens. 1A, 0.1% (2016)	Disinfect. (PT1,2,3,4); Preserv. (PT6,11,12,13)	0.1%; not in aerosols (1989)
Iodopropynyl butylcarbamate; 3-iodo-2-propynyl butylcarbamate; IPBC (55406-53-6)	E, H; Skin Sens. 1, 1% (2014)	Preserv. (PT6,7,8,9,10,13)	Rinse-off 0.02%; leave-on 0.01%; deo. 0.0075%; not oral or lip (2007)
Methyldibromo glutaronitrile; 2-bromo-2-(bromomethyl)pentanedinitrile; MDBGN (DBDCB) (35691-65-7)	–	Preserv. (PT6)	– Delisted (2007)
Phenoxyethanol; 2-phenoxyethanol (122-99-6)	H	Disinfect. (PT1,2,4); Preserv. (PT6,13)	1% (1986)

Note: Year when current conc. limits were decided. References and previous limits available in Tables S1 and S2. Current provisions (as by 31 August 2021).

Abbreviations: –, no harmonized CLP classification, no authorisation by the BPR, or not permitted as preservative according to the Cosmetics Regulation; BPR, Biocidal Products Regulation; CLP, Classification, Labelling and Packaging; conc., concentration; deo., deodorant; disinfect., disinfectants; envir., environmental; INCI, International Nomenclature of Cosmetic Ingredients; preserv., preservatives; sens., sensitization.

[a]Harmonized classifications.

[b]Product types (PT) by *main groups* as defined in BPR: *Disinfectants*: PT1 human hygiene, PT2 disinfectants and algaecides, PT3 veterinary hygiene, PT4 food and feed area; *Preservatives*: for PT6 products during storage, PT7 films and coatings, PT8 wood, PT9 fibre, leather, rubber and polymerized materials, PT10 construction material, PT11 liquid-cooling and processing systems, PT12 slimicides, PT13 working or cutting fluid; *Other*: PT21 antifouling products, PT22 embalming and taxidermist fluids.

[c]Closely related sensitizing substance.

[d]The substance and its salts and esters are covered in the Cosmetics Regulation. Various limits for single esters and mixtures of esters.

by the European Commission (EC) on restrictions or other measures and the date when these measures shall apply. In this study, we have reported the year of the EC decision. Some key elements of high relevance for skin exposure to preservatives, sensitization and prevention, are summarized.

2.1 | Hazardous chemicals: GHS and the CLP Regulation

The *Globally Harmonized System of Classification and Labelling of Chemicals* (GHS)[38] provides internationally harmonized hazard classification and labelling of hazardous chemical substances and mixtures of substances, for protection of health and the environment and to facilitate trade. GHS was adopted by the United Nations (UN) in 2002 and has since been implemented in numerous countries, and in 2008 by the EU. The requirements have been implemented in various EU chemicals directives and regulations, which are broader, more binding and with certain stronger requirements than the GHS.

In the EU, the *Classification, Labelling and Packaging* (CLP) Regulation ((EC) No 1272/2008)[3] is based on GHS; the CLP was preceded by the Dangerous Substances Directive (67/548/EEC [DSD])[39] and the Dangerous Preparations Directive (1999/45/EC [DPD]).[40] Since 2015, CLP is the only legislation in the EU for classification and labelling of substances and mixtures and it mandates information to be included in safety data sheets (SDSs) that are further specified in the EU by Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). CLP does not restrict substances; substance use in cosmetic products, food and medicines is not covered by CLP.

Harmonized classification of hazardous substances is decided by the EC and is legally binding. Most classifications are *notified classifications* (also termed 'self-classification') that must be performed by industry when a substance has no harmonized classification. Notified classifications as a skin sensitizer are generally less vigorous than the following harmonized classifications of the same substance (see examples below).

Hazard classification is based on the intrinsic properties of substances to cause harm. Physical, health and environmental hazards are

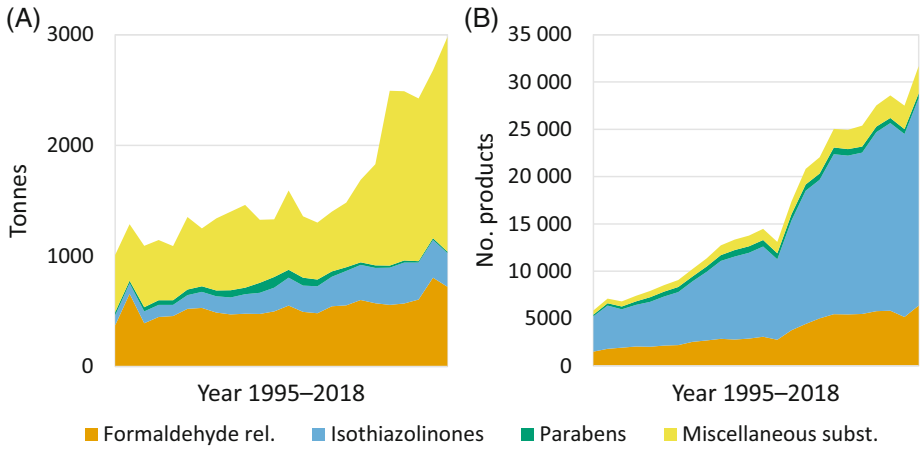


FIGURE 1 Use of selected skin sensitizing preservatives in non-cosmetic products during 1995–2018. Stacked areas displayed by substance groups as (A) tonnes and (B) number of products. Based on annual reports by companies to the Swedish Products Register on import and manufacture. The groups include formaldehyde (<1%) and 5 formaldehyde releasers; 6 isothiazolinones; 5 parabens; and 4 miscellaneous substances (glutaral, IPBC, MDBGN (DBDCB) and phenoxyethanol). The substances are, on regular basis, internationally used for diagnostic patch testing

classified in hazard classes and categories according to agreed classification criteria. The following applies to skin sensitizers: Skin Sensitization category 1, or sub-category 1A or 1B when sufficient data is available, and the hazard statement code H317 (previously R43). Classification of substances for skin sensitization is based on sensitizing potency as shown by human data, and/or animal data (LLNA, GPMT, Buehler assay); currently, available *in vitro/in chemico* methods cannot (yet) be stand-alone tests.

The *generic concentration limit (GCL)* is the 'general' concentration threshold for a substance which triggers the classification for that effect. However, if there is data to show a higher potency of a substance, a *specific concentration limit (SCL)* may be set that then requires classification at a lower concentration than required by the GCL. The GCLs for classification of skin sensitizing substances in a mixture are 1% for Category 1 and sub-category 1B (moderate sensitizers) and 0.1% for sub-category 1A (strong sensitizers). SCLs below the GCL are set when the GCL may be insufficiently protective, and CLP recommends 0.001% for extremely potent skin sensitizers of sub-category 1A.[41]

Only 10 of the 23 skin sensitizing preservatives discussed in this article currently have a harmonized classification as skin sensitizing (Skin Sens.) (Table 1). The current concentration limit for classification is 1% for quaternium-15 *cis* and IPBC, while concentration limits below 1% have been decided for eight of the preservatives with harmonized classification. The first was set in 1996 for formaldehyde (0.2%), followed by benzisothiazolinone (BIT) (0.05%), glutaral (0.5%), MCI/MI (3:1 ratio) (0.0015%) and octylisothiazolinone (OIT) (0.05%). The extremely low limit 0.0015% was decided for MI in 2018, and for dichlorooctylisothiazolinone (DCOIT), OIT (reclassified), and methylbenzisothiazolinone (MBIT) in 2020. Reclassification to a lower limit value has now been done also for glutaral (0.1%) (Tables 1 and S1; Figure 2).

Substances in this article illustrate large differences between previously notified and the harmonized Skin Sens. classifications mentioned above.[42] Further examples on remarkable notified classifications are MCI (without MI; CMIT, CIT) and MDBGN (DBDCB), two potent skin sensitizers still lacking harmonized classification. 96% of 2400 notifications of MCI included Skin Sens., but only 4% as sub-category 1A or a SCL below 1%; only 57% of 1500 notifications of MDBGN (DBDCB) included Skin Sens., and none with a concentration limit below 1%.

Mixtures containing a classified skin sensitizer (either harmonized or notified classification) above the concentration limit for classification must be labelled with a pictogram (exclamation mark) and the hazard statement '*H317*: *May cause an allergic skin reaction*'. Since 1999, mixtures not classified as sensitizing but containing a classified skin sensitizer at a concentration above 10% of the limit for classification shall, according to CLP and its predecessor DPD, have a supplemental hazard label statement: '*EUH208*—"*Contains (name of sensitising substance). May produce an allergic reaction*"'. EUH208 is also mentioned 'elicitation limit'. It was introduced to protect already sensitized individuals that may react below the classification limit.[40]

2.2 | Biocides: BPR

The *Biocidal Products Regulation* (EU) 528/2012 (BPR)[2] entered into force in 2013 and repealed the Biocidal Products Directive (Directive 98/8/EC).[43] In principle, all biocidal active substances must be approved at the EU level, and their use in biocidal products requires authorisation at member state or EU level. The BPR approval is valid for up to 10 years and an application must then be renewed under the BPR review programme, but an approval can be changed earlier. Use in cosmetic products, food and medicines is not covered by the BPR.

Approved active substances can be used only in certain *product types (PT)*; 22 product types are currently specified in Annex V to the BPR.[6,44] Among the 23 preservatives in this article, 15 are currently approved as biocidal active substance. In total, 14 product types are currently allowed for these substances (Table 1) and the most frequent for these are, in descending order, PT6: products during storage ($n = 13$), PT13: working or cutting fluid ($n = 10$) and PT11: liquid-cooling and processing systems ($n = 7$). The three substances with the

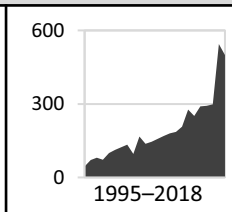
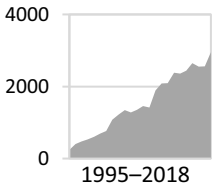
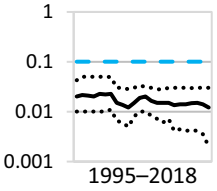
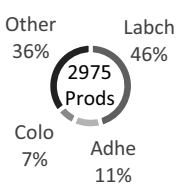
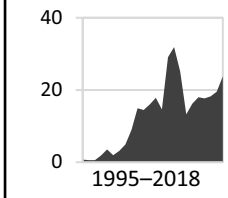
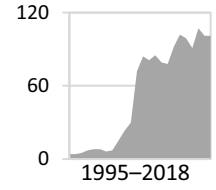
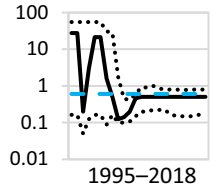
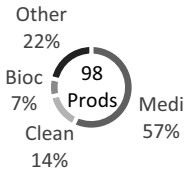
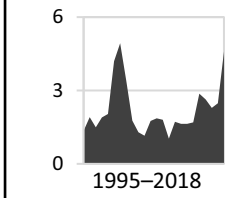
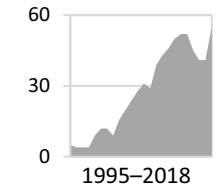
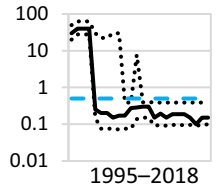
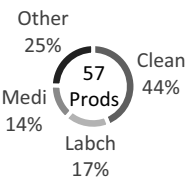
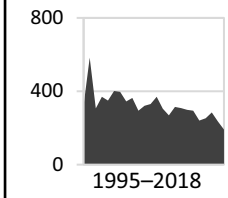
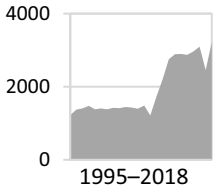
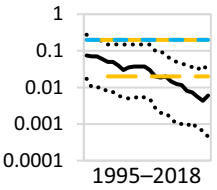
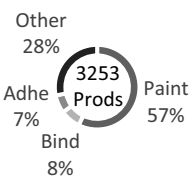
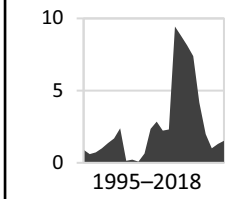
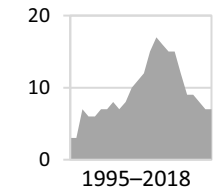
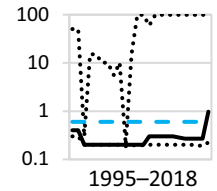
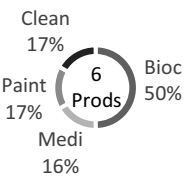
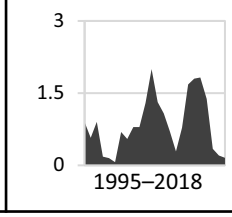
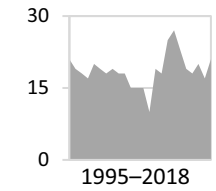
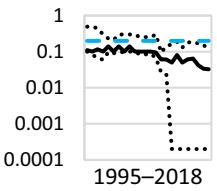
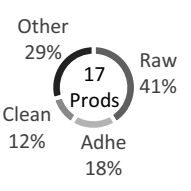
Substance name and CAS no.	Use over 1995–2018			Use in 2018
	a) Tonnes	b) No. products	c) Use conc., classif. and cosmetic limits (%, log)	d) Major product categories; no. products (%)
FORMALDEHYDE AND FORMALDEHYDE RELEASERS				
Bronopol 52-51-7				
DMDM hydantoin 6440-58-0				
Diazolidinyl urea 78491-02-8				
Formaldehyde (<1%) 50-00-0				
Imidazolidinyl urea 39236-46-9				
Quarternium-15 4080-31-3				

FIGURE 2 Data on use of skin sensitizing preservatives in non-cosmetic products during 1995–2018, based on annual reports by companies to the Swedish Products Register. Import and manufacture by weight, number of products and use concentrations (median, Q1, Q3), and major product categories are shown. Harmonized classification limits as skin sensitizing (H317) and information limits (EUH208) according to the Classification, Labelling and Packaging Regulation (CLP) and concentration limits in cosmetics are depicted. Abbreviations: conc., concentration; classif., classification; *Major product categories*: Adhe, adhesives; Bind, binding agents; Bioc, biocides (non-agricultural pesticides); Clean, cleaning products (cleaning/washing agents); Colo, colouring agents; Cool, cooling agents for metal processing; Cur, curing agents (hardeners); Fillag, filling agents; Labch, laboratory chemicals; Medi, medicine/pharmacia (pharmaceuticals); Paint, paint and varnish; Plant, plant protection agents (agricultural pesticides); Polish, polishing agents; Raw, raw materials and intermediate products; Surfag, surface active agents; Surftr, surface treatment for paper, cardboard and other non-metals

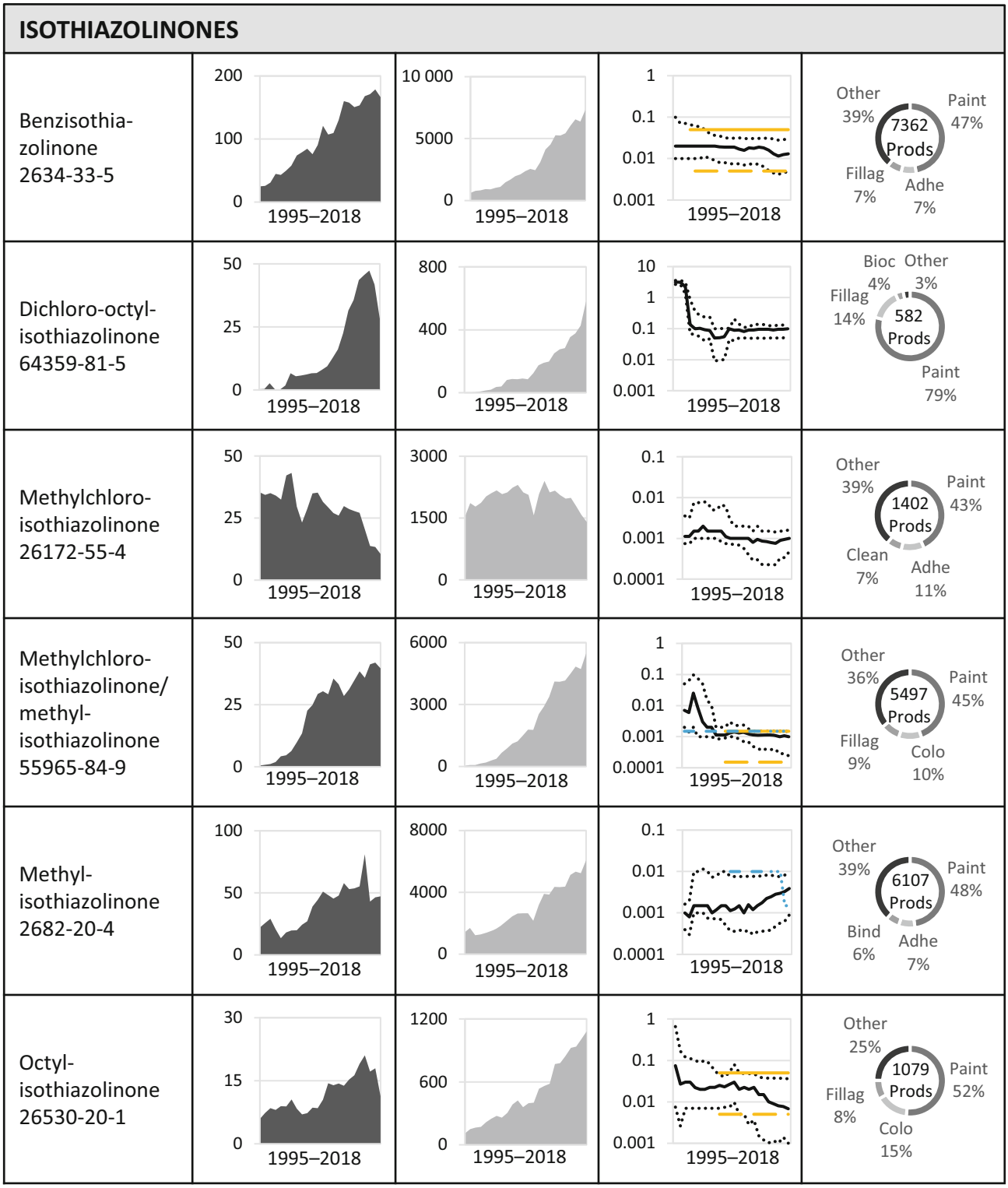


FIGURE 2 (Continued)

broadest range of approved use are glutaral (8 PTs), BIT (7 PTs) and OIT (7 PTs).

A harmonized classification proposal on active substances should, according to the BPR, have been submitted before approval of the substance. This is not yet, however, the case for MDBGN (DBDCB).[45] Specific conditions for protection of workers, consumers and the general public, beyond the CLP label requirements, can also be set for authorisation of biocidal products on national or EU level. Examples are label information on the risk of skin sensitization irrespective of concentration (e.g., IPBC in PT6),[46] and certain restrictions on use

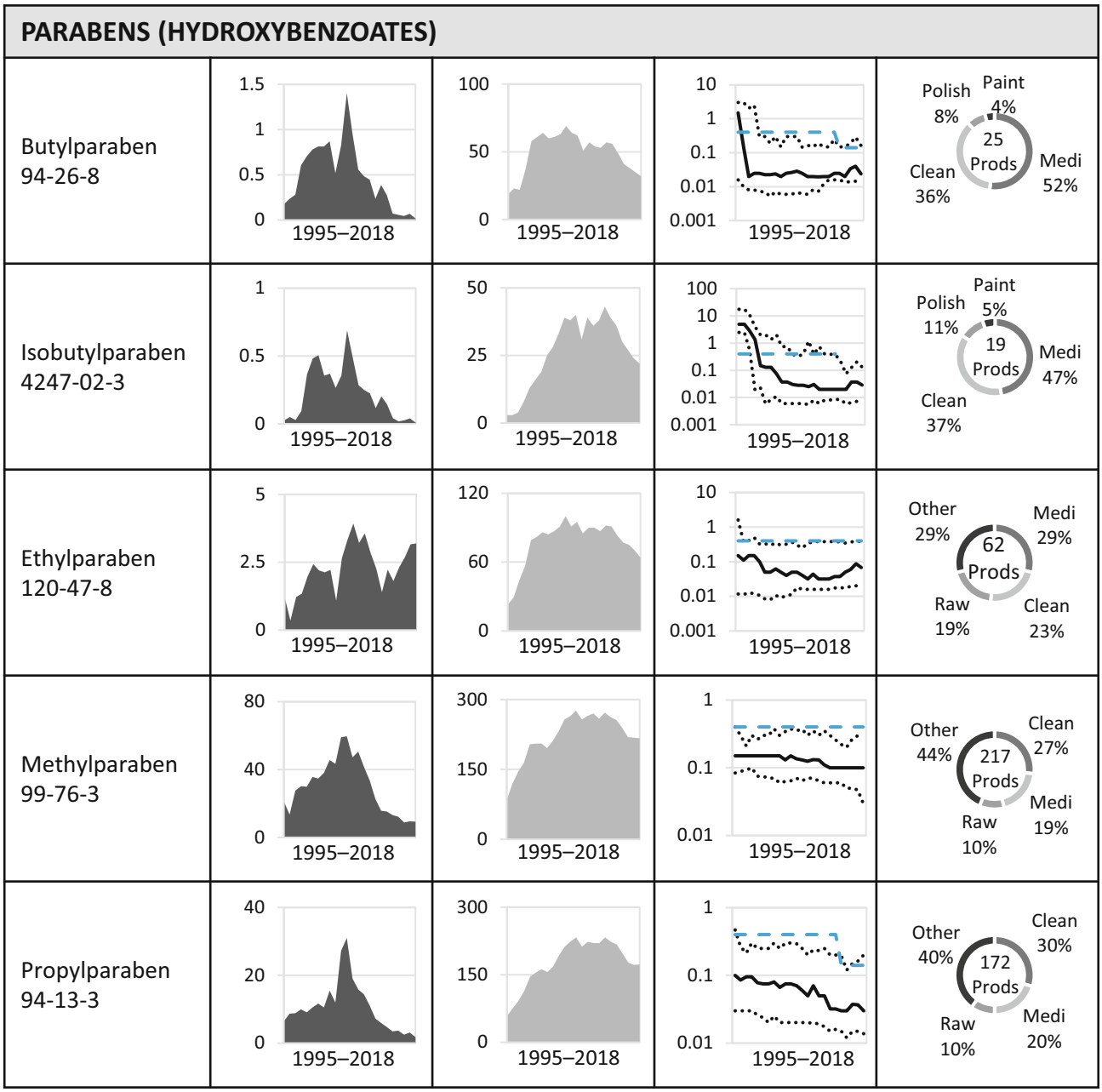


FIGURE 2 (Continued)

concentration above the classification limit for Skin Sens. (e.g., MCI/MI in PT6).[47]

2.3 | Cosmetics: Cosmetics Regulation

The *Regulation on Cosmetic Products* (1223/2009/EC)[48] entered into force in 2013, replacing the Cosmetics Directive (76/768/EEC).[49] It covers a spectrum of product types, including colour cosmetics, hair dyes, deodorants, sunscreens, shampoos, creams, wet wipes and soaps. Annex II lists substances prohibited in cosmetic products, and Annex V lists preservatives allowed in cosmetics, maximum use concentrations and warnings. Examples of warnings are 'contains formaldehyde' where formaldehyde in the product is >0.05%, 'not for children <3 years', 'not for nappy area' or 'contains glutaral'. Except for fragrance substances, since 1997, all ingredients, must be listed on the packaging irrespective of concentration, using the International Nomenclature of Cosmetic Ingredients (INCI).[50] The CLP label requirements and the BPR do not apply to cosmetic products.

To date, 13 of the 23 substances discussed in this article are allowed for use in cosmetic products; 5 have been prohibited or delisted since 2007 (formaldehyde, quaternium-15, quaternium-15 *cis*, isobutylparaben, MDBGN (DBDCB)); and 4 are not permitted (BIT, DCOIT, OIT and MBIT are not listed in Annex V) (Table 1). The

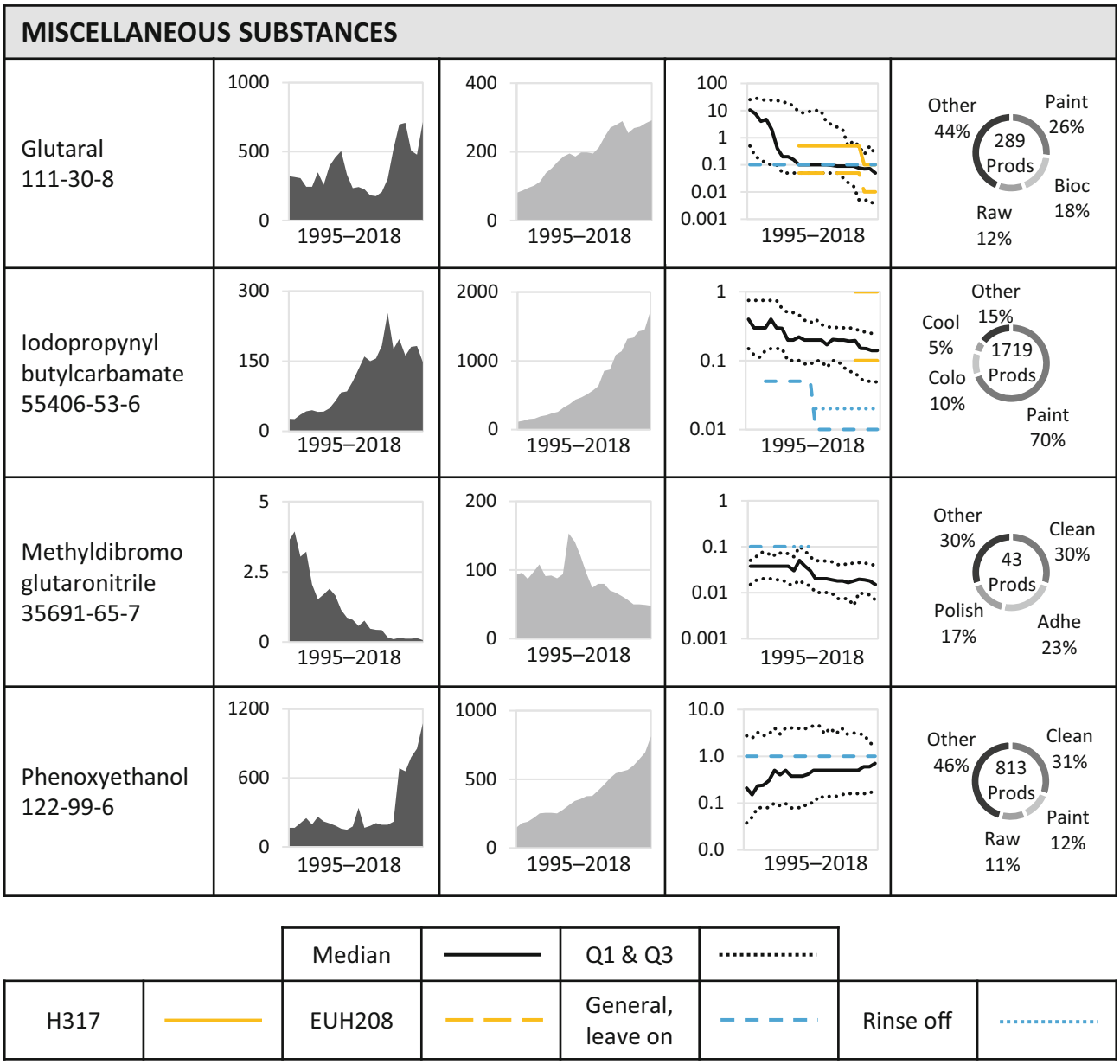


FIGURE 2 (Continued)

following have been prohibited in cosmetics owing to their classification as CMR substances: formaldehyde (category 1B), quaternium-15 and quaternium-15 *cis* (category 2) (2019); and isobutylparaben (2014) owing to insufficient information by industry for evaluation of safety.

Many of the use concentration limits were initially set during the 1980s and only a few have been changed since then (Tables 1 and S2; Figure 2). Severe restrictions have been introduced following massive skin sensitization events (epidemics of contact allergy and allergic contact dermatitis) in the consumer, for example, the limits for MCI/MI and MI were decreased to 0.0015% and their use was restricted to rinse-off cosmetic products; MDBGN (DBDCB) was restricted to rinse-off cosmetic products, and then prohibited (delisted).

2.4 | Some other EU legislations

REACH, Regulation (EC) No 1907/2006 REACH[51] entered into force in 2007. The main aims of the legislation are to improve protection of human health and the environment from risks by chemicals, and to strengthen competitiveness of the EU chemicals industry. Manufacturers, importers and distributors in the EU must identify and manage the risks linked to the substances they manufacture and market in the EU, and they must inform users about risk management for safe use. REACH also addresses risk communication, substitution and restrictions.

REACH requires that industry applies the CLP criteria for classification and labelling, and that SDSs are provided for occupational users and distributors when a substance or mixture meets the

criteria for classification.[52] Information must be given in SDSs concerning skin sensitizing substances (e.g., H317 and EUH208). It is important to understand that SDSs do not list all the ingredients in mixtures or products (articles), which is often erroneously assumed; only classified substances above certain limit values are listed. SDSs are not intended for consumers but may be made available to them.

One aim of REACH is that the most hazardous substances shall be *substituted* with less dangerous substances. Some hazardous substances are considered of very high concern (SVHC), for example, carcinogenic, mutagenic or toxic for reproduction (CMR) and substances that are persistent, bioaccumulative and toxic (*PBT or vPvB*), and on case-by-case basis. Two substances in this article (Table 1) are categorized as SVHC and are included in the candidate list for authorisation; glutaral owing to respiratory sensitizing properties, and butylparaben owing to endocrine modifying properties.

Authorities can *restrict* the use of hazardous substances if industry cannot manage the risks and some substances are *restricted* under REACH (Annex XVII).[53] The restrictions of nickel in prolonged contact with skin, and chromium (VI) in leather and cement are examples familiar within dermatology.

The Detergents Regulation (Regulation (EC) No 648/2004)[54] covers soaps and surfactants intended for washing and cleaning, except cosmetic products. Specific labelling, including information on preservatives irrespective of concentration, and by the same terminology as for cosmetic products (INCI) is required. The CLP label requirements do apply to detergents.

Medicinal products for human use (Directive 2001/83/EC),[55] *veterinary medicinal products* (Regulation (EU) 2019/6),[56] and *medical devices* (Regulation (EU) 2017/745)[57] may contain preservatives in excipients. There are no lists on allowed, restricted, or banned substances, but the products must meet general standards on risk versus benefit. Preservatives in medicinal products for human use must be stated on the label, but the terminology may vary.

3 | USE IN NON-COSMETIC PRODUCTS AND TEMPORAL TRENDS

3.1 | Materials and methods

3.1.1 | The Swedish Products Register

The Products Register of the Swedish Chemicals Agency gathers information by manufacturers and importers of chemical products to Sweden.[58] Parts of the register are publicly available. The use of chemical products (substances and mixtures) at >100 kg/year must be reported by importers and manufacturers (currently approximately 3000 companies) to the Products Register. Currently, the Products Register contains information on more than 200 000 chemical products. It does not contain data on use in cosmetic products or food. The Nordic SPIN database, and the Danish Product Registry and PROBAS database, contain similar data.[59,60] Owing to national differences in required reporting, the data are not directly comparable with the Swedish Products Register.

3.1.2 | Selection of substances

The skin sensitizing preservatives included in the European, North American and/or International baseline series for patch testing, and a few additional, closely related sensitizing substances were selected for the present study (Table 1).[8] General criteria for inclusion in the European baseline series[7] are that at least 0.5%–1.0% of routinely patch tested patients have contact allergy to the substance. Several carbamates, thiurams and some mercapto-compounds, more commonly used as rubber chemical accelerators, are skin sensitizing and routinely included in patch testing, but they were not included in this article. They may be used as fungicides, but such use has not been reported to the Swedish Products Register.[58]

3.1.3 | Data and statistics

Data on well-known skin sensitizing preservatives (Table 1) for the years 1995–2018 was made available by the Products Register for this study: data on tonnes and number of products, use concentrations; and, for year 2018, major product categories. The total number of reports by companies on import or manufacture of the substances in the study during 1995–2018 was 20 855 (range from 68 to 2762 per substance), mainly in mixtures (Table S3). The fee charged to industry by the Products Register, based on number of products in the annual accounting report, was changed in 2008. This might have affected some reporting of number of products in the following compared with previous years.

When the total value on tonnes or number of products for 1 year deviated more than 100% from the two adjacent years, the mean value was used. This adjustment was done for 15 of 1008 (1.5%) of the reported values (all were for tonnes). Because a major part of formaldehyde is used as raw material, the formaldehyde data was restricted to formaldehyde at a concentration below 1% (in the following mentioned formaldehyde [<1%] when relevant).

Use (tonnes, number of products and use concentrations) is displayed in graphs for overview of temporal trends. Harmonized (legally binding) limits for classification as skin sensitizer (H317) and supplemental hazard statement (EUH208) according to CLP and its predecessor, and maximum concentrations for preservatives in cosmetic products, are indicated (Figure 2; Tables 1, S1 and S2). The main uses of the substances in 2018 by product categories, based on Nordic harmonized product type codes (UCN), are shown (Figure 2; Tables S5 and S6).

The reporting by importers and manufacturers of MCI, MCI/MI and MI use has been inconsistent over the period. The mixture MCI/MI (3:1) may be reported as one substance or as two separate substances. Imported raw materials may be pre-treated with MI at lower concentrations than require identification in SDSs, and imported products may contain various combinations of active

biocidal ingredients. MCI without MI has seldom been used in Sweden. These considerations have been confirmed by the Swedish trade association Kemisk Tekniska Företagen KTF (personal communication by A. Melvås, 7 June 2022).

3.2 | Results

An overview of the reported use (by tonnes and number of products) of the selected preservatives during 1995–2018 is shown by four substance groups in Figure 1. The largest group by tonnes is the miscellaneous substances (compiled of not chemically related substances), and the largest group by number of products is the isothiazolinones. The major changes over time are that the miscellaneous substances group has increased four times by tonnes, and that the group of isothiazolinones has increased seven times by number of products. The group of formaldehyde and formaldehyde releasers has increased modestly, and the group of parabens has been constantly small and declined by tonnes over the period.

3.2.1 | Use by tonnes and number of products 1995–2018

Use of the individual substances are shown in Figure 2 and major findings are summarized below.

The use by tonnes has increased for the formaldehyde releasers 2-nitro-2-propane-1,3-diol (bronopol) and DMDM hydantoin, and it has decreased slightly for formaldehyde (<1%). The trend is difficult to assess for the remaining formaldehyde releasers owing to low number of reports. The use by number of products has increased for all, except for quaternium-15.

The use by tonnes and number of products of the isothiazolinones BIT, DCOIT, MCI/MI, MI and OIT has increased significantly, and the increase by number of products has been exponential or linear. The use of MCI has, according to reporting, decreased; the reporting has, however, been inconsistent and is difficult to assess (see above).

The use by tonnes and number of products of the parabens has been biphasic. Overall, it has increased by tonnes for ethylparaben, and decreased for the remaining parabens, and it has increased by number of products for all.

Use of the substances in the group of miscellaneous substances, which not are chemically related as in the other groups, has changed significantly. The use of MDBGN (DBDCB) has decreased by tonnes and number of products, while the use of glutaral, IPBC and phenoxyethanol has increased.

3.2.2 | Concentrations used (1995–2018) and limit values

Use concentrations (Q1, median, Q3), CLP harmonized classification as skin sensitizer (H317), the supplemental hazard statement (EUH208) and the use concentration limits for cosmetic products are displayed in Figure 2 and listed in Tables 1, S1 and S2. The calculated use concentrations (min, max, Q1, median, Q3), as reported for 2018, may be seen in Table S4.

Four formaldehyde-releasing preservatives, five parabens, MDBGN (DBDCB) and phenoxyethanol have no harmonized classification (H317). Harmonized classification of MI was decided in 2018, and of DCOIT, OIT (revised) and MBIT in 2020; all with the extremely low SCL 0.0015%. Harmonized classification of MCI (without MI) is under preparation. Quaternium-15 *cis* and MBIT were not assessed and are not included in Figure 2.

The median use concentration has, over the years, decreased for all preservatives in the study, except for MI and phenoxyethanol, which have increased. The use concentration of some formaldehyde-releasing preservatives (DMDM hydantoin, diazolidinyl urea), isothiazolinones (DCOIT, MCI/MI, OIT), parabens (butylparaben, isobutylparaben) and of glutaral had a sharp decrease during the first years of the period studied. Others have had a slower decline. The Q1 and Q3 concentrations have generally followed the direction of the median concentration.

The median concentration of all preservatives with harmonized classification (H317) has, after they were classified, been below the classification limit, and considerable amounts of formaldehyde (<1%), BIT, OIT, glutaral and IPBC have been below the EUH208 limit (supplemental allergy hazard statement) as indicated by Q1 concentrations below this limit (Figure 2; Tables 1 and S4). Thus, warning labelling as skin sensitizing has been required only for minor parts of the used amounts, and information on presence of the preservatives on labels or in SDSs is often not required.

3.2.3 | Major product categories (2018)

The preservatives most used in 2018 by tonnes and number of products, respectively, were 2-nitro-2-propane-1,3-diol (bronopol) (498 tonnes, 2975 products); BIT (166 tonnes, 7362 products); MCI/MI (39 tonnes, 5497 products); MI (47 tonnes, 6107 products); glutaral (692 tonnes, 289 products); and phenoxyethanol (1073 tonnes, 813 products) (Table S5). Use of the individual substances by major product categories and number of products are shown in Figure 2 and Table S5. Major findings are summarized below. The product categories are used for reporting to the Swedish Products Register (Table S6); they are not identical to the product types (PTs) defined by BPR (Table 1 footnote).

The four product categories with the largest number of products (n) containing any of the studied preservatives were paints ($n = 13\,731$), adhesives ($n = 1651$), filling agents (e.g., putty, sealant) ($n = 1189$) and cleaning products ($n = 544$).

The most frequently used preservatives in *paints* were, in descending order: BIT, MI, MCI/MI, formaldehyde, IPBC, MCI, OIT and DCOIT. Correspondingly, for *adhesives*: BIT, MI, 2-nitro-2-propane-1,-3-diol (bronopol), formaldehyde and MCI; for *filling agents*: BIT, MCI/MI, OIT and DCOIT; and for *cleaning products*: phenoxyethanol, MCI, methylparaben and propylparaben (Figure 2; Table S5). Paints was the largest product category for use of all isothiazolinones in the study. Likewise, cleaning products and medicines were the two largest (however small) categories for the parabens (Figure 2; Table S5).

4 | DISCUSSION

Global use of and contact allergy to preservatives and other biocides has increased dramatically during recent decades. Annual reports to the Swedish Chemicals Agency's Products Register by manufacturers and importers of chemical products show massive increase during 1995–2018 in consumption of the most frequently skin sensitizing preservatives. It is obvious from the above review that the EU legislative framework, including hazard identification, risk assessment and risk management of preservatives and other biocides, is complex, split and sometimes conflicting. This is also what we (I.R.W. and C.L.) have experienced when working as experts on sensitization, risk assessment and classification to the EC and its agencies. Legislation may be vertical rather than horizontal across sectors; in other words, not harmonized.

Although use of biocides brings benefits, consumers, workers, dermatitis patients and the environment may experience negative effects from their use, but do not have the means to change this. Key stakeholders are industry, regulators and to some extent dermatology.

The massive increase in use volume (tonnes), number of products and product types containing various isothiazolinones has resulted in global epidemics of contact allergy to MCI/MI and MI, and eventually (tardy intervention) in legislative attempts to reduce skin exposure and sensitization by the Cosmetics Regulation, CLP and BPR. The use of BIT, DCOIT and OIT has also increased massively, but as they have not been permitted in cosmetics, they have often not attracted general attention by dermatologists. Their main use is in paints, but they are also used in products which do not have label information or SDS, including textile, leather and rubber articles, which has attracted attention lately.[29,33,36] We expect that the use concentration of MI, DCOIT and OIT will decrease significantly following harmonized classification as Skin Sens. 1A with a classification limit of 0.0015% (MI in 2018, DCOIT and OIT in 2020), as it did for MCI/MI (2004). In addition, various new isothiazolinone substances lacking harmonized classification as skin sensitizer are increasingly used.[35]

The impact on health of the increasing use of 2-nitro-2-propane-1,3-diol (bronopol), glutaral and IPBC remains to be assessed.

We assume that the rapid decrease in use concentration of some substances around 1995–2000 was related to the increasing use of isothiazolinones, and that the overall decrease in use concentrations during 1995–2018 likely was related to introduction of several harmonized classifications with decreasing concentration limits. We do not know to what extent combinations of various preservatives (isothiazolines and other types) has contributed to the decrease.

Since 1995, the decrease in use of MDBGN (DBDCB) in non-cosmetic products has been substantial in terms of volume (tonnes) and, since 2008, in terms of number of products, but its use is not zero. MDBGN (DBDCB) was finally prohibited in all types of cosmetic products in 2008 with its ban in rinse-off cosmetic products. According to BPR, it is allowed as preservative in various products, including detergents, paints and adhesives. We fear that use in non-cosmetic products will increase again, as industry currently is promoting its use.[45] MDBGN (DBDCB) does not yet have a harmonized classification and may thus be undisclosed on labels and in SDSs.

Parabens have been under discussion for decades.[61] They have been used mainly for medicinal products, cosmetics, detergents and as food additives. Several of the used parabens are known skin sensitizers, but they are relatively weak sensitizers.[62] Patients with stasis eczema, leg ulcers and atopic dermatitis are the groups mainly affected by paraben allergy. The Scientific Committee for Consumer Safety assessed other concerns regarding toxicity of different parabens.[63,64]

Patients, workers and consumers need to be able to identify potentially harmful substances in products that may contact their skin. This is also essential for treating dermatologists and other healthcare professionals, and for employers who are responsible for the work environment. Industry should know the substances and concentrations they use. EU regulators and national authorities need to use their authority to improve protection of health, personal and environmental safety. We suggest how some of the increasing use trends, shortcomings and obstacles may be met by strategies and demands already existing in some EU legislations.

4.1 | Major challenges and implications for stakeholders

4.1.1 | Contact allergy, diagnosis and prevention of disease

Avoidance of further exposure to a skin sensitizer is crucial to sensitized individuals for avoidance of allergic contact dermatitis. Industry should be obliged to give information about content on request by healthcare professionals managing patients, as this is required for diagnosing and advising patients.

Dermatologists and healthcare professionals need to be aware that information on the presence of preservatives in non-cosmetic products may not appear on labels, packages or SDSs, and that numerous skin sensitizing preservatives and other biocides beyond the baseline series are used in chemical products and various articles for consumer and occupational use. Patch testing with additional preservatives may be required to identify the cause of allergic contact dermatitis. Testing with products and ingredients may also be needed.

All currently commercially available patch test preparations may not be optimal for diagnostic patch testing. For example, the concentrations of formaldehyde, MCI/MI, MI and MDBGN (DBDCB) have been adjusted (generally increased); the preparations of 2-nitro-2-propane-1,3-diol (bronopol), BIT and IPBC may require change; and there is limited experience with numerous substances beyond baseline series.

Human (clinical) evidence may be of great importance in classification of skin sensitizers (see Section 4.1.3). It is, therefore, important that healthcare professionals publish quality scientific articles on skin sensitization to biocides, including CAS number and other identifiers

of the source, description of the exposure, clinical course, patch test results for cases and non-exposed controls. Single cases, occupational groups, epidemiological and experimental studies all contribute to knowledge.

4.1.2 | Reduction of preservative consumption is highly warranted

It is often stated by industry, dermatologists and others, that it is necessary to use preservatives in water-based products to avoid growth of microbes and to prevent disease. It is also often stated that a mixture of various preservatives at low concentration is preferred over fewer at higher concentration, to avoid development of resistance and skin sensitization. There are, however, drawbacks to this.

Risks caused by preservatives and other biocides include the risk of resistance to biocides, antibiotics and other antimicrobial substances. Biofilm in sewage and sludge, contaminated soil, groundwater and aqueous environment, and influence on organisms are serious effects. Many aspects have been reviewed in depth in a scientific opinion on behalf of the EC.[65] The topic is of extremely high concern according to European Chemicals Agency (ECHA), Organization of Economic Cooperation and Development (OECD) and World Health Organization (WHO) but is outside the scope of this article.[66–69]

Combinations of various isothiazolinones and other preservatives in biocidal products and in mixtures (chemical products) are frequent. This contributes to the risk of polysensitization by exposure to multiple sensitizers and risk of cross-reactivity by the increasing use of chemically closely related substances, particularly isothiazolinones.[30] The ability to work of painters with contact allergy to isothiazolinones is seriously affected, when almost all water-based paints contain one or more isothiazolinones.[35] The companies BASF, Lanxess, Thor GmbH and Troy Chemical are among the largest manufacturers and suppliers in Europe of some of the biocides in this study.[70] They market numerous brands and various combinations of isothiazolinones, 2-nitro-2-propane-1,3-diol (bronopol), IPBC and glutaral.

Numerous alternative techniques to reduce or avoid the use of preservatives are available, including smart packaging and dispensing to limit contamination or oxidation during use, controlling pH to limit growth, using solid formulations instead of water-based, and cleaner water and improved techniques during manufacture. Some water-based paints without isothiazolinones or other preservatives exist and are marketed at countries such as Belgium, Denmark, Germany and Sweden.[24,36]

4.1.3 | EU legislations can be better used for prevention of skin disease

Undisclosed use of preservatives and other biocides cause severe obstacles. Current EU legislations may provide existing solutions to this by the Cosmetics Regulation, Detergents Regulation, CLP, BPR and REACH.

Preservatives are among the most potent and frequently skin sensitizing substances.[71–74] No safe use concentrations for elicitation reactions have been shown for frequent skin sensitizers.[75–77] Harmonized classification as Skin Sens. is present for only a few sensitizing preservatives. Notified classifications are often far too generous for prevention of skin sensitization and elicitation and are thus not clinically relevant. To set sufficiently protective harmonized classifications as Skin Sens. should be of high priority. Scientifically published human data on skin sensitization in epidemiological, experimental and workplace studies, selected patient groups and single cases is important for evaluation of the skin sensitizing potency (see also Section 4.1.1). Studies on skin exposure assessment are expected to contribute increasingly.[78]

Labelling (H317 and EUH208) and SDS information about sensitizers in mixtures (chemical products) are directly linked to the CLP classification limit (see Section 2 above). Concentrations below the current EUH208 limit will remain undisclosed on labels and in SDSs, if not otherwise is decided in BPR, which is done for e.g. IPBC (PT6).[46] We suggest that industry, despite current legal requirements, shall give information in SDSs, on packages and labels about presence of all preservatives irrespective of concentration.

Imported treated articles with active biocidal substances can only indirectly be regulated by the BPR by specifying defined uses of the active biocidal substance in the approval. Such articles may be placed on the EU market as no product authorisation will take place for imported treated articles. This gap can be used to avoid authorisation and labelling requirements by BPR and CLP, respectively.[45,79] Compliance with the EU chemicals legislations and enforcement of legislation varies between EU member states, and thus also the related protection of health and safety, and the environment. Import to EU and online trade are areas of special concern. A regulation on how to harmonize market surveillance entered into force in 2021 and will, hopefully, strengthen compliance and enforcement.[80]

It is encouraging that ECHA and the EC are giving increasing attention to the harm caused by skin sensitization and the need to restrict skin sensitizing chemicals by a broad approach. Recent examples are the REACH restrictions on all classified skin sensitizers in tattoo inks and permanent make-up,[81] and the proposed restrictions for textile, leather and so forth, in contact with the skin.[82]

We suggest that some principles used under various EU legislations are applied, for example:

1. That full ingredient labelling of all preservatives and other biocides, irrespective of classification, shall be used for all mixtures (chemical products). This is mandatory for preservatives in detergents and cosmetic products.
2. That "*EUH208—'Contains (name of sensitising substance). May produce an allergic reaction'*" shall be used for all substances classified as Skin Sens., irrespective of concentration in the mixture; or with a new EUH number if initially applied only on biocides. This is mandatory for chromium VI in cement (EUH203), isocyanates (EUH204) and epoxy constituents (EUH205).

3. That CAS numbers may be used as substance identifier in addition to chemical or INCI names, to promote transparency and understanding.
4. That REACH restrictions and CLP classifications are applied on group level for closely related skin sensitizing biocides, for example, owing to the increasing use of isothiazolinone compounds, some lacking harmonized classification as Skin Sens. The group approach is used for parabens in the Cosmetics Regulation (Table 1) and it is under discussion by the EC for numerous substance groups, including some skin sensitizers.[83]

4.2 | Strengths and limitations

The main strengths of our study are that it is the first study reporting temporal trends in use of several skin sensitizing preservatives in non-cosmetic products, and, in parallel depicts key elements in the EU legal framework. The assessed substances are among the most frequently identified skin sensitizers internationally. Generalizability of the results is considered good for Europe owing to the common legal framework concerning chemicals and cosmetics. We have not, however, been able to compare the results with other countries because reporting obligations differ too much between countries for reliable comparison.

Limitations are that it is not known how accurate the reporting by industry to the Swedish Products Register has been. One major problem is that reporting of MCI, MCI/MI and MI was inconsistent, resulting in data partly difficult to interpret. We have not had access to data on combinations of preservatives in various products, for example, isothiazolinones, formaldehyde releasers, IPBC and/or phenoxyethanol. Such combinations are frequent and would be of interest to assess.

5 | CONCLUSION

- The massive increase in use of skin sensitizing preservatives and other biocides is alarming. The relatively few substances in this study represent only a 'tip of the iceberg'. Urgent action to reverse this development is needed for protection of human health and the environment;
- Knowledge about exposure and skin sensitization to preservatives has mainly been related to cosmetic products, while their use in non-cosmetic products is broad, frequent and increasing but often undisclosed;
- EU chemicals legislations, per se, may affect industry to reduce the use of preservatives and the risk of skin sensitization, provided that the requirements set are relevant in relation to the hazard and exposure conditions, and efficient market surveillance. Prevention would improve by better coordination between legislations (horizontal legislation).

AUTHOR CONTRIBUTIONS

Carola Lidén: Conceptualization; data curation; investigation; methodology; validation; visualization; writing – original draft preparation; writing – review and editing. **Niklas Andersson:** Formal analysis; validation; visualization; writing – review and editing. **Ian White:** Validation; visualization; writing – review and editing.

ACKNOWLEDGEMENTS

The authors thank The Swedish Chemicals Agency for valuable help throughout the project by performing analyses and providing data from the Products Register, and for guidance on the Products Register. The authors also thank the Swedish Chemicals Agency for guidance on EU chemicals legislations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Lidén C, Andersson N, White IR. Preservatives in non-cosmetic products: Increasing human exposure requires action for protection of health. *Contact Dermatitis*. 2022;87(5):389-405. doi:10.1111/cod.14181