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Review Article

International Comparison of Criteria for Evaluating Sensitization of PRTR-Designated Chemical Substances

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Abstract

In this study, we aim to compare the criteria for sensitizers among national organizations in various countries and international organizations, and to specify whether each Pollutant Release and Transfer Register (PRTR)-designated chemical substance is a sensitizer by each organization. The definition of sensitizing chemicals and the designation of respective sensitizers according to the PRTR law, Japan Society for Occupational Health (JSOH), American Conference of Governmental Industrial Hygienists (ACGIH), European Union (EU), and Deutsche Forschungsgemeinshaft (DFG) were studied. Of the 435 PRTR-designated chemical substances, 15 are listed as sensitizers according to the PRTR law, 16 as sensitizers of the airway and 21 as sensitizers of the skin by JSOH, 12 as sensitizers (no discrimination) by ACGIH, 19 (airway) and 85 (skin) by EU, and 15 (airway) and 43 (skin) by DFG. Only 9 substances were designated as sensitizers by all these organizations. The variation in the designation of sensitizers is accounted for by the differences in the classification criteria and grouping of chemical substances. JSOH limits the definition of sensitizers to substances that induce allergic reactions in humans and uses only human data. Other organizations utilize not only human evidence but also appropriate animal tests. In addition, EU designates an isocyanate as a sensitizer except those for which there is evidence showing that they do not cause respiratory sensitivity. The worldwide enforcement of the globally harmonized system (GHS) of classification and labeling of chemicals could promote not only the consistent designation of sensitizers among national and international organizations, but also the development of testing guidelines and classification criteria for mixtures.

Key words: sensitizer, risk assessment, chemical substances, PRTR, GHS

Introduction

According to a survey conducted by the World Allergy Organization's Speciality and Training Council (1), about 22% of the population in 33 countries is estimated to suffer from some form of allergic disease. The prevalence of allergy in Japan is 40%, and is the highest among those countries. Recently, many studies have reported an increase in the occurrence of allergic diseases (2, 3). Foods, ticks, fungi, and pollen are well-known causes of allergy. However, occupational and environmental chemicals also account for some proportion of allergic diseases. To prevent chemical allergies, it is essential to identify the chemical substances that cause sensitization and to eliminate such sensitizers from daily life.

In Japan, the Law Concerning the Reporting, etc. of Release to the Environment of Specific Chemical Substances and Promoting Improvements in Their Management (Pollutant Release and Transfer Register law (PRTR) law) has been enforced since 1999. The purpose of this law is to promote improvements in the management of specific chemical substances and to prevent any impediment for environmental protection by requiring businesses handling such substances to report the release of these substances into the environment and to provide technical information on the properties and handling of such substances. This law regards "Class I Designated Chemical Substances" (total of 354 substances) as substances

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that are harmful to human health and the ecosystem (including substances that deplete the ozone layer), and are recognized to continuously exist in the environment over considerably wide areas. “Class II designated chemical substances” (total of 81 substances) are defined similarly to Class I substances but are anticipated to continuously exist in the environment over considerably wide areas if there are increases in the amounts manufactured, imported or used.

Some of the PRTR-designated chemical substances have sensitizing effects. However, the substances designated as sensitizers differ according to the organization or country. In this study, we compared the criteria used to define sensitizers in different organizations in Japan, the United States, European Union and Germany, and specified whether each chemical substance designated by the PRTR law is sensitizer by the respective organizations.

Methods

The meaning of sensitizing chemicals was studied was defined by the PRTR law (4), Japan Society for Occupational Health (JSOH) (5), American Conference of Governmental Industrial Hygienists (ACGIH) (6), European Union (EU) (7), and Deutsche Forschungsgemeinshaft (DFG) (8). Each of the 435 PRTR-designated chemical substances (Class I: 354 and Class II: 81) was to be or not to be a sensitizer or not by the respective organizations mentioned above.

Results

1) Criteria of sensitization in each organization

The criteria for sensitization that are used by PRTR, JSOH, ACGIH, EU, and DFG are shown in Tables 1 to 5, respectively.

Table 1 Selection criteria for sensitizers by Law Concerning the Reporting, etc. of Release to the Environment of Specific Chemical Substances and Promoting Improvements in Their Management (Pollutant Release and Transfer Register law (PRTR law)) (9)

Sensitizers were selected using the following criteria:

1) All substances in group 1 and group 2 of airway sensitizers as defined by JSOH and/or

2) Substances with any evidence in Environmental Health Criteria (EHC), Bangalore Urban Agglomeration (BUA); Advisory Committee on Existing Chemicals of Environmental Relevance of German Chemical Society), European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC), Screening information data set (SIDS), Chemical substances hazard sheet (10), among those indicated with “SEN”, and sensitization by ACGIH or with “R42” (sensitizer by inhalation) by EU.

Table 2 The Japan Society for Occupational Health (JSOH) selection criteria for sensitizers

The airway and skin sensitizers are classified into Group 1 substances which induce allergic reactions in humans and Group 2 substances which probably induce allergic reactions in humans. Recommendation of occupational exposure limits for the occupational sensitizers does not necessarily consider either prevention of sensitization or allergic reaction.

Airway sensitizers

Group 1

1) There are epidemiological studies that clearly show a relationship among the exposure status, respiratory symptom, specific antibody, and allergic diathesis,

and

2) There are case reports of patients with respiratory symptoms which satisfy either of the following conditions from different research institutes.

1. There is a relationship between exposure and pulmonary symptoms as well as detection of the specific antibody against the substance or positive data from an intracutaneous test.

or

2. There is a relationship between exposure and pulmonary symptom as well as positive results from the specific inhalation-challenge test. However, there must be direct or indirect evidence which supports the conclusion that the positive results are not caused by non-allergic reaction.

Group 2

The criteria for Group 1 are similarly applied, but the sensitization has not necessarily been proved in epidemiological studies.

Skin sensitizers

Group 1

1) There are epidemiological studies that clearly demonstrated the relationship among exposure status, symptoms of contact dermatitis, and the patch test (skin sticking examination).

and

2) There are case reports that studied the relationship between the symptoms of dermatitis and patch tests using appropriate methods from different research institutes.

Group 2

The criteria for Group 1 are similarly applied, but the sensitization is not necessarily proved in epidemiological studies.

Table 3 American Conference of Governmental Industrial Hygienists (ACGIH) selection criteria for sensitizers (6)

The designation “SEN” in the “Notations” column refers to the potential for an agent to produce sensitization, as confirmed by human or animal data. For those Threshold Limit Values (TLVs) that are based upon sensitization, they are meant to protect workers from induction of this effect. These TLVs are not intended to protect those workers who have already become sensitized. In the work places, respiratory, dermal, or conjunctival exposures to sensitizing agents may occur. Similarly, sensitizers may evoke respiratory, dermal, or conjunctival reactions. At this time, the notion does not distinguish between sensitization involving any of these organ systems. The absence of “SEN” notation does not signify that the agent lacks the ability to produce sensitization but may reflect the paucity or inconclusiveness of scientific evidence.

Table 4 European Union (EU) selection criteria for sensitizers (7)

Sensitization by inhalation

R42: May cause sensitization by inhalation.

— if there is evidence that the substance or preparation can induce specific respiratory hypersensitivity.

— where there are positive results from appropriate animal tests, or

— if the substance is an isocyanate, unless there is evidence that the specific isocyanate does not cause respiratory hypersensitivity.

Comments regarding the use of R42:

Human evidence

Evidence that the substance or preparation can induce specific respiratory hypersensitivity will normally be based on human experience. In this context hypersensitivity is normally seen as asthma, but other hypersensitivity reactions such as rhinitis and alveolitis are also considered. The condition will have the clinical character of an allergic reaction. However, immunological mechanisms do not have to be demonstrated.

When considering the evidence from human exposure, it is necessary for a decision on classification to take into account in addition to the evidence from the cases:

— the size of the population exposed,

— the extent of exposure.

The evidence referred to above could be:

— clinical history and data from appropriate lung function tests related to exposure to the substance, confirmed by other supportive evidence which may include:

  — a chemical structure related to substances known to cause respiratory hypersensitivity,

  — an in vivo immunological test (e.g., skin prick test),

  — an in vivo immunological test (e.g., serological analysis)

  — studies indicating other specific but non-immunological mechanisms of action, e.g., repeated low-level irritation, pharmacologically mediated effects, or

  — data from a positive bronchial challenge test with the substance conducted according to accepted guidelines for the determination of a specific hypersensitivity reaction.

Clinical history should include both medical and occupational history to determine a relationship between exposure to a specific substance or preparation and development of respiratory hypersensitivity. Relevant information includes aggravating factors both in the home and workplace, the onset and progress of the disease, family history and medical history of the patient in question. The medical history should also include a note of other allergic or airway disorders from childhood, and smoking history.

The results of positive bronchial challenge tests are considered to provide sufficient evidence for classification on their own. It is however recognized that in practice many of the examinations listed above will already have been carried out.

Substances that elicit symptoms of asthma by irritation only in people with bronchial hyperactivity should not be assigned to R42.

Animal studies

Data from tests which may be indicative of the potential of a substance or preparation to cause sensitization by inhalation in humans may include:

— IgE measurements (e.g., in mice), or

— specific pulmonary responses in guinea pigs.

Sensitization by skin contact

R43: May cause sensitization by skin contact

— if practical experience shows the substance or preparation to be capable of inducing sensitization by skin contact in a substantial number of persons, or

— where there are positive results from an appropriate animal test.

Comments regarding the use of R43:

Human evidence

The following evidence (practical experience) is sufficient to classify a substance or preparation with R43:

— positive data from appropriate patch testing, normally in more than one dermatological clinic, or

— epidemiological studies showing allergic contact dermatitis caused by the substance or preparation. Situations in which a high proportion of those exposed exhibit characteristic symptoms are to be looked at with special concern, even if the number of cases is small, or

— positive data from experimental studies in man

The following is sufficient to classify a substance with R43 when there is supportive evidence:

— isolated episodes of allergic contact dermatitis, or

— epidemiological studies where chance, bias or confounders have not been ruled out fully with reasonable confidence.

Supportive evidence may include:

— data from animal tests performed according to existing guidelines, with a result that does not meet the criteria given in the section on animal studies but is sufficiently close to the limit to be considered significant, or

— data from non-standard methods, or

— appropriate structure-activity relationships.

Animal studies

Positive results from appropriate animal tests are:

— in the case of the adjuvant type test method for skin sensitization or in the case of other adjuvant-type test methods, a response of at least 30% of the animals is considered positive,

— for any other test method a response of at least 15% of the animals is considered positive.

Table 5 Deutsche Forschungsgemeinschaft (DRG) selection criteria for sensitizers (8)

a. Criteria for the assessment of contact allergens

The allergological evaluation is based on a variety of information which must be seen as providing different qualities of evidence.

1) **Sufficient evidence** of an allergenic effect is provided by valid results from **either** i) **or** ii):

i) effects in man

— studies in which numerous clinically relevant cases of sensitization (i. e. association of symptoms and exposure) were observed in tests with large collectives of patients in at least two independent centres, or

— epidemiological studies which reveal a relationship between sensitization and exposure, or

— case reports of clinically relevant sensitization (association of symptoms and exposure) for more than one patient from at least two independent centres

or

ii) results of animal studies

— at least one positive result in an animal study without adjuvant carried out according to accepted guidelines, or

— positive results from at least two less well-documented animal studies carried out according to accepted guidelines, one of which did not use adjuvant.

2) An allergenic effect can be considered **probable** on the basis described in i) **and** ii) below:

i) effects in man

— studies in which numerous clinically relevant cases of sensitization (association of symptoms and exposure) were observed in tests in just one centre, or

— studies in which numerous cases of sensitization without details of clinical relevance were observed in tests with large collectives of patients in at least two independent centres

and

ii) results of animal studies

— a positive result in an animal study with adjuvant carried out according to accepted guidelines, or

— positive results from in vitro studies, or

— evidence from structural considerations based on sufficiently valid results for structurally closely related compounds.

3) An allergenic effect is **not sufficiently documented**, but also not excluded, when only the data listed below are available:

— insufficiently documented case reports, or

— only one positive result in an animal study with adjuvant carried out according to accepted guidelines, or

— positive results in animal studies which were not carried out according to accepted guidelines, or

— evidence from studies of structure-effect-relationships or from in vitro studies.

b. Criteria for the evaluation of respiratory allergens

The kinds of data which may be used in the evaluation of respiratory allergens are listed below; here too the different kinds of data provide different qualities of evidence.

1) Sufficient evidence of allergenic effects of a substance in the airways or the lungs is provided by valid data from:

— studies or case reports of a specific hyperreactivity of the airways or the lungs which are indicative of an immunological mechanism from more than one patient and at least two independent testing centres. In addition, the (clinical) symptoms or adverse effects on the function of the upper or lower airways or the lungs must be shown to be associated with the exposure to the substance.

2) An allergenic effect can be considered probable on the basis of the results listed below:

— one single case report of a specific hyperreactivity of the airways or the lungs

and

— other indications of sensitizing effects, e. g., a close structure-effect relationship with known airway allergens.

3) An allergenic effect is not sufficiently documented, but also not excluded, when only the data listed below are available:

— epidemiological studies which demonstrate an increased incidence of symptoms or impaired function in exposed persons, or

— studies or case reports of a specific hyperreactivity of the airways or the lungs in only one patient, or

— studies or case reports of sensitization (e.g., detection of IgE) without accompanying symptoms or impairment of function causally associated with the exposure,

or

— positive results of animal studies, or

— structure-effect relationships with known respiratory allergens.

c. Designation of a substance as an allergen

Whether or not it is necessary to designate a substance as an allergen in the List of MAK (maximale Arbeitsplatz-Konzentration) and BAT Values (Biologischer Arbeitsstoff-Toleranz-Wert) is determined on the basis of the available evidence of allergenic effects and, when possible, also on the basis of the expected levels of exposure.

- The substances characterized according to the criteria in Section a) or b) as belonging in Categories 1) or 2) are generally designated as allergens with “Sa”, “Sh”, “Sah” or “SP”.

— Substances for which these criteria are fulfilled are also designated with an “S” when the observed sensitization is associated mainly with cofactors which are (only) relevant under workplace conditions (e.g. (previous) damage to the skin caused by chemical or physical agents).

- On the other hand, substances are not designated with an “S” when

— in spite of extensive handling of the substance, very few (well-documented) cases of sensitization are observed, or

— the observed cases of sensitization are mainly associated with cofactors which are not relevant under workplace conditions (e.g. the presence of eczema on the lower leg), or

— the criteria of Section a) or b) resulted in classification of the substance in category 3).

The criteria are to be seen as guidelines for an intelligible evaluation of the data but in certain special cases their strict application may not be obligatory.

Table 6 Comparison of criteria for sensitization

Organization	Information	Region of sensitization	Symbol	Meaning
PRTR*[1]	Humans or animals	Airway	1	Sensitization
JSOH*[2]	Humans	Airway and skin	Group 1	Induces allergic reactions in humans
			Group 2	Probably induces allergic reactions in humans
ACGIH*[3]	Humans or animals	No discrimination	SEN	Potential of an agent to produce sensitization as confirmed from human and animal data
EU*[4]	Basically humans, but including animals in some conditions and chemical structure	Airway	R42	May cause sensitizaiton by inhalation
		Skin	R43	May cause sensitization by skin contact
DFG*[5]	Basically humans, but including animal information in some conditions	Skin	Sh	Causes allergic reaction on the skin and the mucosa close to the skin
		Airway	Sa	Causes airway sensitization
		Skin	SP	Causes photocontact sensitization

*[1] PRTR: Pollutant Release and Transfer Register.
*[2] JSOH: The Japan Society for Occupational Health.
*[3] ACGIH: American Conference of Governmental Industrial Hygienists.
*[4] EU: European Union.
*[5] DFG: Deutsche Forschungsgemeinschaft.

The PRTR law restricts the designation of sensitizers to only airway sensitization substances. JSOH limits the designation of sensitizers that induce an allergic reaction in humans. JSOH uses human data only. The designation of substances as sensitizers by ACGIH is based on confirmation from human and animal data even though it is aimed to protect workers from the induction of the effects. EU also uses not only human evidence but also appropriate data from animal tests. In addition, if the substance is an isocyanate, unless there is evidence that the specific isocyanate does not cause respiratory sensitivity, the substance is classified as a sensitizer. In DFG, the designation of substances as allergens is mainly based on human studies; however, some allergens are designated as sensitizers only on the basis of sufficient data from animal tests. The symbols used for designating sensitizing substances also differ according to the respective organizations. The meaning of each symbol is shown in Table 6.

2) Sensitizers classified by each organization

The list of PRTR substances defined as sensitizers by various organizations is shown in Table 7. Among the 435 PRTR-designated chemical substances, 15 are listed as sensitizers according to PRTR law. JSOH (5) designates 18 substances as airway occupational sensitizers and 30 as skin sensitizers. 11 airway sensitizer substances and 12 skin sensitizer substances are classified into Group 1, and 7 airway sensitizer substances and 18 skin sensitizer substances are classified into Group 2, according to the validity of evidence about them. Of the total number of occupational sensitizers designated by JSOH, 16 substances (airway) and 21 substances (skin) are listed in the PRTR law. ACGIH (6), EU (7), and DFG (8) define 25, 719, and 201 substances as sensitizers, respectively. 12 substances designated by ACGIH, 19 (airway) and 85 (skin) substances designated by EU, and 15 (airway) and 43 (skin) substances designated by DFG are listed in the PRTR law.

Although all these organizations define sensitizers as substances that cause specific respiratory hypersensitivity (e.g., asthma, rhinitis, and alveolitis) and/or sensitization by skin contact in humans and/or animals, only 9 substances were commonly designated as sensitizers by all these organizations. These substances are as follows: formaldehyde, methyl methacrylate (MMA), phthalic anhydride, methylene bisphenyl isocyanate (MDI), ethylenediamine, maleic anhydride, glutaraldehyde, trimellitic anhydride (TMA), hexamethylene diisocyanate (HDI), and toluene-2,4- or toluene-2,6-diisocyanate.

Discussion

The criteria for classifying chemical substances as sensitizers are not completely the same among the organizations reviewed in this study. Subtle differences in these criteria cause variation in the designation of chemical substances as sensitizers.

The carcinogenicity of chemical substances has also been reviewed by national organizations in various countries and by international organizations, for example, JSOH, ACGIH, the United States Environmental Protection Agency (EPA), National Toxicology Program (NTP), DFG, EU, the International Agency for Research on Cancer (IARC), and the International Labour Office (ILO). The evaluation criteria used to determine the carcinogenicity of each chemical substance are almost completely consistent in these organizations. All these organizations evaluate carcinogenicity on the basis of data from human and experimental animal studies and supporting evidence and not the carcinogenicity potency of the substance. Because the number of epidemiological studies concerning certain chemical substances is limited, it is thought that all these organizations referred to almost the same reports to collect evidences, which resulted in the evaluations criteria being similar.

In contrast, the evaluation of supporting evidence for sensitizing chemical substances is not consistent. Not only

Table 7 International comparison of sensitizers desinated by various organizations

PRTR No.	Substance	CAS No.	PRTR	JSOH (2004)		ACGIH (2004)		EU (2004)		DFG (2004)		
			Aiway	Airway	Skin	SEN	TLV*** Basis-Critical Effect(s)	Airway (R42)	Skin (R43)	Airway (Sa)	Skin (Sh)	Photo-contact (SP)
	Class I Designated Chemical Substances											
2	Acrylamide	79-06-1							○			
4	Ethyl acrylate; Acrylic acid ethyl ester	140-88-5					sensitization		○		○	
6	Methyl acrylate; Acrylic acid methyl ester	96-33-3			○ (2)	○			○		○	
7	Acrylonitrile	107-13-1							○		○	
15	Aniline	62-53-3							○			
16	2-Aminoethanol; Ethanolamine	141-43-5									○	
17	*N*-(2-Aminoethyl)-1,2-ethanediamine; Diethylenetriamine	111-40-0					sensitization		○		○	
23	1-Allyloxy-2,3-epoxypropane; Allyl glycidyl ether	106-92-3					sensitization		○		○	
27	3-Isocyanatomethyl-3,5,5-trimethylcyclohexylisocyanate; IPDI; Isophorone diisocyanate	4098-71-9					asthma, sensitization	○	○	○	○	
29	4,4'-Isopropylidene diphenol; Bisphenol A	80-05-7							○			○
30	Polymer of 4,4-isopropylidenediphenol & 1-chloro-2,3-epoxypropane(liquid); Diglycidylether of BPA; Bisphenol A type epoxy resin (liqid)	25068-38-6							○			
38	*N*-(1-Ethylpropyl)-2,6-dinitro-3,4-xylidine; Pendimethalin	40487-42-1							○			
39	*S*-Ethyl hexahydro-1*H*-azepine-1-carbothoate; molinate	2212-67-1							○			
42	Ethylene oxide	75-21-8			○ (2)							
46	Ethylenediamine	107-15-3	○	○ (2)	○ (1)		sensitization	○	○	○	○	
48	Zinc *N*,*N*'-ethylenebis(dithiocarbamate); Zineb	12122-67-7							○			
49	Manganese *N*,*N*'-ethylenebis(dithio-carbamate); Maneb	12427-38-2							○		○	
50	Complex compound of manganese *N*,*N*'-ethylenebis(dithiocarbamate) & zinc *N*,*N*'-ethylenebis(dithiocarbamate); Manzeb; Mancozeb	8018-01-7							○			
51	1,1'-Ethylene-2,2'-bipyridiniumdibromide; Diquat	85-00-7							○			
54	Epichlorohydrin	106-89-8							○		○	
56	1,2-Epoxypropane; Propylene oxide	75-56-9				○						
57	2,3-Epoxypropyl phenyl ether	122-60-1				○			○		○	
65	Glyoxal	107-22-2				○			○		○	
66	Glutaraldehyde	111-30-8	○	○ (1)	○ (1)	○	sensitization	○	○	○	○	
68	Chromium & Chromium (III) compounds	—	○	○ (2)*	○ (1)*							
69	Chromium (VI) compounds	—	○					○	○		○ **	
	Lead chromate (VI)	7758-97-6										
	Chromium (VI) trioxide	1333-82-0						○	○			
	Potassium dichromate	7778-50-9						○	○			
	Potassium chromate	7789-00-6							○			
	Ammonium dichromate	7789-09-5						○	○			
	Sodium dichromate	10588-01-9						○	○			
72	*p*-Chloroaniline	106-47-8							○			
73	*m*-Chloroaniline	108-42-9									○	
75	2-Chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine; Atrazine	1912-24-9							○			
82	2-Chloro-2',6'-diethyl-*N*-(methoxy-methyl)acetanilide; Alachlor	15972-60-8							○			
83	1-Chloro-2,4-dinitrobenzene	97-00-7									○	

Table 7 (continued)

PRTR No.	Substance	CAS No.	PRTR	JSOH (2004)		ACGIH (2004)		EU (2004)		DFG (2004)		
			Aiway	Airway	Skin	SEN	TLV*** Basis-Critical Effect(s)	Airway (R42)	Skin (R43)	Airway (Sa)	Skin (Sh)	Photo-contact (SP)
100	Cobalt & its compounds	—	○	○ (1)*	○ (1)*		asthma	○	○	○	○	
115	*N*-Cyclohexyl-2-benzothiazolesulfenamide	95-33-0							○			
131	2,4-Dichlorophenoxy acetic acid; 2,4-D	94-75-7							○			
135	1,2-Dichloropropane	78-87-5			○ (2)*							
137	1,3-Dichloropropene	542-75-6							○		○	
138	3,3'-Dichlorobenzidine	91-94-1							○			
148	*O*-Ethyl *S*,*S*-diphenyl phosphorodithioate; Edifenphos	17109-49-8							○			
161	2,3-Dihydro-2,2-dimethyl-7-benzo[b]furyl *N*-(dibutylamino)thio-*N*-methylcarbamate; Carbosulfan	55285-14-8							○			
167	Dimethyl-2,2,2-trichloro-1-hydroxyethylphosphonate; Trichlorfon	52-68-6							○			
174	3,5-Diiodo-4-octanoyl oxybenzonitrile; Ioxyniloctanoate	3861-47-0							○			
175	Mercury & its compounds	1582-09-8			○ (1)*						○	
181	Thiourea	62-56-6									○	○
194	*O*-3,5,6-Trichloro-2-pyridyl-*O*,*O*-dimethylphosphorothioate; Chlorpyrifos-methyl	5598-13-0							○			
198	1,3,5,7-Tetraazatricyclo[3.3.1.1^{3,7}]decane; Hexamethylenetetramine	100-97-0						○	○		○	
199	Tetrachloroisophthalonitrile; Chlorothalonil	1897-45-6							○		○	
202	Tetrahydromethylphthalic anhydride; Methyl cyclohexene-dicarboxylic ananhydride; MTHPA	11070-44-3		○ (1)				○	○	○		
204	Tetramethylthiuramdisulfide; Thiram; TMTD; Bis(dimethylthiocarbamoyl) disulfide	137-26-8							○		○	
207	Copper salts (water-soluble, except complex salts)				○ (2)*							
212	2,4,6-Trichloro-1,3,5-triazine	108-77-0							○			
215	2,2,2-Trichloro-1,1-bis(4-chlorophenyl) ethanol; Kelthane; Dicofol	115-32-2							○			
218	1,3,5-Tris(2,3-epoxypropyl)-1,3,5-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione; 1,3,5-Triglycidyl-S-triazinetrione	2451-62-9					sensitization		○			
220	α,α,α-Trifluoro-2,6-dinitro-*N*,*N*'-dipropyl-*p*-toluidine; Trifluralin	1582-09-8							○			
226	*p*-Toluidine	106-49-0							○		○	
228	2,4-Diaminotoluene; 2,4-Toluenediamine	95-80-7							○		○	
231	Nickel	7440-2-0	○	○ (2)*	○ (1)*				○	○	○	
232	Nickel compounds	—							○	○	○	
244	Picric acid	88-89-1					sensitization				○	
249	Zinc bis(*N*,*N*-dimethyl dithiocarbamate; Ziram	137-30-4							○			
253	Hydrazine	302-1-2			○ (2)*				○		○	
254	Hydroquinone	123-31-9			○ (2)				○			
258	Piperazine; Hexahydropyrazine; Diethylenediamine	110-85-0	○	○ (2)				○	○	○	○	
262	*o*-Phenylenediamine	95-54-5			○ (1)				○		○	
263	*p*-Phenylenediamine	106-50-3			○ (1)		sensitization		○		○	
264	*m*-Phenylenediamine	108-45-2			○ (1)				○			
265	*p*-Phenetidine; 4-Ethoxyaniline	156-43-4							○			

PRTR No.	Substance	CAS No.	PRTR	JSOH (2004)		ACGIH (2004)		EU (2004)		DFG (2004)		
			Aiway	Airway	Skin	SEN	TLV*** Basis-Critical Effect(s)	Airway (R42)	Skin (R43)	Airway (Sa)	Skin (Sh)	Photo-contact (SP)
267	3-Phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate; Permethrin	52645-53-1							○			
270	Di-*n*-butyl phthalate	84-74-2			○ (2)							
276	Methyl *N*-[1-(*N*-*n*-butylcarbamoyl)-1*H*-2-benzimidazolyl]; Benomyl	17804-35-2							○			
293	Hexamethylene diisocyanate; HDI	822-6-0	○	○ (1)			sensitization	○	○	○	○	
294	Beryllium & its compounds	—	○	○ (1)*	○ (2)*				○	○	○	
300	1,2,4-Benzene tricarboxylic 1,2-anhydride; Trimellitic acid 1,2-anhydride; Trimellitic anhydride; TMA	552-30-7	○	○ (1)			sensitization		○	○		
302	Pentachloronitrobenzene; PCNB; Quintozene	82-68-8							○			
310	Formaldehyde	50-0-0	○	○ (2)	○ (1)	○			○		○	
312	Phthalic anhydride	85-44-9	○	○ (1)		○		○	○	○		
313	Maleic anhydride	108-31-6	○	○ (2)	○ (2)	○	asthma	○	○	○	○	
316	2,3-Epoxypropyl methacrylate; Glycidyl methacrylate; GMA	106-91-2							○			
317	2-(Diethylamino)ethyl methacrylate; DEMA	105-16-8							○			
318	2-(Dimethylamino)ethyl methacrylate; DMMA	2867-47-2							○			
319	*n*-Butyl methacrylate; *n*-Butyl-α-methylacrylate	97-88-1							○		○	
320	Methyl methacrylate; MMA	80-62-6	○	○ (2)	○ (2)	○			○		○	
321	Methyacrylonitrile	126-98-7							○			
324	Methyl isothiocyanate; Isothiocyanato methane	556-61-6							○			
332	3-Methyl-1,5-di(2,4-xylyl)-1,3,5-triazapenta-1,4-diene; Amitraz	33089-61-1							○			
334	6-Methyl-1,3-dithiolo[4,5-*b*]quinoxalin-2-one; Quinomethionate	2439-1-2							○			
338	Methyl-1,3-phenylene diisocyanate; *m*-Tolylene diisocyanate; Tolylene diisocyanate	26471-62-5		○ (1)	○ (2)	○	sensitization	○	○	○		
340	4,4'-Methylenedianiline	101-77-9							○		○	
341	Methylenebis(4,1-cyclohexylene) diisocyanate	5124-30-1					sensitization	○	○			
349	1,2-Dibromo-2,2-dichloroethyl dimethyl phosphate; Naled	300-76-5				○						
350	Dimethl 2,2-dichlorovinyl phosphate; 2,2-Dichlorovinyl dimethyl phosphate; Dichlorvos	62-73-7				○			○			
	Class II Designated Chemical Substances											
6	*p*-Aminophenol	123-30-8									○	
21	*O*-6-Chloro-3-phenyl-4-pyridazinyl *S*-*n*-octyl thiocarbonate; Pyridate	55512-33-9							○			
29	2-(2,4-Dichlorophenyl)-1-(1*H*-1,2,4-trazol-1-yl)-2-hexanol; Hexaconazole	79983-71-4							○			
34	4,6-Dinitro-*o*-cresol	534-52-1							○			
43	1,1-Dimethylhydrazine; *N*,*N*-dimethylhydrazine	57-14-7									○	
74	Methylhydrazine	60-34-4									○	
78	Methylenebis(4,1-phenylene) diisocyanate; pure MDI	101-68-8	○	○ (1)			sensitization	○	○	○	○	
	total number of substances defined as sensitizers		15	16	21	12	sensitization, asthma: 16	19	86	15	43	2

(1): Group 1
(2): Group 2
* Evaluation does not necessarily apply to all individual chemicals within the group.
** (inhalable fraction), with the exception of those practically insolbul in water such as lead chromate, barium chromate.
*** Threshold Limit Value.

sensitizers but also irritants induce bronchial asthma or dermatitis. The differences in individual susceptibility will also affect the evaluation of evidence. Not all individuals develop allergic reactions in response to sensitizers. When very few cases of sensitization are observed, even though a report on a particular case is well documented, the substance involved might not be designated as a sensitizer, depending on the organization.

Another reason for the differences in designation is the difference in the grouping of substances. For example, hexavalent chromium compounds are expressed as chromium (VI) compounds without CAS number in the PRTR law (4). JSOH does not distinguish chromium compounds according to their respective compounds but groups them all as “chromium” with a footnote stating that the evaluation does not necessarily apply to individual chemicals within the group (5). Six individual chromium compounds, namely, chromium (VI) trioxide (chromic anhydride), lead chromate (VI), potassium dichromate, potassium chromate, ammonium dichromate, and sodium dichromate are separately reviewed by EU (7). ACGIH divides hexavalent chromium compounds into water-soluble Cr VI compounds and insoluble Cr VI compounds (6). The category used by DFG is chromium (VI) compounds ((inhalable fraction), with the exception of those that are practically insoluble in water, such as lead chromate, and barium chromate, and four individual chemical names are shown: chromium (VI) oxide, chromium oxychloride, chromium trioxide, and chromyl chloride) (8). Because the potency of sensitization differs depending on the individual chemical, the evaluation of chemicals is thought to differ according to what chemicals are reviewed as representatives of the group.

According to the above-mentioned reason, only 9 substances were designated as sensitizers by all the above-mentioned organizations.

In 1992, the United Nations Conference on the Environment and Development (UNCED) adopted a system for the harmonization of the classification and labeling of chemicals as one of 6 program areas to strengthen national and international efforts related to the environmentally sound management of chemicals (12). The globally harmonized system (GHS) of classification and labeling of chemicals aimed to establish harmonized criteria for classifying substances and mixtures according to their health, environmental, and physical hazards and harmonized communication elements, including the requirements for labeling and safety data sheets. The organization for Economic Cooperation and Development (OECD) is responsible for reviewing and implementing policies on health and environmental hazards (designated as a focal point organization on the basis of its work in the area of testing guidelines and for reviewing other chemical issues. The work of this organization was later expanded to include the formulation of classification criteria for mixtures and chemical preparations).

In GHS (UN 2005), the classification criteria for respiratory sensitizers (Category 1) are

1) if there is evidence in humans that the substance can induce specific respiratory hypersensitivity and/or
2) if there are positive results from an appropriate animal test;

and those for contact sensitizers (Category 1) are

1) if there is evidence in humans that the substance can induce sensitization by skin contact in a substantial number of persons, or
2) if there are positive results from an appropriate animal test.

The details of these criteria are also mentioned in GHS (13). However, the classification criteria for mixtures are not completely stated.

It is expected that the development of testing guidelines, the consistent designation of sensitizers, and the classification criteria for mixtures will be discussed further after the enforcement GHS.

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