



Evaluation for skin sensitization based on published literatures (existing information) of major PRTR designated chemical substances in Japan

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ABSTRACT

Of the 354 substances designated as class I under the Pollutant Release and Transfer Register (PRTR) law in Japan, we reviewed the sensitization data of the selected 144 substances and analyzed it from various aspects comparing human and animal data, determining the relationship between skin sensitization and chemical structure and comparing the various international organizations.

Although most of them were expected to be hazardous substances, 49 out of the 144 substances lacked both human and animal sensitization data. Positive substances accounted for 69% and 42% of the substances for which sensitization data were available in the case of humans and animals, respectively.

A correlation was observed between the chemical structures of the substances and sensitization, despite the relatively few substances examined in this study and the limited homogeneity of the collected data. In particular, epoxides clearly had sensitizing potentials and more than half of carboxylic esters or dicarboxyl anhydrides, aliphatic aldehydes, and aromatic compounds with at least two hydroxyl groups also had sensitizing potentials.

Also, this study clearly demonstrated the lack of consistency across the sensitization assessment criteria adopted by different countries or among those adopted by the same country on the basis of different laws or administrative measures.

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1. Introduction

Most symptoms of allergy caused by chemical substances, such as perfumes, dyes, disinfectants, and metals, are classified under the category of delayed-type allergy, which has long been known as contact allergy and is mediated by cellular immunity. Some chemical substances induce airway allergies, which are classified as immediate-type allergies. In either case, exposure of workers or consumers to target sensitizers must be avoided as much as possible, and these sensitizers need to be replaced with less-sensitizing substances or must be used safely by completing a risk assessment. From this standpoint, it is important that we collect information concerning sensitization of various chemicals and assess their sensitizing potentials.

Classifications established by various organizations, such as the Japan Society for Occupational Health (JSOH), American Conference of Governmental Industrial Hygienists (ACGIH), Deutsche Forschungsgemeinschaft (DFG), and European Union (EU) are useful sources of information on sensitization. The skin sensitization expert group of Deutsche Bundesgesundheitsamt (BGA) (reorganized into the German Federal Institute for Risk Assessment (BfR) in 2002) (hereafter referred to as BfR expert group) designated 244 out of

956 substances examined as sensitizers and ranked them according to the strength of sensitization (Schlede et al., 2003).

However, a lack of consistency has been identified across the classification results obtained in different countries as well as those obtained from the same country on the basis of different laws or administrative measures. An international comparison of the classification results of PRTR-designated chemical substances evaluated by JSOH, ACGIH, DFG, and EU revealed that only nine substances, i.e., formaldehyde, methyl methacrylate, phthalic anhydride, methylenebis(4,1-phenylene) diisocyanate, ethylenediamine, maleic anhydride, trimellitic anhydride, glutaraldehyde, and hexamethylene diisocyanate, were designated as sensitizers in common by all four organizations (Murakami et al., 2007). This result demonstrated that the classification criteria for sensitizers, unlike those for carcinogens, are not consistent among organizations.

Thus, regardless of the presence or absence of sensitizing potentials, it is essential to examine existing data on the sensitizing potentials of chemical substances in order to analyze the differences in classification criteria among the various international organizations as well as understand the basis for globally harmonized assessment. The outcome of this examination will have far-reaching impacts on the current situation. This is because data concerning human health toxicity and ecological toxicity are being streamlined through international efforts such as the Globally Harmonized System of Classification and Labelling of Chemicals (GHS)

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and EU's newly established Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH).

In Japan, the Pollutant Release and Transfer Register (PRTR) law was enforced in fiscal year (FY) 2002, and 354 substances have been designated as class I under this law. In the present study, we selected 144 class I-designated substances on the basis of their toxicity, amount manufactured/imported, etc., and examined the existing data on sensitization. From FY 2001 to FY 2006, the authors' institution, namely, the Chemical Evaluation and Research Institute, Japan (CERI), conducted a hazard assessment project termed "Chemical Risk Assessment and Development of Risk Assessment Methods" at the request of the New Energy and Industrial Technology Development Organization, Japan (NEDO). The results of the project were organized such that they could be domestically shared (CERI and NEDO, 2007). In the present paper, we reviewed the sensitization data of the 144 substances and analyzed it from various aspects, comparing human and animal data, determining the relationship between sensitization and chemical structure and comparing the various international organizations.

2. Materials and methods

2.1. Target substances

The 144 target substances were selected from those subjected to hazard assessment in the NEDO project. Substances with higher priorities were preferentially selected, provided that the priorities were calculated based on the hazard category adopted at the designation of PRTR class I substances and PRTR emission data (Sado-tomo et al., 2006).

2.2. Information sources for skin sensitization

We searched through the existing evaluation documents, databases, and literature databases listed in Table 1 by Chemical Abstract Services (CAS) number.

Table 1

List of information sources for skin sensitization.

Documents

- IPCS, International Program on Chemical Safety: Environmental Health Criteria (EHC)
- IPCS, International Program on Chemical Safety: Concise International Chemical Assessment Document (CICAD)
- IPCS, International Program on Chemical Safety: Joint Meeting on Pesticide Residues (JMPR), monographs and evaluations
- IARC, International Agency for Research on Cancer: IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans
- OECD, Organization for economic co-operation and development: Screening Information Data Set (SIDS) Initial Assessment Report
- EU, European Union: Risk Assessment Report
- ECETOC, European Chemical Industry Ecology & Toxicology Centre: Technical Report; Joint Assessment of Commodity Chemicals
- The Chemical Evaluation and Research Institute, Japan: Hazard Data Book for Chemical Substances
- The Chemical Evaluation and Research Institute, Japan and National Institute of Technology and Evaluation: Chemical Substances Hazard Assessment Report/Initial Risk Assessment Report
- Ministry of Environment, Japan: Initial Risk Assessment Report Vols. 1–4
- GDCh BUA: German Chemical Society-Advisory Committee on Existing Chemicals of Environmental Relevance, BUA Report
- Environment Canada, Health Canada: Priority Substances List Assessment Report, Canadian Environmental Protection Act (CEPA)
- Australian Department of Health and Aging: Priority Existing Chemical Assessment Report, National Industrial Chemicals Notification and Assessment Scheme (NICNAS)
- ACGIH, American Conference of Governmental Industrial Hygienists: Documentation of the threshold limit values and biological exposure indices, seventh ed.
- US ATSDR, Agency for Toxic Substances and Disease Registry: Toxicological Profile
- US NTP CERHR, National Toxicology Program Center for the Evaluation of Risks to Human Reproduction: Report
- US NTP, National Toxicology Program: Technical Report

Data searches

- EU, European Union: International Uniform Chemical Information Database (IUCLID)
- Ministry of the Environment, Japan: PRTR data database
- US EPA: Integrated Risk Information System (IRIS), National Library of Medicine

Literature searches

- NLM, National Library of Medicine: Toxicology Literature Online (TOXLINE)
- SRC, Syracuse Research Corporation: Toxic Substance Control Act Test Submission database (TSCATS)

Classification for sensitization by some organizations

- EU, European Union
- PRTR, Pollutant Release and Transfer Register law in Japan
- JSOH, The Japan Society for Occupational Health
- ACGIH, American Conference of Governmental Industrial Hygienists
- DFG, Deutsche Forschungsgemeinschaft

2.3. Classification of the substances on the basis of the evidence from human and animal studies

On the basis of the evidence collected in humans and animals, we assessed the skin sensitizing potentials of the target substances. Table 2 shows the criteria adopted for classifying the substances on the basis of the evidence from human and animal studies. According to the criteria, the substances were classified as either positive, negative, equivocal, or no data available.

The currently available international guideline is the OECD test guideline 406 "Skin Sensitization." After its revision in 1992, the guideline recommends two methods for testing skin sensitization to chemicals (contact hypersensitivity induction potential), i.e., the guinea pig maximization test (GPMT) and the Buehler Test (OECD, 1992). The mouse ear swelling test (MEST) and the Local Lymph Node Assay (LLNA) have also been added to the OECD test guidelines as methods approved for primary screening of skin sensitizers (OECD, 2002). Therefore, we emphasized on the results obtained by the GPMT, Buehler Test, LLNA, and MEST, which are recommended by the current OECD test guidelines and we required at least one positive result from the four tests to have positive in animal data. However, to have negative we required two or more negative results from the four tests because we should consider a substance as a non-sensitizer carefully. We also took into consideration the results of tests performed according to other methods when assessing the skin sensitizing potentials of the substances.

We also classified substances which produced positive results at least in human or animal studies as skin sensitizers in this study.

2.4. Chemical structurally based classification

We also discussed the relationship between the chemical structures and sensitizing potentials of the target substances. We focused on chemical structures regarded as sensitization-related structures, i.e., epoxy, amines or amides, aldehydes, carboxylic

Table 2

Criteria based on evidence from human and animal data.

(1) Human data	
Positive	There is evidence in humans that the substance can lead to sensitization by skin contact. Evidence should include any of the following: • Positive data from patch testing, normally obtained in more than one dermatology clinic • Well documented episodes of allergic contact dermatitis, normally obtained in more than one dermatology clinic • Epidemiological studies showing allergic contact dermatitis caused by the substance • Positive data from experimental studies in man
Negative	There is negative evidence in human that the substance can lead to sensitization by skin contact. Negative evidence should include two or more of the following: • Patch testing • Well documented episodes of allergic contact dermatitis, normally obtained in dermatology clinic • Epidemiological studies showing allergic contact dermatitis caused by the substance • Negative data from experimental studies in man
Equivocal	Not fit in both positive and negative
No data available	
(2) Animal data	
Positive	There is at least one positive result from an appropriate animal test • Guinea Pig Maximization test • Buehler Guinea Pig Test • Local Lymph Node Assay • The Mouse Ear Swelling Test (MEST)
Negative	There are two or more negative results from an appropriate animal test • Guinea Pig Maximization test • Buehler Guinea Pig Test • Local Lymph Node Assay • The Mouse Ear Swelling Test (MEST)
Equivocal	Not fit in both positive and negative
No data available	

acids, aromatic hydroxyl groups, and halogenated compounds (Barratt et al., 1994a,b). Isocyanates are also regarded as sensitization-related structures but were excluded from the study due to their scarcity among the 144 substances. Alcoholic hydroxyl groups were also examined to represent structures that are not considered to have sensitization-related structures.

3. Results

3.1. Human and animal sensitization data for the 144 substances

The human and animal sensitization data for the 144 substances is summarized in Table 3. The complete set of sensitization data for all substances is presented in Appendix A.

Human sensitization data were available for 68 substances, among which 47, 9, and 12 were classified as positive, negative, and equivocal, respectively. Among the 144 substances examined,

animal data were available for 80 substances, among which 34, 7, and 39 were classified as positive, negative, and equivocal, respectively. Among the substances for which sensitization data were available, there was a high proportion of positive substances, i.e., the amount being 69% and 42% in the case of humans and animals, respectively.

The data from human and animal studies is compared in Table 4. Of the 144 substances, substances 19 and 3 were consistently positive and negative, respectively, in both humans and animals. Very few substances showed inconsistent results between human and animal studies; only one substance was positive in humans but negative in animals, and it was the reverse in the case of one other substance. Forty-nine (34%) out of the 144 substances lacked both human and animal data regarding sensitization.

3.2. Relationship between the characteristic chemical structures and skin sensitization

We discussed the relationship between the characteristic chemical structures of the examined substances and skin sensitization. We focused on the chemical structures regarded as sensitization-related structures, i.e., epoxy, amines or amides, aldehydes, carboxylic acids, aromatic hydroxyl groups, and halogenated compounds (Barratt et al., 1994a,b). Alcoholic hydroxyl groups were also examined to represent structures that are not considered to have sensitization-related structures. The number of substances containing the individual chemical structures and the number and percentage of skin sensitizers are summarized in Table 5. Skin sensitizers were defined as substances that were positive at least in human or animal studies in the present study.

All eight epoxide compounds examined in this study were classified as skin sensitizers. Of the 17 amines or amide substances, 13 were found to be skin sensitizers. Five of eight aldehydes were classified as skin sensitizers. This demonstrated that skin sensitizers could be found at high proportions among substances containing these structures. In contrast, the proportion of skin sensitizers was low among halogenated compounds (8 out of 34). None of the

Table 3

Summary of human and animal data in the 144 chemical substances.

Human data (68 chemical substances)			Animal data (80 chemical substances)		
Positive	Negative	Equivocal	Positive	Negative	Equivocal
47 (69%)	9 (13%)	12 (18%)	34 (42%)	7 (9%)	39 (49%)

Table 4

Comparison between sensitization data from human and animal studies.

		Human data				
		Positive	Negative	Equivocal	No data	Total
Animal data	Positive	19	1	2	12	34
	Negative	1	3	1	2	7
	Equivocal	17	4	5	13	39
	No data	10	1	4	49	64
	Total	47	9	12	76	144

Table 5
Relationship between the characteristic chemical structures and skin sensitization.

Chemical structure (): number of substances	Number of skin sensitizers classified in this study ^a (%)	Number of substances without any data available (%)
Epoxides (8)	8 (100)	0 (0)
Amines or Amides (17)	13 (76)	1 (6)
Aldehydes (8)	5 (63)	2 (25)
Carboxylic acids ^b (24)	13 (54)	5 (20)
Aromatic hydroxyl groups (8)	4 (50)	1 (12)
Halogenated compounds (34)	8 (24)	17 (53)
Alcoholic hydroxyl groups (9)	0 (0)	1 (12)

^a Based on evidence from human and/or animal data.

^b Carboxylic acid, carboxylate ester and dicarboxylic anhydride are included.

nine compounds with alcoholic hydroxyl groups were classified as skin sensitizers.

3.3. Comparison with the classification data from various international organizations

The classification results of the 144 substances based on human and animal data were compared with the classification data from various international organizations in Table 6. Of the 19 substances that were consistently positive in both humans and animals, 16 and 15 were classified as skin sensitizers (R43) by EU and DFG, respectively. The BfR expert group classified 14 of these substances into three ranks: A, B, and C, according to their allergenic potency (A: significant contact allergen, B: solid based indication for contact allergenic effects, C: insignificant contact allergen or questionable contact allergenic effect). We have listed the BfR work for the purpose of reference because it is useful. But attention needs to be paid to the fact that it did not follow any national or international classification guideline and so would be expected to have produced some anomalies. Among the 43 substances that were positive in either human or animal studies, relatively few were classified as sensitizers by any of the organizations. Moreover, among the 33 substances that had positive data in neither humans nor animals, or among the 49 substances without any data available in either humans or animals, very few were classified as sensitizers by any of the organizations.

4. Discussion

4.1. Existing data concerning skin sensitization by 144 substances

In the present study, we reviewed the existing data concerning skin sensitization by 144 substances. Since these chemical substances were designated as class I under the PRTR law in Japan, most of them were expected to be hazardous substances. Positive

substances accounted for 69% and 42% of the substances for which sensitization data were available in the case of humans and animals, respectively; this demonstrated that substantial proportions of the 144 substances were potential skin sensitizers. Thus, though sensitization is an important parameter that should be checked while assessing potentially hazardous substances, 49 out of the 144 substances lacked both human and animal sensitization data. Sensitization is not included in the items to be checked in the OECD/SIDS program. Many sensitization cases have been reported in recent years, reflecting the increased risk of exposure to sensitizers, not only in occupational but also residential areas. For potentially hazardous substances that are manufactured in large amounts, e.g., those designated as class I under the PRTR law in Japan, LLNA or MEST test data should be collected and made available for those who require it for primary screening.

4.2. Relationship between the characteristic chemical structures and skin sensitization

In order to discuss the relationship between the chemical structure and toxicity, toxicity data homogenous in terms of test conditions, etc., must be collected for as many substances as possible. Despite the relatively few substances examined in this study and the limited homogeneity of the collected data, a correlation was observed between the chemical structures of the substances and sensitization. In particular, epoxides clearly had sensitizing potentials and more than half of carboxylic esters or dicarboxyl anhydrides, aliphatic aldehydes, and aromatic compounds with at least two hydroxyl groups also had sensitizing potentials. These structures commonly show a high reactivity, readily reacting with substituents in proteins (Landsteiner and Jacobs, 1935; Buehler, 1965; Magnusson and Kligman, 1969; Kimber and Basketter, 1992; Divkovic et al., 2005). Sensitization occurs as a result of the immune response to denatured proteins, etc. The marked sensitizing potentials of epoxides and aliphatic aldehydes can be attributed to their high reactivity with amino groups in proteins; these structures readily induce an addition reaction that leads to protein denaturation. None of the substances having alcoholic hydroxyl groups showed any sensitizing potential; this could be attributed to their poor reactivity with biopolymers, which is in contrast to the sensitizing structures.

New approaches such as those based on the structure–activity relationship have currently been developed as alternatives for the existing methods for hazard assessment of chemicals. As described above, most sensitizers have structures that readily react with proteins, suggesting that sensitization is closely related to structure. Therefore, sensitization should be suitably assessed on the basis of the structure–activity relationship, in contrast to other hazard criteria. According to the workshop on skin sensitization, which was held as a part of the project on the harmonization of

Table 6
Comparison between the results in this study and skin sensitizers designated by various organizations.

Results in this study (): number of substances	PRTR ^{a,b}	JSOH (2007)	ACGIH (2007) ^c	EU (2007)	DFG (2007)	BfR expert group ^d		
						A	B	C
Positive in both humans and animals (19)	6	7	6	16	15	10	3	1
Positive in only humans (28)	2	6	3	9	7	4	2	1
Positive in only animals (15)	2	0	2	7	3	0	2	1
Positive in neither humans nor animals (33)	0	1	1	4	1	0	2	3
No data available in either human or animal (49)	0	0	0	1	1	0	0	1

^a Only airway sensitization was taken into consideration.

^b Central Environmental Council, Ministry of the Environment, Japan (2000). About designation of class I designated chemical substances and class II designated chemical substances on the base of "Act on confirmation, etc. of release amounts of specific chemical substances in the environment and promotion of improvements to the management thereof." (Report) (in Japanese).

^c Both airway and skin sensitization were taken into consideration.

^d Schleder et al. (2003).

Table A.1

PRTR No. (1)	Substance	CAS No.	Chemical structure	Animal data ^a				Human data ^a	Skin sensitizer in this study ^b	PRTR (2007)	_JSOH (2007)	EU (2007)	ACGIH (2007)	DFG (2007)	BR expert group Schiede et al. (2003) ^c	
				Maximization test												
				Buchler test	LLNA	MEST	Others									
				Results												
Under the revised law																
*: PRTR class II substances																
Under the revised law	Zinc compounds (water-soluble)	–														
	Acrylamide	79-06-1	Amines or amides	×	×	ND	ND	ND	×	○						
	Acrylic acid	79-10-7	Carboxylic acids	○	ND	ND	ND	ND	△	○	ND			Sh		
	Ethyl acrylate	140-88-5	Carboxylic acids, α,β -unsaturated esters	○	×	ND	ND	ND	ND	△	○			Sh	B	
	2-(Dimethylamino)ethyl acrylate	2439-35-2	Carboxylic acids, α,β -unsaturated esters	○	ND	ND	ND	ND	ND	○	ND					
	Methyl acrylate	96-33-3	Carboxylic acids, α,β -unsaturated esters	○	ND	ND	ND	ND	○	○		Skin 2	SEN	Sh	B	
	Acrylonitrile	107-13-1	Aldehydes	○	ND	ND	ND	ND	ND	○	ND			Sh	B	
	Acrolein	107-02-8	Aldehydes	×	ND	ND	ND	ND	△	○						
	Bis(2-ethylhexyl) adipate	103-23-1	Carboxylic acids	ND	ND	ND	ND	ND	×	ND						
	Acetaldehyde	75-07-0	Aldehydes	ND	ND	ND	ND	ND	ND	ND	ND					
	Acetonitrile	75-05-8	Aldehydes	ND	ND	ND	ND	ND	ND	ND	ND					
	2,2'-Azobisisobutyronitrile	78-67-1	Aldehydes	×	ND	ND	ND	ND	×	△	○					
	Aniline	62-53-3	Amines or amides	○	ND	ND	ND	ND	△	○	○			Sh	B	
	2-Aminoethanol	141-43-5	Amines or amides, alcoholic hydroxyl	ND	ND	ND	ND	ND	ND	ND	ND			Sh		
	N-(2-Aminoethyl)-1,2-ethanediamine (diethylenetriamine)	111-40-0	Amines or amides	○	ND	ND	ND	ND	ND	○	○			Sh	A	
	Allyl alcohol	107-18-6	Alcoholic hydroxyl	ND	ND	ND	ND	ND	ND	ND	ND			Sh		
	1-Allyloxy-2,3-epoxypropane	106-92-3	Epoxides	ND	ND	ND	ND	ND	ND	ND	○				A	
	n-Alkylbenzenesulfonic acid and its salts (alkyl C = 10–14)	–		○	△	ND	ND	ND	ND	○	×					
	Antimony and its compounds	–		ND	ND	ND	ND	ND	ND	ND	△					
	Isoprene	78-79-5	Aromatic hydroxyl	ND	ND	ND	ND	ND	ND	ND	ND					
	4,4'-Isopropylidenediphenol (bisphenol A)	80-05-7	Aromatic hydroxyl	ND	ND	ND	ND	ND	ND	△	△				B	
	Polymer of 4,4'-isopropylidenediphenol and 1-chloro-2,3-epoxypropane (liquid)	25068-38-6	Epoxides, aromatic hydroxyl, halogenated compounds	○	ND	ND	ND	ND	ND	ND	○				SP	A
	2-Imidazolidinethione	96-45-7	Epoxides, aromatic hydroxyl, halogenated compounds	ND	ND	ND	ND	ND	ND	ND	○					
	Ethylbenzene	100-41-4	Epoxides	ND	ND	ND	ND	ND	ND	△	○					
	Ethylene oxide	75-21-8	Epoxides	ND	△	ND	ND	ND	ND	△	○					
Ethylene glycol	107-21-1	Alcoholic hydroxyl	ND	ND	ND	ND	ND	ND	ND	ND		Skin 2				
Ethylene glycol monoethyl ether	110-80-5	Alcoholic hydroxyl	ND	ND	ND	ND	ND	ND	ND	ND						
Ethylene glycol monomethyl ether	109-86-4	Alcoholic hydroxyl	ND	ND	ND	ND	ND	ND	ND	ND						
Ethylenediamine	107-15-3	Amines or amides	○	○	△	ND	ND	ND	ND	○		Airway 2 Skin 1	R42/R43	Sah	A	
Ethylenediaminetetraacetic acid	60-00-4	Epoxides, halogenated compounds	×	ND	ND	ND	ND	ND	ND	△	○					
Epichlorohydrin	106-89-8	Epoxides, halogenated compounds	○	ND	ND	ND	ND	ND	○	○				Sh	A	
1,2-Epoxypropane (propylene oxide)	75-56-9	Epoxides	ND	ND	ND	ND	ND	ND	×	△	○					
2,3-Epoxypropyl phenyl ether	122-60-1	Epoxides	ND	ND	ND	ND	ND	ND	○	△	○					
1-Octanol	111-87-5	Alcoholic hydroxyl	ND	ND	ND	ND	ND	ND	ND	ND		R43	SEN	Sh	A	
ε-Caprolactam	105-60-2	Alcoholic hydroxyl	×	ND	ND	ND	ND	ND	ND	ND						
2,6-Xylenol	576-26-1	Aromatic hydroxyl	ND	ND	ND	ND	ND	ND	ND	ND						
Xylene	1330-20-7	Aldehydes	ND	ND	ND	ND	ND	ND	ND	ND						
Glyoxal	107-22-2	Aldehydes	○	○	ND	ND	ND	ND	×	○	○			Sh	A	
Glutaraldehyde	111-30-8	Aldehydes	○	ND	ND	ND	ND	ND	×	○	○			Sah	A	
Cresol	1319-77-3	Aromatic hydroxyl	○	ND	ND	ND	ND	ND	○	○						
o-Chloroaniline	95-51-2	Amines or amides, halogenated compounds	×	ND	ND	ND	ND	ND	ND	△	ND					
p-Chloroaniline	106-47-8	Amines or amides, halogenated compounds	○	ND	ND	ND	ND	ND	△	○		R43				

Continued on next page

(continued on next page)

Table A.1 (continued)

PRTR No. (:)	Substance	CAS No.	Chemical structure	Animal data ^a	Buehler test	LLNA	MEST	Others	Results	Human data ^a	Skin sensitizer in this study ^a	PRTR (2007)	JSOH (2007)	EU (2007)	ACGIH (2007)	DFG (2007)	BIR expert group (2003) ^c
Under the revised law				Maximization test								Airway	Airway 1 or 2	R42: Airway	SEN	Sa: Airway	
substances																Sh: Skin	
																Sa: Airway	
																Sh: Skin	
																Sa: Airway	
																SP:	
																Photocontact	
74 (-)	Chloroethane	75-00-3	Halogenated compounds	ND	ND	ND	ND	ND	ND	ND	○						
77 (94)	Chloroethylene (vinyl chloride)	75-01-4	Halogenated compounds	ND	ND	ND	ND	ND	ND	ND	ND						
80 (98)	Chloroacetic acid	79-11-8	Carboxylic acids, halogenated compounds	ND	ND	ND	ND	ND	ND	ND	ND						
89 (109)	o-Chlorotoluene	95-49-8	Halogenated compounds	×	×	ND	ND	ND	ND	ND	×						
91 (123)	3-Chloropropene (allyl chloride)	107-05-1	Halogenated compounds	ND	ND	ND	ND	ND	ND	ND	ND						
93 (125)	Chlorobenzene	108-90-7	Halogenated compounds	ND	ND	ND	ND	ND	ND	ND	ND						
95 (127)	Chloroform	67-66-3	Halogenated compounds	ND	ND	ND	ND	ND	ND	ND	ND						
96 (128)	Chloromethane (methyl chloride)	74-87-3	Halogenated compounds	ND	ND	ND	ND	ND	ND	ND	ND						
101 (133)	2-Ethoxyethyl acetate	111-15-9	Carboxylic acids	ND	ND	ND	ND	ND	ND	ND	ND						
102 (134)	(ethylene glycol monoethyl ether acetate)	108-05-4	Carboxylic acids	ND	○	ND	ND	ND	ND	ND	○						
103 (135)	Vinyl acetate	110-49-6	Carboxylic acids	ND	ND	ND	ND	ND	ND	ND	ND						
108 (144)	2-Methoxyethyl acetate	-	Carboxylic acids	ND	ND	ND	ND	ND	ND	ND	ND						
109 (145)	(ethylene glycol monomethyl ether acetate)	-	Carboxylic acids	ND	ND	ND	ND	ND	ND	ND	ND						
112 (149)	Inorganic cyanide compounds (except complex salts and cyanates)	100-37-8	Alcoholic hydroxyl	×	ND	ND	ND	ND	ND	ND	ND						
113 (150)	Tetrachloromethane	56-23-5	Halogenated compounds	×	ND	ND	ND	ND	ND	ND	ND						
114 (154)	1,4-Dioxane	123-91-1	Halogenated compounds	×	ND	ND	ND	ND	ND	ND	ND						
116 (157)	Cyclohexylamine	108-91-8	Halogenated compounds	ND	ND	ND	ND	ND	ND	ND	ND						
117 (158)	1,2-Dichloroethane	107-06-2	Halogenated compounds	ND	ND	ND	ND	ND	ND	ND	ND						
118 (159)	1,1-Dichloroethylene (vinylidene dichloride)	75-35-4	Halogenated compounds	ND	ND	ND	ND	ND	ND	ND	ND						
119 (24 *)	cis-1,2-Dichloroethylene	156-59-2	Halogenated compounds	ND	ND	ND	ND	ND	ND	ND	ND						
120 (160)	trans-1,2-Dichloroethylene	156-60-5	Halogenated compounds	ND	ND	ND	ND	ND	ND	ND	ND						
128 (167)	3,3-Dichloro-4,4'-diaminodiphenylmethane	101-14-4	Amines or amides, halogenated compounds	ND	ND	ND	ND	ND	ND	ND	ND						
135 (178)	1,4-Dichloro-2-nitrobenzene	89-61-2	Halogenated compounds	×	ND	ND	ND	ND	ND	ND	ND						
139 (181)	1,2-Dichloropropane	78-87-5	Halogenated compounds	ND	ND	ND	ND	ND	ND	ND	ND				SEN		
140 (181)	o-Dichlorobenzene	95-50-1	Halogenated compounds	ND	ND	ND	ND	ND	ND	ND	ND						
145 (186)	p-Dichlorobenzene	106-46-7	Halogenated compounds	○	ND	ND	ND	ND	ND	ND	ND						
157 (200)	Dichloromethane (methylene dichloride)	75-09-2	Halogenated compounds	ND	ND	ND	ND	ND	ND	ND	ND						
160 (-)	Dinitrotoluene	25321-14-6	Halogenated compounds	○	ND	ND	ND	ND	ND	ND	ND						
166 (224)	Diphenylamine	122-39-4	Alcoholic hydroxyl	ND	ND	ND	ND	ND	ND	ND	ND						C
172 (232)	2-(Di-n-butylamino)ethanol	102-81-8	Alcoholic hydroxyl	×	ND	ND	ND	ND	ND	ND	ND						
177 (240)	N,N-Dimethyldodecylamine N-oxide	1643-20-5	Aldehydes	ND	ND	ND	ND	ND	ND	ND	ND						
181 (245)	N,N-Dimethylformamide	68-12-2	Aldehydes	ND	ND	ND	ND	ND	ND	ND	ND						
182 (245)	Styrene	100-42-5	Aldehydes	ND	ND	ND	ND	ND	ND	ND	ND						
187 (255)	Selenium and its compounds	-	Amines or amides	ND	ND	ND	ND	ND	ND	ND	ND						
197 (255)	Thiourea	62-56-6	Amines or amides	×	ND	ND	ND	ND	ND	ND	ND						
198 (258)	Decabromodiphenyl ether	1163-19-5	Halogenated compounds	ND	ND	ND	ND	ND	ND	ND	ND						
200 (262)	1,3,5,7-Tetraazatricyclo[3.3.1.1(3,7)]decane (hexamethylenetetramine)	100-97-0	Halogenated compounds	○	ND	ND	ND	ND	ND	ND	ND						
202 (265)	Tetrachloroethylene	127-18-4	Halogenated compounds	ND	ND	ND	ND	ND	ND	ND	ND						
203 (-)	Tetrafluoromethylphthalic anhydride	11070-44-3	Carboxylic acids	ND	ND	ND	ND	ND	ND	ND	ND						
205 (270)	Tetrafluoroethylene	116-14-3	Halogenated compounds	ND	ND	ND	ND	ND	ND	ND	ND						
206 (271)	Terephthalic acid	100-21-0	Carboxylic acids	ND	ND	ND	ND	ND	ND	ND	ND						
208 (-)	Dimethyl terephthalate	120-61-6	Carboxylic acids	ND	ND	ND	ND	ND	ND	ND	ND						
210 (280)	Trichloroacetaldehyde	75-87-6	Aldehydes, halogenated compounds	ND	ND	ND	ND	ND	ND	ND	ND						
211 (281)	1,1,2-Trichloroethane	79-00-5	Halogenated compounds	ND	ND	ND	ND	ND	ND	ND	ND						
218 (291)	Trichloroethylene	79-01-6	Halogenated compounds	ND	ND	ND	ND	ND	ND	ND	ND						
222 (66 *)	1,3,5-Tris(2,3-epoxypropyl)-1,3,5-triazine-2,4,6-(1H,3H,5H)-trione	2451-62-9	Epoxides	○	ND	ND	ND	ND	ND	ND	ND						
223 (295)	Tribromomethane (bromofom)	75-25-2	Halogenated compounds	ND	ND	ND	ND	ND	ND	ND	ND						
224 (297)	3,5,5-Trimethyl-1-hexanol	3452-97-9	Alcoholic hydroxyl	ND	ND	ND	ND	ND	ND	ND	ND						
227 (300)	1,3,5-Trimethylbenzene	108-67-8	Alcoholic hydroxyl	ND	ND	ND	ND	ND	ND	ND	ND						
	Toluene	108-88-3	Alcoholic hydroxyl	ND	×	ND	ND	ND	ND	ND	ND						

approaches to the assessment of risks from exposure to chemicals led by IPCS (International Programme on Chemical Safety) in 2005–2006, sensitization assessment methods based on the structure–activity relationship have not been validated for the purpose of hazard confirmation. However, some methods are effective in evidence weighting or initial screening (van Loverena et al., 2008). Additionally, the correspondence of sensitization properties with structural alerts, such as carboxylic esters, etc. is better than nothing, because they are often, but not always, associated with chemical reaction mechanisms of protein binding. For example esters can in some cases act as acylating agents, in some cases can act as activating groups for Michael acceptors, but in many cases they do neither (Aptula and Roberts, 2006; Roberts et al., 2007). When utilizing sensitization assessment methods based on the structure–activity relationship, we must acknowledge the limited potential of the existing methods based on the structure–activity relationship at this time, but reaction mechanistic alerts would be a useful approach to apply.

4.3. International comparison of sensitizers

The classification criteria for sensitizers are known to vary among various international organizations (Murakami et al., 2007). The classification criteria adopted by various international organizations can be roughly divided into two groups. The criteria adopted by ACGIH and JSOH limit the definition of sensitizers to substances that induce sensitization in humans and employ only human data obtained from case reports, epidemiological data, or volunteer experiments. On the other hand, EU and German MAK assess the potential of chemicals as sensitizers and employ not only data from human case reports but also results from animal studies that comply with appropriate standards and results from in vitro tests and structure–activity relationship studies, but conditionally. In other words, the ACGIH-type criteria assesses whether chemicals induce sensitization in humans upon exposure in the work area, while the EU-type criteria assess the sensitizing potentials of the chemicals. Regarding the 19 substances that were consistently positive in both humans and animals, the EU, DFG, and BfR Expert Groups classified a majority of these substances as sensitizers, while ACGIH and JSOH classified only a few of them as sensitizers, demonstrating the marked difference among classification criteria adopted by the various organizations. Moreover, although sensitization was adopted as an index for designating class I substances under the PRTR law, only airway sensitization was taken into consideration; skin sensitization was disregarded since the actual environmental concentration of the substances was low. The present classification based on skin sensitization classified 62 out of 144 substances as sensitizers, which largely deviated from PRTR designation, where only 14 out of 354 substances were designated as sensitizers.

The study clearly demonstrated the lack of consistency across the sensitization assessment criteria adopted by different countries or among those adopted by the same country on the basis of different laws or administrative measures. Such inconsistency makes it difficult for the workers or consumers to understand the classification results, and this result in nontariff barriers in international trades in chemicals. Increasing the explicitness and efficiency of classification by removing such barriers is thus the first step in realizing appropriate management of chemical substances, and this issue must be regarded as a global priority. An example of a worldwide initiative in this regard is GHS, i.e., the global harmonization of classification and labeling (UN, 2003). Regarding the sensitizer classification according to GHS, an assessment of both skin and respiratory sensitization must be conducted. In order to improve GHS classification, the existing data need to be widely shared, and harmonization of sensitization classification criteria

must be discussed. The GHS approach will play a major role to solve the above problems.

The number of PRTR-designated chemical substances in Japan has increased from 354 to 463 following the revision of the enforcement order of the law in November 2008 (MOE, 2008). Continuous efforts on the expansion of the scope of substances targeted for toxicity data collection and examination of the obtained results should facilitate global harmonization of assessment and effective use of the existing structure–activity relationship models.

In conclusion, of the 354 substances designated as class I under the Pollutant Release and Transfer Register (PRTR) law in Japan, we reviewed the sensitization data of the 144 substances and analyzed it from various aspects. Although most of them were expected to be hazardous substances, 49 out of the 144 substances lacked both human and animal sensitization data. Regardless of the presence or absence of sensitizing potentials, it is essential to examine existing data on the sensitizing potentials of chemical substances in order to analyze the differences in classification criteria among the various international organizations as well as understand the basis for globally harmonized assessment. The outcome of this examination will have far-reaching impacts on the current situation, because data concerning human health toxicity and ecological toxicity are being streamlined through international efforts such as GHS and EU's newly established REACH.

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Appendix A

See Table A.1.

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