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Existing test data for the Act on Registration & Evaluation, etc. of Chemical Substances

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Objectives In this study, the possibility of using existing test data provided in Korea and elsewhere for the registration of chemical substances was examined. Data on 510 chemical substances that are among the first subject to registration under the "Act on the Registration and Evaluation, etc. of Chemical Substances (K-REACH)" were analyzed.
Methods The possibility of using existing data from 16 reference databases was examined for 510 chemical substances notified in July 2015 as being subject to registration.
Results Test data with the reliability required for the registration of chemical substances under the K-REACH constituted 48.4% of the required physicochemical characteristics, 6.5% of the required health hazards, and 9.4% of the required environmental hazards.
Conclusions Some existing test data were not within the scope of this research, including data used for registration in the European Union (EU). Thus, considering that 350 of these 510 species are registered in EU Registration, Evaluation, Authorisation & Restriction of Chemicals, more test data may exist that can be utilized in addition to the data identified in this study. Furthermore, the K-REACH states that non-testing data (test results predicted through Read Across, Quantitative Structure- Activity Relationships) and the weight of evidence (test results predicted based on test data with low reliability) can also be utilized for registration data. Therefore, if methods for using such data were actively reviewed, it would be possible to reduce the cost of securing test data required for the registration of chemical substances.

Keywords Act on the Registration & Evaluation, etc. of Chemical Substances, Environmental hazards, Human hazards, Phase-in substance, Physical and chemical properties

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Introduction

The "Act on the Registration and Evaluation, etc. of Chemical Substances (K-REACH)" was enforced on January 1, 2015. Pursuant to the Act, any person who produces or imports over 1 ton of an existing chemical substance subject to registration, or any quantity of a new chemical substance, should register that chemical with the National Institute of Environmental Research [1]. The existing chemical substances subject to registration are expected to number approximately 2000 species, and the test data that should be submitted for registration vary according to the tonnage produced or imported (15 items required for 1 to 10 tons, 26 items for 10 to 100 tons, 37 items for 100 to 1000 tons, and 47 items for over 1000 tons) [2]. If these test data were all commissioned to test agencies, it is expected that the following expenses would be incurred: about 35 million Korean won (KRW) per substance for 1 to 10 tons; 96 million KRW per substance for 10 to 100 tons; 410 million KRW per substance for 100 to 1000 tons; and about 1.03 billion KRW per substance for over 1000 tons [3,4]. In order to minimize the expenses of registering existing chemical substances, the K-REACH only requires data for a single substance to be acquired once, and that data can be used across several registrations for that particular substance. Furthermore, previously generated test data can be used for registration if permission is granted from the owner of the test data, either for a fee or free of charge.

Meanwhile, non-testing data (test results predicted through Read Across, Quantitative Structure- Activity Relationships [QSARs], etc.) can also be used as registration data [5]. Considering that most of the existing chemical substances subject to registration have been produced or imported in excess of 1000 tons, the cost of producing test data for 2000 existing chemical substances subject to registration is expected to be nearly 2.06 trillion KRW. The extent to which this expense could be reduced depends on the amount of test data that already exists and the cost of using such data. In this regard, we examined 510 existing chemical substances that are subject to registration as notified in July 1, 2015, to identify the amount of existing test data that could be utilized when registering chemical substances in accordance with the K-REACH [6].

Materials and Methods

Research Objective

Of the 510 existing chemical substances subject to registration as notified in July 2015, 47 items of test data (13 items for physicochemical properties, 15 items for health hazards, and 19 items for environmental hazards) required for their registration pursuant to the K-REACH were examined.

Research Method

Sixteen reference databases (DBs) were selected from Korea and elsewhere, which provided existing test data for chemical substances. The presence of existing test data (47 items) was examined for the 510 chemical substances subject to registration (Table S1).

Criteria for the Applicability of Existing Test Data for Registration

The existing test data provided by 16 reference DBs from Korea and elsewhere were examined to determine if they were prepared based on the good laboratory practice (GLP) regulations of Organization for Economic Cooperation and Development (OECD). The reliability was assessed based on the results. Where data were verified objectively, e.g., published in GLP regulations of OECD or Science Citation Index, which are international test guidelines, the reliability was designated as 1. If the case did not correspond to a reliability of 1 but the test methods were provided in detail and the study was scientifically acceptable, a reliability of 2 was given. If an unauthorized test method was used or the test was scientifically unacceptable, a reliability of 3 was given. In terms of the test items (1 item for physicochemical properties, 15 items for health hazards, and 14 items for environmental hazards) only the test data corresponding to reliability 1 were likely to be recognized as registration data as stipulated in the K-REACH, which only accept test data produced in accordance with GLP regulations. For the other test items (12 for physicochemical properties and 5 for environmental hazards), test data corresponding to a reliability of 1 and 2 are highly likely to be recognized as registration data. Thus, these criteria were used when applying test data as registration data.

Results

Possibility of Utilizing Existing Test Data for Physicochemical Properties

Among the existing test data on physicochemical properties, 1.9% of the required data were present at reliability 1, 50.4% were at reliability 2, 0.6% were at reliability 3, and 47.1% had no existing test data. It was assumed that only the data classified as reliability 1 would be recognized as registration data for the octanol-water partition coefficient, in accordance with the K-REACH, while for other test items, existing test data corresponding to reliability 1 and 2 would be recognized for registration. Based on this, the applicability of existing test data for physicochemical properties would be 48.4% (Table S2).

Applicability of Existing Test Data for Health Hazards

Among the existing test data for health hazards, 6.5% of the required data was present at reliability 1, 30.2% was at reliability 2, 0.2% was at reliability 3, and for 63.1%, there was no existing test data. Under the assumption that only existing test data with reliability 1 would be recognized for registration according to the K-REACH, the applicability of existing test data for health hazards would be 6.5% (Table 1).

Applicability of Existing Test Data for Environmental Hazards

Among the existing test data on environmental hazards, 5.4% of the required data was present at reliability 1, 17.3% was present at reliability 2, 0.1% was present at reliability 3, and for 77.2% no test data was available. It was assumed that existing test data with reliability 1 and 2 would be recognized as registration data for hydrolysis according to the pH and confirmation of degradation products, adsorption/desorption screening, additional information on the behavior/dynamics of degradation products, and additional information on adsorption/desorption, in accordance with the K-REACH. For other test data, only existing data with a reliability of 1 would be recognized as registration data. On this basis, the applicability of existing test data for environmental hazards would be 9.6% (Table 2).

Table 1. Analysis of existing test data for health hazards

Item	Required data present as existing test data (%)				
	Total	Reliability 1	Reliability 2	Reliability 3	No data
Acute oral toxicity	510 (100)	36 (7.1)	240 (47.1)	2 (0.4)	232 (45.5)
Acute dermal toxicity	510 (100)	18 (3.5)	180 (35.3)	3 (0.6)	309 (60.6)
Short-term repeated dose toxicity (28 d)	510 (100)	21 (4.1)	108 (20.6)	0 (0.0)	381 (74.7)
In vivo skin irritation	510 (100)	45 (8.8)	207 (40.6)	1 (0.2)	257 (50.4)
In vivo eye irritation	510 (100)	42 (8.2)	231 (45.3)	2 (0.4)	235 (46.1)
Skin hypersensitivity (*in vivo*)	510 (100)	34 (6.7)	113 (22.2)	3 (0.6)	360 (70.6)
Ames	510 (100)	64 (12.5)	256 (50.2)	1 (0.2)	189 (37.1)
In vitro chromosomal abnormality	510 (100)	34 (6.7)	170 (33.3)	1 (0.2)	305 (59.8)
In vitro mammalian cell gene mutation	510 (100)	16 (3.1)	120 (23.5)	0 (0.0)	374 (73.3)
In vivo genotoxicity (micronucleus of red blood cell, bone marrow and chromosomal abnormality)	510 (100)	35 (6.9)	147 (28.8)	1 (0.2)	327 (64.1)
Additional genotoxicity (transgenic mice, comet test)	510 (100)	7 (1.4)	61 (12.0)	0 (0.0)	442 (86.7)
Screening for reproductive/developmental toxicity	510 (100)	24 (4.7)	163 (32.0)	1 (0.2)	322 (63.1)
Prenatal development toxicity test	510 (100)	25 (4.9)	127 (24.9)	0 (0.0)	358 (70.2)
Second generation reproductive toxicity test	510 (100)	12 (2.4)	60 (11.8)	0 (0.0)	438 (85.9)
Carcinogenicity test	51 (100)	84 (16.5)	130 (25.5)	0 (0.0)	296 (58.0)
Total	7650 (100)	497 (6.5)	2313 (30.2)	15 (0.2)	4825 (63.1)

Table 2. Analysis of existing test data for environmental hazards

Item	Required data present as existing test data (%)				
	Total	Reliability 1	Reliability 2	Reliability 3	No data
Short-term toxicity test in fish	510 (100)	80 (15.7)	210 (41.2)	0 (0.0)	220 (43.1)
Short-term toxicity test in invertebrate (water flea)	510 (100)	91 (17.8)	202 (39.6)	0 (0.0)	217 (42.5)
Growth inhibition test on water plants (algae)	510 (100)	60 (11.8)	129 (25.3)	0 (0.0)	321 (62.9)
Long-term toxicity test in fish	510 (100)	8 (1.6)	87 (17.1)	0 (0.0)	415 (81.4)
Long-term toxicity test in invertebrate (water flea)	510 (100)	29 (5.7)	91 (17.8)	0 (0.0)	390 (76.5)
Activated sludge respiration inhibition test	510 (100)	35 (6.9)	19 (3.7)	0 (0.0)	456 (89.4)
Short-term toxicity test in plants	510 (100)	8 (1.6)	78 (15.3)	0 (0.0)	424 (83.1)
Long-term toxicity test in plants	510 (100)	3 (0.6)	40 (7.8)	0 (0.0)	467 (91.6)
Earthworm (short-term) toxicity	510 (100)	13 (2.5)	45 (8.8)	0 (0.0)	452 (88.6)
Earthworm (long-term) toxicity	510 (100)	5 (1.0)	26 (5.1)	0 (0.0)	479 (93.9)
Long-term toxicity test in invertebrate	510 (100)	0 (0.0)	9 (1.8)	0 (0.0)	501 (98.2)
Bio-degradability (ready)	510 (100)	112 (22.0)	110 (21.6)	1 (0.2)	287 (56.3)
Bio-degradability (inherent)	510 (100)	39 (7.6)	17 (3.3)	2 (0.4)	452 (88.6)
Hydrolysis according to pH (hydrolysis)	510 (100)	6 (1.2)	174 (34.1)	0 (0.0)	330 (64.7)
Confirmation of degradation products	510 (100)	0 (0.0)	14 (2.7)	1 (0.2)	495 (97.1)
Bioaccumulation in aquatic species (fish)	510 (100)	30 (5.9)	212 (41.6)	0 (0.0)	268 (52.5)
Additional information regarding behavior/dynamics of degradation products	510 (100)	0 (0.0)	1 (0.2)	0 (0.0)	509 (99.8)
Adsorption/desorption screening	510 (100)	5 (1.0)	209 (41.0)	0 (0.0)	296 (58.0)
Additional information regarding adsorption/desorption	510 (100)	0 (0.0)	4 (0.8)	0 (0.0)	506 (99.2)
Total	9690 (100)	524 (5.4)	1677 (17.3)	4 (0.1)	7485 (77.2)

Discussion

The applicability of using existing test data based on 16 reference DBs from Korea and elsewhere was analyzed for 510 chemical species notified as being subject to registration in July 2015. Physicochemical properties were confirmed to have 48.4% applicability, which is somewhat high, while health hazards had 6.5% applicability and environmental hazards has 9.6%. Most of the existing test data provided by the reference DBs are not owned by the institutes providing the relevant DBs, who provide a summary and source of the test results. Thus, if the scope of this study is limited to the reference DBs identified, more existing test data may be utilized than is reported here. However, considering that currently about 350 of 510 species are registered in EU-REACH, more existing test data might be utilized in addition to that identified here, since some existing test data was not within the scope of this study (e.g., EU registration data). Furthermore, the K-REACH regulates non-test data (test results predicted

through Read Across, QSARs, etc.), and the weight of evidence (test results predicted based on test data with low reliability) can also be utilized as registration data. It is therefore necessary to actively review the methods for utilizing such data. For reference, among the EU-REACH registration data (166876 cases as of October 1, 2013, announced by Eurpean Chemical Agency), test data were only submitted as registration data for 46.2% health hazards and 32.5% environmental hazards. Based on these considerations, chemical companies aiming to register existing chemical substances under the K-REACH would be able to reduce registration expenses by using a range of methods to utilize existing test data and non-testing data (Read Across, QSARs, etc.).

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Conflict of Interest

The authors have no conflicts of interest associated with material presented in this paper.

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Table S1. The 16 reference databases

Reference database	Website address	Provided test data		
		Physicochemical properties	Health hazard	Environmental hazard
NCIS (Korea)	ncis.nier.go.kr/ncis.jsp	○	○	○
Safety test (Korea)	ncis.nier.go.kr/ncis.jsp	○	○	○
OECD SIDS (EU)	www.chem.unep.ch/irptc/sids/OECDSIDS/indexcasnumb.htm	○	○	○
GHS classification result (EU)	esis.jrc.ec.europa.eu/index.html	○	○	○
GHS classification result (Korea)	ncis.nier.go.kr/ghs/search/toxic_contain_chem_label.jsp	○	○	○
ECB IUCLID (EU)	esis.jrc.ec.europa.eu/	○	○	○
HSDB (US)	toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen·HSDB	○	○	○
IPCS EHC (EU)	http://www.inchem.org/pages/ehc.html	-	○	○
ATSDR (US)	www.atsdr.cdc.gov/toxprofiles/index.asp	-	○	-
Japanese safety assessment report (Japan)	www.safe.nite.go.jp/english/sougou/view/TotalSrchInput_en.faces	-	○	○
CCRIS (US)	toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CCRIS	-	○	-
GENETOX (US)	toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?GENETOX	-	○	-
EPA IRIS (US)	cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showsubstanceList	-	○	-
ECOTOX (US)	cfpub.epa.gov/ecotox/quick_query.htm	-	-	○
Chemical DB (US)	ull.chemistry.uakron.edu/erd/	○	-	-
ChemID Plus (US)	chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp	○	-	-
Total	16	9	13	10

NCIS, National Chemicals Information System; OECD, Organization for Economic Cooperation and Development; SIDS, Screening Information Data Set; GHS, Globally Harmonized System; EU, European Union; European Chemical Bureau; IUCLID, International Uniform Chemical Information Database; HSDB, Hazardous Substances Data Bank; IPCS EHC, International Programme on Chemical Safety Environmental Health Criteria; ATSDR, Agency for Toxic Substances and Disease Registry; CCRIS, Chemical Carcinogenesis Research Information System; GENETOX, Genetic Toxicology Data Bank; EPA IRIS, US Environmental Protection Agency Integrated Risk Information System.

Table S2. Analysis of existing test data for physicochemical properties

Item	Required data available as existing test data (%)				
	Total	Reliability 1	Reliability 2	Reliability 3	No data
State of substance	510 (100)	3 (0.5)	391 (76.7)	0 (0.0)	116 (22.7)
Melting point/freezing point	510 (100)	15 (2.9)	368 (72.2)	2 (0.4)	125 (24.5)
Boiling point	510 (100)	7 (1.4)	314 (61.6)	2 (0.4)	187 (36.7)
Relative density	510 (100)	6 (1.2)	212 (41.6)	6 (1.2)	286 (56.1)
Vapor pressure	510 (100)	15 (2.9)	317 (62.2)	1 (0.2)	177 (34.7)
Solubility	510 (100)	19 (3.7)	377 (73.9)	1 (0.2)	113 (22.2)
Grain size analysis	510 (100)	1 (0.2)	0 (0.0)	0 (0.0)	509 (99.8)
Octanol-water partition coefficient	510 (100)	31 (6.1)	257 (50.4)	0 (0.0)	222 (43.5)
Dissociation constant	510 (100)	2 (0.4)	104 (20.4)	0 (0.0)	404 (79.2)
Viscosity	510 (100)	0 (0.0)	158 (31.0)	0 (0.0)	352 (69.0)
Inflammability	510 (100)	16 (3.1)	238 (46.7)	13 (2.5)	243 (47.6)
Explosiveness	510 (100)	5 (1.0)	318 (62.4)	8 (1.6)	179 (35.1)
Oxidative degree	510 (100)	3 (0.6)	289 (56.7)	7 (1.4)	211 (41.4)
Total	6630 (100)	123 (1.9)	3343 (50.4)	40 (0.6)	3124 (47.1)