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Getting the SMILES right: identifying inconsistent chemical identities in the ECHA database, PubChem and the CompTox Chemicals Dashboard†

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Chemical databases containing information on substances and their identities are important and useful tools, used in many areas of chemistry and cheminformatics. Errors or inconsistencies in the identities of substances in the databases are a major problem, as they can make QSAR predictions inaccurate, make chemical hazard and risk assessments erroneous, and cause problems for the ordering of chemicals and analytical standards. In the present study, we checked the entries of all mono-constituent organic substances registered under REACH (more than 8500 substances) in the database of the European Chemicals Agency (ECHA), PubChem and the CompTox Chemicals Dashboard and flagged compounds with inconsistent chemical identifiers. In total 736 inconsistent entries, and 48 additional entries where the substance identity was not clear, were identified. This shows that data curation activities are still not sufficient in the databases and that more work needs to be done. Additionally, the identified inconsistent entries were analyzed to understand what kind of mismatches have been introduced in the databases and to avoid these mismatches in the future. Data gathering and processing is described in detail in the current study so that further studies can continue with this work for additional substances and databases. In this way, the study makes an important contribution towards improved and more trustworthy databases.

Environmental significance

The substances fully registered under REACH are all manufactured in and/or imported to the European Economic Area at more than 1 tonne per year. In terms of tonnage, these are the most important industrial chemicals in Europe, and it is therefore crucial that their chemical identities are correctly listed. However, the analysis of more than 8500 registered mono-constituent organic substances has shown that CAS Registry Numbers and structures of 346 entries did not match in the database of the European Chemical Agency. Inconsistent entries were also found in other databases for these substances. This shows that current data curation activities are still not sufficient in chemical databases and that more work is urgently needed in this area.

Introduction

Chemical hazard and risk assessment for the thousands of chemicals that are currently on the market or are intended to be put on the market faces various challenges, starting from basic information about chemical identity and chemical properties.[1,2] Traditionally, experimental studies have been used to determine chemical property data, but data from read-across and quantitative structure–activity relationships (QSARs) are increasingly used as well. The fourth report on the use of alternatives to testing on animals for the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) in Europe showed that in 2019 on average 27% of the data in the registrations submitted to the European Chemicals Agency (ECHA) under REACH came from experimental studies, 25% from read-across, 2.6% from QSARs, and 3.7% from weight of evidence. The rest were either data waivers, test proposals or had no information.[3] Especially for read-across and QSARs, it is critical that the information about the substances that is used as input to these estimation methods is correct. This includes the line notation of the chemical structure, *e.g.*, as Simplified Molecular-Input Line-Entry System (SMILES) or International Chemical Identifier (InChI) string, the Chemical Abstracts Service Registry Number™ (CAS RN™) and the chemical name and applies to the reference substances in read-across as well as to the substances of interest. Young *et al.* (2008)[4] looked into various databases and found that 0.1% to 3.4% of the chemical structures in the databases were incorrect. Several scientific

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articles have addressed the importance of chemical structure curation in cheminformatics and QSAR modelling since then,[5–10] but there are still two important open issues. First, most articles have looked at data curation workflows, *i.e.*, how data retrieved from a database can be curated to make them suitable for QSAR development. Only few studies really identified and published the incorrect data in the original databases. For example, Waldman *et al.* (2015)[7] mentioned that the errors they discovered have been corrected. However, they did not search systematically for errors in larger databases. Gadaleta *et al.* (2018)[6] investigated large datasets and also reported the rejected substances. However, they did not report the original database, *i.e.*, the sources, of the incorrect entries and it is unlikely that these entries have been corrected in the original databases. Similarly, Young *et al.* (2008)[4] identified incorrect structures but did not publish the structures for each database explicitly. Second, new substances are added to the databases regularly, so curating the databases is an ongoing process.

Based on these examples, it can be assumed that there is still a relevant number of incorrect or inconsistent entries in chemical databases. One of the most important databases for chemicals in Europe is the ECHA database, which contains information on substances registered under the REACH Regulation and are manufactured in and/or imported to the European Economic Area at more than 1 tonne per year. The information in the ECHA database originates from the registrants themselves and is supposed to be updated regularly.[11] Investigations by ECHA itself but also by the German Environment Agency revealed that quite a high percentage of the data submitted under REACH are not compliant with the REACH regulations.[12–15] When we started to look into the database in more detail, we also found a range of inconsistencies in the chemical identities. The aim of the present study was therefore to systematically identify inconsistent chemical identities of organic substances in the ECHA database[16] as well as in PubChem[17] and the CompTox Chemicals Dashboard.[18] Inorganic and organometallic compounds have additional complications with regard to line notation representations and will be treated in a separate study. PubChem and the CompTox Chemicals Dashboard database were chosen as they are two of the largest publicly available databases and because it was possible to retrieve information from these two databases for a large number of substances (semi-)automatically. The commercial database SciFinder^{n} [19] that is operated by the Chemical Abstract Service (CAS) was used to cross-check cases where the chemical identities in the ECHA database, PubChem and/or the CompTox Chemicals Dashboard did not agree.

Methods

Selection of substances

The substances investigated in this study are those that have been fully registered under REACH (as of April 2022) and that are organic and mono-constituent. NONS (for "notification of new substances", which are substances notified before REACH entered into force) were also included in the assessment; intermediates were excluded. Substances whose production has been ceased or whose registration dossier is no longer valid were included if the information on the substances was still available on the ECHA website (and thus publicly accessible). Table 1 shows the number of substances for the entire database and the different subgroups. The majority of the registration dossiers from REACH contained information on the "origin" of the substance (organic/inorganic/organo-metallic/petroleum product) as well as on the composition (mono-constituent/multi-constituent/UVCB). However, for around 19% of the substances, this information was missing and there was no entry for origin and/or composition. In order not to overlook substances, we deselected the unsuitable substances instead of selecting the targeted ones (see Table 1). Remaining substances that were not organic and mono-constituent were subsequently excluded manually. Table 1 shows that 37% of all registered substances (excluding those that are only intermediates) are mono-constituent and organic and do not have the word "reaction" in their name. This set of 8590 substances was included in the present study.

Table 1 Overview of the number of substances registered under REACH as of April 2022. UVCB: unknown or variable composition, complex reaction product or biological materials

	Number of substances	Percentage compared to all
ECHA database – all	23 184	100%
Not inorganic, not an element, not a petroleum product[a], not organo-metallic	20 702	89%
Additionally, not UVCB, not multi-constituent	16 156	70%
Additionally, with full registration or NONS	10 753	46%
Additionally, without 'reaction' in the name	10 529	45%
Additionally, without those removed manually that had no entry under origin and/or composition but were not organic and mono-constituent	8590	37%

[a] Products such as gasoline, kerosene (jet-fuel), diesel fuel, lubricants, paraffin wax and bitumen that are manufactured from crude oil using a range of refining processes.

Chemical identifier

Table 2 gives an overview of, and provides some details on, the chemical identifiers mentioned in this study. To systematically identify inconsistent chemical identities in a database, at least two chemical identifiers are needed: one that represents the chemical structure and one that can be used to verify the entry in another database. In the present study, we used the SMILES for the structural representation and the CAS RN™ for the verification. The chemical names were not used/verified systematically, because many names are provided in the ECHA database as non-IUPAC names and cannot automatically be converted into a structure. The ECHA guidance document for the identification and naming of substances under REACH and

Table 2 Overview of the chemical identifiers used in this work

Chemical identifier	Abbreviation in full	Description
IUPAC name	International Union of Pure and Applied Chemistry (IUPAC) name	Name of the substance based on IUPAC nomenclature rules
EC number	European Community (EC) number	Unique seven-digit identifier that was assigned to substances for regulatory purposes within the EU
CAS RN™	Chemical Abstracts Service (CAS) Registry Number™	Unique numerical identifier assigned by the CAS to every chemical substance or compound whose existence has been proven
DSSTox substance ID	Distributed structure-search-able (DSS) toxicity substance identifier (DTXSID)	Unique identifier for substances; used mainly in the CompTox Chemicals Dashboard. Substances here are single chemicals, mixtures or polymers
DSSTox compound ID	DSS toxicity chemical identifier (DTXCID)	Unique identifier for chemical structures; used mainly in the CompTox Chemicals Dashboard
SID	PubChem Substance ID	Unique identifier for substances[a]; used mainly in PubChem
CID	PubChem Compound ID	Unique identifier for compounds[a]; used mainly in PubChem
Molecular formula	—	Numbers of each chemical element in a molecule; the Hill notation was used for a uniform order of the elements; does not contain structural information
Isomeric SMILES	Isomeric simplified molecular-input line-entry system	Line notation for describing the structure of chemicals; 'isomeric' means that it contains isotopic and chiral specifications; one structure can be described by more than one (isomeric) SMILES string even if the canonical SMILES is used[b]
InChI string	IUPAC International Chemical Identifier string	Standardized way to encode molecular information; uses *layers* of information; is a unique representation
InChIKey	IUPAC International Chemical Identifier Key	Hashed version of the full InChI string that has always 27 characters and allows for easy web searches
2D structure	2-Dimensional structure of the molecule	Structure created from the SMILES *e.g.*, *via* Smi2Depict (https://re.edugen.wiley.com/cgibin/Smi2DepictWeb.py); unique representation

[a] In the PubChem terminology, a substance is a chemical sample description provided by a single source and a compound is a normalized chemical structure representation found in one or more contributed substances. [b] Canonical SMILES represent a unique representation for a particular molecule. However, the original procedure of Weininger *et al.* (1988)[21] did not include a treatment of stereochemistry. Various algorithms have therefore been developed for generating canonical SMILES all of which differed from each other.[22]

CLP[20] states that the IUPAC name should be used for the registration of a substance under REACH. However, this is not always respected, and some substances are registered with trade names (*e.g.*, JASMONITRILE) or other non-IUPAC names. We checked the chemical names therefore only for those substances where CAS RN™ and SMILES were not consistent in the ECHA database. Inconsistencies between the name and the given structure are also possible for substances where CAS RN™ and SMILES match. However, this was not checked further.

Data gathering

ECHA database. For substances registered under REACH, the IUPAC name and very often the EC number, CAS RN™, molecular formula, SMILES and InChI string are provided on the ECHA website. For some of the substances, these pieces of information are confidential business information and not available to the public. There are, for example, 91 substances where "No public or meaningful name is available" is stated. An additional 480 substances have no SMILES in the ECHA database. In most cases, however, this does not pose a problem for the identification of the substances, because the CAS RN™ is available and uniquely identifies the substance. However, for 44 substances (0.5% of all substances in this study) neither CAS RN™ nor SMILES (nor InChI string) are available. These substances can then only be identified by their name, which is not always unambiguous, and the structure cannot always be deduced from the name. Such cases would be *e.g.*, CS 372 (EC number 434-940-1), SUNA (EC number 414-360-5) or custom

yellow #2 (no EC number publicly available, substance ID 100.127.049).

Systematic automated data collection activities (including scraping, data mining, and extraction and re-utilization) of the whole or a substantial part of the ECHA website and the ECHA databases are prohibited. It is therefore not possible to retrieve the registered data directly form the ECHA website. General information on the substances including their CAS RN™, registered tonnage band, composition and origin can be downloaded from **https://echa.europa.eu/information-on-chemicals/registered-substances**. However, the SMILES is not available *via* this website and also not available *via* the study results, which can be downloaded in IUCLID format.[23] We therefore contacted ECHA and obtained a list of the registered substances with the available IUPAC names, EC numbers, CAS RNs™, molecular formulas and SMILES notations in January 2021. Additional SMILES codes were obtained manually from the website in February and May 2022, after which SMILES were available for 94% of all organic mono-constituent organic substances. Almost all substances could be identified by an EC number (99.5% of the 8590 substances used in the present study). However, in the dataset provided by ECHA in January 2021, only 73% of the substances had CAS RNs™. After cross-checking with the other databases, different manual checks and updates in the ECHA database, we were able to allocate CAS RNs™ to 88% of the finally investigated substances.

CompTox Chemicals Dashboard. The CompTox Chemicals Dashboard is a part of a suite of databases and web applications developed by the US Environmental Protection Agency's Chemical Safety for Sustainability Research Program. It contains over 900 000 chemicals which can be accessed online in batch mode. The data in the CompTox Chemicals Dashboard have been manually curated to identify conflicts between identifiers.[24] Possible input parameters for the batch search are the chemical name, CAS RN™, InChIKey, DTXSID or DTXCID. Possible outputs are CAS RN™, InChIKey, IUPAC name and SMILES.

PubChem. PubChem is an open chemistry database operated by the National Institutes of Health (NIH) in the US. It contains more than 110 million individual chemical structures. The entries in PubChem can be accessed *via* HTTP request (Power User Gateway (PUG) Representational State Transfer (REST)). Possible input parameters to the HTTP request include SID, CID, chemical name, SMILES, InChI string, InChIKey and molecular formula. Searches with the CAS RN™ can be performed *via* the name field. Possible outputs include the whole record or the synonyms as JSON or XML file. The whole record contains, for example, the isomeric SMILES; the listed synonyms very often contain the CAS RN™.

SciFinder^n. SciFinder^n is a commercial database operated by the Chemical Abstracts Service. It contains more than 262 million substances and related information, including their chemical names, structures, and CAS RNs™. The information in the database that stems from journals and patents is manually curated by CAS experts. Unfortunately, a search for substances is only possible for one substance at a time. Also, there are some systematic errors in the SMILES of substances with several components in SciFinder^n. The stoichiometry of a substance in SciFinder^n is only given in the molecular formula (and the name), but not in the SMILES string. Thus, a "disodium" compound in SciFinder^n contains only one Na^+ in the SMILES string although the stoichiometry says two. Additionally, salts are shown without charge and with an additional hydrogen on the molecule. An example is potassium perfluorobutanesulfonate, which is given as [K].O=S(=O)(O)C(F)(F)C(F)(F)C(F)(F)C(F)(F)F instead of [K^+].[O–]S(=O)(=O)C(F)(F)C(F)(F)C(F)(F)C(F)(F)F. Despite these (for our case unfavorable) forms of representation, SciFinder^n is one of the best databases available, mainly because the data are extensively manually curated.

Data gathering sequence. The data gathering was conducted in several steps as shown in Fig. 1. The three databases are shown in yellow (ECHA database), green (CompTox Chemicals Dashboard) and gray (PubChem), respectively. The starting point of the data gathering was the ECHA database. For substances with a CAS RN™ in the ECHA database, it was possible to search *via* the CAS RN™ for the isomeric SMILES in the other databases (PubChem and CompTox Chemicals Dashboard). The chemical identity of substances without CAS RN™ in the ECHA database could only (at least partly) be verified if the SMILES code was available in the ECHA database. In these cases, the SMILES was converted into the InChIKey, and CAS RN™ and isomeric SMILES were retrieved from PubChem and the CompTox Chemicals Dashboard *via* the InChIKey. In cases where the CAS RN™ could be retrieved from one of the databases *via* the InChIKey, the CAS RN™ was used then to search for the isomeric SMILES in the other database as well.

Searching for the InChIKey in the CompTox Chemicals Dashboard and PubChem resulted in CAS RNs™ that are not included in REACH. These CAS RNs™ are marked in green in the ESI-1† to show that they were not provided by the registrants.

Data processing

If more than two of the three databases had an entry for a substance, the isomeric SMILES obtained from the databases were converted into standard InChI strings and standard InChIKeys using Open Babel version 3.1.1 (ref. 25 and 26) and afterwards compared to each other. For substances where the InChI strings did not match, the SMILES were manually inspected *via* Smi2Depict[27] and grouped afterwards. For mismatching structures or disagreeing stereochemistry, SciFinder^n was checked additionally to find the 'correct' structures for the respective CAS RN™. Since the Chemical Abstract Service that operates SciFinder^n also assigns CAS RNs™ to structures and is the only authoritative source of CAS RNs™, we assumed that the CAS RN™ and the structural formula are correctly assigned in SciFinder^n, even if the SMILES strings themselves have some unfavorable representation or are even sometimes incorrect (see the points above).

It is important to note that the check for inconsistencies for the compounds in the ECHA database was only possible if the CAS RN™ was available in the ECHA database. Without CAS

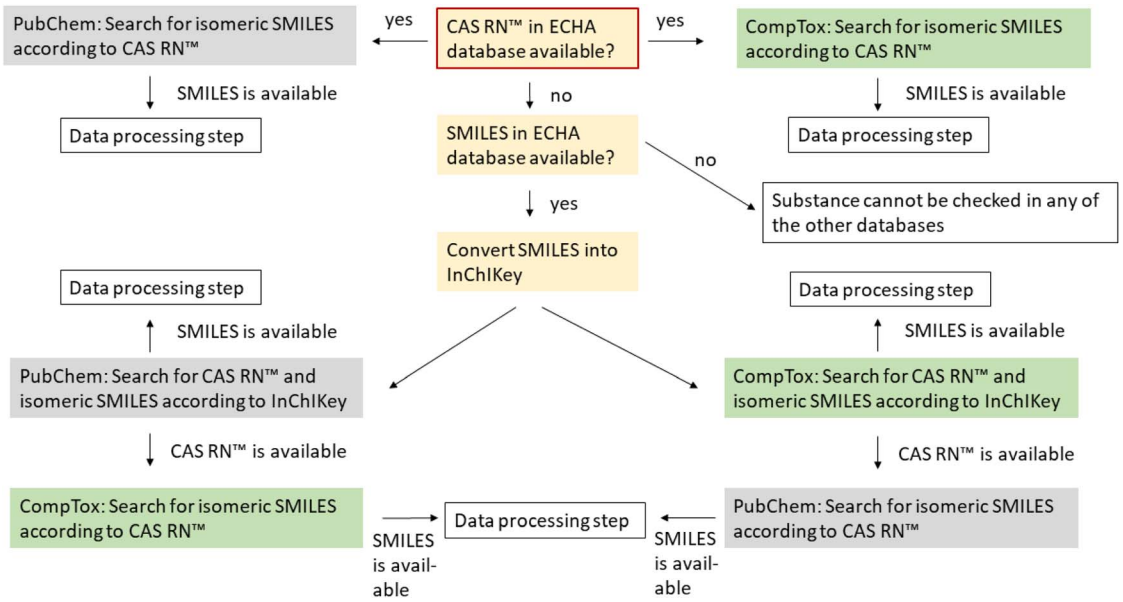

Fig. 1 Data gathering sequence for the isomeric SMILES and CAS RNs™ from PubChem and the CompTox Chemicals Dashboard (here short CompTox). Starting point of the data gathering is the ECHA database (red box). The goal was to obtain the isomeric SMILES from the two databases, PubChem and CompTox Chemicals Dashboard, respectively. The subsequent "data processing step" depends on the availability of SMILES and/or CAS RN™, which is explained in detail in the text under section "Data processing".

RN™, it was only possible to check whether or not the SMILES string itself was internally consistent and whether or not it belonged to a valid chemical structure (if a corresponding structure was found in PubChem or the CompTox Chemicals Dashboard).

For substances with CAS RN™ but no SMILES in any of the databases or a SMILES in just one of the databases, the isomeric SMILES was obtained and/or verified *via* SciFinder^n. To obtain the correct isomeric SMILES in SciFinder^n, the given SMILES in SciFinder^n was taken and manually adjusted for substances with more than one component, taking the stoichiometry and charges in the structural formula and the name into account.

Substances without CAS RN™ and for which the search according to the InChIKey gave no result in PubChem or the CompTox Chemicals Dashboard could not be verified. Here, it was only possible to check whether or not the SMILES string itself was internally consistent and had, *e.g.*, no unusual valence.

Substances where the InChI strings did not match between the databases were assigned to five different groups: (1) inconsistent information on the molecular structure where the assignment could be checked with SciFinder^n; (2) inconsistent information on the molecular structure in at least two databases and no verification possible *via* SciFinder^n; (3) missing *cis*/*trans*-isomer information for alkenes; (4) 'Omitted undefined stereo' warning in Open Babel, *cis*/*trans* isomers are defined for alkenes; (5) tautomers. Tautomers with identical InChI string were marked whenever they were detected in the manual data curation.

For substances in group 1, it was further specified which aspect is inconsistent. The seven different possible specifications were: inconsistency related to the molecular structure itself; no stereochemistry information in the ECHA database while SciFinder^n has some for the corresponding CAS RN™; deviating stereochemistry; available stereochemistry information in the ECHA database while SciFinder^n has none for the corresponding CAS RN™; inconsistency related to the *cis*/*trans* isomer; substances with unusual valence *e.g.*, unpaired electrons; and substances registered as polymer while the SMILES represents a monomer.

For substances in the ECHA database that belonged to group 1, the so-called 'brief profiles' of the ECHA database were checked again manually in June 2022 to find out whether or not the brief profiles of the substances had been updated in the meantime.

An important point for the ECHA database and substances in group 1 is that only the registrants know which substance they intended to register. It is possible that they included a correct SMILES (and maybe name) in the registration but a wrong CAS RN™, but it is also possible that they included the correct CAS RN™ but wrong SMILES. We therefore also converted the names for the substances in group 1 from the ECHA database into structures (using Marvin Sketch 22.18) and compared the structural formulas converted from the names to the structures obtained *via* the CAS RN™ and those given in the ECHA database directly.

Results & discussion

Identified entries in the various groups

Table 3 gives an overview of the investigated substances and the number of substances in the different groups. In total 8590 substances were checked. Of these, 346 (4.3%), 197 (3.0%) and 193 (2.8%) substances had inconsistent chemical identifiers in

Table 3 Overview of the investigated substances and of the number of substances in the different groups. 8590 substances were investigated in total. Group 1: inconsistent information on the molecular structure where the assignment could be checked with SciFinder^n; group 2: inconsistent information on the molecular structure in at least two databases and no verification possible *via* SciFinder^n; group 3: missing *cis*/*trans*-isomer information for alkenes; group 4: 'Omitted undefined stereo' warning in Open Babel, *cis*/*trans* isomers for alkenes are defined

	ECHA database		CompTox Chemicals Dashboard		PubChem	
	Number of substances with SMILES	Percentage	Number of substances with SMILES	Percentage	Number of substances with SMILES	Percentage
Total	8109		6564		6989	
Group 1	346	4.3%	197	3.0%	193	2.8%
Group 2	21	0.3%	9	0.1%	18	0.3%
Group 3	115	1.4%	141	2.1%	68	1.0%
Group 4	1722	21%	2112	32%	1532	22%

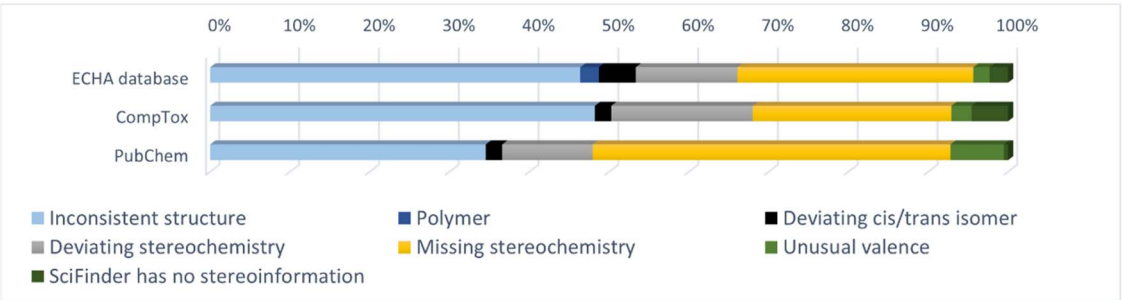

Fig. 2 Percentages of the different types of errors and inconsistencies for the substances in group 1.

the ECHA database, the CompTox Chemicals Dashboard and PubChem, respectively (group 1). In addition, 21, 9, and 18 substances had differing identifiers in the databases, but it was not possible to check the identities in SciFinder^n (group 2). Table 3 lists additionally the number of substances with missing *cis*/*trans*-isomer information for alkenes in each database (group 3) and the number of substances where Open Babel gave the warning 'Omitted undefined stereo' that was not due to missing *cis*/*trans*-isomer information for alkenes (group 4).

Fig. 2 shows the percentages of the different types of errors and inconsistencies in group 1. In PubChem, most of the inconsistent entries in group 1 were due to missing stereochemistry whereas in the CompTox Chemicals Dashboard and the ECHA database most of the entries in group 1 were due to inconsistent structures. There are also some errors/inconsistencies in group 1 that occurred for many substances. These included (a) substances where the net charge was not zero; (b) substances with LiH, NaH, KH, MgH_2 or CaH_2 as additional components (instead of counterions) and (c) substances with two or more components while the CAS RN™ only corresponded to one of these components (only in the ECHA database). The investigated substances with their chemical identifiers are provided in the ESI-1,† divided into single substances and substances with multiple components (*e.g.*, salts). The ESI-2† shows the inconsistent structures from the ECHA database in 2D in order to make it easier to correct the entries.

Crosschecking of the substance identify in the ECHA database *via* the chemical name

Fig. 3 shows the results for the name-to-structure conversion for the substances in group 1 of the ECHA database. For 31% of the substances, the name could not be converted into a structure. In most of the cases this was due to errors in the chemical name. In a few cases, the trade name was given and no structure at all could be generated from the trade name. For 39% of the substances, the name corresponded to the CAS RN™ and for 16% of the substances to the SMILES code. For the remaining 14% of the substances, the structures generated from the name did not correspond to the CAS RN™ nor to the SMILES.

Discussion on the applied method

Errors such as unusual valence, net charge is not zero, polymer with monomer SMILES and missing *cis*/*trans* isomers can be detected independently of other databases and it has been requested in the past that database operators should check for those errors.[10] Other errors such as inconsistent or missing stereochemistry and inconsistent structures are harder to detect. In the present study, comparing the entries in two or three databases has been proven very useful. It only fails if all the databases have the same (inconsistent) entry. Unfortunately, the option to check all substances against SciFinder^n only works to a limited extent, even though we currently consider SciFinder^n to be the most reliable reference database. A direct comparison is however complicated by the fact that

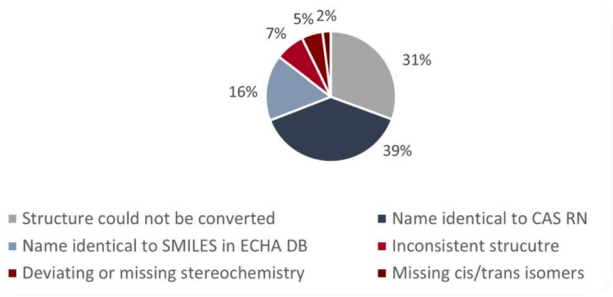

Fig. 3 Name-to-structure conversion for the 346 substances in group 1 of the ECHA database.

SciFinder^{n} represents substances with disconnected structures differently than the other databases.

The prerequisite for the comparison of the structures between the databases is in any case a second identifier that is independent of the structure. In the present study, the CAS RN™ was used as second identifier. For substances without a CAS RN™ in the ECHA database, the comparison was less meaningful. In these cases, it could only be checked if the InChIKey from the ECHA database existed in one of the other databases. However, this was not a confirmation that the structure in the ECHA database is correct. The chemical name was only checked for a few substances because many names could not be converted to structures.

Completeness of the check

The semi-automated review of the SMILES in the three databases revealed quite some errors and inaccuracies. However, all three databases are regularly updated, which means that some of the errors might have been corrected since we obtained the data, while others may have been newly introduced. At the time of the submission of this article, the SMILES from PubChem and the CompTox Chemicals Dashboard were quite current as they were retrieved in February 2022. The SMILES from the ECHA database were retrieved more than two years before the publication of this article. In order to at least partially take into account the updates in the ECHA database, all SMILES from the ECHA database for substances in group 1 were manually rechecked (and corrected if necessary) in June 2022. Surprisingly, for 28 substances the inconsistent SMILES had been removed from the ECHA database. In six other cases, however, the SMILES had been adjusted.

Significance of the various errors

We divided the identified inconsistencies in the three databases into four groups (see Table 3). The first group contains substances with inconsistent structures as well as substances with inconsistent or missing information on their stereochemistry. SMILES where either single atoms, parts of the molecule or the whole substance are incorrect can lead to significant errors in QSAR predictions. Young *et al.*[4] showed for example that using an O atom instead of the correct S atom in CAS RN™ 34643-46-4, a substance where Young *et al.* found an inconsistent SMILES/CAS RN™ assignment, resulted in the octanol–water partition coefficient (K_{OW}) to be off by 75%. Similar, the omission of a cyano group from CAS RN™ 15301-48-1 leads to a 48% difference in the mean absolute error for the K_{OW} and an extra carbon in one of the rings of CAS RN™ 60207-93-4 to a difference of 91%. Furthermore, using incorrect SMILES in the training sets of QSARs can lead to less accurate predictions and thus weaker QSARs.[4] It has also been shown that organic salts can have different toxicity values compared to their neutral forms.[4] The omission or addition of counterions can therefore have an important effect on the evaluation of a substance. Incorrect CAS RNs™, in turn, can lead to errors in the purchasing and using of chemicals and standards. It is therefore of great importance that CAS RNs™ and structures are correct in the databases.

The first group also includes substances with deviating or missing information on their stereochemistry. Stereoisomers are mainly important in biological systems and are therefore studied in great detail in clinical pharmacology and pharmacotherapeutics.[28] However, this does not mean that they can be ignored for industrial chemicals as also these substances interact with biological systems. For example, bioaccumulation but also toxicity and degradation may differ between enantiomers.[29–32] Enantiomers are therefore also not regarded equal under REACH.[20] It is therefore important to also pay attention to the stereochemical information when substances are registered and when information is transferred between databases.

Substances that are registered as polymers but have the SMILES of the monomer are mainly an issue in the ECHA database. So far, polymers are exempted from the provisions on registration of Title II of REACH (Article 2(9)),[33] however the monomer substances of the polymer have to be registered under REACH. For the substances identified in this work, it seems that the monomers were correctly registered, but under the name (and partly also the CAS RN™) of the polymer.

The second group of incorrect substances contains those substances where we were not able to identify the correct structure. Also, for this group, it would be important to recheck these substances and either correct the structures or the CAS RNs™. The chemical name should also be consistent with the other two identifiers.

The third group contains substances with missing *cis*/*trans*-isomer information for alkenes. Similar to the inconsistent or missing stereoisomers in group 1, the *cis*/*trans* isomerism might be important in biological systems. Missing information on *cis*/*trans* alkene isomers occurred in percentages from 1.0% (PubChem) to 2.1% (CompTox Chemicals Dashboard), showing that the problem is not huge, but still relevant.

The missing stereochemistry information in the fourth group had various reasons. In some cases, these are missing *cis*/*trans*-isomer information for N=N or N=C bonds which are shown as *E*/*Z* but in most cases are non-specific and could be represented as crossed bonds. In other cases, chirality for specific stereocenters was not defined in the original SMILES/InChI strings and Open Babel had to omit the stereochemistry definition even if it correctly identified a stereocenter in the

structure. This can be problematic as two chemicals with two different three-dimensional conformations would be represented with the same SMILES/InChI, creating confusion when the databased is queried on the basis of the molecular structure.

Obstacles with checking the databases

One of the biggest problems in cross-checking substances is that there is no unique chemical identifier that is present in all databases. Almost all substances in the ECHA database have an EC number, but the EC number is only partially available in PubChem and the CompTox Chemicals Dashboard. For the chemical name, on the other hand, it is not always possible to convert the chemical name to a structure if non-IUPAC names are used (Fig. 3). From the other identifiers (Table 2) it is only the CAS RN™ that is at least partially available in all three databases. However, the CAS Registry is a proprietary database, and access to most of the data was possible in the past only *via* a paid service such as SciFinder or STN®. A subset of 8000 substances has been accessible since 2009 *via* the CAS Common Chemistry database, which is an open web resource provided by CAS.[34] This dataset was expanded in 2021 to 500 000 chemical substances[35] and thus now offers free access to a relatively large number of substances in the CAS Registry®. The continued expansion and updating of the CAS Common Chemistry database are critical to the reliable use of CAS RN™ in regulatory systems in the future.

Another challenge for the identification of inconsistent chemical structures are tautomers. When comparing standardized InChI strings, tautomers must be manually identified, because the standardized InChI strings can differ for tautomers. InChI strings can be converted to detect the keto–enol tautomerism (*e.g.*, in the tool that the IUPAC provides to generate InChI strings), however this may produce non-standard InChI (*i.e.*, starting with 'InChI=1/' instead of 'InChI=1S/') and other types of tautomerism may not be addressed and standardized and still appear as mismatching structures.[22] A related issue are nitro groups that are sometimes represented in the SMILES and the InChI string with a pentavalent nitrogen and sometimes with charge-separated groups. Moreover, many different formats of SMILES exist (*e.g.*, kekulized, canonical, QSAR-ready) and it is not always clear which is the one reported in the various databases or if a standardization of the molecular structure has been done at all.[22,36] It has been pointed out that this issue as well as others could be solved with standardization rules for chemistry databases.[10]

The biggest obstacle, however, is that one must first understand that databases contain errors and that the structures need to be checked before working with them. Williams and Ekins have pointed out in several articles that there is an urgent need for data curation in public databases.[10,37] This is to improve the quality of the databases, but also because errors have been found to proliferate from databases such as PubChem to other databases on the internet when the content is downloaded and reused.[37] Here we have made the first step for a part of the substances that are registered under REACH to uncover inconsistencies in the ECHA database as well as in the CompTox Chemicals Dashboard and PubChem. For the latter two databases, it is now up to the database operators to also fix these inconsistencies. For the ECHA database, this might be more complicated as only the registrants know what substance they intended to register and are responsible for most data. For this reason, the registrants would need to correct their dossiers first – either by adjusting the CAS RN™ or structure – before the data can be corrected in the ECHA database. To facilitate this process, we present the inconsistent structures in the ESI-2† to this article and hope that this will help to make the correction process faster. An exception are substances that were already listed in the European Inventory of Existing Commercial Chemical Substances (EINECS), the European List of Notified Chemical Substances (ELINCS) and the No-Longer Polymers (NLP) list.[20] These are substances whose EC number begins with 2, 3, 4 or 5. The registrants cannot correct errors in EINECS/ELINCS/NLP (*i.e.*, change the associated name and/or CAS RN) because these are closed inventories.[38] To change them, a process would have to be opened at ECHA to issue a new list number with new name, and possibly a CAS RN™ associated.

Beside this, more work is still needed on the identification of inconsistent identifiers. We have only checked 37% of the substances registered under REACH and probably the easier ones. The same check would need to be performed for multi-constituent substances and UVCBs as well as (ECHA internally) for those substances where the SMILES is confidential and not available in the public domain. Also, the chemical names would need to be checked systematically. The CAS Common Chemistry database could be very useful here as it can now also be accessed *via* an application programming interface (API). However, the same systematic errors that occur in SciFinder^n also occur in the CAS Common Chemistry database and these would have to be managed appropriately in a fully automatic check. However, we think it is worth the effort because it will help to evaluate chemicals in a better and more trustworthy way.

Conclusions

Young *et al.*[4] reported already in 2008 that in between 0.1% and 3.4% of the chemical structures in chemical databases are incorrect. Unfortunately, this still holds true and although there have been efforts to correct inconsistent entries, there is still a substantial number of errors in chemical databases, even in official ones, and users have to carefully check identifiers and structures before working with them. This also shows that more efforts should be dedicated to finding and correcting inconsistent chemical identifier in chemical databases. This could and should be done by the database operators, but should also be supported by scientists working with these databases. Addressing mistakes in publicly available databases is an iterative process that benefits from the inputs and feedbacks of users that find errors and inconsistencies in the data. There are quite some publications on data curation workflows, but it would also be important to report the identified inconsistent entries back to the database operators. An important conclusion is that finding a way to unequivocally represent the

chemical structure is not an easy task and most likely errors and inconsistencies will always be found in chemical databases. Different types of SMILES and InChI notations exist because chemicals can exist in different states and forms. Database operators must provide information as clear and accurate as possible, but the final users have to make sure that the identifiers and the structure representation of the intended chemical are correct and appropriate for the context in which they are operating. Cross checking the information in multiple independent databases is a recommended good practice, but it is important to be aware that different databases may have different standardization rules and practices. For the future, we recommend (a) that database operators check their entries (CAS RN™ and SMILES) against other databases (such as the CAS Common Chemistry database) to identify inconsistent entries; (b) the standard use of name-to-structure conversion tools in databases to check the consistency of chemical names; and (c) that users of databases always double-check information that is important to them in a second database.

Author contributions

Method development and data curation were mainly done by JG. MS and KM contributed to the method development and data analysis. All authors contributed to writing and reviewed the final manuscript. Funding was acquired by MS.

Conflicts of interest

There are no conflicts to declare.

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