Exponential growth of new chemicals and evolution of information relevant to risk control

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Summary. The number of new chemicals synthesized and marketed increases exponentially. The database CAS REGISTRY at present contains more than 33 million organic and inorganic substances. However, the little information regarding the potential hazard associated with a large amount of chemicals is an old known problem in the European Union and also in the United States. This critical problem may find a solution in the collaboration of the different involved countries and in a planned task setting at international level. Both in the United States (*e.g.*, the "Gore Initiative") and in European Union (the REACH policy) a big effort has been dedicated to this solution, within standardized procedures and an appropriate collaboration.

Key words: chemical control, risk management, hazardous substances.

Riassunto *(Crescita esponenziale di nuove sostanze chimiche ed evoluzione dell'informazione per il controllo dei rischi)*. Il numero di sostanze chimiche sintetizzate e commercializzate cresce in modo esponenziale. La banca dati del Chemical Abstract Service (CAS REGISTRY) contiene attualmente oltre 33 milioni di sostanze organiche e inorganiche. La limitata disponibilità di dati sui pericoli potenziali associati a un gran numero di sostanze chimiche è un problema antico e comune, sia all'Unione Europea sia agli Stati Uniti, che può trovare una soluzione a livello internazionale nella collaborazione tra i diversi paesi coinvolti e in una distribuzione pianificata dei compiti. Gli Stati Uniti (con la cosiddetta iniziativa Gore) e l'Unione Europea (con la politica REACH) hanno dedicato un grande impegno alla ricerca di una soluzione attenendosi a metodologie armonizzate a livello mondiale e nell'ambito di appropriate collaborazioni.

Parole chiave: gestione del rischio, controllo delle sostanze chimiche, sostanze pericolose.

The overall growth of new chemicals synthesized or isolated annually is extremely high and steadily rising. The database CAS REGISTRY (www.cas.org), produced by Chemical Abstracts Service, a division of the Chemical Society that since 1907 identifies univocally chemicals, at present includes more than 33 million organic and inorganic substances and over 59 million sequences (January 2008). This database is updated daily and, as an average, approximately 4000 new substances are added each day.

The data from *CAS Statistical Summary 1907-2006* show that the growth of chemicals progressively included has followed an exponential increase *(Table1)* [1].

As shown by the above *Table 1*, the number of substances progressively registered by the Chemical Abstract Service has increased of about 420-fold, from about 212 thousands in the year 1965 up to about 88.7 millions in the year 2006, in agreement with an exponential trend (statistically significant). The yearly average increase rate may be estimated in the order of 12-16%. However, some variability exists for this parameter in different time periods. At the very beginning, in the years between 1965 and 1970, the increase has been remarkably high and in the order of about 7.6-fold over 5 years (about 51% per year, from 211 934 up 1 601 933) while for the 1970-1990 period the increase has been of about 6.6-fold over 20 years (around 9% per year, from 1 601 933 to 10 575 961). The increase between 1990 and 2000 has been around 2.7-fold over 10 years (about 9% per year, from 10 575 871 up to 28 499 942). In the 1999-2004 period the increasing rate has been about 3.5-fold over 5 years (about 28% per year, from 22 468 564 up to 77 801 625); in this period, in particular in the years 2003 and 2004 the highest numbers of registered substances are reported (respectively, 15 459 282 and 17 326 060). Lastly, it is worthwhile noticing that from the year 2004 to the year 2006, the increase, equal to 1.14-fold is comparatively very low (about 7% per year, from 77 801 625 up to 88 758 285). Clearly, due to the extremely high numbers of chemicals in the last decade, even a relatively small yearly percent increase may correspond to a number in the order of millions. However, the yearly increase rates emerging for the 2004-2006 periods, considerably lower than the ones of previous periods may

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Table 1 | *Growth of the CAS Chemical Registry System [1]*

Year	Substances registered	Substances registered on file at year end
1965	211 934	211 934
1970	288 085	1 601 933
1980	353 881	5 141 872
1990	663 342	10 575 961
1995	1 196 334	14 594 302
1998	1 679 913	18 919 806
1999	3 548 161	22 468 564
2000	6 031 378	28 499 942
2003	15 459 282	60 475 565
2004	17 326 060	77 801 625
2005	6 412 458	84 214 083
2006	4 544 202	88 758 285

suggest some possible flattening of the trend of the new chemicals registered.

It is worthwhile underlining that the chemicals actually introduced into the environment and marketed are only a small part of the ones registered by the CAS system, and that the ones at high production volume (HPVC), presumably constitute only a minor fraction. An estimate of possible future trends of new chemicals production and introduction in the market might be of main interest for planning, at the worldwide level, the organization of the data production systems on the chemical hazards and risks, of the related evaluation and assessment activities, of the information systems and of the whole other necessary resources.

Lastly it should be noticed that the high numbers of new chemicals registered per year, and within them of new chemicals marketed or intended to be marketed, intrinsically imply a great difficulty for the related safety assessment, which requires a considerably high time consuming work. This justifies the delays in information production hereafter discussed.

In fact, the information regarding the potential hazards is relatively poor for a considerable amount of these chemicals.

In the US, the verified lack of information about chemical agent risks (commonly called "data gaps") stimulated in 1976 the adoption of the Toxic Substance Control Act (TSCA) [2]. Many studies confirmed this data gap. In 1984, a study of the US National Academy of Sciences/National Research Council showed that for only a 22% of the US High Production Volume of chemicals (HPV) the "minimal toxicity data" were available [3] (minimal toxicity data include basic information as acute and chronic toxicity, developmental and reproductive toxicity, mutagenicity as a key indicator of carcinogenicity, ecotoxicity and environmental fate). This condition did not significantly improve in the following 13 years. In fact, in 1998 a report of the US Environmental Protection Agency indicated that no information on toxicity was available for 43% of HPV chemicals produced or imported in US (an amount higher than 1 million tons per year) and that a full set of toxicity data was available only for a 7% of the whole [4].

The lack of data on the chemical hazard is an old known problem also in the European Union, as also underlined by several studies, indicating a condition comparable with that of the United States:

- in 1990, an analysis of chemical control in the EU showed lack of information on the use and toxicity of the existing chemicals, also examining the downstream uses [5];
- in 1996, an international review of the risk assessment of chemicals confirmed the same condition [6];
- a detailed analysis carried out by the European Chemicals Bureau led to the same conclusions on the lack of information concerning the high production volume of chemicals (HPVC) (exceeding a production volume of 1000 tonnes/year), pointing out significant gaps: *e.g.*, for only a 14% of the EU HPVC data were available (publicly available) concerning the "Base Set" (*i.e.*, the minimum information on dangerous properties of substances, required under the EU regulations for assessing the risks of new industrial chemicals according to the Directive 67/548/EEC, Annex VIIA). Moreover, for 65% of the EU HPVC, the available information was less then the "base set", and for 21% no data existed at all (no data on toxicity tests on humans and on the environment) [7];
- in 2000, the Danish Environmental Protection Agency (Danish EPA) carried out a study aimed at determining the extent of the available data on the hazards for the about 100 000 substances included in the European Inventory of Existing Commercial Chemical Substances (EINECS), analyzing two of the world largest sources of publicly available test data (RTECS, 2000 and AQUIRE, 1994). Among the conclusions presented by the Danish EPA *(Table 2)*, it is underlined that the information on the dangerous properties of chemicals was incomplete or even

Table 2 | *Available data for some parameters from the Danish EPA study on AQUIRE and RTECS for over 100 000 listed substances (as percentages) [8]*

Acute toxicity	13.4 %
Toxic to reproduction	2.5 %
Mutagenicity	3.9 %
Carcinogenicity	1.8 %
Danger to the aquatic environment	3.5 %

AQUIRE = AQUatic Toxicity Information Retrieval, United States Environmental Protection Agency.

RTECS: Registry of Toxic Effects of Chemical Substances, The National Institute of Occupational Safety and Health, Washington, DC.

lacking at all, and that for about 90% of the 100 000 substances listed in the EINECS only few data on toxicological tests on experimental animals were available [8].

The lack of data on the hazardous properties of chemicals is a key element and has stimulated different initiatives and policies:

- in the United States, the so called "Gore initiative", finalized to fill the gaps in the public access to basic health and emissions information, aims at completing testing of 2800 high production volume chemicals by 2004 (www.epa.gov/history/topics/earthday/09.htm). The initiative, regarded as the first approach to systematically obtain toxicological and eco-toxicological information about the most abundant existing chemicals on the US market, concerns high production volume chemicals, chemicals to which children are most exposed and PBTs, (Persistent, bioaccumulative toxic pollutants) or are persistent in the environment with bioaccumulative properties;
- the European Union recently developed a new chemical policy for industrial chemicals control called REACH (Registration, Evaluation, and Assessment of CHemicals). The REACH legislation, entered into force on June 2007, has the ambitious expectation to fill the knowledge gaps for about 30 000 substances [9] (*i.e.,* those produced or marketed in quantities above 1 ton/year) stimulating the collection of existing data but also the production of new data in order to fill the data gaps. REACH regulation intends to create a central database on information about chemicals, which will be located in the European Agency of Chemical Substances (ECHA), recently settled in Helsinki. It removes the present distinction between "New" and "Existing" chemicals and move large part of responsibility in evaluating and managing the risks of chemicals from the governments to the industry;
- the international cooperation presently existing allows that results from studies on the dangerous properties of chemicals performed in the US, in the European Community and in other Countries (provided they have been obtained according to the Good Laboratory Practices and using internationally recognised protocols) will be shared without the need of being repeated. This is the important consequence of the adoption of a globally harmonized testing methodology. Accordingly, test results of the Screening Information Data Set (SIDS) programme (the "High Production Volume Chemicals Programme", www.cefic.org/activities/hse/mgt/hpv/hpvinit.htm) of the Organisation for Economic Co-operation and Development (OECD) the International Council of Chemical Associations (ICCA) High Production Volume Chemicals (HPVC) Programme will be taken into account to reduce the number of tests to be performed in the EU [9].

The above discussion suggests a substantially critical condition, due to the "explosion" of the number of the new chemicals produced during the last decades. It is evident that the studies and experimental tests on the relevant hazards/risks cannot follow the same increasing trend, because of the necessity of a very high amount of expertise, human and technological resources, experimental laboratory activity, and of an appropriate time for carrying out various and not simple experiments and tests, as well as for the result evaluation and the consequent decision making.

The solution of this problem may arise from a technological/methodological improvement, and, in particular, from international cooperation and distribution of tasks and related costs, presently existing. A scale of priority is also considered, in order to progressively resolve the most urgent cases (*e.g.*, HPV Chemicals).

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