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Integrating process safety with molecular modeling-based risk assessment of chemicals within the REACH regulatory framework: Benefits and future challenges

Amanda Lewis, Nikolaos Kazantzis *, Ilie Fishtik, Jennifer Wilcox

Department of Chemical Engineering, Worcester Polytechnic Institute, Worcester, MA 01609-2280, USA

Abstract

Registration, evaluation and authorization of chemicals (REACH) represents a recent regulatory initiative by the European union commission to protect human health and the environment from potentially hazardous chemicals. Under REACH, all stakeholders must submit (thermo)physical, thermochemical, and toxicological data for certain chemicals. The commission's impact assessment studies estimate that the costs of REACH will be approximately 3–5 billion Euros. The present study advocates the systematic incorporation of computational chemistry and computer-assisted chemical risk assessment methods into REACH to reduce regulatory compliance costs. Currently powerful computer-aided ab initio techniques can be used to generate predictions of key properties of broad classes of chemicals, without resorting to costly experimentation and potentially hazardous testing. These data could be integrated into a centralized IT decision and compliance support system, and stored in a retrievable, easily communicable manner should new regulatory and/or production requirements necessitate the introduction of different uses of chemicals under different conditions. For illustration purposes, ab initio calculations are performed on heterocyclic nitrogen-containing compounds which currently serve as high energy density materials in the chemical industry. Since investigations of these compounds are still in their infancy, stability studies are imperative regarding their safe handling and storage, as well as registration under REACH.

Keywords: Chemicals regulation; Computational chemistry; Chemical process safety; Molecular modeling; Chemical risk

1. Introduction

Registration, evaluation and authorization of chemicals (REACH) form the acronym representing a recent complex regulatory and legislative initiative originally developed and introduced by the European union commission, that aims at protecting human health and the environment from potentially hazardous classes of chemicals. At the same time, REACH aims at stimulating innovation and R&D activity towards the design of safer chemicals and processes, thus enhancing corporate responsibility, as well as promoting competition within the European chemical industry [1–3]. Given the inherent inefficiency and antinomies of the current regulatory framework for chemicals in Europe [1,2], REACH not only represents a comprehensive regulatory policy framework for the management of chemical in the European union (EU), but is also compatible with World Trade Organization (WTO) rules and directives. As a result REACH, will eventually have a much broader impact on chemicals policy and regulation initiatives as they begin to be implemented on a worldwide scale [1–4]. Indeed, REACH policies are going to affect a quite broad group of manufacturers, importers and downstream users of chemical substances [2]. Under the aforementioned regulatory framework, all stakeholders must submit (thermo)physical, thermochemical, toxicological data, as well as the results of risk assessment studies for all chemicals involved through the submission of detailed technical dossiers [2,3,5]. The latter will be thoroughly evaluated by state authorities in all member states of the European union, as well as by the newly established European chemical agency (ECA), and authorization will be issued accordingly for the use and storage of the most hazardous classes of chemicals [2,3,5]. In light of the new legislation and chemicals policy, various impact assessment studies undertaken on behalf of the European commission provide estimates for the associated costs induced by REACH within the range of 3–5 billion Euros [6]. Particular emphasis is placed

* Corresponding author. Tel.: +1 508 831 5666; fax: +1 508 831 5853.
E-mail addresses: alewis@wpi.edu (A. Lewis), nikolas@wpi.edu (N. Kazantzis), ifishtik@wpi.edu (I. Fishtik), jwilcox@wpi.edu (J. Wilcox).

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on the reduction of the associated regulatory compliance costs within the REACH framework for small to medium-sized enterprises (SMEs) due to their limited resources [2,6]. Taking into account the above considerations, the present study aims at the development of a framework that advocates the systematic incorporation of process safety practices through the use of molecular modeling techniques in order to develop a cost-effective comprehensive computer-assisted chemical risk assessment scheme and integrate it into a centralized supervisory IT-system, the latter being the regulation support system administered by ECA and the European Chemicals Bureau (ECB).

According to the proposed approach, current powerful computer-aided molecular modeling techniques can be used in order to develop and validate quantitative structure-activity relationships (QSARs) [7,8], through which one could computationally generate predictions of key (thermo)physical, thermochemical, and toxicological properties for broad classes of chemicals, as well as assess the associated chemical risks under different conditions without resorting to costly experimentation and potentially hazardous testing. In addition, the computer-based investigations will allow for the reduction of scientifically less sound trial-and-error type of risk assessment and management practices that could induce fines and unnecessary litigation. The computationally generated data, QSARs and risk assessment results could be integrated into the centralized information management and regulation support system of ECA and ECB, as well as the overall compliance plan and IT-systems of corporations. Preferably, they would be stored in a format that renders the pertinent information retrievable; easily transferable/communicable while facilitating its flow between the various stakeholders should new regulatory and/or production requirements and strategic goals necessitate the introduction of different uses of chemicals under different conditions. Consequently, the preparation of the content of the detailed technical dossiers and compliance to requirements under REACH becomes easier, cost-effective, operationally transparent and amenable to adaptation to new market conditions and regulatory norms. Indeed, preliminary and rather promising results on the cost-saving potential of QSARs under REACH were recently released, further corroborating the intuitive benefits of incorporating process safety and molecular modeling-based risk assessment of chemicals into the new regulatory framework [7–10]. Within the above context and in order to illustrate the proposed approach, molecular modeling investigations based upon quantum mechanics are performed on a heterocyclic nitrogen compound that has recently emerged in the literature due to its promise of serving as a high energy density material (HEDM) in the chemical industry. Since investigations of heterocyclic nitrogen compounds of this type are still in their infancy, stability studies are imperative so that knowledge can be gained regarding their safe handling and storage, as well as their registration under REACH. The present work is the first to examine the formation enthalpy of this novel compound from a theoretical perspective. Future work will involve the examination of other emerging HEDMs in the literature.

The present paper is organized as follows: Section 2 contains a description of the main features, structure and requirements of the new regulatory framework and policy for chemical substances in the EU known as REACH, as well as the main results and findings of recent impact assessment studies on the chemical industry. A few thoughts and ideas on integrating process safety and molecular modeling-based risk assessment of chemicals within REACH, along with the associated benefits and future challenges are presented in Section 3. The proposed ideas are illustrated through a molecular modeling case study in Section 4, followed by some concluding remarks are in Section 5.

2. REACH: a new regulatory and policy framework for chemicals in the European union

It is widely recognized, that the current regulatory framework for the management of chemicals in Europe is inadequate and inefficient [1–3]. In particular, it has not resulted in sufficient information or sound chemical risk assessment practices pertaining to the effects of certain chemicals on human health and the environment. Furthermore, whenever the associated risks of these substances have been identified, the implementation of risk management measures has been unacceptably slow [1–3]. Furthermore, the current framework has adversely affected patterns of research activity and innovation, causing the European chemical industry to lag behind its main counterparts in the US and Japan [1–3].

The currently used regulatory framework makes a clear distinction between the so-called existing and new chemicals. Approximately 100,000 chemicals have been introduced to the global market before 1981 and are termed as existing chemicals, with approximately 3000 been introduced after 1981 and termed as new ones [1,2]. While new chemicals have to undergo extensive testing before entrance into the market, there are no such provisions and comprehensive directives for existing chemicals. The current regulatory framework in the EU requires information on only high volume existing chemicals to be submitted and only public authorities in member states are responsible to determine which of them need further examination [1–3]. As a result, these procedures have been proven to be bureaucratically tedious and inefficient. Current legislation requires manufacturers and importers of chemicals to provide information on the chemicals they use and store, but does not impose similar obligations on downstream users (such as industrial users and formulators) unless the substance is classified [1,2]. Clearly, reliable information on the uses of chemical substances is currently difficult to obtain and information about exposure associated with downstream uses of chemicals is generally scarce. Within the existing framework, new chemicals ought to be notified and tested in production volumes as low as 10 kg/year. This has inhibited R&D activities, undermined invention efforts for new substances, and stifled innovation in the European chemical industry, encouraging the continued use of existing chemicals that current regulation compliance requirements render easier to use and less costly [1,2].

In light of the aforementioned remarks, a revision of the current legislative framework for chemicals in the EU becomes imperative. In response to this need, the EU commission introduced a preliminary White Paper [1], which outlined the main

strategic goals and policy measures for the development of a new regulatory framework for chemicals in Europe. This new ambitious piece of proposed legislation became known under the acronym REACH (registration, evaluation and authorization of chemicals). Following extensive consultations with major stakeholders, including governments, industry and non-governmental organizations (NGOs), a comprehensive piece of legislation emerged on 29 October 2003 through the commission's initiatives and put forward for consideration by the European Parliament and Council for possible adoption under the so-called co-decision procedure [2]. The commission's proposal represents an ambitious model of sustainable development by simultaneously pursuing objectives along three main axes: economic (industrial competitiveness), social (public health protection and job creation), and environmental. The proposal also represents a visible piece of evidence of a growing trend towards increasing corporate responsibility on global regulation requirements, as well as industry-led evaluation and understanding of the risks of chemical exposure and the associated effects on the environment.

At this point, let us present the most salient features of REACH [2]. In the EU, all chemical substances that are manufactured or imported in volumes exceeding one metric tonne on an annual basis per manufacturer or importer (tonnage) must be registered. The registration procedure requires the submission of a technical dossier which contains fundamental information on the chemical's (thermo)physical, thermochemical, and toxicological properties and uses. It is important to notice that all dossiers will be evaluated and checked. When this procedure is complete, the chemical is considered to be registered and can continue to be used until further evaluation is deemed appropriate. One could single out two special classes of chemical substances that are exempt from current REACH registration requirements for rather obvious reasons: chemical substances solely used and stored for R&D purposes and polymers. Under the proposed legislation, a European chemical agency (ECA) will be established in Helsinki, Finland that will undertake the management of the technical, scientific and administrative aspects of REACH and the data-base of chemical information. The ECA will also ensure that REACH functions well and maintains its credibility and transparency with all stakeholders.

Chemical substances that are manufactured in volumes exceeding 100 metric tonnes per year will be evaluated by state authorities in EU member states and appropriate institutions, who may ask for additional testing and risk assessment studies to be conducted. The newly established ECA will ensure consistency across institutions and state agencies in member states during the evaluation process. The ECA will also provide the requisite IT-capacity and communication protocols for data sharing in order to minimize costs. Furthermore, under REACH, certain chemical substances which are characterized as "substances of very high concern" (carcinogenic mutagenic and toxic to reproduction; persistent bio-accumulative and toxic; persistent organic pollutants) ought to be authorized for specific uses and conditions.

An integral part of the October 2003 REACH proposal pertains to the need of a comprehensive extended impact assessment of the new regulatory framework and the induced cost structure on the competitiveness and innovation capacity of the European chemical industry [6]. Over 40 impact assessment studies have been carried out and made a significant contribution towards a better assessment and understanding of the changes needed in order to achieve a balanced and workable solution for REACH. Let us now briefly examine the main findings that resulted from these studies, starting with the regulatory compliance cost structure. The direct costs induced by REACH are estimated to be within the range of 3–5.2 billion Euros over the first 11 years after the entry into force of the new regulatory framework [6,11]. While the costs induced by the new regulatory framework are certainly real, all impact assessment studies suggest that they are also manageable [6,11]. Further improvement of the testing methods through the development of more efficient practices will result in additional cost reduction. On the other hand, all these studies have also shown that the benefits associated with REACH are substantial [6,11]. In agreement with world bank estimates, these studies indicate that the positive public health and occupational impact of REACH will lead to potential health benefits and savings evaluated at approximately 50 billion Euros over a 30-year period due to the reduced burden associated with various diseases caused by chemicals.

It should be pointed out, that SMEs can be particularly affected by REACH due to their limited financial capacity, resources and weaker market position that can pose major challenges to their regulatory compliance efforts [6]. However, SMEs play a strategically important role in the EU economy and the European chemical industry. In light of this recognition, REACH has already introduced lighter requirements since most SMEs are likely to fall into the category of downstream users. Moreover, SMEs that produce substances are likely to find themselves within the lower tonnage bands, on which lighter regulatory requirements are imposed. Innovative research-oriented SMEs could also take advantage of the exemption scheme for R&D-used chemicals offered by REACH. Finally, the benefits associated with the development of a comprehensive user-friendly IT-support system that will be administered by ECA (and developed in consultation with all stakeholders) will be considerable.

The regulatory compliance cost structure and the aforementioned findings of the various impact assessment studies of REACH provide ample motivation for the development of new approaches. These approaches could improve the cost efficiency of the new regulatory framework while maintaining the overall objectives of REACH. In the present paper, the incorporation of process safety practices and molecular modeling-based risk assessment techniques for chemical substances within REACH is advocated as a potential means to enhance its cost efficiency, functionality, transparency, and most importantly, improve and strengthen the scientific/technical basis of a comprehensive chemicals policy. In the following section, it is argued that the above approach may entail considerable benefits to the adoption and actual implementation of REACH, and at the same time, pose interesting challenges and opportunities for further reflection towards the constant refinement and improvement of the new chemicals policy.

3. Integrating process safety and molecular modeling within REACH: benefits and future challenges

It is now widely recognized that knowledge of the hazards and risks posed to human health and the environment by broad classes of existing chemicals is unacceptably poor, incomplete and inconsistent [1–3]. Even a significant fraction of High Production Volume Chemicals (HPVCs) have not been subjected to systematic testing and risk assessment. As a result potential hazards associated with the production, use, and storage of HPVC's cannot be carefully evaluated or properly managed [1–3,5]. The situation appears to be even more problematic in the cases of new chemicals, including non-HPVCs, for which the lack of data on property characterization and risk assessment has reached alarming levels [1–3,5]. Consequently, there is an immediate need to develop a comprehensive chemicals policy framework that ensures the intensification of regulatory compliance efforts and the systematic generation of sound scientific data for new and existing chemical substances. This is precisely one of the basic tenets and main objectives of REACH. The benefits associated with the generation of reliable scientific data are two-fold:

(i) They enable a more insightful and thorough risk assessment of chemicals to be conducted that would lead to the development of the most appropriate and cost-effective risk management measures ensuring the safe use and storage of chemical substances.
(ii) They partly eliminate and confidently address the uncertainties associated with the specification of the proper level of protection of human health and the environment by strengthening the decision- and policy-making process, avoiding unnecessary "conservativeness" in their respective frameworks, as well as costly layers of "over-regulation".

Typically, the type of data needed to be generated in order to serve the main policy objectives of an ambitious framework such as REACH could be classified into three main categories [12–14]:

(i) Data pertaining to key (thermo)physical and thermochemical properties of substances such as flammability, explosivity, vapor pressure, auto-ignition temperature, calorimetric and thermodynamic properties, etc.
(ii) Data pertaining to the biological activity of chemical substances such as carcinogenicity, toxicity, mutagenicity, and reproductive toxicity, etc.
(iii) Data associated with the ecological effects and environmental fate of chemical substances such as aquatic toxicity, degradation, bioaccumulation, soil and sediment sorption, etc.

The above data are customarily generated through [12–14]:

(i) Laboratory tests and experimental studies by resorting to animal testing (in vivo) and/or cell cultures (in vitro).
(ii) The establishment of qualitative structure-activity relationships (SARs) or quantitative structure-activity relationships (QSARs).

In the present study the focus is placed on QSARs and the role of molecular modeling techniques in their establishment and validation. QSARs also have the potential to reduce regulatory compliance costs and animal testing under REACH. For these reasons, let us view QSARs as mathematical representations through which quite complex relationships between intrinsic molecular structural characteristics of a substance and its chemical and biological activity can be modeled [7,9,10]. The intrinsic molecular characteristics that define the structure of a chemical substance play the role of "independent variables" often called molecular descriptors. The data associated with the observed chemical and biological activity/behavior of substances (please see the above classification of different types of data) represent the values of the "dependent variables" of QSARs [7,9,10,14]. It should be pointed out, that the values of descriptors can be obtained either through experimental studies (which are non-trivial and quite often technically impossible) or calculated with the aid of currently available software packages that allow a thorough quantum-mechanical description and insightful molecular modeling of the chemical of interest [7–10,14,15]. Typical examples of molecular descriptors are dipole moment, charge-bond strength, delocalizability index, mid-point potential, highest positive and negative charge, highest and lowest molecular orbitals, etc [9,10]. Using molecular descriptor data for chemical substances and data obtained through direct observation, QSARs can be developed by applying techniques such as regression analysis, neural networks (typically back-propagation modeling methods) and various classification methods [14]. A preliminary QSAR is typically developed on the basis of a training set of data, and later verified using a validation set of data. It should be emphasized that data obtained using computational chemistry and molecular modeling techniques are systematically used for both training and validation purposes when QSRAs are developed [9,10,14]. Having developed and appropriately validated QSARs, the benefits engendered by their use are two-fold:

(i) Predictions can be generated about the chemical and biological activity of substances. These can then be adopted for chemical management, risk assessment, classification and labeling purposes, and become naturally integrated into a regulatory framework such as REACH.
(ii) Useful information will be able to be extracted on how facets of chemical and biological activity are affected by specific inherent structural (molecular) characteristics of the substance under consideration.

The above advantages become even more pronounced in the case of untested and poorly characterized chemical substances that need to be registered and carefully managed under REACH. They also apply in cases where new safer substances need to be designed and produced.

Let us now consider, in a more concrete manner, the benefits that can be drawn by integrating the use of computational

chemistry, molecular modeling and QSARs into the overall regulatory framework of REACH. In accordance to article 23 of the proposed regulatory and policy framework of REACH, vertebrate animal testing should be viewed only as a last resort for the attainment of the main registration and evaluation objectives [2]. Recent analysis performed by ECB scientists suggests that approximately 3.9 million additional animal tests could be potentially used in order to comply with REACH regulation requirements if alternative approaches are not pursued [7,8]. As mentioned in Section 2, the pursuit of alternative cost-effective, scientifically sound testing, and risk assessment methods for chemical substances could significantly reduce and control the regulatory compliance cost structure under REACH. Both EU authorities and ECB quickly responded to an initiative and proposal put forward by the Institute for Health and Consumer Protection (IHCP) for the development of intelligent testing strategies (ITS) [16]. ITS will form a new comprehensive framework aiming at making current testing practices cost-effective and less demanding on the number of animal tests needed. This can be attained by promoting an integrated testing scheme that rationally uses a multitude of alternative approaches, where computational chemistry and QSARs will have a prominent role [16]. Emphasis is placed on the need for more coordinated efforts between industry and regulatory authorities on the development, validation and use of QSARs in the spirit promoted by the REACH legislation and the paradigm of increasing corporate responsibility that it advocates [7,8,14]. Besides the potential of significantly reducing the number of animal tests, computational chemistry and QSARs exhibit the potential to rationalize (and quite often expedite) testing, priority setting and risk assessment procedures for chemical substances. This is done by eliminating the need for additional tests under certain conditions and/or providing scientifically supported guidance towards the selection of the appropriate testing methods and risk management measures. Preliminary results of recent studies undertaken by ECB suggest that 1.3–1.9 million test animals could be saved if QSARs are adopted, and substantial cost savings of the order of 1 billion Euros could be achieved through the above ITS scheme [7,8]. The latter figure far exceeds the estimated 10 million Euros cost associated with industry developing its own QSARs and documenting them through the IT-support system [7,8].

One could mention the opportunity for the enhancement of the innovation capacity of the chemical industry in alignment with the special incentives provided by the REACH legislation to design and synthesize new and safer chemicals. This is a task that could significantly be facilitated through computational chemistry techniques and a judicious use of QSARs. These can be proven to be advantageous in cases where certain substance withdrawal and extensive reformulation becomes likely under REACH, and innovation is critical for the introduction of new substances and risk management methods into the market. Studies mentioned in Section 2 suggest that there are additional benefits associated with the use of computational chemistry. Furthermore, certain SMEs can benefit by the use of computational chemistry tools and QSARs, thus reducing costs, eliminating redundant testing, and rationalizing risk management practices under REACH requirements.

The integration of computational chemistry, molecular modeling and QSARs under the REACH framework poses considerable scientific, technical, implementation and legislative challenges. The latter fall beyond the scope of the present paper. The first major challenge pertains to various validation procedures for QSARs developed with the aid of computational chemistry that can be universally accepted by decision-makers and regulation authorities as reliable and practically useful [7,8,14]. The organization for economic co-operation and development (OECD) made the first attempt to address these challenges [17]. Even though OECD ensured homogeneity of standards and consistency of criteria by explicitly advocating the use of sound scientific practices and methods [17], the above efforts have not yet resulted in a practical, transparent validation framework that would bring the broadest possible consensus amongst policy makers, various QSAR users and regulators [14,18]. The above project should receive immediate priority since QSARs (and the associated computational chemistry tools) could be directly used to support decision-making and regulatory actions in the management of chemicals [12,13,18]. They need to exhibit relative simplicity in generating predictions, and the domain of their validity, their prediction uncertainty and degree of reliability concerning certain classes of chemicals must be reported in an unambiguous manner as well [14,18]. Statistical methods used for the development and validation of QSARs need to become available in order to ensure transparency and allow future refinements and extensions. Critical to the above efforts, would be the recognition that QSARs developed for the prediction of health effects of chemicals substantially differ from the ones used for the prediction of ecological and environmental effects due to the fundamental differences in the nature of the respective endpoints, the associated data as well as the availability of reliable dose– or exposure–response relationships [12,13,18].

A major future challenge related to a cost-effective implementation of the REACH regulatory framework is the development and design of a comprehensive user-friendly IT decision-support system. It would require access by both industry and regulatory authorities, and facilitate their respective decision-making process [2,16]. The decision-support system should be supported and centrally administered by an independent organization whose neutrality would ensure transparency and fairness to all stakeholders involved. The system, while administered by ECA, will be scientifically and technically supported by ECB as well [2,16]. Preliminary efforts are already in progress and made under the "umbrella" of the so-called REACH-IT project, whose primary aim is the design of an IT-support system that efficiently serves the main regulation requirements of REACH by engaging industry, regulatory authorities and other decision-makers in the chemicals legislation domain. Currently, that main software tools that support decision-making and risk assessment of chemical substances in the EU are the European chemical substances information system (ESIS), the International Uniform Chemicals Information Database (IUCLID) and the European union system for the evaluation of substances (EUSES) [16]. They all would require refinement in order to support the new REACH regulation requirements, become integrated into the overall REACH-IT structure, and reflect the new realities in

the European regulatory landscape for chemicals [16]. A specific QSAR decision-support system needs to be developed and become accessible through the internet. Such a decision-support system will become an indispensable part of the overall REACH-IT platform and ECB has already formed a working group to study and address the above problem and the associated challenges [16]. It becomes apparent that further challenges lie ahead as the new IT and decision-support system for REACH should also facilitate communication and ensure uninterrupted flow of information along the supply chain in order to reduce regulatory compliance costs. The technical challenge becomes the problem of harmonization of different data formats that could be exchanged between various platforms and IT decision-support systems.

4. The theoretical prediction of the thermochemical property, formation enthalpy: determining the stability of emerging heterocyclic nitrogen compounds

Ab initio investigations were carried out at the G3 level of theory [19] and the isodesmic approach [20] was employed for the theoretical prediction of the formation enthalpy for the heterocyclic nitrogen compound, 3,6-di(azido)-1,2,4,5-tetrazine (C_2N_{10}). These thermochemical predictions allow for the development of QSARs from which the stability of these emerging high energy density materials (HEDM) can be determined. All molecular orbital calculations were carried out using Gaussian 98 and Gaussian 03 software packages [21].

G3 theory developed by Curtiss et al. [19], was chosen to calculate the unknown heat of formation of C_2N_{10}. It is an improved version of G2 and is more accurate when calculating heats of formation [19,22]. More specifically, G3 has been successful in prediction heats of formation data for compounds containing a significant number of carbon, nitrogen, and oxygen atoms [19,22]. Since the current work concerns a compound containing 2 carbon atoms and 10 nitrogen atoms, this composite method was a logical choice for maximizing the accuracy of the theoretical predictions. Not only is the G3 theory computationally less expensive than G2, CCSD(T), and QCISD(T) levels of theory, but it also uses considerably less computational time due to the changing basis sets [19,23–26].

G3 theory begins with an optimized geometry calculation for the species of interest the second order Moller Plesset perturbation theory, MP2, and then uses this optimized geometry for calculating single-point energies (SPE) at higher levels of theory, e.g., MP4, QCISD(T), and HF [19]. The optimized geometry calculation was carried out using the MP2(FU) method with the 6-31G(d) basis set. "FU" refers to "full" and insinuates that all of the electrons are included in the electron correlation calculation. Electron correlation becomes important when considering second-row atoms such as carbon and nitrogen [19,27].

The following SPE calculations are performed on the MP2(FU)/6-31G(d) optimized geometry of the heterocyclic C_2N_{10} compound: MP4(FC)/6-31G(d), MP4(FC)/6-31 + G(d), MP4(FC)/6-31G(2df, p), QCISD(T, FC)/6-31G(d), and MP2(full)/G3Large. "FC" refers to "frozen core" and implies that inner-shells are excluded from the electron correlation calculation, making the calculations less time consuming. The G3Large basis set is an extended Pople basis set which includes both polarization and diffuse functions [19]. These energies are presented in Table 1.

Table 1 also lists the three correction factors that are considered in the G3 theory, i.e. spin-orbit (SO) correction, higher level correction (HLC), and zero-point energy (ZPE) correction. Previous studies have shown that molecular SO correction provides no overall improvement in the accuracy of energy calculations [19]. The compound of focus, C_2N_{10} and all the reference species are molecules making the SO correction negligible. The HLC is calculated using the following equation:

$$-An_\beta - B(n_\alpha - n_\beta) \quad \text{or} \quad -Cn_\beta - D(n_\alpha - n_\beta) \tag{1}$$

where n_β and n_α are the numbers of β and α valence electrons, respectively, A the correction for paired electrons in molecules, B the correction for unpaired electrons in molecules, C the correction for the paired electrons in atoms, and D is the correction for unpaired electrons in atoms.

The total G3 energy, E_0, is calculated through the evaluation of (2),

$$E_0(\text{G3}) = E[\text{MP4(FC)/6-31G(d)}] + \Delta(+) + \Delta(\text{2df, p}) + \Delta(\text{QCI}) + \Delta + \Delta(\text{HLC}) + \text{ZPE} \tag{2}$$

Table 1
G3 energy contributions and total energies for reference species and C_2N_{10} in Hartrees

Reference species	MP4(FC)/6-31G(d)	Δ(+)	Δ(2df, p)	Δ(QCI)	Δ	Δ(HLC)	ZPE	E_0(G3)
NH_3	−56.2897578	−0.0902997	−0.1294505	−0.0823403	−0.0073612	−0.025544	0.036162	−56.589
C_6H_6	−231.5317459	−0.0140679	−0.015932	−0.0169012	−0.3253073	−0.09579	0.106636	−232.042
C_5H_5N	−247.5529126	−0.0159325	−0.1827884	0.0016899	−0.332379	−0.09579	0.094161	−248.084
ortho-$C_4H_4N_2$	−263.5418548	−0.0169012	−0.183451	0.0034666	−0.3396753	−0.09579	0.080691	−264.094
meta-$C_4H_4N_2$	−263.5768182	−0.0173593	−0.1839439	0.0025901	−0.3398136	−0.09579	0.081767	−264.129
$C_3H_3N_3$	−279.6033974	−0.0186248	−0.1853779	0.0031899	0.0031899	−0.09579	0.069467	−280.178
N_2H_2	−110.3333922	−0.0080926	−0.08196	−0.0007504	−0.1293291	−0.038316	0.029317	−110.563
N_2H_4	−111.471453	−0.0191261	−0.1096655	−0.0012444	−0.1365662	−0.044702	0.051904	−111.702
CH_3N	−94.3455203	−0.0079219	−0.0791078	−0.0013048	−0.1213373	−0.038316	0.042294	−94.551
N_3H	−164.3708911	−0.0105692	−0.1056388	0.0093907	−0.1905183	−0.051088	0.021857	−164.697
[a]C_2N_{10}	−621.838054	−0.0333763	−0.0333763	0.8851032	−1.0700452	−0.185194	0.05943	−622.182

[a] Due to the computational expense of the SPE calculations for C_2N_{10} the G3 theory was modified as detailed in the text.

where

$$\Delta(+) = E[\text{MP4(FC)/6-31 + G} - \text{MP4(FC)/6-31G(d)}] \quad (3)$$

$$\Delta(\text{2df, p}) = E[\text{MP4(FC)/6-31G(2df, p)} - \text{MP4(FC)/6-31G(d)}] \quad (4)$$

$$\Delta(\text{QCI}) = E[\text{QCISD(T, FC)/6-31G(d)} - \text{MP4(FC)/6-31G(d)}] \quad (5)$$

$$\Delta = E[\text{MP2(FU)/G3Large} - \text{MP2(FC)/6-31(2df, p)} - \text{MP2(FC)/6-31 + G(d)} + \text{MP2(FC)/6-31G(d)} \quad (6)$$

All calculations for the reference species were carried out using Gaussian 03, while supercomputing resources equipped with Gaussian 98 were employed for the compound of interest, C_2N_{10} [21]. The computing requirements to carry out the G3 SPE calculations on C_2N_{10} were exceeded and modifications to both ab initio methods and basis sets were implemented as follows:

$$\text{MP4(FC)/6-31G(d)//MP2(FU)/6-31G(d)} \rightarrow \text{MP4SDQ(FC)/6-31G(d)//MP2(FU)/6-31G(d)} \quad (7)$$

$$\text{MP4(FC)/6-31 + G(d)//MP2(FU)/6-31G(d)} \rightarrow \text{MP4SDQ(FC)/6-31 + G(d)//MP2(FU)/6-31G(d)} \quad (8)$$

$$\text{MP4(FC)/6-31G(2df, p)//MP2(FU)/6-31G(d)} \rightarrow \text{MP4SDQ(FC)/6-31 + G(p, d)//MP2(FU)/6-31G(d)} \quad (9)$$

$$\text{QCISD(T, FC)/6-31G(d)//MP2(FU)/6-31G(d)} \rightarrow \text{QCISD}(T)\text{/6-31G////MP2(FU)/6-31G(d)} \quad (10)$$

For the SPE calculations (7) and (8), the basis set size was consistent, but the fourth order perturbation theory, MP4 was carried out to include single, double, and quadruple excitations, neglecting the triple excitations. MP4, also known as MP4SDTQ, is more computationally rigorous since it also includes the triple excitations [28]. The basis set for the SPE calculation (9) was reduced by an f polarization function on each of the carbon and nitrogen atoms in C_2N_{10}, but increased by an additional diffuse function on each of these atoms. For the SPE calculation (10), QCISD was carried out fully, including all electrons in the correlation energy, and the basis set used was reduced by a d polarization function on each of the carbon and nitrogen atoms of C_2N_{10}. The total theoretically predicted G3 energies are converted to heats of formation using the experimentally available formation enthalpies of the reference species via the isodesmic approach.

The total ab initio enthalpies of the species are usually converted into enthalpies of formation employing various reaction schemes such as atomization [29], isodesmic [20], homodesmic [30], bond separation [31], group equivalent [32], group additivity [33], ring conserved isodesmic reactions [34], etc. The procedure is illustrated next employing the isodesmic reaction schemes. Let B_0 be the species for which the ab initio enthalpy of formation is sought. Based on the structure of B_0, i.e., type of bonds, a set of molecules $B_1, B_2, \ldots, B_q$ referred to as reference species is selected such that: (a) ideally, the experimental enthalpies of formation of $B_1, B_2, \ldots, B_q$ are known with high accuracy, and (b) the species $B_1, B_2, \ldots, B_q$ involve all of the bonds present in B_0. Normally, the number of species q is such that only one reaction that preserves the type and number of bonds, and, referred to as isodesmic reaction may be generated. Let this reaction be:

$$\rho = \sum_{i=1}^{q} \nu_i B_i + \nu_0 B_0 = 0 \quad (11)$$

where the stoichiometric coefficients are assumed to be positive for products and negative for reactants. Let $\Delta H_{\text{f},i}^{\text{exp}}$ ($i = 1, 2, \ldots, q$) be the experimental enthalpies of the reaction enthalpy changes expressed via the enthalpies of formation and total ab initio enthalpies

$$\sum_{i=1}^{q} \nu_i \, \Delta H_{\text{f},i}^{\text{exp}} + \nu_0 \, \Delta H_{\text{f},0}^{ai} = \sum_{i=1}^{q} \nu_i H_i^{ai} + \nu_0 H_0^{ai} \quad (12)$$

This gives

$$\Delta H_{\text{f},0}^{ai} = \frac{1}{\nu_0} \left(\sum_{i=1}^{q} \nu_i H_i^{ai} + \nu_0 H_0^{ai} - \sum_{i=1}^{q} \nu_i \, \Delta H_{\text{f},i}^{\text{exp}} \right) \quad (13)$$

To improve the accuracy in the enthalpy of formation of the species B_0 it is desirable to choose a larger set of reference species. In this case, however, the number of possible isodesmic reactions involving B_0 and reference species exceeds one. Since there are no rules to select chemical reactions in a complex, multiple chemical reaction system, one has to face the problem of arbitrariness of chemical reactions. The problem may be fixed employing the concept of stoichiometric uniqueness of chemical reactions. According to this concept only the shortest reactions are allowed. By "shortest" it is meant that if a species is eliminated from a reaction, there is no way to balance the reaction employing only the remaining species. Such reactions were deduced from chemical thermodynamics and were called response reactions (RERs) [35]. Thus, in this general case, the procedure may be briefly summarized as follows. Our starting point is the so-called bond matrix:

$$\boldsymbol{\pi} = \begin{array}{c} \begin{matrix} P_1 & P_2 & \ldots & P_s \end{matrix} \\ \begin{bmatrix} \pi_{01} & \pi_{02} & \ldots & \pi_{0s} \\ \pi_{11} & \pi_{12} & \ldots & \pi_{1s} \\ \pi_{21} & \pi_{22} & \ldots & \pi_{2s} \\ \ldots & \ldots & \ldots & \ldots \\ \pi_{q1} & \pi_{q2} & \ldots & \pi_{qs} \end{bmatrix} \end{array} \begin{matrix} B_0 \\ B_1 \\ B_2 \\ \ldots \\ B_q \end{matrix} \quad (14)$$

where π_{ki} ($k = 1, 2, \ldots, s$; $i = 0, 1, 2, \ldots, q$) is the number of a specified type of bonds P_k ($k = 1, 2, \ldots, s$) between the elements. If rank $\boldsymbol{\pi} = s$, an isodesmic RER involves no more than

$s+1$ species. Clearly, one of these species should always be B_0 while the remaining s species are selected from the list of q reference species. If the s reference species involved in a RER are $B_{i_1}, B_{i_2}, \ldots, B_{i_s}$ $(1 \le i_1 < i_2 < \cdots < i_s \le q)$ the general equation of an isodesmic RER is [36]:

$$\rho(B_0, B_{i_1}, B_{i_2}, \ldots, B_{i_s}) = \begin{vmatrix} \pi_{01} & \pi_{02} & \ldots & \pi_{0s} & B_0 \\ \pi_{i_1,1} & \pi_{i_1,2} & \ldots & \pi_{i_1,s} & B_{i_1} \\ \pi_{i_2,1} & \pi_{i_2,2} & \ldots & \pi_{i_2,s} & B_{i_2} \\ \ldots & \ldots & \ldots & \ldots & \ldots \\ \pi_{i_s,1} & \pi_{i_s,2} & \ldots & \pi_{i_s,s} & B_{i_s} \end{vmatrix} = 0 \quad (15)$$

Similar equations are valid for the enthalpy changes of the isodesmic RERs expressed via the enthalpies of formation of the species:

$$\Delta H_\rho^{\mathrm{f}} = \begin{vmatrix} \pi_{01} & \pi_{02} & \ldots & \pi_{0s} & \Delta H_{\mathrm{f},0}^{ai} \\ \pi_{i_1,1} & \pi_{i_1,2} & \ldots & \pi_{i_1,s} & \Delta H_{\mathrm{f},i_1}^{\mathrm{ext}} \\ \pi_{i_2,1} & \pi_{i_2,2} & \ldots & \pi_{i_2,s} & \Delta H_{\mathrm{f},i_2}^{\mathrm{exp}} \\ \ldots & \ldots & \ldots & \ldots & \ldots \\ \pi_{i_s,1} & \pi_{i_s,2} & \ldots & \pi_{i_s,s} & \Delta H_{\mathrm{f},i_s}^{\mathrm{exp}} \end{vmatrix} \quad (16)$$

and the total ab initio enthalpies at 298 K

$$\Delta H_\rho^{ai} = \begin{vmatrix} \pi_{01} & \pi_{02} & \ldots & \pi_{0s} & H_0^{ai} \\ \pi_{i_1,1} & \pi_{i_1,2} & \ldots & \pi_{i_1,s} & H_{i_1}^{ai} \\ \pi_{i_2,1} & \pi_{i_2,2} & \ldots & \pi_{i_2,s} & H_{i_2}^{ai} \\ \ldots & \ldots & \ldots & \ldots & \ldots \\ \pi_{i_s,1} & \pi_{i_s,2} & \ldots & \pi_{i_s,s} & H_{i_s}^{ai} \end{vmatrix} \quad (17)$$

For a certain isodesmic RER the enthalpy of formation of B_0 is evaluated by solving the equation $\Delta H_\rho^{\mathrm{f}} = \Delta H_\rho^{ai}$ for $\Delta H_{\mathrm{f},0}^{ai}$. The final enthalpy of formation of B_0 is determined as the average over a complete set of isodesmic RERs.

As an example, consider the evaluation of the ab initio enthalpy of formation of C_2N_{10}. The structural formula of this species as well as a set of possible reference species is presented in Fig. 1. As can be seen C_2N_{10} involves five types of bonds, namely, C–N, C=N, N–N, N=N and N≡N. The simplest species that involve the last three types of bonds are hydrazine (N_2H_4), diazene (N_2H_2) and hydrogen azide (HN_3). Since these species also involve the bond N–H, it is necessary to add at least one reference species that involve this type of bond, e.g., ammonia (NH_3). The only species that involve the bonds C–N and C=N and for which accurate thermochemical data are available are methanimine (CH_3N), pyridine (C_5H_5N), pyridazine, 1,3-diazine ($C_4H_4N_2$) and 1,3,5-triazine ($C_3H_3N_3$). The last three species involve additionally, C=C and C–H bonds that can be balanced with benzene (C_6H_6). Thus, the isodesmic reaction scheme for C_2H_{10} involves 10 reference species and a total of nine types of bonds as shown in Fig. 1.

It is important to note that there have been very few investigations involving C_2N_{10}. To the authors' knowledge this species has not been isolated in the laboratory and, therefore, no experimental data exists for it. In addition, there were limited experimental gas-phase thermochemical data available for the reference species. In particular, the experimental formation enthalpy for CH_3N has an error bar associated with it of ± 8 kcal/mol. Although the current investigation does not examine the effect of the complete error range, it will be considered in future work. For the compound, N_2H_4, there were multiple experimental formation enthalpies available from the NIST–JANAF thermochemical database [37,38] and the most recently investigated in the literature was used in the calculations for the current work.

The bond matrix generated based on this selection of reference species is presented in Table 2. It may be easily checked that the rank of the bond matrix is equal to 8 and, consequently, only 8 types of bonds from a total of 9 are linearly independent.

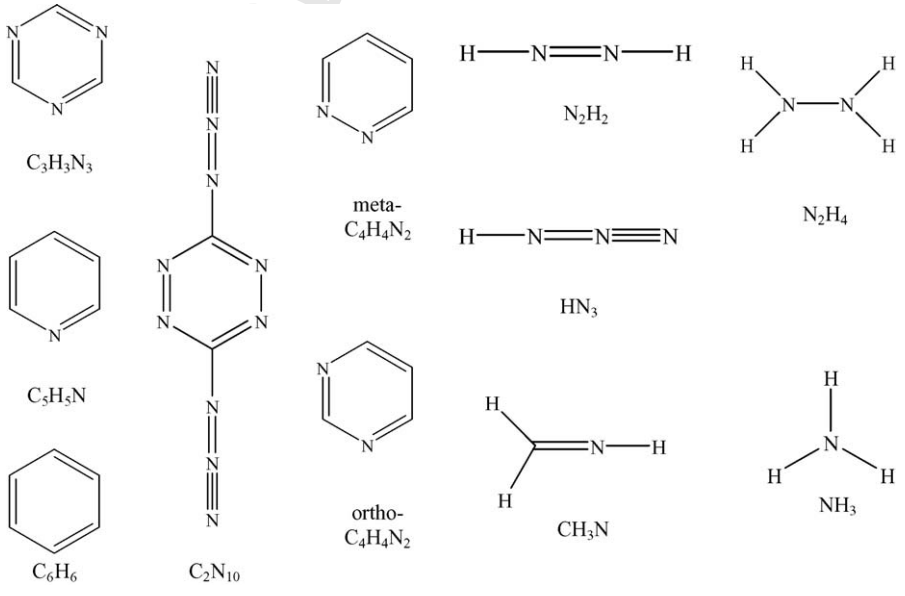

Fig. 1. Reference species used for the formation reactions of the compound, 3,6-di(azido)-1,2,4,5-tetrazine (C_2N_{10}).

Table 2
The bond matrix for the isodesmic reaction scheme used to evaluate the an initio enthalpy of formation of C_2H_{10}

	Bonds								
	N≡N	N=N	N–N	C=N	C–N	N–H	C–H	C–C	C=C
Species									
C_2N_{10}	2	3	1	2	4	0	0	0	0
C_6H_6	0	0	0	0	0	0	6	3	3
C_5H_5N	0	0	0	1	1	0	5	2	2
$C_4H_4N_2$[a]	0	0	1	2	0	0	4	2	1
$C_4H_4N_2$[b]	0	0	0	2	2	0	4	1	1
$C_3H_3N_3$	0	0	0	3	3	0	3	0	0
CH_3N	0	0	0	1	0	1	2	0	0
N_2H_2	0	1	0	0	0	2	0	0	0
HN_3	1	1	0	0	0	1	0	0	0
N_2H_4	0	0	1	0	0	4	0	0	0
NH_3	0	0	0	0	0	3	0	0	0

[a] Pyridazine.
[b] 1,3-Diazine.

Further, a RER involves no more than 8 + 1 = 9 species, one of which should be C_2N_{10}. The remaining 8 species may be selected from a total of 10 reference species in 10!/8!/2! = 45 ways, i.e., the total number of isodesmic RERs does not exceed 45 and can be generated using Eq. (5). In reality, due to a specific stoichiometric structure of the system, only four RER out of 45 are stoichiometrically distinct. These are,

$$3N_2H_4 + 4C_3H_3N_3 + 3N_2H_2 + 6HN_3 \rightarrow 6NH_3 + 6CH_3N + 3C_2N_{10} \quad (18)$$

$$3N_2H_4 + 8C_4H_4N_2 + 3N_2H_2 + 6HN_3 \rightarrow 6NH_3 + 6CH_3N + 4C_5H_5N + 3C_2N_{10} \quad (19)$$

$$3N_2H_4 + 6C_4H_4N_2 + 3N_2H_2 + 6HN_3 \rightarrow 6NH_3 + 6CH_3N + 2C_6H_6 + 3C_2N_{10} \quad (20)$$

Table 3
Experimental enthalpies of formation of the reference species and the total ab initio enthalpies of the species at 298 K

Species	$\Delta H_{f,i}^{exp}$ (kcal/mol)[a]	$H_{f,i}^{ai}$ (Hartrees)
C_2N_{10}	x	−622.1821363
C_6H_6	19.8	−232.0416795
C_5H_5N	33.5	−248.0839516
$C_4H_4N_2$[b]	66.5	−264.0935147
$C_4H_4N_2$[c]	46.7	−264.1293679
$C_3H_3N_3$	53.9	−280.1779842
CH_3N	16.5	−94.5512141
N_2H_2	50.7[d]	−110.5625233
HN_3	71.6[e]	−164.6974577
N_2H_4	22.8	−111.7022568
NH_3	−10.9	−56.5885915

[a] Ref [39].
[b] Pyridazine.
[c] 1,3-Diazine.
[d] Ref [40].
[e] Ref [41].

$$3N_2H_4 + 12C_5H_5N + 3N_2H_2 + 6HN_3 \rightarrow 6NH_3 + 6CH_3N + 8C_6H_6 + 3C_2N_{10} \quad (21)$$

It should be noticed that from two different species with the same brutto-formula $C_4H_4N_2$ but different structures, i.e., pyridazine and 1,3-diazine, only the second appears in the isodesmic RERs.

Once a complete set of RERs is available, the enthalpy of formation of C_2N_{10} may be readily evaluated using the formalism described above. The necessary experimental gas-phase thermochemical data along with the ab initio-generated gas-phase output data is presented in Table 3. Using these data, the enthalpies of formation of C_2N_{10} obtained from the above four isodesmic RERs are: 739.042, 744.493, 743.444 and 740.296 kcal/mol, respectively, that gives an average value of 741.819 kcal/mol.

5. Concluding remarks

Registration, evaluation and authorization of chemicals (REACH) represents a recent regulatory and policy framework for chemicals proposed by the European union commission to protect human health and the environment. The commission's impact assessment studies estimate that the direct costs of REACH will be of the order of 3–5 billion Euros. In light of the above considerations, a few ideas and thoughts were presented advocating the development of a framework that allows for the systematic incorporation of molecular modeling and computer-assisted risk assessment methods of hazards posed by chemicals into REACH to reduce regulatory compliance costs. According to the proposed approach, currently available and powerful computer-aided molecular modeling techniques can be used to computationally generate predictions of key (thermo)physical, thermochemical, and toxicological properties of wide classes of chemicals, without resorting to costly experimentation and potentially hazardous testing. The above computationally generated data could be integrated into a centralized IT decision and compliance support system. To illustrate the proposed approach, a molecular modeling investigation was presented

as an example. The investigation involved the theoretical formation enthalpy prediction for the novel heterocyclic nitrogen compound, 3,6-di(azido)-1,2,4,5-tetrazine (C_2N_{10}), that might have promise as a stable HEDM. Stability calculations involving nitrogen-containing HEDMs of this type require prior thermochemical knowledge, such as formation enthalpies. Due to the potential instability of these compounds, very few experimental studies are available. It is quite possible that molecular modeling investigations will serve as the bridge to understanding the behaviour and activity of these types of compounds. This knowledge can then be applied to methods involving their safe handling and storage, as well as their registration under REACH.

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