



Questions and answers  
on measurement  
implications of REACH  
and CLP

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# Questions and answers on measurement implications of REACH and CLP

July 2010

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# 1. Introduction

## 1.1 Intended readership

This advice is mainly intended for businesses of all kinds, and particularly SMEs, that are required to comply with the REACH Regulation<sup>1</sup>. It also aims to help those obliged to notify classification and labelling for a wider range of substances under the CLP Regulation<sup>2</sup>. Moreover, scientists, SIEFs<sup>3</sup> and consortia, trade associations, regulators, consultants and some general enquirers may find it useful to consider the measurement implications of these Regulations.

We welcome feedback, corrections, and suggestions for improvement.

## 1.2 Scope

The first REACH registration deadline for phase-in substances<sup>4</sup> - 30 November 2010<sup>5</sup> - is fast approaching. Moreover, many more companies will face the obligation to register in 2013 and 2018. This Q&A document continues to foster awareness that correct substance identity is pivotal for successful registration, and addresses key practical requirements.

Experience to date shows that the European Chemicals Agency (ECHA) attaches the highest significance to correct substance identity, which forms the foundation of most REACH processes, including decisions about hazard testing as well as enforcement. Dossiers on REACH substances are being rejected unless they comply closely with the Agency's substance identity requirements and expectations. It is clear that this emphasis will continue, being the only way to ensure that other REACH actions are well-defined. Thus over the coming three years ECHA aims to 'Ensure to the extent possible that the substance identity of the submitted dossiers is correct so that information and regulatory action on substances is targeted and well understood by industry and authorities'<sup>6</sup>.

The CLP Regulation, which gives effect in the European Union (EU) to the United Nations Globally Harmonised System of Classification and Labelling of Chemicals (GHS), is closely aligned with REACH. We are mindful that measurement may be needed to underpin the CLP classification of many substances due to be notified to ECHA by 3 January 2011, even if they are not subject to REACH registration. In the light of data gathered during the pre-registration phase of REACH, ECHA recognises that the first version of the public classification and labelling inventory may contain many entries with insufficient substance identity, but will be seeking to rectify this by 2013.<sup>6</sup>

In places, this document goes beyond REACH registration issues in seeking to share understanding of wider measurement requirements arising under REACH and CLP. Developing a picture of the overall role of measurement science should help compliance and enforcement activities to be planned as cost-effectively as possible.

However, as time and resources are limited, a number of topics likely to have measurement implications are either not covered or discussed only briefly in this version. Examples include polymers, nanomaterials, crystalline forms, substances in articles, strictly controlled conditions for intermediates, and requirements for analysis to support hazard and exposure assessment. We may extend coverage in future if there is demand. We have not covered the legislation and guidance on

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<sup>1</sup> Regulation (EC) No 1907/2006 *concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)* as amended. Current consolidated text: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2006R1907:20090627:EN:PDF>

<sup>2</sup> Regulation (EC) No 1272/2008 *on classification, labelling and packaging (CLP) of substances and mixtures* as amended. Original act: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:EN:PDF>

<sup>3</sup> Substance information exchange fora (REACH Regulation, Article 29)

<sup>4</sup> As defined by REACH Article 3(20). In general terms, substances that the previous regulatory framework treated as 'existing', which are now coming under detailed scrutiny for the first time

<sup>5</sup> This deadline applies to high-tonnage and certain high-hazard substances, as detailed in Article 23(1) of the REACH Regulation

<sup>6</sup> ECHA, *Draft multi-annual work programme 2011-2013*. 12 March 2010: [http://echa.europa.eu/doc/consultations/work\\_programme/mb\\_03\\_2010\\_public\\_consultation\\_mawp\\_2011\\_2013.pdf](http://echa.europa.eu/doc/consultations/work_programme/mb_03_2010_public_consultation_mawp_2011_2013.pdf)

REACH restrictions because we believe it is relatively clear<sup>7</sup>, but there, as elsewhere, feedback on any measurement-related issues is very welcome.

### 1.3 How we developed this document

In the UK, the Government Chemist<sup>8</sup> has a long-standing duty to advise on the analytical science implications of policy, standards and regulation. Over the last year, feedback from stakeholders, including questions raised at our open event in November<sup>9</sup>, continued to suggest that there are significant uncertainties about the measurement implications of REACH. We therefore undertook to develop further advice based on case studies with industry.

As before<sup>10,11,12</sup>, we appointed an independent consultant<sup>13</sup> to profile measurement issues relating to REACH compliance for several industrial chemical products, in conjunction with companies involved in their supply. Broadly, we considered three further cases as follows:

- An inorganic mineral that disperses and degrades in water
- An unstable multi-constituent organic substance
- An aqueous extract of a plant material.

This document utilises the consultant's findings, together with our own experience arising from involvement with REACH since the early days of policy development. To safeguard confidentiality, we discuss lessons learnt from the industry case studies only in the broadest terms - in fact, only as far as is necessary to derive, validate or illustrate advice.

The measurement implications of REACH are ultimately determined by the legislation, supported by official technical guidance documents<sup>14</sup>; in addition, the ECHA Substance Identity Workshop<sup>15</sup> provided valuable context. We consulted the EU and ECHA sources extensively whilst preparing this document.

**We cannot guarantee that our advice will meet existing or future regulatory requirements. Readers should consult the legal texts, the technical guidance documents published by ECHA, and if appropriate seek their own specific advice.**

The Government Chemist function is funded by the UK Department for Business, Innovation and Skills through the National Measurement Office.

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<sup>7</sup> ECHA, Existing restrictions webpage: [http://echa.europa.eu/reach/restriction/existing\\_restriction\\_en.asp](http://echa.europa.eu/reach/restriction/existing_restriction_en.asp)

<sup>8</sup> The Government Chemist: <http://www.governmentchemist.org.uk/>

<sup>9</sup> *Better analysis: one giant leap toward REACH compliance*. Held in partnership with Humber Chemical Focus and the University of Hull Environmental Technologies Centres of Industrial Collaboration (ETCIC), Hull, 12 November 2009: <http://www.governmentchemist.org.uk/Events.aspx?m=93&amid=830>

<sup>10</sup> Francis J, Scott R and Selby M, Analytical issues relating to chemical substance identity under REACH (March 2008, LGC/GC/2007/016): <http://www.governmentchemist.org.uk/Publications.aspx?m=77&amid=474>

<sup>11</sup> Francis J, Scott R and Selby M, Analytical issues relating to chemical substance definition under REACH (March 2009, LGC/RT/2009/015): <http://www.governmentchemist.org.uk/Generic.aspx?m=77&amid=730>

<sup>12</sup> Francis J, Analytical issues relating to chemical substance definition under REACH: supplement on dyes (March 2009, LGC/RT/2009/016): <http://www.governmentchemist.org.uk/Generic.aspx?m=77&amid=731>

<sup>13</sup> Denehurst Chemical Safety Ltd

<sup>14</sup> ECHA, Guidance documents: [http://guidance.echa.europa.eu/guidance\\_en.htm](http://guidance.echa.europa.eu/guidance_en.htm)

<sup>15</sup> Held in Helsinki, 1 December 2009: [http://echa.europa.eu/news/events/substance\\_identity\\_workshop\\_2009\\_en.asp](http://echa.europa.eu/news/events/substance_identity_workshop_2009_en.asp)

## 2. Questions and answers on measurement implications of REACH and CLP

### 2.1 General

#### 2.1.1 How should I find out about REACH measurement requirements?

The primary sources are the REACH Regulation as amended<sup>16</sup>, and ECHA guidance<sup>14</sup> - particularly the technical guidance document (TGD) on identification and naming<sup>17</sup>. Authoritative advice may be obtained from the UK Competent Authority helpdesk<sup>18</sup>, or from ECHA<sup>19</sup>. The Substance Identity Workshop held in December 2009<sup>15</sup> is a useful source of advice provided directly by ECHA on some of the key measurement requirements.

Intermediaries, including trade associations and reputable independent consultants, are helping to interpret the specific implications of REACH. The UK Government Chemist's role is limited to impartial scientific advice on the analytical measurement implications, and stems from a generic responsibility to advise within our field of expertise rather than from a specific mandate under REACH.

#### 2.1.2 What are the main areas of analytical requirement?

We have been evaluating this question throughout the development of REACH. The legislation depends on analytical measurement in so many ways that we still cannot provide an exhaustive answer, but key areas include:

1. First and foremost, establishing substance identity for the purposes of a REACH registration, or another regulatory submission such as a PPORD notification<sup>20</sup> or an inquiry<sup>21</sup>. Substance identity requirements apply both for substances of well defined composition and UVCBs<sup>22</sup>
2. Showing whether different industrial chemicals are the same REACH substance, and establishing a single joint composition (in addition to the substance identity required from each individual registrant)
3. Providing evidence of structural similarity between substances, to support the read-across of valuable data on physicochemical, toxicological and ecotoxicological properties<sup>23</sup>
4. Deciding which substances qualify as polymers
5. Deciding whether a product is chemically identical to a substance found in nature
6. Process and pre-release quality control to check that substances, mixtures and articles comply with restrictions, limits on SVHC<sup>24</sup>, and potentially authorisation conditions
7. Checking that a variable product continues to meet the specification for a single substance
8. Filling gaps in supply chain data, such as for imported materials - for example, establishing whether they are products of a chemical reaction or deliberate mixtures, before proceeding to

<sup>16</sup> ECHA, REACH legislation: [http://echa.europa.eu/legislation/reach\\_legislation\\_en.asp](http://echa.europa.eu/legislation/reach_legislation_en.asp)

<sup>17</sup> ECHA, Guidance for identification and naming of substances under REACH, June 2007:

[http://guidance.echa.europa.eu/docs/guidance\\_document/substance\\_id\\_en.pdf](http://guidance.echa.europa.eu/docs/guidance_document/substance_id_en.pdf)

<sup>18</sup> HSE, UK REACH Competent Authority: <http://www.hse.gov.uk/reach/compauth.htm>

<sup>19</sup> ECHA, ECHA helpdesk: [http://echa.europa.eu/help/echahelp\\_en.asp](http://echa.europa.eu/help/echahelp_en.asp)

<sup>20</sup> ECHA, Guidance on Scientific Research and Development (SR&D) and Product and Process Oriented Research and Development (PPORD), February 2008: [http://guidance.echa.europa.eu/docs/guidance\\_document/ppord\\_en.pdf](http://guidance.echa.europa.eu/docs/guidance_document/ppord_en.pdf)

<sup>21</sup> Where required prior to registration in accordance with Article 26 of the REACH Regulation

<sup>22</sup> UVCB substances: substances of unknown or variable composition, complex reaction products or biological materials (ECHA, Guidance for identification and naming of substances under REACH, page 10)

<sup>23</sup> Read-across is about predicting hazard properties from chemical structure or reactivity, rather than inferring substance identity or sameness from physicochemical properties (cf. REACH Annex XI section 1.5)

<sup>24</sup> Substances of very high concern, as defined in Title VII of the REACH Regulation

substance identity and the question of whether different suppliers actually deliver the same substance

9. In hazard studies - particularly innovative alternatives to in vivo testing - measuring the dose (identity and stability of the test material) and response (substance transformation and effect)
10. To support toxicokinetic studies as required, for example to improve the robustness of a read-across hypothesis<sup>25</sup>; and in research on the fundamental mechanisms of toxicity (toxicodynamics)
11. Validation and improvement of exposure models by measuring real datasets, typically using environmental or biological samples taken under carefully chosen conditions
12. Regular monitoring of emissions and cumulative chemical burdens, for example to build an exposure assessment<sup>26</sup>, or provide evidence of compliance with the strictly controlled conditions required for the manufacture and use of intermediates
13. Enforcement, such as testing whether a substance is really what it is claimed to be, checking the nature and concentrations of substances in mixtures and articles, and policing restrictions.

### 2.1.3 How can I gauge the level of effort required?

Experience shows that:

- ECHA expects to see certain basic analytical data (spectra, chromatograms). Substance identity needs to be reported in enough detail for the reader to replicate the analysis
- Sufficient work needs to be performed to enable possible discussions about the sameness of substances, or read-across with similar ones
- The behaviour of a substance in water and biotic conditions needs to be known, to allow environmental fate and toxicokinetic assessments to be made (the exact requirements may depend on tonnage).

### 2.1.4 How can analytical science help counteract compliance costs?

Analytical measurement can offer benefits over and above bare compliance with the law. It can:

- Provide evidence that a substance is exempt from registration
- Show that certain hazard tests are not required
- Be a crucial component of alternatives to costly and undesirable animal testing
- Show that a product is suitable for specialised, high value uses, or has wider market potential.

A planned approach to the analytical work is advisable to:

- Minimise costly replication, by optimising the experimental design and relative timing of studies
- Avoid paying urgency premiums, and potential enforcement penalties.

### 2.1.5 What about quality assurance?

Compliance with good laboratory practice (GLP) is not a legal requirement for the analytical work. ECHA intends to accept appropriate data generated by in-house laboratories. The level and form of quality assurance that ECHA does expect will become clearer as industry gains more experience with submitting dossiers. Meanwhile we recommend that analytical work conforms with GLP principles, such as internal checking, sign-off by responsible persons and record-keeping.

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<sup>25</sup> Cf. ECHA, Evaluation under REACH - progress report 2009. ECHA-10-R-001-EN, 25 February 2010, chapter 3.1.2.4: [http://echa.europa.eu/doc/progress\\_report\\_2009.pdf](http://echa.europa.eu/doc/progress_report_2009.pdf)

<sup>26</sup> An exposure assessment may be needed to justify the waiving of ecotoxicity tests - cf. ECHA, Waiving information requirements. Webinar, 10 December 2009 - slide 29: [http://echa.europa.eu/doc/press/webinars/waiving\\_information\\_requirements\\_wim\\_de\\_coen\\_echa.pdf](http://echa.europa.eu/doc/press/webinars/waiving_information_requirements_wim_de_coen_echa.pdf)

Although not explicitly required by ECHA, we suggest that confidence in the analytical data could be underpinned by explaining arrangements for the accreditation of laboratory work, staff qualifications and training, how methods were validated, use of appropriate certified or matrix-matched reference materials, the nature and meaning of control experiments, and the handling of measurement uncertainty.

### 2.1.6 Will REACH be enforced in relation to specific substances and mixtures?

The evidence so far is that enforcement will be highly specific and targeted.

The first joint REACH project co-ordinated by ECHA's Forum for Exchange of Information on Enforcement finished at the end of 2009. It focused on checking for the registration or pre-registration of phase-in substances; safety data sheets (SDS) were also inspected. Preliminary data showed that 850 inspections were delivered across 28 countries. The next joint enforcement project will focus on formulators of mixtures. This is conceived as a logical extension of enforcement focused on manufacturers and importers (which is ongoing). Most mixtures are sold on to article producers, but others are consumer products, e.g. detergents, paints, personal care. On-site inspections are planned for 2011.<sup>27</sup>

The UK REACH Competent Authority is launching intelligence-led, substance-specific inspection campaigns. These focus on the duty to register - the 'no data, no market' principle - but are likely to extend to checking compliance with other REACH duties.<sup>28</sup> REACH restrictions are also being enforced in a substance-specific, risk-based manner, and early examples have been publicised.<sup>29</sup>

### 2.1.7 How can science-based disputes be resolved?

Under REACH, there is no officially prescribed referee function<sup>30</sup> devoted to disputes about analytical measurement, whether these arise within industry or between businesses and the enforcement authorities. The Manual of Decisions<sup>31</sup> compiled under the former Notification of New Substances (NONS) legislation may help to resolve some technical points, e.g. as to what spectral and chromatographic details need to be reported.

ECHA has provided information concerning procedural disputes over data sharing.<sup>32</sup> Related guidance suggests that consortium agreements could contain clauses covering dispute resolution.<sup>33</sup>

Dispute resolution in relation to SIEFs has been addressed by an independent legal group<sup>34</sup>. A general finding was that parties will need to deploy imagination and common sense in resolving disputes over REACH implementation.

In the UK, the REACH Enforcement Regulations 2008 point to an arbitration mechanism for determining compensation, or a formal appeals process, in certain circumstances.<sup>35</sup>

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<sup>27</sup> ECHA, Forum decides on checking how formulators comply with REACH. News alert ECHA/NA/09/34, 14 December 2009: [http://echa.europa.eu/doc/press/na\\_09\\_34\\_forum\\_20091214.pdf](http://echa.europa.eu/doc/press/na_09_34_forum_20091214.pdf)

<sup>28</sup> HSE, Enforcement activities of the UK REACH Competent Authority: <http://www.hse.gov.uk/reach/ourwork.htm>

<sup>29</sup> UK REACH Competent Authority (Environment Agency), Environmental aspects of the enforcement of REACH in the UK: [http://www.governmentchemist.org.uk/dm\\_documents/091123RichardHawkins\\_XdQCE.pdf](http://www.governmentchemist.org.uk/dm_documents/091123RichardHawkins_XdQCE.pdf)

<sup>30</sup> Along the lines of the functions fulfilled by the Government Chemist under national legislation to improve safety and protect the public, such as the Food Safety Act 1990, the Agriculture Act 1970 and the Medicines Act 1968

<sup>31</sup> European Commission Joint Research Centre - Institute for Health and Consumer Protection - former European Chemicals Bureau, Manual of decisions for implementation of the sixth and seventh amendments to Directive 67/548/EEC on dangerous substances (Directives 79/831/EEC and 92/32/EEC) - non-confidential version, EUR 22311 EN, July 2006: [http://ecb.jrc.ec.europa.eu/DOCUMENTS/New-Chemicals/Manual\\_of\\_decisions.pdf](http://ecb.jrc.ec.europa.eu/DOCUMENTS/New-Chemicals/Manual_of_decisions.pdf)

<sup>32</sup> ECHA website, Data sharing. 18 May 2010: [http://echa.europa.eu/datasharing\\_en.asp](http://echa.europa.eu/datasharing_en.asp)

<sup>33</sup> ECHA, Guidance on data sharing, September 2007, section 10.7:

[http://guidance.echa.europa.eu/docs/guidance\\_document/data\\_sharing\\_en.pdf](http://guidance.echa.europa.eu/docs/guidance_document/data_sharing_en.pdf)

<sup>34</sup> NautaDutilh, SIEFs and dispute resolution, May 2009, reference 9000001 1 P 467324 / 13 (55049):

<http://chemicalwatch.com/downloads/NautaDutilh%20SIEFs%20and%20dispute%20resolutions.pdf>

<sup>35</sup> Statutory Instrument 2008 No. 2852: [http://www.opsi.gov.uk/si/si2008/pdf/uksi\\_20082852\\_en.pdf](http://www.opsi.gov.uk/si/si2008/pdf/uksi_20082852_en.pdf)

Parties are of course free to seek the opinion of an independent expert. The resolution of some questions, such as around substance sameness, may hinge on an impartial review of analytical data, or on definitive measurement. Recourse to an independent expert may work best if the parties can agree in advance how they will respond to the opinion.

### **2.1.8 Can REACH support science-based innovation and growth?**

ECHA expects to see spectra and chromatograms resulting from the more routine, readily interpretable measurement techniques, which is unsurprising given the scope and timetable for REACH implementation. This does not exclude the submission of data derived from more innovative techniques. Indeed, substance identity requirements will need to be met using whatever techniques and data are scientifically suitable.

The ECHA guidance on mono-constituent and multi-constituent substances does state that 'Spectroscopic and analytical methods are subject to continuous change. Therefore, it is the responsibility of the registrant to present appropriate spectral and analytical data.'<sup>36</sup> For UVCB substances, the guidance highlights the part played by developing insight into how to use methods.<sup>37</sup>

We should not forget that sample preparation is a major factor in determining the validity of spectroscopic and chromatographic techniques, as well as in their smooth running, ease of interpretation and clarity of reporting. Sample preparation continues to offer a great deal of scope for innovation - for example, through novel solvents, optimised chemistries, bio-based and affinity separations, and robust automation. Equally, analytical instrument manufacturers can play a key part in growing capability to tackle complex measurement issues, as well in enabling the generation of valid data more cost-effectively.

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<sup>36</sup> ECHA, Guidance for identification and naming of substances under REACH, pages 24 and 26

<sup>37</sup> ECHA, Guidance for identification and naming of substances under REACH, page 38

## 2.2 Specific

### 2.2.1 What is a REACH substance?

REACH assumes that a substance is not a pure element or compound. Unless a substance is in the natural state, it is effectively whatever results from the manufacturing process, including both (wanted) constituents and (unintended) impurities. The legal definition takes this understanding into account:

'substance: means a chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition'<sup>38</sup>.

As implied by this definition, additives and solvents (including water) should be removed as far as practical when establishing substance identity, unless needed to stabilise the substance.

Substances, including those that result from a chemical reaction, are distinct from mixtures. There is no intentional chemical reaction when a mixture is made.

### 2.2.2 How are substances grouped - and does it matter?

Substances are either 'well defined' by chemical composition, or 'of unknown or variable composition, complex reaction products or biological materials' (UVCB)<sup>39</sup>.

Well defined substances include those that are:

- Mono-constituent: A mono-constituent substance is 'As a general rule, a substance, defined by its composition, in which one main constituent is present to at least 80% (w/w)'<sup>40</sup>
- Multi-constituent: 'As a general rule, a substance, defined by its composition, in which more than one main constituent is present in a concentration  $\geq 10\%$  (w/w) and  $< 80\%$  (w/w)'<sup>40</sup>
- Defined by more than the chemical composition (e.g. some crystalline forms).

These groups and subgroups are important in that they affect the naming of the substance and the mechanics of submitting data to ECHA. The 10 % and 80 % limits in the above definitions are flexible under some circumstances, provided that the registrant justifies the course taken.

Even if a substance is initially ill-defined, registrants are expected to try as far as possible to present it as multi-constituent rather than UVCB.

### 2.2.3 Are natural products exempt?

Substances occurring in nature, and which are not chemically modified, may be exempt from registration if they are also non-hazardous.<sup>41</sup> Measurement may be needed to determine whether any allowable<sup>42</sup> processing leads to chemical changes.

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<sup>38</sup> REACH Regulation, Article 3(1)

<sup>39</sup> ECHA, Guidance for identification and naming of substances under REACH, Chapter 4.1

<sup>40</sup> ECHA, Guidance for identification and naming of substances under REACH, Chapter 2.2

<sup>41</sup> ECHA, Guidance for Annex V - Exemptions from the obligation to register. Version 1, ECHA-10-G-02-EN, 31 March 2010 - pages 18 and 27: [http://guidance.echa.europa.eu/docs/guidance\\_document/annex\\_v\\_en.pdf](http://guidance.echa.europa.eu/docs/guidance_document/annex_v_en.pdf)

<sup>42</sup> Cf. REACH Regulation, Article 3(39)

## Case study

In one of the cases we encountered, a plant material is roasted to obtain a water extract that contains valuable organic fragrance compounds. Registration may not be required if it can be shown that the extract is non-hazardous, and that the constituents retained in it are unchanged by roasting - even though some volatile compounds, which can be regarded as impurities, may have been lost.

The extract cannot be dried without losing valuable constituents, so the solvent (water) can be regarded as part of the REACH substance. This extract is a UVCB substance containing a wide variety of other constituents, including sugars and complex carbohydrates, amino acids, low molecular weight alkyl acids, and inorganic salts. Many of these can support microbial growth, so analytical samples were prepared under sterile conditions.

IR was performed on the plant extract and the crushed plant source material. In both cases, complex spectra were obtained. However, after using the instrument software to subtract the IR signal of water, the spectra appeared the same, suggesting that the extraction process does not chemically modify the natural constituents.

HPLC and GC methods were developed for some of the key constituents, including the main fragrance compound. These constituents can be regarded as measurable indicators of any chemical change that occurs during extraction. In addition, the concentrations of various metals, which are typically present in plant material as counter-ions, were compared by inductively coupled plasma atomic emission spectroscopy (ICP-AES); evidence that no new metals are present after extraction could provide a further indication of identity with the plant source material.

The exemption for substances occurring in nature does not extend to synthetic versions. However, a synthetic form of the main fragrance compound is commercially available, and has been used in medicinal products. On the strength of analytical work (in this case GC-MS) to establish the extent and nature of similarities between the two forms, hazard data already available for the synthetic molecule could help to justify waiving some test requirements if the plant extract does have to be registered.

### 2.2.4 How detailed does the analysis need to be?

All constituents and impurities<sup>43</sup> (including isomers and by-products) which are known to make up 1 % or more of a substance should be identified and quantified. In addition, impurities should be identified and quantified wherever the product owner is aware that they pose a potential risk - even below 1 % where they affect the hazard classification and/or PBT<sup>44</sup> assessment of the substance. It is also important to highlight the total number and concentration range of unknown impurities.

Additives which cannot be removed prior to analysis should be identified and quantified. Unless they have a stabilising function, treat them as impurities.

For REACH, quantification means providing the typical concentration, together with the upper and lower limits. The unit of concentration (typically w/w) needs to be selected in IUCLID<sup>45</sup>, so laboratories should be made aware before planning the analysis that they are constrained in this respect by the software options available.

At least 99 %, and ideally 100 %, of the substance should be accounted for. Any unknown impurities need to be listed, with their concentration ranges, in order to complete the mass balance. In practice, we find that it is generally feasible to establish the purities of relatively refined chemicals in the range of 99-100 % with uncertainties in the region of 0.5 % or below. For the avoidance of later doubt, we suggest that laboratories could record and retain evidence (such as extract and

<sup>43</sup> An impurity, or unintended constituent, typically makes up less than 10 % (w/w) of the bulk.

<sup>44</sup> Persistent, bioaccumulative and toxic

<sup>45</sup> International Uniform Chemical Information Database - the software platform that enables REACH and other regulatory dossiers to be prepared: <http://iuclid.echa.europa.eu/>

residue weights) showing that all fractions of the sample have been analysed so as to give a mass balance of the entire substance.

## 2.2.5 What are the core measurements required by the regulator?

The requirements in Annex VI section 2 of the REACH Regulation must be met unless a science-based justification is provided. Most have been carried forward from earlier EU chemicals legislation.

ECHA guidance<sup>46</sup> points in particular to:

- Ultraviolet-visible absorption (UV-Vis) spectra (at pH range of 4-9 if water soluble<sup>47</sup>)
- Infrared (IR) spectra
- Nuclear magnetic resonance (NMR) spectra and/or<sup>48</sup> mass spectrometry (MS) data
- Gas chromatography (GC) and/or high-performance<sup>49</sup> liquid chromatography (HPLC).

The spectral data are intended to confirm structure, and the chromatographic methods to confirm composition, of the substance. Although more sophisticated techniques may be needed to meet substance identity requirements, it is proving important to show ECHA that UV-Vis, IR, proton (or possibly carbon) NMR and appropriate chromatographic methods have at least been attempted. We recognise that it is scientifically valid to challenge any requirement for unnecessary data. Indeed, the REACH Regulation permits registrants to provide a justification where it does not appear scientifically necessary to give information of this kind<sup>50</sup>. However, if any of the above spectra or chromatographic data cannot be provided, there must be a scientific reason. There are few valid reasons not to supply the spectra - lack of access, or suggesting that they are meaningless, has not proven acceptable. Existing data may be unfit for purpose or subject to ownership issues, but, unless otherwise shown, regulators are likely to assume that the registrant can generate their own directly relevant data using the core measurement techniques.

## 2.2.6 Are there specific information requirements for each technique?

ECHA expects to receive certain details about each of the standard techniques:

- For UV-Vis, the concentration of the test substance, cuvette path length, solvent
- For IR, details of sample preparation
- For NMR, operating frequency, nucleus, concentration of test substance, solvent, internal standard, range (which must be suitable - typically 15 ppm for proton NMR), chemical shift integrals
- For GC or LC, the specific method for the substance in hand, including the experimental set-up, preparation of solutions and identity of standards. The details should include the column type, length and diameter; injection volume; mobile phase/carrier gas; GC temperature programme; flow rate; concentrations of HPLC standard solutions; detection technique; and run time.

Quantitation procedures should be fully reported. For example, a table of data could show the assignment of constituents to chromatographic peaks, and the use of peak areas, standards and calibration curves.

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<sup>46</sup> ECHA, Guidance for identification and naming of substances under REACH, pages 24, 26, 29 and 38

<sup>47</sup> Requirement to investigate pH range established through experience with regulatory submissions

<sup>48</sup> Cf. REACH Regulation, Annex VI, section 2.3.5. At present, NMR is generally viewed as definitive by ECHA, but the use of MS could be justified on a case-by-case basis

<sup>49</sup> The REACH Regulation itself (Annex VI, section 2.3.6) specifies a high-pressure liquid chromatogram. We believe the terms to be interchangeable for REACH purposes

<sup>50</sup> Annex VI, note 1 and section 2

## 2.2.7 What other data may be needed?

Depending on circumstances, including the chemistry of the constituents, and particularly if the core techniques listed in Annex VI section 2 of the REACH Regulation are unsuitable, ECHA will look for complementary data which help to confirm structure and define the whole substance, for example:

- NMR based on other elements present, e.g. carbon, phosphorus or fluorine. For example,  $^{13}\text{C}$  NMR may indicate the ratio of positional isomers present in a multi-constituent substance. ECHA has recognised the value in making good use of information-rich NMR spectra<sup>51</sup>, and of more advanced experiments such as DEPT<sup>52</sup> in contributing to molecular structure determination
- Valid constituent separation techniques other than GC and HPLC to confirm the composition
- For inorganic substances, elemental analysis such as atomic absorption spectroscopy (AAS) or X-ray fluorescence (XRF). Also crystallographic techniques, such as powder X-ray diffraction (XRD), which will usually be needed to confirm the name of a mineral
- Measurement of metals and other counter-ions, e.g. by potentiometric titration
- Karl Fischer test for water
- Thermal analysis.

However, registrants do not have to develop specialised analytical techniques which would require additional investment. From ECHA's point of view, industry is responsible for selecting appropriate methods and showing that they are suitable; justification should be provided for non-standard techniques. The details provided should be sufficient for the method to be reproduced, including for example sample preparation, instrument operating characteristics, calibration of the method, and quantification of results.

## 2.2.8 Should I measure isomers?

The concentrations of isomers should be submitted, whether they occur in a characteristic ratio within a multi-constituent substance, or are present as impurities.

For optical isomers, see question 2.2.15.

## 2.2.9 Do ionic substances present special problems?

ECHA expects all parts of a substance, including the inorganic counter-ions of organic moieties, to be identified and quantified. The identity of ions needs to be chemically specific - for example, chloride or another specific halide should be named, rather than simply reported as  $\text{X}^-$ .

### Case study (continued under Question 2.2.17)

A silicate substance - essentially a mineral material - is used as a flocculant and clarity enhancer for personal care and domestic products. It contains sparingly soluble particles, so the exchange of internal counter-ions with water may be restricted. This could bias some measurement methods. Best efforts are required to establish the identity of the substance, with appropriate use of data on the particle structure itself or the composition in pure water<sup>53</sup>. A destructive elemental analysis technique such as AAS can be used to establish the empirical formula, but does not specifically confirm the arrangement of the atoms and ions in the intact substance. XRD provided basic fingerprint data, suitable for discussing sameness between commercial products in the context of SIEF formation. More information was obtained by employing dialysis to drive the dissociation of

<sup>51</sup> ECHA, Substance identity webinar for Lead Registrants, 25 January 2010: [http://echa.europa.eu/news/webinars\\_en.asp](http://echa.europa.eu/news/webinars_en.asp)

<sup>52</sup> Distortionless enhancement by polarisation transfer in  $^{13}\text{C}$  NMR

<sup>53</sup> The latter is perhaps more relevant, if it reflects the use of the substance and its potential distribution in the environment. A substance as defined by Article 2(1) of the REACH Regulation excludes 'any solvent which may be separated without affecting the stability of the substance or changing its composition'

the substance toward completion; the ionic composition of the dilute dialysate was then determined by highly sensitive inductively coupled plasma mass spectrometry (ICP-MS).

Beyond substance identity, the potential bioavailability of the counter-ion may have implications for biota or environmental systems. Bioavailability of the bulk of the substance could also be affected by structural changes resulting from ion exchange with the wide range of charged species potentially present in natural media. Further studies of the substance, including its behaviour in hard and soft waters, acidic and alkaline media, may therefore depend on the analytical monitoring of ionic concentrations and exchange trends over time.

### **2.2.10 Can I rely on traditional methods, low resolution data, 'fingerprinting'?**

We believe that all these data sources can play a valuable part in REACH compliance, but in many cases they are unlikely to provide enough information to complete and submit a dossier successfully.

Some traditional methods are highly sensitive and specific. Provided that they are appropriately validated, in our view they could be scientifically justifiable if they can be applied to hazardous constituents or impurities which may occur in a substance at levels of concern.

Low resolution data and 'fingerprint' patterns derived from any applicable technique could be used to evaluate the sameness of substances from different companies, and thus contribute to SIEF formation. This would limit the initial disclosure of compositional detail - or at least, its assignment to chemical structure - with the advantage that pre-SIEF discussions could progress while collaborators build trust, or participating competitors develop suitable data protection arrangements. However, pattern-matching approaches are often based on libraries of spectra built up over many years, and caution in their use is appropriate when it comes to decision making. We recommend validation of the primary reference underlying any significant library match.

'Broad brush' data could also help provide a shared profile of the substance for the joint registration dossier. Low resolution profiling may give clear-cut evidence as to the presence or absence of a key constituent that would affect the EC Inventory name and number of the substance. Likewise, having just enough data to quantify a key impurity may facilitate the sharing of hazard testing data, or help determine the CLP classification.

### **2.2.11 What substance identity data must each individual registrant provide?**

The identities of the main constituents, which contribute to the substance name, are usually the same for all members of a SIEF, but their concentration ranges may differ. Registrations may cover products derived from a variety of starting materials and processes, so the impurity profiles may differ in nature as well as concentration.

Each individual registrant's dossier needs to include data on their substance, as manufactured:

- Purity, based on the concentrations of the main constituents
- Impurities.

The individual specification should be within the scope of the material used for hazard tests on the substance. Registrants will be aware that the impurity profile can provide clues to production methods, including the starting materials, solvents, catalysts and other processing aids, and may choose to flag certain details of the submission as confidential.

## 2.2.12 How to report variability in the substance specification?

In real life, the concentrations of all constituents will be subject to some degree of variability. The concentration ranges of the constituents should be provided. Also, more than one composition can be reported, for example to reflect different grades of a single substance, or manufacturing sites.<sup>54</sup>

It is not usually necessary to prove variability by submitting multiple chromatograms. However, if the same substance is obtained from different suppliers, any differences in the impurity profiles should at least be described.

## 2.2.13 How to establish the identity of a UVCB substance?

In this case, there is no hard and fast distinction main constituents and impurities. Registrants are expected to carry out the usual spectroscopic and chromatographic analyses, and to provide whatever evidence they can about the make-up of each constituent, aiming to report its identity, typical concentration and range. This is expected for constituents amounting to 10 % or more of the substance. All constituents that affect classification and/or PBT assessment should also be identified. Unknown constituents should be described generically - for example, in groups based on clear features of the analytical data (e.g. by chain length, functional group, or double bonding pattern).

## 2.2.14 How can substance stability issues be tackled?

Instability can 'move the goalposts' during substance identity studies, and is likely to be even more of a problem during hazard testing under a range of environmental and biological conditions. Precautions will be needed throughout sampling, transportation, storage, sample preparation and measurement to preserve the 'dossier substance'<sup>55</sup> both qualitatively and quantitatively. Breakdown products are likely to complicate the analytical data, and may need to be considered when assessing the fate and consequent risk associated with the dossier substance. Destructive methods of analysis will be of limited value in this situation because they will tend to blur the distinction between a substance and its breakdown products.

Part of the analytical chemist's skill lies in knowing which sources of uncertainty in the measurement process may be significant for a particular substance, and how to control them. Experienced scientists will be able to recognise and control the potential effect of variables such as timing, temperature, pH, moisture, air, dilution, the sample container, interactions between constituents and impurities, and stabilising additives. Laboratory procedures can often be performed under cryogenic, desiccative or anoxic conditions. Control experiments can be performed to monitor and compensate for substance breakdown.

### Case study

One of the substances we studied was manufactured by reacting several starting materials in a particular order, as is often done to produce functional organic structures that perform specific tasks in mixtures such as lubricants, paints and adhesives. This complex structure was unstable in water and damp air, reverting back to starting materials including amines and alcohols. Results from the standard substance identification techniques - UV-vis, IR, NMR and chromatography - were difficult to interpret (although HPLC was of some use to confirm the partition coefficient and adsorption coefficient range). Performing UV-vis over a range of pH values established that the substance was more stable under alkaline conditions. HPLC-MS was subsequently performed at pH 8 in 20:80 (v/v) water:acetonitrile. The results provided evidence for the theoretical structure and degradation pathways of the substance, but it remained challenging to assign peaks between the dossier substance, residual starting materials and similar breakdown products.

<sup>54</sup> ECHA, Data submission manual - Part 18 - How to report the substance identity in IUCLID 5 for registration under REACH. ECHA-10-B-27-EN, June 2010, chapter 2.3.Q&A8:  
[http://echa.europa.eu/doc/reachit/dsm18/substance\\_id\\_report\\_iuclid\\_en.pdf](http://echa.europa.eu/doc/reachit/dsm18/substance_id_report_iuclid_en.pdf)

<sup>55</sup> I.e. a substance which is subject to registration through a SIEF, or where applicable to the inquiry procedure or a PPOD notification.

For toxicological and environmental assessment, HPLC studies were refocused on breakdown products, including alkylamines and water-soluble alcohols. The data provided sufficient evidence that the substance would break down rapidly in water. Thus the results of hazard tests performed on the breakdown products (as well as the starting materials for the synthesis, which are of similar structure) could be read across<sup>56</sup> to the dossier substance, and only a few additional procedures are required, such as *in vitro* irritation and *Daphnia* immobilisation. Bacterial sludge inhibition and biodegradation tests, which are easy and inexpensive, will also be carried out to confirm that read-across is appropriate.

### 2.2.15 Should I determine optical isomers?

If different optical isomers exist, yes - they count as separate constituents of the substance<sup>57</sup>. IUCLID includes an 'Optical activity' field which prompts for an overview, while further data can be given as part of the description of analytical methods. The format of the reported data may depend on the number of chiral centres in the substance and on the measurement techniques. Modern techniques are often based on the interaction of the constituents with chiral media.

If polarimetry is used, we suggest that laboratories could record the magnitude and sign of the optical rotation for the substance, and provide an interpretation in terms of the proportions of stereoisomers. Measurements on fractions of the substance may be needed to complete the breakdown of its optical activity. Accompanying data would include the measurement conditions - optical wavelength (particularly if not 589 nm), optical path length, concentration of the measurand, solvent, temperature - and other details of the method, e.g. instrument, sample preparation, blanks, standards and controls, replication, concentration dependence.

### 2.2.16 Should I generate data on surface chemistry?

New requirements for safety data sheets, which amend REACH Annex II, state that appropriate and available safety information on surface chemistry should be indicated.<sup>58</sup> We would welcome views on the need to develop advice about suitable analytical approaches.

### 2.2.17 Are there special requirements for substances in the nanoform?

In 2007, ECHA guidance stated: 'The current developments in nano-technology and insights in related hazard effects may cause the need for additional information on size of the substances in the future. The current state of development is not mature enough to include guidance on the identification of substances in the nanoform in this TGD.'<sup>59</sup>

Clearly the situation is evolving, and likely to continue doing so. ECHA recently published guidance on data submission for nanomaterials.<sup>60</sup>

#### Case study (see also Question 2.2.8)

One issue will be the clear definition of substances within scope. For example, at concentrations below 1 000 mg L<sup>-1</sup>, mixtures of a certain silicate substance with water are clear, but could be described as nano-suspensions because the substance does not fully dissociate into the dissolved state. A side-effect of this colloidal character is that chromatography cannot be performed; the value of UV-Vis, IR and NMR is also questionable, as meaningful interpretation may prove challenging. At present we are unsure whether such a substance might be regarded as in the nanoform.

<sup>56</sup> Read-across is the inference of properties using information from structurally related substances (REACH Regulation, Article 13; Annex XI section 1.5; and *passim*)

<sup>57</sup> ECHA, Data submission manual - Part 18 - How to report the substance identity in IUCLID 5 for registration under REACH. Chapter 2.3.Q&A4

<sup>58</sup> Regulation (EU) No 453/2010 amending Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), Section 3 (pages 7 and 27):

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:133:0001:0043:EN:PDF>

<sup>59</sup> ECHA, Guidance for identification and naming of substances under REACH, page 28

<sup>60</sup> ECHA, IUCLID 5 guidance and support - Nanomaterials in IUCLID 5.2. Version 1.0, 1 June 2010:

<http://iuclid.echa.europa.eu/index.php?fuseaction=home.documentation#reachmanual>

## 2.2.18 ECHA looks for consistent substance identity data. What does this mean?

Registrations are made through the dedicated IUCLID software. ECHA is liable to reject a submission unless the data entered in the substance identity fields (1.1, 1.2 and 1.4) of the IUCLID dossier preparation software are consistent, and enable the substance composition to be verified. For example, the substance name (IUCLID section 1.1) and substance identity summary (section 1.2) need to take account of the number and concentration of identified components. If reported techniques yield different types of compositional data, for example on counter-ions or certain groups of constituents, this should be explained.

The Agency will also check that substance identity - including constituents, impurities, additives, analytical data and the description of methods - is consistent between registrants, within each joint registration for a single substance, as well as between different registrations which perhaps ought to be for the same substance. But it is not mandatory for all registrants of a single substance to use the same methods.

## 2.2.19 Have you any practical tips on submitting analytical reports?

Based on current experience, we recommend:

- Use the same sample for all analytical work if possible. Otherwise, establish sameness by analysing all available samples at the same time (under identical measurement conditions)
- Record the substance name (consistent with the nomenclature to be used for registration), a batch number or laboratory code with dates, identity of the facility where the analysis took place, and details of equipment, sample preparation, and methods. A certificate of analysis format could be used to structure the information
- ECHA is liable to reject dossiers unless they contain all the standard spectra, and as much detail as is necessary to replicate the measurements - particularly for quantitative procedures such as chromatography
- Write analytical reports as if they were intended for the sales manager - they need to be legible, relatively easy to understand, and show that they relate to the material actually being supplied; structures and reaction mechanisms are also good as they will help provide a picture of the substance and possible by-products
- Try to get all the spectra into one report to attach to the IUCLID file. Although it is possible to create repeat blocks to add separate files, in practice a single spectra report is the best way. The chromatography and other analysis should again be condensed into a single report and attached to the IUCLID section asking for these details.

## 2.2.20 What measurement is required for a CLP notification?

The CLP obligation to notify classification and labelling to ECHA applies to a wider range of substances than REACH.<sup>61</sup> The identity data that actually need to be submitted for each substance within this scope are a subset of the REACH requirements, as they are specified by section 2.1 to 2.3.4 of REACH Annex VI.<sup>62</sup> The notification must include at least one entry defining a composition (i.e. listing constituents, impurities and additives) for the whole substance<sup>63</sup>, including qualitative and quantitative data. The underlying evidence base, consisting of spectra, chromatograms and a self-sufficient description of the analytical methods, does not need to be submitted. However, we suggest that laboratories do record and retain all the underlying details, in case the authorities ask to inspect them.

<sup>61</sup> ECHA, Practical guide 7: How to notify substances in the Classification and Labelling Inventory. ECHA-10-B-01-EN, 19 May 2010 - chapter 2.2: [http://echa.europa.eu/doc/publications/practical\\_guides/pg\\_7\\_clp\\_notif\\_en.pdf](http://echa.europa.eu/doc/publications/practical_guides/pg_7_clp_notif_en.pdf)

<sup>62</sup> ECHA, Introductory guidance on the CLP Regulation. ECHA-09-G-01-EN, 25 August 2009 - page 78: [http://guidance.echa.europa.eu/docs/guidance\\_document/clp\\_introduutory\\_en.pdf?vers=24\\_08\\_09](http://guidance.echa.europa.eu/docs/guidance_document/clp_introduutory_en.pdf?vers=24_08_09)

<sup>63</sup> ECHA, Data submission manual - Part 12 - How to prepare and submit a classification and labelling notification using IUCLID. ECHA-10-B-02-EN, March 2010, chapter 5.4: [http://echa.europa.eu/doc/reachit/data\\_submission\\_manual\\_12\\_c&l.pdf](http://echa.europa.eu/doc/reachit/data_submission_manual_12_c&l.pdf)

The whole substance should be accounted for by the composition data. The upper and lower bounds of the concentration range for each constituent should, as far as possible, be provided.<sup>64</sup> If applicable, provide information on the optical activity and typical ratio of (stereo)isomers.<sup>65</sup>

Preparations for a classification and labelling notification may involve some hazard testing, particularly for physicochemical properties. If so, it may also be necessary to measure and record data showing that the test material is representative of the notified substance.

If different classifications are submitted for the same substance, the reasons should be given.<sup>62</sup> The justification may hinge on data concerning impurities that are relevant for the classification.

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<sup>64</sup> ECHA, Practical guide 7, chapter 4.3

<sup>65</sup> ECHA, Data submission manual - Part 12, chapter 5.6

### 3. Request for feedback

We hope this advice is a useful starting point. Please be aware that any decision to update and improve the document may depend on your feedback. Amendments and comments of all kinds would be most welcome. Please contact:

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We would particularly like to hear about any measurement-related topics and issues that you would like to see addressed in a second edition.