Comments on the draft recommendation of substances for inclusion in Annex XIV

Substance name: N,N-Dimethylformamide (DMF)

Consultation deadline 23 September 2013

General comments

General comments on the recommendation to include the substance in Annex XIV, including the prioritisation of the substance:

The European Diagnostic Manufacturer's Association (EDMA) would like to comment on the prioritisation of N,N-Dimethylformamide (DMF) for possible inclusion in Annex XIV of Regulation 1907/2006/EEC (REACH).

EDMA requests ECHA to recommend against inclusion of DMF on Annex XIV and instead consider other risk management options for DMF as part of the class of polar aprotic solvents, for the following reasons:

- The IVD sector uses only small quantities of DMF under strictly controlled industrial and laboratory conditions;
- Substitution is challenging and might be considered possible only for another polar aprotic solvent which is already listed as a substance of very high concern;
- Both application for Authorisation and actual substitution would be burdensome for our industry which is more than 90% SME– seeking substitution would impact hundreds of IVDs on an individual basis, triggering extensive and complex re-validation and re-registration processes for each assay.

Use and exposure

In vitro diagnostic medical devices (IVDs) provide medically useful diagnostic information by examination of a specimen derived from the human body.

The IVD industry contributes a fraction of the total use of DMF in the EU. Of the total EU volume (10,000 – 100,000 t/y), the IVD sector use is under 15 t/y, or < 0.15%.

DMF is used in the manufacture of IVDs, both as a process chemical and as a component of the final product. This submission focusses on the use of DMF as a process chemical (given that IVDs have an exemption from the requirement to apply for Authorisation where DMF is a component of the final product). EDMA notes that Authorisation could however affect supply of DMF for use in the final IVD.

European Diagnostic Manufacturers Association
Rue Joseph II, 40 - 1000 Brussels
Tel. +32 2 772 22 25
Fax. +32 2 772 23 29
edma@edma-ivd.eu
www.edma-ivd.eu
N° d'entreprise:
VAT BE 0445 309 182

Known as a 'universal solvent', DMF is used in diverse IVD technologies including manufacture of synthetic chromogenic substrates, synthetic diagnostic peptides, diagnostic dyes, conjugates and dissolution of stabilizers used in IVDs. Using synthetic antibodies or synthetic antigens instead of living, actively infectious antigens means running a diagnostic test without risk of infection.

DMF is one solvent in a class of solvents called 'polar aprotics'. Other aprotic solvents include N-methylpyrrolidone (NMP), N,N-dimethylacetamine (DMAc), N,N-dimethylacetamide, and dimethylsulfoxide (DMSO). They are solvents that dissolve both polar reactants (such as ions) and nonpolar compounds (such as hydrocarbons). Polar aprotics are also miscible in a wide range of organic solvents including water.

These two properties of DMF - ability to dissolve polar reactants and miscibility with water - are the key to the role of DMF in IVD reagents. DMF is required to solubilize small polar molecules called "coupling agents" which link antibodies to other proteins (enzymes used in the detection systems of diagnostic products). At the same time, the proteins being linked (or "conjugated") are soluble in water. DMF provides an environment in which the polar coupling agents are dissolved and can actually link the aqueous proteins.

The REACH Descriptor Process categories which best describe the use of DMF in the manufacture of final IVDs and components used in IVDs are 'PROC 15 – Use as a laboratory reagent', PROC 3 –Use in closed batch process (synthesis or formulation) and PROC 19 – Intermediate. This is a consequence of the small quantities involved at the workplace. DMF is used under closed processes or in fume hoods with no or minimum exposure to the worker and environment well under the indicative occupational exposure limit for DMF set by Directive 98/24.EC. This limited exposure meets the requirements of national legislation such as COSHH in the UK or Ireland's Control of Substances Hazardous to Health Regulations 2003. National legislation follows Community legislation relating to Workers' health legislation: Chemical Agents Directive 98/24/EC, Carcinogens and Mutagens Directive 2004/37/EC and Council Directive 92/85/EEC.

In the wider industry, DMF is used not only in the manufacture of IVDs but also manufacture for:

- Research and development products manufactured under laboratory conditions and where the final product does not contain DMF. These end products are used by cancer research institutes, medical research organisations, universities and pharmaceutical companies to investigate cellular disease processes, with a view to developing better diagnostic tools, pharmaceuticals and therapies;
- Non-IVD industries producing commercially marketed diagnostic tests for forensic or veterinary purposes.

Substitution

Due to its unique properties, it would be difficult or impossible depending on the assay in question, to substitute DMF for another polar aprotic solvent. DMF offers sufficient solubility of many inorganic reagents (e.g. salts, acids & bases) to facilitate chemical reactions that would not be feasible or robust in many other organic solvents. While the possibility for substitution cannot be ruled out, trials already performed within the industry have reported lack of success. As noted in the ECHA background document, safer alternatives are not available. The only possible substitute in an IVD would be another polar aprotic solvent of sufficient strength and characteristics– however these have the same intrinsic properties with respect to reproductive toxicity.

Footnote 3 in the Background Document for DMF notes that the lack of availability of substitutes was not taken into account for prioritisation of DMF for potential inclusion on Annex XIV. At the same time, application for Authorisation necessitates testing to find substitutes where possible. EDMA points out that a regulatory measure to prioritise DMF for Annex XIV is particularly inappropriate when the only potential alternatives are other polar aprotic solvents. Without alternatives, our only options as an IVD Industry would be to repeatedly apply for Authorisation – a costly and resource-intensive exercise as is explained below – or exit the market for valuable but lower revenue generating products or move manufacturing out of the EU. A different risk management option which does not force substitution should be found which regulates uncontrolled exposure of all polar aprotic solvents rather than providing a different regulatory solution for each substance.

Application for Authorisation would mean conducting studies to see whether or not substitution is possible. Because each IVD assay is performed for different analytes on different biological human samples for different sensitivity and specificity parameters, candidate substitutes would need to be tested for on an assay-by-assay basis. It would necessitate extensive studies to screen candidate replacements to ensure no change in product performance – in particular sensitivity and specificity testing. Without sufficient testing, the risk arises to have either false negative or false positive tests, which has tremendous and possibly fatal consequences for patients and the health of the population.

Should an appropriate substitute be found, the next step would be re-validation testing performed on an assay-by-assay basis. Re-validation means:

- Testing of large populations of patients to ensure rare variations in the blood proteins of some patients would not interfere with the safe diagnostic performance of the test, leading to potentially fatal consequences for the individual patient, e.g. in a malaria or gonorrhoea test;
- Full stability trials on 3 lots of the reformulated component to ensure the replacement did not adversely impact the products' shelf lives. In many cases, accelerated stability tests will

neither be practicable nor possible necessitating real time tests which may result in additional chemical wastes and delays in product availability of 1-2 years. Without a stable IVD with shelf life which lasts months or even years, diagnostic tests cannot be manufactured centrally and transported across the healthcare market in Europe and globally;

- Relicensing in certain markets both EU and non-EU, leading to protracted introduction time and a complex implementation pathway for the products;
- The huge cost to IVD products for validation and registrations could mean decisions to remove some products from the market or manufacture outside EU;
- Considerable time and resources to implement a portfolio re-design per impacted product diverted from re-investment into further innovation in diagnostic testing.

Application for Authorisation would necessitate the IVD industry checking if substitution is possible. This check would necessitate the extensive sensitivity, specificity and stability testing described above. Therefore the application for Authorisation itself would be a significant burden on our industry which would potentially be prohibitive, jeopardizing the supply of IVDs for health institutions, blood banks and patients.

Furthermore, IVD manufacturing is impacted during this same timeline by the proposed prioritisation of 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated (4-tert-OPnEO) which, if listed on Annex XIV, would considerably increase the complexity and time needed to address identification of substitutes and redesign products. In some cases, both (sets of) substances are included in the manufacture or formulation of the finished IVD products. It is not feasible for one industry to plan for the substitution of multiple different substances that are used in IVDs on the basis that global supply of these devices must be maintained and where validation processes (if viable alternatives exist) are estimated to take up to 10 years for a single substitution. The complexity of preparing for several substitutions would significantly impact the IVD industry.

Distortion of EU market and disproportionate impact on SMEs

As over 90% of the European IVD industry is made up of SMEs, the disproportionate cost of applying for Authorisation and in particular the necessity to divert R&D resources into seeking substitution – would fall on those least able to pay for it. Suppliers may choose not to apply for Authorisation in order to market the relatively small volumes of DMF used by the IVD industry, the amount of material being too small to justify the cost. The cost of application could fall wholly on the IVD industry.

Authorisation would affect the ability of European companies to compete in our own market. Third country manufacturers exporting IVDs into Europe and using DMF as a process chemical would be unaffected by the Authorisation requirement. Europe has a strong IVD manufacturing base however this measure could encourage manufacturing to move outside of the EU. It is important that the

healthcare industry continues to have access to DMF at rates determined by the market in order for Europe to maintain its leadership in healthcare innovation.

Any substitution (if possible) would trigger re-validation and re-registration of hundreds of products. The €10.8 billion market revenue generated by the European IVD industry only makes up 0.8% of total health care expenditure in the EU (2011 figures), however Member States could see costs rise considerably or access to new innovative products disrupted regardless if Authorisation is granted or a substitute is found. Because re-validation/verification and re-registration would be required for impacted IVDs the substitution requirements of authorisation would hit SMEs disproportionately, affect the competitiveness of European IVD manufacturing and impact on the availability and cost of diagnostic medical products.

The cost and resources needed for re-validating/verifying hundreds of IVDs manufactured in Europe due to the use of relatively small quantities of DMF – for which the only substitute would be another polar aprotic solvent – seems disproportionate indeed to the intended policy outcome which is to manage the exposure risk to worker health and safety. This is already strictly controlled in IVD manufacturing under laboratory conditions and according to EU and national legislation governing exposure of dangerous chemicals. Given the hugely positive impact which the use of DMF has for diagnostics and healthcare and the lack of feasible alternative for a non-SVHC substance, EDMA requests that ECHA find a different risk management option for DMF and indeed for the group of polar aprotic solvents.

Transitional arrangements (Application date(s) and Sunset date(s))

Comments on the proposed dates:

EDMA does not support Authorisation as the most appropriate risk management option for the reasons mentioned under the 'General Comments' section. If the EU should regardless decide to proceed with including DMF on REACH Annex XIV, the IVD sector would require a 7-10 years' transition time considering the hundreds of products which would be impacted, the majority SME nature of our sector, and the extensive re-validation and re-registration required both in the EU and internationally.

IVD manufacturing is impacted during this same timeline by the proposed prioritisation of 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated (4-tert-OPnEO) which, if listed on Annex XIV, would considerably increase the complexity and time needed to address identification of substitutes and redesign products. In some cases, both (sets of) substances are included in the manufacture or formulation of the finished IVD products. EDMA therefore requests longer transitional arrangements on the basis that the IVD sector might need to apply for Authorisation for two or more substances critical to the sensitivity and specificity of our diagnostic tests. It is not feasible for one industry to plan for the substitution of multiple different substances that are used in IVDs on the basis that

global supply of these devices must be maintained and validation processes are estimated to take up to 10 years for a single substitution. Should both (sets of) substances be listed on Annex XIV, the IVD industry would potentially need much longer than 10 years to test for candidates and engage in re-validation/registration processes.

Hints:

for more details on the approach used by ECHA for determining the proposed Application dates and Sunset dates, see the document approach for preparing draft Annex XIV entries – section "Transitional arrangements"

please note that the present lack of alternatives to (some of) the uses of a substance or the time estimated to change industrial processes and finalise transition to alternatives is no viable reason for prolonging the application dates or sunset dates for the substance or some of its uses. Such information is however important information to be included in a potential authorisation application, if the substance is included in Annex XIV.

Uses (or categories of uses) exempted from the authorisation requirement (including product and process oriented research and development (PPORD) and maximum tonnage for that)

EDMA does not support Authorisation as the most appropriate risk management option for the reasons mentioned under the 'General Comments' section.

If the EU should regardless decide to proceed with including DMF on REACH Annex XIV, EDMA would request an exemption to use DMF as a process chemical. According to Article 58(2) of REACH:
"[u]ses or categories of uses may be exempted from the authorisation requirement provided that, on the basis of the existing specific Community legislation imposing minimum requirements relating to the protection of human health or the environment for the use of the substance, the risk is properly controlled."

EDMA considers that ECHA should take into account the following directives as they represent specific Community legislation imposing minimum requirements for the protection of human health:

1. Council Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work, in conjunction with Commission Directive 2009/161/EU establishing a third list of indicative occupational exposure limit values in implementation of Council Directive 98/24/EC and amending Commission Directive 2000/39/EC.

Directive 98/24/EC establishes (Article 1(1)) "minimum requirements for the protection of workers from risks to their safety and health arising, or likely to arise, from the effects of chemical agents that are present at the workplace or as a result of any work activity involving chemical agents". Particularly, the Directive applies where (Article 1(2)) "hazardous chemical agents are present or may be present at the workplace".

The minimum requirements of Directive 98/24/EC are established by introducing, amongst others, "indicative occupational exposure limit values for the protection of workers from chemical risks" (Article 3(2)). These limits are adopted at EU level; however, Member States should "take into account" (Article 3(3)) these indicative limit values when establishing national occupational exposure limit values.

Directive 2009/161 lays down such specific limit values in its Annex. DMF is among the substances for which such specific limit values are established. Indeed, as highlighted by the Swedish Chemicals Agency in the Annex XV dossier to identify DMF as an SVHC, "DMF is included in the third list of indicative occupational exposure limit values (IOEL) set up by Commission Directive 2009/161/EU of 17 December 2009".

2. Council Directive 92/85/EEC on the introduction of measures to encourage improvements in the safety and health at work of pregnant workers and workers who have recently given birth or are breastfeeding (tenth individual Directive within the meaning of Article 16 (1) of Directive 89/391/EEC).

Directive 92/85 aims at encouraging "improvements in the safety and health at work of pregnant workers and workers who have recently given birth or who are breastfeeding" (Article 1(1)). It does so by providing that the Commission should "draw up guidelines on the assessment of the chemical, physical and biological agents and industrial processes considered hazardous for the safety or health of workers within" (Article 3(1)). These guidelines must serve as a basis for each employer to conduct an assessment on "the nature, degree and duration of exposure, in the undertaking and/or establishment concerned, of workers" (Article 4(1)). If the result of such assessment reveals a risk for the safety or health of workers, the employer shall "take the necessary measures to ensure that, by temporarily adjusting the working conditions and/or the working hours of the worker concerned, the exposure of that worker to such risks is avoided."

In short, Directive 92/85 in conjunction with Directive 2009/161 establishes minimum requirements relating to the protection of human health resulting from the use of DMF. These requirements guarantee that the risks from the use of DMF are properly controlled, particularly when DMF is used at the workplace, or as a result of a work activity involving chemical agents.

In this respect, EDMA notes that, having regard to the conclusions of ECHA's Draft background document for DMF, the main reason for prioritising DMF for inclusion in Annex XIV of REACH is the potential for significant workers exposure at some stages of the industrial processes.

Therefore, while not supporting Authorisation as the most appropriate risk management option, EDMA considers that, should ECHA recommend the inclusion of DMF in Annex XIV of REACH, this should include an exemption for its use at the workplace, or as a result of a work activity.

If the EU should regardless decide to proceed with including DMF on REACH Annex XIV, an exemption for PPORD up to 10 tons per annum would be required.

Hints:

*mention clearly the **use(s)** or categories of uses that are proposed to be exempted*

*mention the **Community legislation** which is considered to justify the proposed exemption(s)*

*please note the explanations on **preconditions** to fulfilled for considering exemption of uses from authorisation (see the document on approach for preparation of draft Annex XIV entries – section "Uses or categories of uses exempted from the authorisation requirement")*

*if the proposed exemption regards product and process oriented research and development (PPORD), first check whether the use falls indeed under the definition of **PPORD**, and if so include the maximum tonnage proposed to be exempted and provide a justification for your proposal*

*if a use falls under the **generic** exemptions from authorisation, there is no need to propose an additional specific exemption.*

Review periods for specific uses

Comments on uses for which review periods should be included in Annex XIV, including reasons for that:

EDMA does not support Authorisation as the most appropriate risk management option for the reasons mentioned under the 'General Comments' section. If the EU should regardless decide to proceed with including DMF on REACH Annex XIV, the IVD sector would require review periods of 7-10 years in length considering the hundreds of products which would be impacted, the majority SME nature of our sector, and the extensive re-validation and re-registration required both in the EU and internationally.

Hints:

please note that all authorisation decisions will include a case specific review period, based on concrete case specific information provided in the applications for authorisation

if you consider that review periods for certain use(s) should already be included as entry in Annex XIV and not decided upon case by case, then mention clearly the respective use(s), the proposed review period(s), and sufficient information justifying the setting of an upfront review period