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N,N-Dimethyl Formamide European Restriction Demands Solvent Substitution in Research and Development

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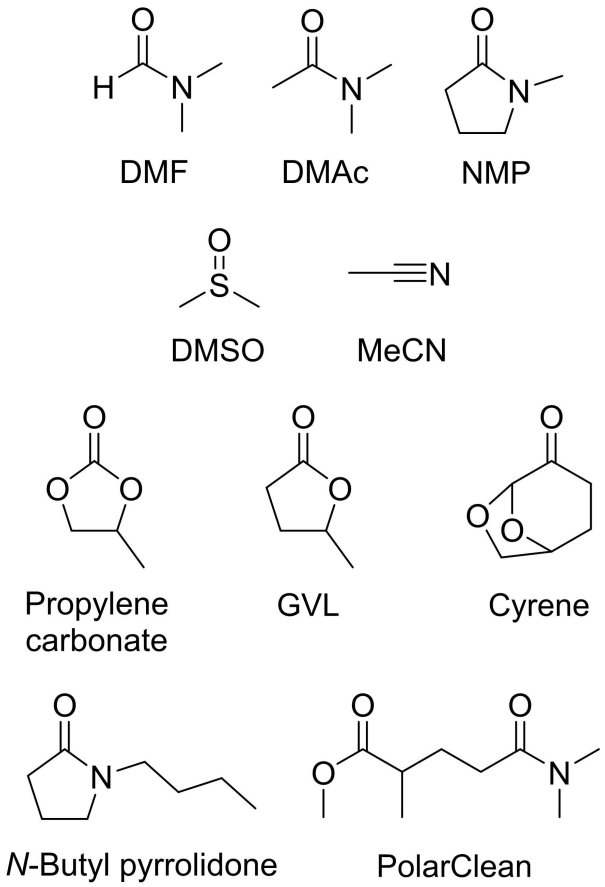
As of December 2023, the use of common solvent *N,N*-dimethyl formamide (DMF) will be restricted in the European Union because of its reproductive health hazard. Industrial facilities must comply with stricter exposure limits, and researchers are recommended to find alternative solvents. Here we explain the restrictions on DMF, which disciplines are affected, and how to substitute DMF to keep research and development commercially relevant.

Solvent properties

N,N-Dimethyl formamide (DMF) is a dipolar aprotic solvent with varied uses across the polymer and fine chemical industries. Known since the nineteenth century,[1] DMF came into widespread use as a solvent in the mid-twentieth century, especially for the production of polyacrylonitrile fibres.[2] The market for DMF is currently 20–30 thousand tonnes per annum within the EU,[3] making it the most commonly used amide solvent, with a lower price and lower boiling point than the structurally similar *N,N*-dimethyl acetamide (DMAc) and *N*-methyl pyrrolidone (NMP) (Scheme 1). DMF, DMAc, and NMP are all considered to be reprotoxic and are labelled with the health hazard statement 'H360D: May damage the unborn child'.

The physical properties of DMF and the other dipolar aprotic solvents (liquid range, density, viscosity, surface tension, water-octanol partition coefficient, flash point, autoignition temperature, electrical conductivity) are comfortably within the bounds established by common solvents (see Supporting Information, Figure S1). What sets dipolar aprotic solvents apart, making them indispensable to the chemical industries, is their polarity (Figure 1). Dipolar aprotic solvents are defined by their high relative permittivity and are also non-protogenic.[4] Described in terms of the Hansen solubility parameters, the dipolarity (δ_P) of dipolar aprotic solvents is greater than other categories of solvents. Only chlorinated and aromatic solvents have greater dispersion (δ_D) forces, and their hydrogen bonding (δ_H) interactions are the strongest of the aprotic solvents. These characteristics make DMF capable of dissolving polar substances including salts and functionalised polymers. The Kamlet–Abboud–Taft solvatochromic parameters describe solvent polarity in relation to chemical phenomena such as reaction rate



Scheme 1. The chemical structure of *N,N*-dimethyl formamide (DMF) and related solvents. DMAc, *N,N*-dimethyl acetamide; NMP, *N*-methyl pyrrolidone; DMSO, dimethyl sulphoxide; MeCN, acetonitrile; GVL, γ-valerolactone. PolarClean is methyl-5-(dimethylamino)-2-methyl-5-oxopentanoate.

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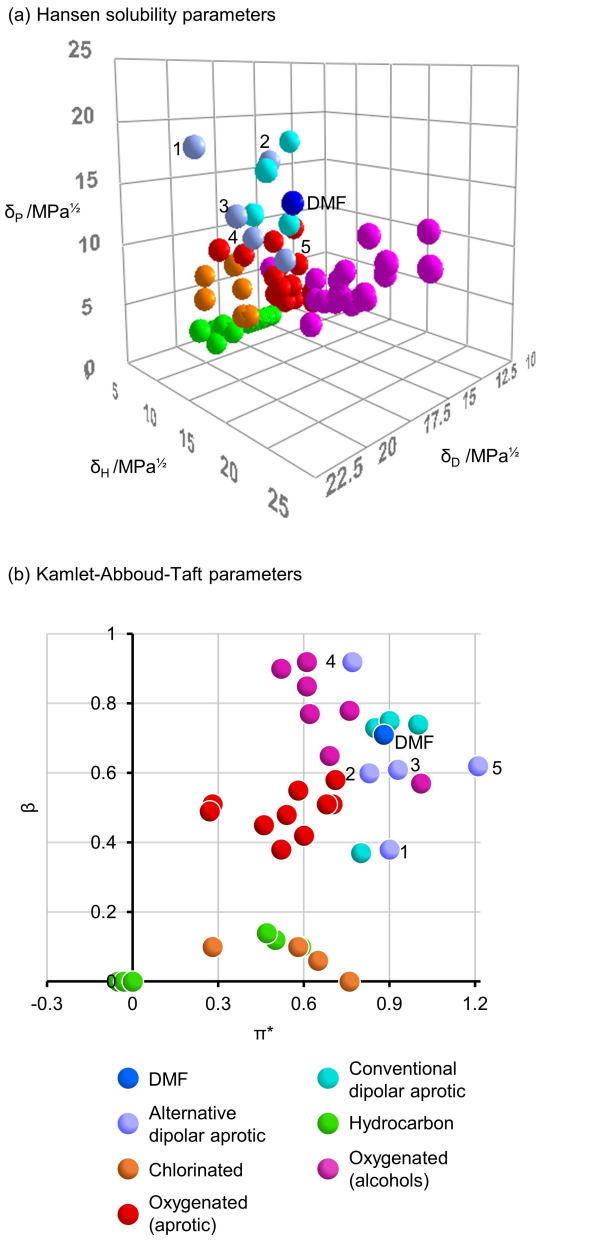


Figure 1. Solvent polarity maps. (a) Hansen solubility parameters. (b) Kamlet-Abboud-Taft solvatochromic parameters. Key: 1, propylene carbonate; 2, γ-valerolactone; 3, Cyrene; 4, *N*-butyl pyrrolidone; 5, PolarClean; blue: DMF; cyan: other dipolar aprotic solvents (DMAc, NMP, dimethyl sulphoxide, acetonitrile); green: hydrocarbon solvents; orange: chlorinated solvents; red: aprotic oxygenated solvents; magenta: protic oxygenated solvents. Data is tabulated in the Supporting Information.

constants. High dipolarity (π*) and high hydrogen bond accepting ability (β) is observed for DMF and the other dipolar aprotic solvents. Thus, reactions that require the stabilisation of electronic charges or protogenic species benefit from the polarity of dipolar aprotic solvents.

Dipolar aprotic solvent health hazards

Although the benefits of DMF are significant, it's reproductive toxicity is well established.[5,6] Damage to the liver is another health concern associated with exposure to DMF.[2,7] This has led to regulatory action being implemented to restrict the use of DMF. Since its introduction in 2007, the European REACH regulation has introduced stricter controls over the use of hazardous substances. One of the chemical categories that has been under scrutiny is solvents.[8,9] It is already illegal for DMF to be present in consumer products e.g. paint removal products,[10] and stricter exposure limits are being introduced for professional settings.[11] From 12th December 2023, DMF shall not be manufactured, used, or marketed unless exposure is limited to 6 mg/m^3 (2 ppm) for exposure by inhalation and 1.1 mg/kg/day for dermal exposure. These thresholds are lower (and therefore stricter) than previous national exposure limits.[7] The EU restriction on DMF use follows the principles used in the restriction of NMP,[9] namely the introduction of stricter exposure limits rather than prohibiting its use. This is because of the perception that the only valid substitutes for DMF are the similarly reprotoxic amides DMAc and NMP etc.[12] Eventually, all the amide solvents are likely to be restricted within the EU in a similar way to DMF and NMP.[13] Conversely, no such action is scheduled for the UK,[14] and DMF is not amongst the ongoing or completed risk evaluations under the USA Toxic Substances Control Act (TSCA).[15]

Academic and R&D uses of DMF

Efforts must be made to avoid using DMF in discovery phase chemistry to avoid regulatory issues or late-stage solvent substitution at pilot scale or beyond. To identify the chemistries most affected by restrictions on the use of DMF, a survey of solvent use in selected journals was conducted with SciFinder^n (see Supporting Information, Figure S2).[16] This exercise revealed that DMF is commonly used at discovery chemistry level, especially in the multi-step synthesis of bioactive molecules. A reaction in DMF is reported within articles published in *Journal of Medicinal Chemistry* and *European Journal of Medicinal Chemistry* at a rate of 4–10 reactions per paper and is increasing The use of DMF is less common in *ChemSusChem* (which publishes sustainable chemistry) but has tripled over ten years (Figure 2). At larger scales (ascertained via the journal *Organic Process Research & Development*), DMF use remains quite common despite the optimisation required to move processes towards pilot plant stage.

To better understand how DMF is used as a solvent in discovery chemistry, a more detailed literature search was conducted (using SciFinder^n), organised by reaction category. Covering the years 2013–2022, examples of DMF being used as a solvent in reaction chemistry exceeded 2 million instances.[16] This is comparable to the frequency that DMAc, NMP, acetonitrile and DMSO combined were used over the same time period. Carbonyl addition was found to be the most common type of transformation, especially amidations which

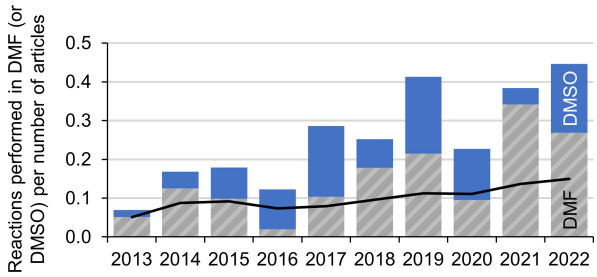
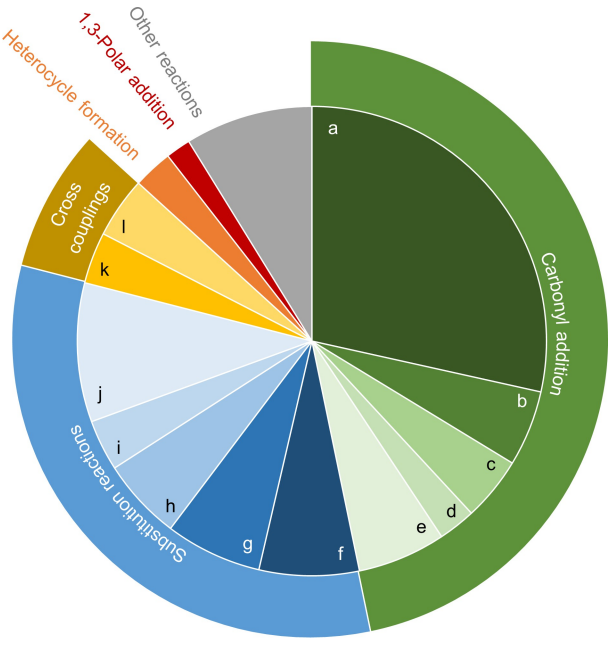


Figure 2. Reaction survey reporting DMF (and DMSO in solid blue) use by average occurrence in reactions per article published in ChemSusChem. Rolling average shown as line. Data for 2022 was incomplete at the time of the survey. See the Supporting Information for further details.

accounted for 28% of reported DMF use (Figure 3). A reliance on DMF for peptide synthesis is suggested, including protection and deprotection strategies, with transamidation and amide hydrolysis also amongst the most frequent applications of DMF. Nucleophilic substitution is also a common use of DMF, roughly equal between S_NAr (and related) reactions, nucleophilic substitution by nitrogen nucleophiles and nucleophilic substitution by oxygen nucleophiles.[17] To a lesser extent, cross couplings are also a popular use of DMF,[18] especially the Suzuki–Miyaura reaction.

It is important to know whether DMF is the main solvent option in the transformations it is commonly used for, which makes the investigation of alternative solvents important, or if there are more common solvent choices, in which case DMF substitution is trivial. DMF is the most popular solvent for amidations and transamidations, typical S_N2 reactions, and amide alkylations (Figure 4). Only for ester hydrolysis (excess water being preferred, not shown in Figure 4) and Suzuki-Miyaura type cross couplings (which are tolerant of many solvents) is DMF a minor solvent.[19] It is interesting that DMF is far more commonly used than DMAc or NMP, even at small scale where cost is less of an issue. DMSO is relatively common for S_NAr reactions and acetonitrile (MeCN) is used across many reactions, but still DMF use is much more prevalent. With a much lower boiling point and weaker hydrogen bonding, synthetic methods may need to be adjusted to accommodate MeCN as a replacement for DMF.

Through the analysis presented in Figure 3 and Figure 4, it can be surmised that DMF substitution in research and development is best focused on amidation and related chemistries. Carbonyl additions are accelerated by low polarity, non-hydrogen bonding solvents,[20] so actually DMF will only need to be used in amidations when solubility is paramount. Most importantly, this includes Solid Phase Peptide Synthesis (SPPS). The SPPS strategy involves the use of a polymeric (solid) protecting group for the *C*-terminal carboxylic group. The solvent must solvate this peptide-resin and cause sufficient swelling to permit access of the free amino termini of the resin-bound peptide chains by the reactants.[21] Low solvent viscosity is important for the efficient diffusion of the solvent into the



a. Amidation
b. Transamidation
c. Amide hydrolysis
d. Ester hydrolysis
e. Other carbonyl addition
f. S_NAr (and couplings)
g. S_N2 (amines)
h. S_N2 (alcohols)
i. Amide *N*-alkylation
j. Other substitutions
k. Suzuki reaction
l. Other cross-couplings

Figure 3. Relative frequency of DMF use in different chemical transformations, grouped by type of transformation.

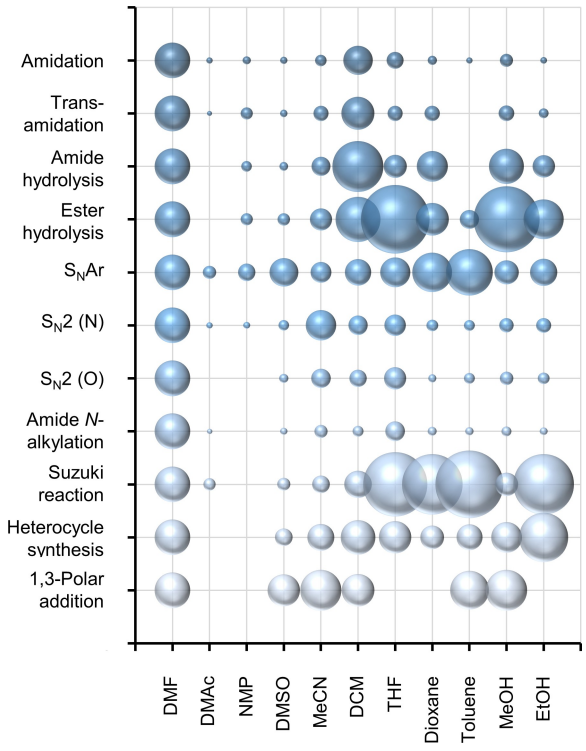


Figure 4. The relative popularity of solvents for the most common uses of DMF in synthetic chemistry (sourced from SciFinder^n). Bubble area represents the number of reported uses compared to DMF between 2013 and 2022. Nucleophilic substitution is divided into amine (N) and alcohol (O) nucelophiles. Literature search definitions are given in the Supporting Information.

solid support. Then, the amino acid sequence can be elongated by repetitive amidation of the incoming amino acid with the α-amino temporally protected with a 9-fluorenymethyloxycarbonyl (Fmoc) group. Removal of the Fmoc group is then necessary to continue the peptide synthesis.[22]

Since the implementation of SPPS with cross-linked polystyrene resins, the amidation steps have typically been carried out in DMF (and to a lesser extent NMP). The preferred Fmoc removal protocol usually requires 20% piperidine-DMF/NMP, and intermediate washings of the resin to remove excess reagents is performed with neat DMF/NMP.[23] So far, a single solvent able to replace DMF/NMP has not been identified, the mixtures of ethyl acetate (EtOAc) with *N*-butyl pyrrolidone or DMSO being the most promising candidates.[24–26]

Industry uses of DMF

N,*N*-Dimethyl formamide accounts for over half of conventional dipolar aprotic solvent use reported in patents (see Supporting Information, Figure S3). The major industry uses of DMF include pharmaceuticals, the production of polyurethane materials, and the spinning of synthetic fibres. Polyurethane coating processes and membrane fabrication have an extra year to comply with the DMF REACH restriction, and the dry and wet spinning of synthetic fibres (e.g. polyacrylonitrile) has a 2 year extension.[11] Within pharmaceuticals, the production of peptide-based Active Pharmaceutical Ingredients (APIs) is very susceptible to regulation controlling the use of DMF because SPPS is the method of choice for essentially all peptide drug discovery projects through to manufacturing. Although water would be the ideal solvent from the perspective of safety and environmental impact, its use in SPPS has been limited to the synthesis of short peptides in an academic context.[27–29] Its implementation in an industrial setting would require a total change of the SPPS paradigm with the concourse of a total different set of protecting groups,[30] and polymeric supports,[31] including the development of bespoke aqueous surfactants.[32] Instead, a number of alternative organic solvents have been investigated, including 2-methyltetrahydrofuran (2-MeTHF),[33] GVL,[34] *N*-butyl pyrrolidone,[35,36] propylene carbonate,[37] methyl-5-(dimethylamino)-2-methyl-5-oxopentanoate (Polarclean),[38] and *N*-octyl pyrrolidone.[39] Most of these solvents have showed better results when used with a polyethylene glycol based solid support, e.g. TengaGel,[40] and ChemMatrix,[41] that are more hydrophilic than the standard polystyrene support. The use of solid supports other than polystyrene has the drawbacks of higher cost and lesser availability, especially in the large amounts needed for commercial peptide production. Higher temperatures are also commonly required to reduce the otherwise high viscosity of the alternative SPPS solvents, adding further practical and economic limitations on the use of alternative solvents at larger scales. However, pharmaceutical manufacturing (and petrochemicals) are already understood to operate within the new DMF exposure limits, and so will not be required to take additional action.[42]

The use of water as a solvent has been resurgent for the preparation of small molecules, especially for micellar reactions. Cross-coupling reactions form the backbone of many small compounds and are often performed in dipolar aprotic solvents such as DMF.[18] Kilogram-scale Suzuki–Miyaura cross-coupling reactions have been successfully performed in water using the surfactant TPGS-750-M to create a hydrophobic micellar environment.[43,44] To avoid reaction solvent altogether, the use of mechanochemistry for aromatic nucleophilic substitution has been developed by the AbbVie pharmaceutical company,[45] meaning the use of dipolar aprotic solvents once synonymous with this class of reaction can be avoided. A ball mill can be used to combine the reactants, sometimes with novel reactivity,[46] and for production scale, reactive extrusion can permit continuous flow mechanochemistry.[47]

Dry and wet spinning of synthetic fibres involves dissolving a polymer in a solvent, then extruding it to form fibres. Dry spinning uses hot air to dry the fibres while wet spinning fibres are extruded into a non-solvent. DMF is the standard solvent for producing polyacrylonitrile fibres by both dry and wet spinning techniques. Polyacrylonitrile fibres are used to make textiles and the majority of carbon fibres.[48,49] It appears that the substitution of DMF in the production of polyacrylonitrile fibres is not viable. The sector is prepared to provide respiratory protective equipment for workers in order to comply with the new exposure limits.[3,42] Various arguments have been provided by manufacturers against the substitution of DMF, including supply chain disruption and cost.[50] Dimethyl sulphoxide (DMSO) has been tested as an alternative to DMF, preferred to the traditional sodium thiocyanate solutions,[51] but ultimately there were insurmountable problems caused by the higher boiling point and viscosity of DMSO, as well as coagulation of the polymer solution.[42] However, academic research indicates that DMSO is suitable for the (wet) spinning of polyacrylonitrile fibres,[52] especially if the moisture content is limited to improve solubility.[53]

The fabrication of productive polyurethane coatings and polyurethane membranes commonly uses DMF as the casting solvent.[12] The relevant regulatory dossiers do not contain much information on why DMF is used and whether there is an alternative.[42] Academic research has identified a number of viable solvents,[54] including blends of solvents tailored to suit different commercial polyurethane products.[55] Some commercial polyurethane coatings are already produced with water-borne coating technologies.[56,57] Bio-based dipolar aprotic solvents Cyrene and γ-valerolactone (GVL) can be used as co-solvents for polyurethane dispersions in water.[58] Conversely, some new, renewable alternatives to standard polyurethane materials continue to use DMF as a processing solvent.[59]

Solvent substitution

It is important to understand the hazards associated with potential DMF replacements to avoid unsatisfactory solvent substitutions. For example, the use of DMAc to replace DMF (temporarily) avoids regulatory control, but because both are

reprotoxic a hazard to health remains. The safety, health hazards, and environmental impact of solvents can be illustrated with a solvent selection guide. The CHEM21 solvent selection guide has been used here (Figure 5).[60] Various properties are considered to create a score in each category, with low scores being preferable. Dipolar aprotic solvents tend to have high flash points that reduces safety risks. Alternatives to DMF (propylene carbonate, Cyrene, GVL, PolarClean, *N*-butyl pyrrolidone) also have high flash points. None of the solvents have any particular environmental hazards (aside from the consequences of being VOCs), and so the environmental impact is derived from the energy cost to distil the solvent for recovery. Dipolar aprotic solvents tend to have high boiling points and energy intensive distillations due to their strong intermolecular interactions. The CHEM21 solvent selection guide considers the neoteric dipolar aprotic solvents to be problematic because of their high boiling points. More importantly, valid substitutes for DMF shall not be reprotoxic or possess equally dangerous hazards. The alternative solvents included in Figure 5 only have minor health hazards, such as eye irritation.

Changes to methodologies may be needed to accommodate solvent substitutions, and this should be pursued, instead of dismissing safer solvents as inferior when reactions have been optimised in DMF or another undesirable solvent.[61–65] Newer technologies, such as micellar reaction environments,[66–67] or solvent-free systems such as powder coatings,[68] are proven but widespread adoption seems to be hindered by the need for initial investment and new expertise.

In the context of peptide synthesis, the development or binary or even ternary solvents is seen as the most promising approach.[24–26] The use of solvent mixtures may improve reaction performance but solvent recovery and separation may be compromised and so it remains important to evaluate the impact of solvent substitution from cradle to grave. Telescoped reactions have also been devised to reduce solvent use, minimising risk and waste.[69] Furthermore, the development of the so-called Liquid-Phase Peptide Synthesis (LPPS) methodology, where a soluble tag is used instead of the solid support, retains the advantages of SPPS but with a great reduction in solvent consumption.[70] Advantageously, LPPS is much more flexible with respect to solvent selection because all reaction stages take place in solution without needing to consider resin swelling.

Generally, the integrated optimisation of a reaction procedure, evaluating solvent and other reaction parameters concurrently, must be performed to arrive at the most advantageous conditions.[71] The greater availability of machine learning and other computational methods is making reaction optimisation easier and more reliable than ever before,[72] and maximising solvent suitability and greenness must be at the forefront of these endeavours.

Solvent	Safety	Health	Enviro.	Ranking
DMF	3	9	5	Hazardous
DMAc	1	9	5	Hazardous
NMP	1	9	7	Hazardous
DMSO	1	1	5	Recommended
MeCN	4	3	3	Recommended
PC	1	2	7	Problematic
Cyrene	1	2	7	Problematic
GVL	1	2	7	Problematic
PolarClean	1	2	7	Problematic
NBP	1	2	7	Problematic

Figure 5. Extract of the CHEM21 solvent selection guide for conventional and alternative dipolar aprotic solvents.

Supporting Information

The authors have cited additional references within the Supporting Information.[73–85]

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: *N*,*N*-Dimethyl formamide · DMF · REACH · solvent · substitution

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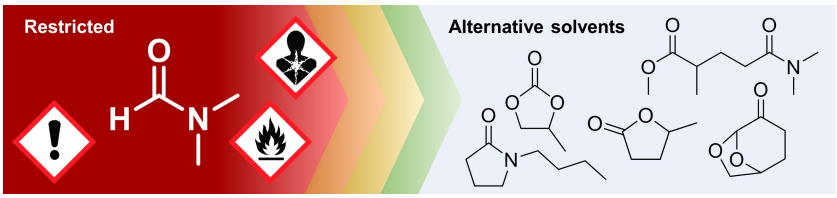

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_N,N_-Dimethyl Formamide European Restriction Demands Solvent Substitution in Research and Development

Time for a change. The use of *N,N*-dimethyl formamide (DMF) will be restricted in the European Union from December 2023 because of its reproductive health hazard. Now is the time to replace DMF in fundamental research so that future processes are not reliant on an obsolete, hazardous solvent.