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Green Solvent Selection for Emulsifiable Concentrate Agrochemical Formulations

Ana Pacheco, Thomas Attard, David Calvert, James Bullock, James H. Clark, James Sherwood,* and C. Robert McElroy*

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ABSTRACT: Emulsifiable concentrates are a common form of agrochemical formulation in which a high quantity of active ingredient is typically dissolved in an aromatic hydrocarbon solvent. There are considerable health and environmental hazards associated with the solvents in emulsifiable concentrates, and finding alternatives was deemed worthy of investigation. Using a combination of *in silico* modeling and experimental testing, a number of alternative safer solvents have been tested for the agrochemicals pendimethalin, prochloraz, and pyraclostrobin. Cyclohexanone, diethyl carbonate, ethyl acetate, and dihydrolevoglucosenone (Cyrene) were observed to be effective solvents.

KEYWORDS: *formulations, agrochemicals, solvents, modeling*

INTRODUCTION

Crop protection products represent a highly innovative and expanding sector. The worldwide crop protection market is estimated to be worth $65 billion.[1] Crop protection products are available in a variety of liquid and solid formulations. Emulsifiable concentrates (ECs), a traditional pesticide formulation, are responsible for a quarter of the total global plant protection market.[2] A typical pesticide formulation is composed of at least one active ingredient with a loading of over 20 wt % and a series of inert auxiliaries including surfactants, organic solvents, stabilizers, and preservatives.[3] The solvent is an essential component of an EC, as it ensures the stability of the other ingredients over a suitably wide temperature range and high concentration. It is also important in this application to facilitate the rapid formation of an emulsion upon dilution in water. Aromatic hydrocarbons are typical solvents for ECs. Besides being nonrenewable petrochemicals, aromatic hydrocarbons are volatile organic compounds (VOCs) possessing high flammability and human toxicity.

The environmental sustainability of ECs is very dependent on the choice of solvent because it represents the majority of the formulation. The solvent is perhaps the easiest component of a formulation to replace for two reasons: (i) solubility can be understood in simple thermodynamic terms and modeled to predict the suitability of different solvents, and (ii) the solvent is inert and in general does not directly affect the action of the active ingredient, and therefore, it can typically be substituted without interfering with the purpose of the product. Therefore, greener formulations can be designed by substituting solvents for less hazardous and lower environmental impact alternatives.

Alternative solvents for EC formulations are known but have not been widely adopted. Vegetable oil-derived solvents can be used in agrochemical formulations,[4,5] as can various amides,[6] including Rhodiasolv Polarclean.[7] This work seeks to rationalize green solvent selection for agrochemical active ingredients by using Hansen Solubility Parameters in Practice (HSPiP)[8] and COSMOtherm software.[9] The software was used to model solubility, and the CHEM21 solvent selection guide was used to evaluate greenness,[10] with the ultimate goal of identifying green, high-performance solvents. Three agrochemical active ingredients were chosen for evaluation: pendimethalin (**1**), prochloraz (**2**), and pyraclostrobin (**3**).

EXPERIMENTAL METHODS

Isolation of Active Ingredients. Pyraclostrobin was isolated from its commercial EC formulation by vacuum filtration. A Buchner funnel with a fritted disc attached to a side-arm Erlenmeyer flask was loaded with silica (60 Å, 220−440 mesh size), to which the EC was added and washed with a vacuum applied. Pyraclostrobin was eluted with ethyl acetate−hexane (1:6). The separation progress was monitored by thin-layer chromatography (TLC) using a UV lamp and phosphomolybidic acid stain.

Pendimethalin was isolated by centrifugation. The commercial EC formulation was diluted with the addition of 3 parts of distilled water and added to a volumetric tube which was placed into a Heraeus MEGAFUGE 40R centrifuge at 3500 rpm for 20 min. The precipitate was separated from the supernatant by vacuum filtration, and the recover solid dried at 105 °C.

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Prochloraz was obtained from Lonza Ltd. and used as received.

Solubility Tests. Solutions of the active ingredients in different solvents were prepared at the same concentration as in the commercial formulation (pyraclostrobin at 19.2 wt %, pendimethalin at 36.3 wt %, and prochloraz at 38 wt %) to give an overall sample weight of 1 g. Solubility was assessed after briefly shaking followed by 4 h on a roller mixer. Solubility was assessed visually using the following scoring: (1) full dissolution and clear solution; (2) almost full dissolution, slightly cloudy solution; (3) good dissolution, small amount of solid material remaining; (4) reasonable dissolution but solid material also clearly visible; (5) some dissolution but significant solid remaining; (6) no dissolution. Solubility scores of 1 and 2 were designated as suitable for the purpose of constructing Hansen spheres, unless otherwise indicated.

HSPiP, 5th edition, version 5.3.06, was used to produce Hansen spheres from experimental solubility data. COSMO files were produced using Turbomole at the BP (B88-VWN-P86) density functional theory level with the triple-ζ valence polarized (TZVP) basis set. COSMOthermX (version C30_1705; COSMOlogic GmbH & Co. KG, 2017) was used to visualize the molecular surface charges, σ profiles, and σ potentials and perform the solubility calculations using the default settings (relative screening compared to solvent with the highest solubility in the original set of 10, by mass fraction). Solubility calculations were modeled at 21 °C, with additional values at 4 and −18 °C presented in the Supporting Information.

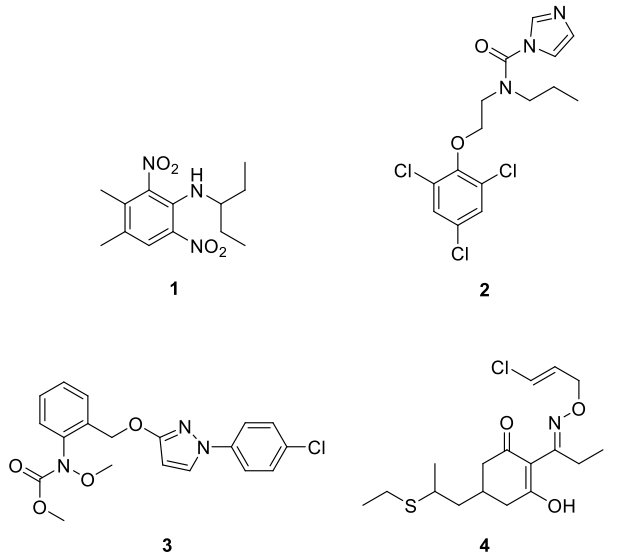
Stability Tests. Stability tests were carried out on solutions of the active ingredients based on guidance in *CIPAC Handbook F* methods MT39, MT46, and MT36.3.[11] Seven-day tests were performed on undisturbed 1 g samples at room temperature (21 °C), 4 °C, and −18 °C, and any solid formation or phase separation was recorded.

RESULTS AND DISCUSSION

Selection of Appropriate Active Ingredients. Four active ingredients were initially chosen for this study (two herbicides and two fungicides): Pendimethalin (**1**), prochloraz (**2**), pyraclostrobin (**3**), and clethodim (**4**) (Scheme 1). **1** is a dinitroaniline herbicide used to control grasses and weeds in cropland. **2** is an imidazole fungicide that is active against a wide range of plant diseases. **3** is a broad-spectrum strobilurin fungicide for cereals. Active ingredient **4** could not be isolated from its EC formulation. Isolated **1**, **2**, and **3** had purities of 99%, 95%, and 91%, respectively, as determined by GC-FID and NMR spectroscopy. Other components of the formulations were not investigated, as the active ingredient was the only product reported in each EC specification.

Solvent Selection. An initial set of 10 solvents was used to investigate the solubilities of active ingredients **1**−**3** (Table 1). All the solvents are recommended or problematic according to the CHEM21 solvent selection guide (avoiding the hazardous and highly hazardous categories).[10] A score of 1 indicates no hazards, while a score of 10 is extremely hazardous across three categories of safety (S), health (H), and environment (E). A variety of polarities were included based on the Hansen solubility parameters of the solvents, these being dispersion forces (δ_D), dipolarity (δ_P), and hydrogen bonding (δ_H). These solvents were also selected as they are all bioderived/bioderivable with the exception of DMPU, although this is recommended as a replacement for NMP and other classical

Scheme 1. Crop Protection Product Active Ingredients



pharmaceutical solvents.[12] As is customary for evaluating solubility with Hansen solubility parameters, the 1 g total weight solutions were ranked 1−6 based on observation, with 1 indicating complete solubility.

The initial solubility tests (entries 1−10, Table 1) showed that cyclohexanone was the only solvent capable of fully dissolving each active ingredient. The least green attribute of cyclohexanone is its environment score of 5, determined by its boiling point of 154 °C, making it a VOC that is reasonably energy-intensive to distill. The only other solvent that completely dissolved **1** was ethyl acetate, which is also considered to be a green solvent. The solubilities of **2** and **3** were high in the majority of the solvents tested.

The solubility data for the initial 10 solvents permitted the construction of Hansen spheres (in green, Figure 1). When the solvents are graphically plotted according to the three Hansen solubility parameters, successful solvents tend to be positioned in a region similar to that of the graph. A sphere can be described that contains the "good" solvents and excludes nonsolvents. The center of the sphere represents the polarity of the solute and can be used to further optimize solvent selection. For active ingredients **2** and **3**, this was successful, defining good solvents as those achieving solubility scores of 1 or 2. The Hansen sphere for **1** is less accurate, as the fit is below 1, *i.e.*, there are good solvents outside the sphere (dotted blue spheres) and a nonsolvent within the sphere (hollow red cube, Figure 1a). This was corrected by only including solvents resulting in solubility scores of 1 within the Hansen sphere (Figure 1b).

The predictive aspects of the modeling were then tested. There are several green and effective solvents for **2** and **3**, so testing was focused on active ingredient **1**. Of the 10 solvents originally screened, only cyclohexanone and ethyl acetate were previously found to produce solubility scores of 1 (equivalent to a ≥36.3 wt % solution). Hansen solubility parameters and COSMO-RS solubility calculations were used to screen potential green solvents, with three candidates selected to extend the testing of **1** and validate the solubility models: butanone (known as methyl ethyl ketone or MEK), 2-methyltetrahydrofuran (2-MeTHF), and dimethyl carbonate. The Hansen solubility values of butanone were calculated to

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Table 1. Hansen Solubility Parameters, Experimental Solubilities, and Greenness Rankings of a Core Set of Solvents (Entries 1−10) and Three Additional Solvents (Entries 11−13)

		Hansen solubility parameters/MPa$^{1/2}$[a]			solubility scores[b]			green scores[c]		
entry	solvent	δ_D	δ_P	δ_H	**1**[d]	**2**[d]	**3**[d]	S	H	E
1	cyclohexanone	17.8	8.4	5.1	1	1	1	3	2	5
2	cyrene	18.9	12.4	7.1	2	1	1	1	2	7
3	D-limonene	17.2	1.8	4.3	3	6	5	4	2	7
4	diethyl carbonate	15.1	6.3	3.5	2	1	1	3	1	3
5	DMPU[e]	17.9	8.4	7.5	5	1	1	1	6	7
6	ethanol	15.8	8.8	19.4	6	1	6	4	3	3
7	ethyl acetate	15.8	5.3	7.2	1	2	1	5	3	3
8	ethyl lactate	16.0	7.6	12.5	5	1	1	3	4	5
9	propylene carbonate	20.0	18.0	4.1	6	1	3	1	2	7
10	γ-valerolactone	16.8	11.4	6.7	5	1	1	1	2	7
11	2-MeTHF[f]	16.9	5.0	4.3	3			6	5	3
12	butanone	16.0	9.0	5.1	1			5	3	3
13	dimethyl carbonate	15.5	8.6	9.7	2			4	1	3

[a]Hansen solubility parameters were taken directly from the HSPiP database.[8] [b]Solubility scores were assessed as described in Experimental Methods. [c]Green scores are from Prat et al.[10] The greenness ranking of γ-valerolactone has been updated since its annex III REACH registration was completed.[13] A default health score of 5 was given in the original paper if a solvent was not REACH-registered. [d]**1**,**2** and **3** refer to the active ingredients pendimethalin, prochloraz, and pyraclostrobin, respectively. [e]DMPU is dimethyl propylene urea. [f]2-MeTHF is 2-methyltetrahydrofuran.

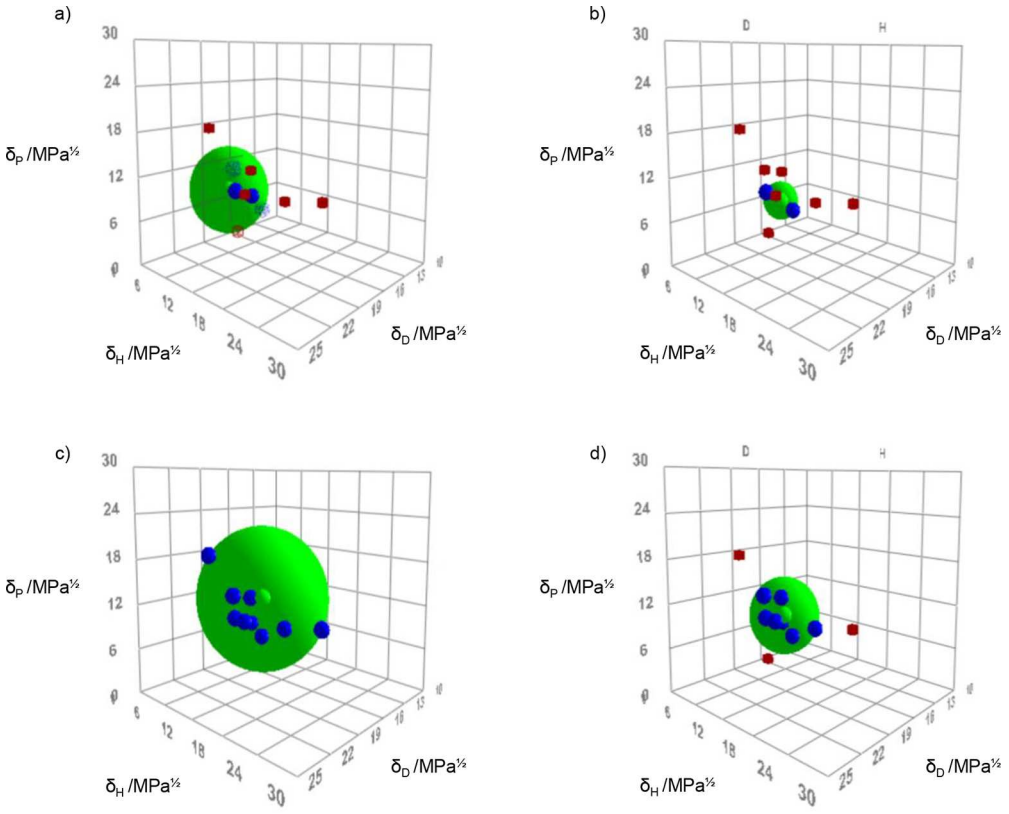

Figure 1. Hansen spheres of (a) substrate **1** including solubility scores of 1 (full dissolution, FD) and 2 (almost full dissolution, AFD, slightly cloudy solution), (b) substrate **1** including solubility scores of 1 (FD) only, (c) substrate **2** including solubility scores of 1 (FD) and 2 (AFD; nonsolvent limonene is obscured by the sphere), (d) substrate **3** including solubility scores of 1 (FD) and 2 (AFD). Solvents imparting the required solubility are represented as blue data points. Nonsolvents are represented with red data points. Green data points represent the solute.

fall within the Hansen sphere of **1** (Figure 1b). Butanone was also predicted by COSMO-RS to outperform the solubilities previously achieved by the initial set of solvents. 2-MeTHF occupies a position in Hansen space just outside the sphere, and dimethyl carbonate is predicted to be a nonsolvent. If the Hansen sphere is defined so that only a solubility score of 1 is acceptable, then the Hansen model was predictive: butanone was observed to be a good solvent, and 2-MeTHF and dimethyl carbonate were not. However, the performance of dimethyl carbonate was superior to that of 2-MeTHF despite their Hansen space coordinates predicting otherwise. Therefore, the predictive quality of the Hansen sphere representing **1** is weak but sufficient to find acceptable solvents. The COSMO-RS solubility calculations were in agreement with

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the Hansen approach, so butanone was correctly identified as a good solvent, but the solubility of **1** in 2-MeTHF was again overestimated compared to dimethyl carbonate (Figure 2).

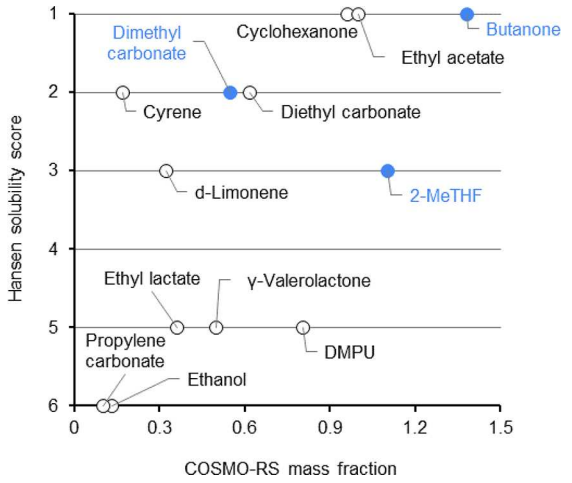

Figure 2. Comparison between experimental solubility (*y* axis, using Hansen solubility scores) and COSMO-RS solubility calculations (*x* axis, calculated values expressed by relative solubility, where 1 is arbitrarily set as the score for the best calculated solubility from the initial set of solvents). Additional solvents are presented with blue (solid) data points.

Experimentally, 2-MeTHF created a dispersion of **1**. Overall, no correlation is found between experimental solubilities and the COSMO-RS predictions (Figure 2). Previous work on the solubility of pesticides in deep eutectic mixtures also found that the predicted solubilities generated by COSMO-RS poorly matched experimental values.[14] It was not necessary to pursue alternative solubility prediction models because greener solvents had been found that fully dissolve **1** in a reasonable timespan (e.g., butanone).

Solvent System Stability. The Collaborative International Pesticide Analytical Council (CIPAC) advocates testing the stability of liquid formulations.[11] Accordingly, the stability of selected solutions was evaluated over 7 days, held at different temperatures (21, 4, and −18 °C). Table 2 lists the lowest temperatures at which the solutions were observed to be stable. Solvents with few hazards and high solubilities of the active ingredients were chosen. Solutions of **1** were not stable below room temperature, with lower temperatures leading to precipitation. Cold storage of **2** and **3** was performed in Cyrene. Alternatively, ethanol is appropriate for active ingredient **2**, and cyclohexanone or ethyl acetate solutions of **3** can also be stored at −18 °C.

Table 2. Lowest Stable Temperatures of Solutions after 7 Days in Storage

	lowest stable temperature/°C		
solvent	**1**	**2**	**3**
cyclohexanone	21	4	−18
cyrene	–[a]	−18	−18
ethanol	–[a]	−18	–[a]
ethyl acetate	21	–[a]	−18
butanone	21	–[b]	–[b]

[a]Low solubility and thus not attempted. [b]Not part of this study.

Solvent Optimization. As Hansen models were shown to be predictive for each active ingredient, a small study was carried out using the solvent optimize function of HSPiP. Two-component solvent mixtures predicted to dissolve the active ingredients **1** and **3** have been postulated from the solvents used in this research. The results are displayed in Table 3, including the ratio between the solute−solvent distance in Hansen space and the sphere radius, known as the "relative energy difference" (RED). Values of RED below 1 indicate that the solvent (or solvent mixture) is located within the Hansen sphere. Solvent systems that suggested a high loading of a solvent already known to function were dismissed (*e.g.*, 97 wt % cyclohexanone, 3 wt % Cyrene for dissolution of **1**). No suitable mixtures were generated for **2** due to the large solubility sphere and the wide range of working solvents. It was found that limonene and propylene carbonate are immiscible, and therefore, this solvent mixture could not be assessed. The design of a solvent mixture for **1** where the components are nonsolvents individually (i.e., 2-MeTHF and Cyrene) but the mixture successfully dissolved the solute was most interesting. This showed, for this active ingredient, that the solubility predictions made via HSPiP are robust, albeit in a limited study.

Table 3. Predicted Optimum Solvent Mixtures

solvent 1	solvent 2	solute	predicted RED	experimental solubility score
limonene (64%)	propylene carbonate (36%)	**1**	0.64	N/A[a]
2-MeTHF (55%)	Cyrene (45%)	**1**	0.74	1
limonene (64%)	propylene carbonate (36%)	**3**	0.78	N/A[a]
cyclohexanone (69%)	propylene carbonate (31%)	**3**	0.89	1

[a]The suggested solvents were immiscible.

CONCLUSION

The solubilities of three agrochemicals were evaluated using Hansen solubility parameters, and the stabilities of those solutions were tested at refrigerator and freezer temperatures. Cyclohexanone can be described as a green, general-purpose solvent for pendimethalin (**1**), prochloraz (**2**), and pyraclostrobin (**3**), although for solutions of **2**, Cyrene and ethanol offered superior low-temperature stability. Compounds **1** and **3** are also highly soluble in ethyl acetate. This set of solvents has minimal hazards and could form the basis of alternative formulations to conventional emulsifiable concentrates that contain toxic hydrocarbon solvents. The prediction of solubility using COSMO-RS was inaccurate. The use of Hansen solubility parameters was preferable, and these parameters were used to contextualize the solubility test results. Next steps for this work would be to include suitable emulsifying surfactant(s) in these promising solvent and agrochemical systems to produce emulsifiable concentrate formulations. These in turn would need to be tested for stability and efficacy.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.3c00211.

NMR data for the purified actives, tabulated relative solubility (mass fraction) calculations, and a general guide to applying HSPiP in similar solubility work (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

James Sherwood − *Green Chemistry Centre of Excellence, Department of Chemistry, University of York, York YO10 5DD, U.K.*; Email: james.sherwood@york.ac.uk

C. Robert McElroy − *Green Chemistry Centre of Excellence, Department of Chemistry, University of York, York YO10 5DD, U.K.; School of Chemistry, University of Lincoln, Lincoln LN6 7DL, U.K.*; orcid.org/0000-0003-2315-8153; Email: cmcelroy@lincoln.ac.uk

Authors

Ana Pacheco − *Green Chemistry Centre of Excellence, Department of Chemistry, University of York, York YO10 5DD, U.K.*

Thomas Attard − *Green Chemistry Centre of Excellence, Department of Chemistry, University of York, York YO10 5DD, U.K.*

David Calvert − *iFormulate Limited, Hull HU12 9SR, U.K.*

James Bullock − *iFormulate Limited, Hull HU12 9SR, U.K.*

James H. Clark − *Green Chemistry Centre of Excellence, Department of Chemistry, University of York, York YO10 5DD, U.K.*; orcid.org/0000-0002-5860-2480

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.oprd.3c00211

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) *Value of the Global Market for Crop Protection 2016 to 2022*. Statista Research Department, 2023. https://www.statista.com/statistics/272493/revenue-of-the-plant-protection-market-worldwide-since-2007/ (accessed 2023-05-22).

(2) *Encyclopedia of Pest Management*; Pimentel, D., Ed.; CRC Press, 2002.

(3) Knowles, A. Recent developments of safer formulations of agrochemicals. *Environmentalist* **2008**, *28*, 35−44.

(4) Chin, C.-P.; Lan, C.-W.; Wu, H.-S. Application of biodiesel as carrier for insecticide emulsifiable concentrate formulation. *J. Taiwan Inst. Chem. Eng.* **2012**, *43* (4), 578−584.

(5) Tran, N. H.; Hieu, T. V. T.; Dang-Bao, T.; Anh, T. T. K. Assessment of methyl ester as a green carrier solvent in pesticide emulsifiable concentrate formulation. *IOP Conf. Ser.: Earth Environ. Sci.* **2021**, *947*, 012031.

(6) Bell, G. A.; Tovey, I. D., Process for producing lactamide compounds, new lactamide compounds and formulations containing lactamide compounds. EP 2001288 B1, 2015.

(7) Randová, A.; Bartovská, L.; Morávek, P.; Matějka, P.; Novotná, M.; Matějková, S.; Drioli, E.; Figoli, A.; Lanč, M.; Friess, K. A fundamental study of the physicochemical properties of Rhodiasolv® Polarclean: A promising alternative to common and hazardous solvents. *J. Mol. Liq.* **2016**, *224*, 1163−1171.

(8) Hansen, C. M. *Hansen Solubility Parameters: A User's Handbook*; CRC Press, 2007.

(9) Klamt, A. The COSMO and COSMO-RS solvation models. *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **2018**, *8* (1), e1338.

(10) Prat, D.; Wells, A.; Hayler, J.; Sneddon, H.; McElroy, C. R.; Abou-Shehada, S.; Dunn, P. J. CHEM21 selection guide of classical—and less classical—solvents. *Green Chem.* **2016**, *18* (1), 288−296.

(11) Martin, A.; Dobrat, W. *CIPAC Handbook F*; Collaborative International Pesticides Analytical Council: Harpenden, U.K., 1994.

(12) Byrne, F. P.; Jin, S.; Paggiola, G.; Petchey, T. H.; Clark, J. H.; Farmer, T. J.; Hunt, A. J.; Robert McElroy, C.; Sherwood, J. Tools and techniques for solvent selection: green solvent selection guides. *Sustainable Chem. Processes* **2016**, *4*, 7.

(13) *Substance Infocard: γ-valerolactone*. European Chemicals Agency, June 9, 2023. https://echa.europa.eu/substance-information/-/substanceinfo/100.003.245 (accessed 2023-09-09).

(14) Wang, J.; Guo, Y.; Liu, F.; Zhang, X.; Wang, W.; Peng, Q. COSMO-RS prediction and experimental verification of deep eutectic solvents for water insoluble pesticides with high solubility. *J. Mol. Liq.* **2022**, *349*, 118139.