GISELA OBREGON GUTIERREZ

SOLVENT ASSESSMENT AND SELECTION IN TERMS OF SUSTAINABILITY, PERFORMANCE, AND COST

Design of a solvent database in a pharmaceutical environment

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Design of a solvent database in a pharmaceutical environment

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Trabalho efetuado sob a orientação de:

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UNIVERSIDADE DO ALGARVE

Faculdade de Ciências e Tecnologia

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Declaration of Authorship

I hereby declare that I am the author of this work, which is original and unpublished. Authors and works consulted are properly cited in the text and listed in the list of references included.

Gisela Obregon Gutierrez

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Resumo

Palavras clave: Ferramenta de seleção de solventes, Avaliação de solventes, Quimica verde, Sustentabilidade

O aumento da consciência ambiental ajudou, desde o final da década de 1980, a mudar o paradigma da remediação para a prevenção de resíduos. A introdução do conceito de química verde e a publicação dos doze princípios na década de 1990s foi importante na indústria farmacêutica, onde normalmente entre 25 e 100 quilos de resíduos são gerados por quilo de produto final (proporção conhecida como o fator E). Na literatura, análises sobre a produção de produtos farmacêuticos referem que solventes e água representam 58% e 28% do total de resíduos do processo, respetivamente, quando comparados a 8% da contribuição das matérias-primas. A redução no uso e a melhoria na seleção de solventes são áreas-chave de oportunidade para reduzir a pegada ambiental da indústria farmacêutica. Neste contexto, vários manuais e guias que pretendem avaliar solventes e facilitar a sua seleção têm sido publicados tanto por empresas privadas (por exemplo, Pfizer, GSK, AstraZeneca) como por grupos de trabalho (por exemplo, ACS GCI-PR, CHEM21).

Em linha com esses esforços, uma nova ferramenta de avaliação e seleção de solventes foi desenvolvida e adaptada ao contexto único da Hovione. O público-alvo foi definido como qualquer pessoa que trabalhe com solventes na empresa, mas principalmente investigadores que procuram escolher solventes para aplicações novas ou para outras já existentes (ou seja, substituição de solventes). A análise da literatura e a abordagem inicial desses investigadores e de outros grupos-chave da empresa, por meio de um questionário e de entrevistas individuais, ajudou a produzir uma relação preliminar de solventes (com mais de 100 solventes), uma lista de prioridades para informações sobre solventes (maior prioridade para informações fisicas, quimicas e propiedades termodinâmicas entre outras, e menor para informação regulatória e custo entre outras) e a primeira lista de campos de informações a serem incluídos na base de dados.

Uma lista final de 50 solventes (com base nos solventes que são atualmente usados e foram usados nos últimos anos na Hovione) foi compilada e serviu de base para a construção da base de dados. Para cada entrada, uma lista mais longa de 49 informações químicas, termodinámicas, ambientais, e regulatórias foi incluída, com base nos campos de informação referidos como importantes pelos investigadores, bem como outros considerados relevantes para começar a criar uma perspectiva holística de cada solvente. Desta forma, em primeiro lugar foi construída

uma base de dados que incluía inúmeras informações diferentes atualizadas para essa lista de 50 solventes.

Além disso, neste contexto de avaliação de solventes e com a intenção de proporcionar aos investigadores mais instrumentos para os ajudar na seleção e substituição de solventes, a ferramenta incorporou um novo método de avaliação unificado com quatro parâmetros menores, considerando o perigo que o solvente representa para a saúde dos trabalhadores ("Health Risk"), o risco à segurança do processo ("Process Safety"), o impacto ambiental ("Environmental Impact), e uma análise de sustentabilidade ("Sustainability"). Cada avaliação contém entre um (no caso do impacto na saúde) a vários fatores (nos outros casos) que formam uma nota final dada a cada análise, na forma de um número numa escala de 1 a 10. Nesta escala, quanto menor o número, melhor é o resultado, ou seja, um menor número indica um impacto menor. Cada avaliação pode ser personalizada pelo utilizador, de forma que é possível priorizar ou até desconsiderar aspectos específicos de cada exercício, mesmo se a ferramenta já propõe valores predefinidos para a ponderação.

A ferramenta oferece ainda uma classificação final para cada solvente, classificando-o como recomendado, problemático, perigoso, ou altamente perigoso. Essa classificação também vem com um formato de quatro cores estilo semáforo (verde, amarelo, vermelho, e vermelho/marrom) associado, para uma leitura mais fácil e rápida. A classificação final para cada solvente depende da existência de códigos de perigo GHS cancerígenos, mutagênicos ou tóxicos para a reprodução (CMR, pelas siglas em inglês), bem como dos resultados das quatro avaliações individuais anteriores (saúde, perigo industrial, impacto ambiental e sustentabilidade).

Em resumo, do total de 50 solventes incluídos na base de dados, o método de avaliação global dos produtos químicos por meio de algoritmos com ponderações pré-definidas resultou na definição de 16 solventes como recomendados, 24 como problemáticos, 5 como perigosos e outros 5 como altamente perigosos. Neste último caso, dos cinco solventes considerados altamente perigosos, quatro foram imediatamente considerados como tal devido à inclusão de pelo menos dois dos códigos de perigo CMR e GHS.

As recomendações finais fornecidas pelos algorítmos incluídos na ferramenta correlacionaram-se bem com as recomendações de outros guias de solventes publicados. É possível sustentar a metodologia e destacar a eficácia da estratégia de avaliação propostas para a obtenção de resultados consistentes com os de outros guias de solventes. Considerando os critérios de importância estabelecidos na Hovione e as características (in)desejadas em solventes, os resultados individuais obtidos fornecem validação adicional da confiabilidade na ferramenta. Os resultados também confirmam o valor previsto da ferramenta no suporte a processos de tomada de decisão informados.

As avaliações parciais (*Health Risk*, *Process Safety*, *Environmental Impact* e *Sustainability*) e as recomendações finais ajudarão os investigadores a comparar os solventes uns com os outros, bem como a considerar medidas de precaução adicionais caso um solvente controverso seja escolhido para uma aplicação. Não obstante, permanecem ainda várias áreas de oportunidade para o desenvolvimento do projeto. Principalmente, será necessário completar alguma informação em falta para avaliar completamente todos os solventes, assim como expandir a base de dados atual para incluir solventes alternativos mais recentes, mais ecológicos, que não estão atualmente em uso na Hovione mas que poderiam ser integrados em novos processos ou em outros já existentes. No entanto, as prioridades serão disseminar a ferramenta na empresa e construir uma interface de utilizador com a qual seja mais fácil a interação.

Por último é importante ter em conta que, devido às limitações de tempo e ao contexto em que o projeto foi desenvolvido, algumas conclusões importantes como importância da adoção desta ferramenta e as possíveis melhorias nos processos decorrentes da sua aplicação ficaram fora do âmbito deste projeto. Contudo é expectável que o feedback sobre a ferramenta e a estratégia de avaliação proposta, fundamental para planear a progressão do projeto fora do âmbito desta tese, esteja disponível em breve.

Abstract

Key words: Solvent selection tool, Solvent assessment, Green chemistry, Sustainability

Increased environmental awareness has, since the end of the 1980s, helped shift the paradigm from waste remediation to waste prevention. The introduction of the green chemistry concept and the publication of the twelve principles in the 1990s has been particularly embraced by the pharmaceutical industry, where typically between 25 and 100 kilograms of waste are generated per kilogram of product (ratio known as the E-factor). In this context, several manuals and guides that intend to evaluate solvents and facilitate their selection have been released, published both by individual companies (e.g., Pfizer, GSK, AstraZeneca) and working groups (e.g., ACS GCI-PR, CHEM21).

In alignment with these efforts, a novel solvent selection and assessment tool was developed, tailored to suit Hovione's unique context. The target audience was defined as anyone working with solvents, but particularly scientists looking to choose solvents for new or existing applications. A list of 50 solvents currently in use in Hovione was compiled and served as the basis for the database. For each entry, a list of 49 various chemical, thermodynamical, environmental, and regulatory data points was included.

Furthermore, the tool incorporated a new unified assessment method across four categories, considering the danger that the solvent poses to workers' health, the risk to the process safety, the environmental impact, and a sustainability analysis. Each evaluation was customizable by the user, in order to prioritize specific aspects of each exercise. In addition, each solvent was then ranked as recommended, problematic, hazardous, or highly hazardous. The final recommendations provided by the algorithms included in the tool correlated well with recommendations from other published solvent guides. These smaller assessments and final recommendations will aid scientists in comparing solvents against each other, as well as help them consider precautionary steps in case a contentious solvent is chosen for an application.

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Abbreviations and Acronyms

ΔH_{vap}	Enthalpy heat of vaporization
ACS	American Chemical Society
ACS GCI PR	American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable
AIChE	American Institute of Chemical Engineers
API	Active Pharmaceutical Ingredient
AZ	AstraZeneca
BP	Boiling point
CMR	Carcinogenic, mutagenic and reprotoxic
Cp	Specific heat capacity
CRW	Chemical Reactivity Worksheet
DCM	Dichloromethane
DIPPR	Design Institute for Physical Properties
ECHA	European Chemicals Agency
EI	Environmental Impact
EMA	European Medicines Agency
EPA	Environmental Protection Agency
FP	Flash point
GCI	Green Chemistry Institute
GHS	Globally Harmonized System
HR	Health Risk
HSE	Health, Safety, and Environmental
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IT	Information Technology
LCA	Life Cycle Assessment
NFPA	National Fire Protection Association
NIST	National Institute of Standards and Technology
NOAA	National Oceanic and Atmospheric Administration
OECD	Organization for Economic Cooperation and Development
OEL	Occupational Exposure Limit
PBT	Persistent, Bioaccumulative, and Toxic

PCA	Principal Component Analysis
PS	Process Safety
SAP	System Applications and Products in Data Processing
SVHC	Substance of Very High Concern
R&D	Research and Development
REACH	Registration, Evaluation, Authorization, and Restriction of Chemicals
T	Temperature
UK	United Kingdom
US	United States
VOC	Volatile Organic Compound
VP	Vapor pressure
vPvB	very Persistent and very Bioaccumulative

1. Introduction

1.1. Green chemistry, E factor, and the 12 Principles of Green Chemistry

Starting in the 1980s, growing concern among the chemical industry led to a paradigm shift regarding the generation of waste and use of hazardous and toxic materials in chemical operations (Sheldon, 2018). The traditional concept of giving more value to chemical processes with higher yields rapidly became obsolete. Instead, the chemical industry started giving preference to maximizing resource efficiency, minimizing waste, and altogether avoiding the use of hazardous and toxic agents in chemical synthesis, championing this as "efficiency in organic synthesis" (Sheldon, 2017). Overall, the chemical industry began recognizing the importance of including the environmental factor when assessing the efficiency of organic synthesis.

At the same time, there was another shift from pollution control and mitigation to pollution prevention. Most importantly, the United States (US) Pollution Prevention Act of 1990 focused attention on the need to avoid, rather than depend on, end-of-pipe waste treatment, and shifted the US Environmental Protection Agency's (EPA) strategy entirely. The idea of a process with less waste as being 'better' was supported by presenting waste prevention not only as good for the environment but also as having an economic edge by circumventing the costs of its treatment and using raw materials more effectively, therefore rendering the process itself more efficient and competitive (Sheldon, 2018).

The culmination of the 1980s's shift of perspective came with groundbreaking moments in the 1990s, of which three are worth mentioning in this context. Firstly, the introduction of the term "green chemistry", by Paul Anastas in 1991, initially synonymously used with "minimum impact chemistry", was promoted by the EPA to describe the design of chemical processes and products that minimized (or avoided altogether) the use of hazardous and toxic substances, favoring renewable raw materials, while also reducing the formation of waste in the manufacture and application of chemical products. That is, green chemistry as a concept focuses primarily on pollution prevention rather than waste remediation (Sheldon, 2017) (Sanderson, 2011).

Secondly, the publishing of the E(nvironmental) Factor by Sheldon in 1992 established a disruptive metric for assessing the environmental impact of manufacturing processes across different segments of the chemical industry by comparing the total mass of waste[1] (including all auxiliary components, for example, solvent losses and chemicals used in the workup) with the mass of final product obtained. The ideal E factor will therefore be zero, but generally a lower value is considered 'better'. While the inclusion of water as waste has been a point of debate in the past, the current trend (and particularly in the pharmaceutical industry) is to include water in the E factor calculation. This trend surges because a major source of waste in the manufacture of chemicals comes from solvent losses. It has been published in literature that solvents and water account for 58% and 28% of the process waste, respectively, when compared to 8% of raw materials (Sheldon, 2018). The E factors for several segments of the chemical industry are shown, as first published in 1992, in Table 1.1 (Sheldon, 2017).

Table 1.1. *E factors in the chemical industry.*

Industry segment	Tonnes per annum	E factor (kg waste per kg product)
Oil refining	$10^6 – 10^8$	< 0.1
Bulk chemicals	$10^4 – 10^6$	< 1 – 5
Fine chemicals	$10^2 – 10^4$	5 – 50
Pharmaceuticals	$10 – 10^3$	25 – >100

It also becomes important to understand that the primary cause of the high E factor in the pharmaceutical industry stems from the difficulty of the processes themselves. The high molecular complexity of Active Pharmaceutical Ingredients (APIs) usually demands a large number of chemical steps to form the molecule from commercially available starting materials. Another important cause is the widespread use of organic solvents and prevailing use of stoichiometric reagents rather than catalysts (Sheldon, 2017). It is key to remember that a lower E factor correlates with a lower API manufacturing cost (as a result of lower process materials input, reduced energy demand, etc.) and reduced waste disposal requirements, among others.

Thirdly, the publication of the 12 Principles of Green Chemistry by Anastas and Warner in 1998 presented an overall guiding element of "benign by design". By providing a framework for designing and improving products, processes, and systems, Anastas and Warner push to reduce the environmental impact of waste and operations, therefore upholding the tenet of green chemistry. Since their introduction, the 12 Principles have become a roadmap to a greener industry. They can be found in Table 1.2 (ACS, 1998).

[1] Where waste was originally defined as "everything but the desired product".

Table 1.2. *The 12 Principles of Green Chemistry.*

1. Prevent waste.	7. Use of renewable feedstocks.
2. Atom economy.	8. Reduce derivatives.
3. Less hazardous synthesis.	9. Catalysis (vs stoichiometric).
4. Design benign chemicals.	10. Design for degradation.
5. Benign solvents & auxiliaries.	11. Real-time analysis for pollution prevention.
6. Design for energy efficiency.	12. Inherently benign chemistry for accident prevention.

1.2. Solvent assessment tools and guides

In the wake of the green chemistry revolution of the 80s and 90s, pharmaceutical companies have taken it upon themselves to limit waste, avoid pollution, and establish safer, more sustainable manufacturing processes. One way in which they have done so is through the publication of solvent assessments and guides, which intend to lead chemists in the selection of greener solvents. Some advocates have said that the most fundamental barrier to a wider adoption of green chemistry is the mindset of the chemists themselves, since scientists are not always taught to see any engineering, product design, or life cycle assessment (LCA) analysis as part of their (usually technical) solvent selection process (Sanderson, 2011). Therefore, the intention of these guides is to expose the chemists to the consequences of using one or another solvent, usually via a three-tier traffic light evaluation of the solvent itself, and to help them aspire to a more benign synthesis.

The first of these solvent guides was published by GSK in 1999 and originally included 35 solvents (Curzons, Constable, & Cunningham, 1999). A further version in 2004 incorporated 47 solvents more and an LCA analysis (Jiménez-González, Curzons, Constable, & Cunningham, 2004). An additional third edition in 2011 further expanded the solvent list to include 110 entries, revised the assessment of the factors that impacted process safety, and added a customized solvent selection guide appropriate for medicinal chemistry and analytical laboratories (Henderson, et al., 2011). In 2015, another guide specific for selecting acids and bases as reagents was announced, incorporating 63 bases and 23 acids (Henderson, Hill, Redman, & Sneddon, 2015). Lastly, a fourth edition of the original solvent selection guide was published in 2016, including a total amount of 154 solvents (Alder, et al., 2016). As of this last edition, solvents were evaluated across four general areas of assessment: waste, environment, health, and safety, each including smaller evaluations, and given a score between 1 and 10, where the lower the number the worse the score is.

Similarly, in 2008, Pfizer published its own solvent selection guide for medicinal chemistry, including 39 solvents and assessing them across three general areas: worker safety, process safety, and environmental and regulatory considerations. The solvents were then classified in one of three groups: preferred, usable, and undesirable. While smaller, the authors shared from the start a positive reception of the guide, as well as immediate positive response to chlorinated solvent and selected ether-reducing campaigns, in their eyes largely due to a “philosophy of encouragement and education rather than obligation and scrutiny” (Alfonsi, et al., 2007).

Sanofi also published its own solvent selection guide in 2013, in which, for a total of 95 solvents, did assessments across occupational health, safety, and environmental hazards, while also considering other concerns (such as legal restrictions or hazardous properties) and ICH[2] limits. Each solvent is then ranked in one of four categories: recommended (green), substitution advisable (yellow), substitution requested (red), and banned (brown) (Prat, et al., 2013).

Solvent selection guides and assessment tools have not been limited only to individual companies, but have also been developed by working groups, such as the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable (ACS GCI PR). The ACS, GCI, and several global pharmaceutical corporations founded in 2005 the ACS GCI PR with the mission to catalyze the implementation of green chemistry and engineering into the business of drug discovery, development, and production through joint cooperation, sharing innovation tools, and education (Jiménez-González, et al., 2011) (Constable, et al., 2007). As of 2023, the ACS GCI PR has 25 members, 19 associate members (including Hovione FarmaCiência), and 2 affiliate members (ACS GCI, n.d.).

AstraZeneca (AZ) published its own solvent selection guide, originally including 47 solvents graded across 10 criteria covering health, safety, and environmental (HSE) analysis with a 1-10 rating for each criterion, where the lower the rating, the least impact. The original guide was then updated in PDF format in collaboration with the ACS GCI PR to include 60 solvents, scoring them across several types of properties, to deliver a final score in a 1-10 scale, where again, the lower the number, the lesser the impact (Ekins, Clark, & Williams, 2012). Furthermore, rework by AstraZeneca in 2016 led to a new solvent tool, including a whooping 272 entries, a massive property database, and a principal component analysis (PCA) model.

[2] International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use.

This new guide has been recreated in collaboration with the ACS GCI PR and is freely available after registration in the ACS GCI PR website (Prat, et al., 2013).

Another working group that came out with its own solvent guide is CHEM21. The Innovative Medicines Initiative (IMI)-CHEM21 public-private partnership is a European consortium promoting sustainable chemical and biological methodologies comprising several pharmaceutical companies, universities, and small to medium enterprises (Prat, Hayler, & Wells, 2014). In 2016 they published their own solvent assessment and selection guide, consisting of 76 solvents scored across HSE criteria on a 1-10 scale, where the bigger number indicates a higher impact. Finally, the solvents are assigned a ranking: recommended, problematic, hazardous, or highly hazardous (Prat, et al., 2016). As of 2023, as the CHEM21 is the latest workgroup-led solvent guide, the official stance of the ACS GCI is to recommend the use of CHEM21's solvent guide.

One last solvent tool worth mentioning is that published in 2019 by Syngenta, which included both practical considerations (such as cost and HSE impact) and technical suitability. Syngenta's tool includes extensive PCA analysis and chemometric property analysis for 209 solvents, although it has not been widely shared and does not consider any ranking of the entries, rather relying on quantitative analysis of properties selected by each user for each application (Piccione, et al., 2019).

An overview of the solvent assessment tools and guides discussed can be found in Table 1.3 and Table 1.4.

Table 1.3. *Solvent selection tools of individual companies.*

	GSK	Pfizer	Sanofi	AZ	Syngenta
Solvent count	154	39	95	47	209
Ranking	**1–3**	**Preferred**	**Recommended**	**1–3**	N/A
	4–7	**Usable**	**Substitution advisable**	**4–7**	N/A
	8–10	**Undesirable**	**Substitution requested**	**8–10**	N/A
			Banned		

Table 1.4. *Solvent selection tools of workgroups.*

	ACS GCI PR	AZ + ACS GCI PR	CHEM21
Solvent count	60	272	76
Ranking	**1–3**	**1–3**	**Recommended**
	4–7	**4–7**	**Problematic**
	8–10	**8–10**	**Hazardous**

1.3. Successes and difficulties in implementing solvent substitution via a simplified solvent guide

Several issues have been highlighted when considering solvent selection guides and solvent recommendations. First of all, related to the construction of the solvent guides and, therefore, their omissions, tools usually fall back on HSE aspects to rank solvents. This of course can be adjustable and commonly varies between guides. Nevertheless, usually all three aspects are weighed equally. It begs to question if one should outweigh the other. To borrow an example, in an analysis of one guide, a peroxide forming ether like diethyl ether ended up ranked as less green than the reprotoxic DMF (Byrne, et al., 2016). Other authors have shone a light on the lack of an economic component in green chemistry. In order to be sustainable, a process must not only be socially and environmentally sustainable, but also economically so (Sheldon, 2018).

Furthermore, in the push to recommend or disregard a solvent, there is a risk for common sense – and the process requirements, the main purpose of a solvent – to be left behind. An exclusive focus on either environmental performance or health risk when creating a solvent shortlist may prove overtly limiting for effective process screening. Process requirements must be considered side-by-side (Diorazio, Hose, & Adlington, 2016). It might be more effective to start with a wider set of solvents and allow the user to filter down through the solvent properties that fulfill the process needs, therefore building a list from a wider set of options. The philosophy of such solvent guides, that provide different criteria and a wealthy collection of data (such as GSK, AZ, and ACS GCI PR) while not providing a clear overall ranking, is to feed chemists and engineers options from which they can then make a choice, after taking into consideration such process requirements (Prat, Hayler, & Wells, 2014).

In line with feeding scientists options, the general consensus in published solvent selection guides is to avoid presenting authoritarian advice. Firstly, such advice would rely, as previously postulated, on the solvent and disregard completely the context in which it would be used (Diorazio, Hose, & Adlington, 2016) (Alfonsi, et al., 2007). Similarly, while some guides attempt to say that one solvent or another should not be used, newer guides or reworks of older ones attempt to make the various HSE trade-offs apparent so the scientist him/herself can have the appropriate freedom and understanding to make the best decisions both for the environment, for the business, and for the process (Jiménez-González, Curzons, Constable, & Cunningham, 2004). Examples of the success of this approach are Pfizer's 50% reduction in chlorinated solvents use over 2 years, and 97% reduction in undesirable ethers (diisopropyl ether in particular), achieved by increasing awareness of solvent issues to scientists (Byrne, et al., 2016).

An additional problem identified with some solvent guides is the lack of an LCA approach. While a proper LCA requires significant investment both in time and resources, evaluating solvents without this analysis could seriously underestimate impacts, conceal trade-offs, and could result in regrettable substitutions. For example, the choice of end life can significantly alter the environmental footprint a solvent might have. For some solvents, like hexane and heptane, incineration with heat recovery might lead to the smallest environmental footprint, while for others, it might be through recovery by distillation, as with THF and acetic acid (Jiménez-González, 2019). Including an LCA analysis in solvent assessment should be the gold standard, and scientists must be aware of the shortcomings of any guide that does not include such an analysis in a final recommendation.

Finally, scientists must also be warned of avoiding a "fits one fits all" approach. It is key not to consider one green solvent as the best fit for any application if it has been considered sustainable for another. What is sustainable in one application might not be so elsewhere (Schuur, Brouwer, Smink, & Sprakel, 2019).

In alignment with the efforts undertaken by other companies in the industry, and in line with Hovione's own Sustainability Agenda, a novel assessment tool is proposed, tailored to suit Hovione's unique context, and integrating sustainability assessment, performance appraisal, regulatory overview, and cost analysis into a unified framework. This tool will aim to provide chemists and other users with hard data to lead their solvent choice shortlisting, while providing a platform for evaluating HSE trade-offs including economic decision-making.

2. Methodology

The execution of this project was separated in two phases, each encompassing a key question. The first phase, centered around laying the groundwork for the tool, is best explained by the question: "what to include?" This first phase will be described in sections 2.1 (what information to include) and 2.2 (which solvents to include) in this chapter. The second phase, centered around the execution and building of the tool, is best explained by the question: "how to deliver?" and is described in sections 2.3 (where to get the data from) and 2.4 (how to holistically assess the solvents).

2.1. Defining priorities, information fields, and delivery method

The objective was to build a tool that would serve its users; therefore, it became a priority to gather feedback from those potential users regarding what their requirements were, what the proposed tool would need to do and what information it would need to cover.

First, valuable analysis of other solvent guides and tools in literature was performed. The intention of this analysis was to create a master list of information fields consistently found across the different solvent tools, reading these data points as priorities in other pharmaceutical companies.

Secondly, to understand the priorities of the scientific and engineering teams in Hovione (as primary potential users of this tool), a questionnaire was generated. This questionnaire was sent out in two waves to working teams inside the R&D structure in Hovione's offices in Portugal[3]. After receiving a total of fifty-eight responses, they were analyzed to understand three key points:

- Which sources do potential users go to for data.
- Which data do potential users look for.
- What type of information do potential users want to see if Hovione had an internal solvent database.

The full questionnaire can be found in Annex A: Questionnaire

[3] The R&D structures in other countries around the world where Hovione is present were disregarded for this initial questionnaire.

During the process of delineating the fields to incorporate into the database, an encounter transpired with a separate team within Hovione. This other team intended to build a database akin to the one planned in this project but tailored to meet the requisites for spray drying within their workgroup. Following the presentation of the project, they graciously augmented the working list of information fields by contributing their own considerations.

Finally, regarding the delivery method, a quick analysis of the capabilities of Hovione and ease of access of different platforms across the organization was done, with great contributions from senior members in the R&D team.

2.2. Defining the solvent list

In order to have a tool that would serve Hovione’s users well, it became key to obtain a comprehensive solvent list on which to build. First, as with the information fields, a deep analysis of published solvent guides was performed. The intention of this analysis was to create a directory of solvents found across the different tools, identify those present most often, and define a first list that would serve as the foundation on which to build the database.

As work progressed, it became evident that the amount of work required to build such a comprehensive database would be extensive. With a view to optimizing efficiency and ensuring the delivery of a well-finished product, it became imperative to streamline the solvent target list, prioritizing the inclusion of solvents already in use in the company. Therefore, a connection was established with Hovione’s Purchasing team, from whom a list encompassing all the solvents utilized at Hovione was requested. This compilation was determined to serve as the starting point of the database.

2.3. Data sourcing

While further discussion of the insights the questionnaire provided will occur in a later chapter, it is relevant to remember that one of the questions posed to scientists was the source of their data. It is only natural that, if one does not trust the origin of the data, one does not trust the data itself. The answers to this section of the questionnaire helped determine a list of trusted data sources that were already routinely accessed by the potential users of the database. By sourcing data from these preferred references, the tool could provide information points that the scientists would trust.

Moreover, one additional key finding of the questionnaire was that every single scientist that answered the questionnaire reported consulting at least two different sources. Pooling several information fields and data outlets into one in-house tool, such as the proposed solvent assessment database, could also help reduce the time spent scouring individual repositories for information.

Therefore, defining which sources would be used to collect the data for the previously defined information fields was greatly led by the scientists themselves, through the questionnaire responses, by pinpointing which sources were already being accessed (mainly, the Dynochem DIPPR[4] Properties database and the ACS GCI PR solvent tool).

For all other information that could not be obtained from one of these two sources, preference was then given to external databases, such as the NIST Chemistry WebBook and PubChem, and software such as CAMEO Chemicals[5] and the Chemical Reactivity Worksheet (CRW)[6]. For information related to regulation, only official sources would be considered up to date, as confirmed by Hovione's Regulatory leader, Paulo Baião (Baião, 2022), such as the European Chemicals Agency (ECHA) and European Medicines Agency (EMA). Lastly, external literature would be consulted for the remaining missing data points.

2.4. Assessment strategy

Once the database was built, the final stage of the project was to create an assessment strategy applicable across the solvent list, starting from the available information, in order to help chemists compare between one solvent and the other. To attain this goal, four individual assessment lanes plus one final recommendation were defined. For each individual assessment, a 1-10 scale with a three-tier traffic light was considered, where the lower the value, the better the assessment. For assessment values 1 through 3, both the assessment value and a green background would be shown. For assessment values 4 through 7, a yellow background would

[4] DIPPR stands for the Design Institute for Physical Properties, a project inside the American Institute of Chemical Engineers (AIChE) and is the name of a database integrated inside the Dynochem software, concentrating thermo-physical properties on an extensive list of solvents (American Institute of Chemical Engineers, n.d.).

[5] Managed by the National Oceanic and Atmospheric Administration (NOAA).

[6] Managed by the AIChE.

be shown. Finally, for assessment values 8 through 10, it would be a red background. These assessment lanes were:

1) Health risk: to consider the risk the exposure to a solvent might have on the worker or general population.
2) Process safety: to consider the ease or risks of working with a solvent, particularly on an industrial level but also applicable to the laboratory.
3) Environmental impact: to reflect the ecotoxicity, bioaccumulative potential, and other effects that a solvent can have on the environment.
4) Sustainability: as a measure of the environmental impact both during sourcing and upon release of the solvent, recoverability, and other sustainability-related repercussions.

Particular care was taken to have informative notes for each assessment in order to brief the users on the comprehensive strategy employed for each individual evaluation and the final recommendation. This approach aims to provide the scientists with a transparent understanding of the assessments' constituent components, methodologies, and factors considered, in order to foster trust and enable a meaningful interpretation of the assessments beyond being fed mere numerical outputs.

Next, detailed explanations on each assessment will be provided, delving into the specific methodologies, variables, and considerations employed, and offering a comprehensive understanding of the overall evaluation process.

2.4.1. Health Risk

The Health Risk (HR) evaluation derived its assessment exclusively from the utilization of Globally Harmonized System (GHS) hazard codes and statements. GHS codes were taken directly from each solvent's Registration Dossier under REACH[7] with ECHA and exist as an information field in the proposed solvent assessment tool. GHS codes fall within three categories: those related to process hazards (H200s minus H281), those related to health hazards (H281 and H300s), and finally those related to environmental hazards (H400s). Supplemental hazard information (EUHs) can be labelled either one of the three types: process (EUH014, 018, 019, 044, 209/209A and 210), health (EUH029 through 208, 211, 212, and 401), and

[7] Registration, Evaluation, Authorization and Restriction of Chemicals.

environmental hazards (EUH401, shared with health). A complete list of GHS codes and hazard statements can be found in Annex B: Full list of GHS hazard codes and statements

For the Health Risk evaluation, each GHS code related to health hazard was attributed a value. This value intends to be a measurement of the danger associated to the GHS and serves as a comparison with other GHS codes. The lower the value, the less danger the code signifies. The values attributed to the different GHS codes derive from a linguistic and impact analysis of the hazard statement themselves.

The analysis was done by individually reviewing all related GHS hazard statements to first understand the key words present in the statements. These words were then grouped into "modifiers" and "effects".

- Modifiers: words, such as ‘may’, ‘can become’, ‘suspected’, etc. that imply that the effect of the hazard statement is not so certain or requires specific conditions to occur.
- Effects: words, such as ‘flammable’, ‘catches fire’, ‘fatal’, ‘cause cancer’, etc. that indicate the impact associated with the hazard statement. Effects can then be subdivided into categories, mainly: the extent of the damage to health (fatal, toxic, or harmful), the damage done (damage to organs, cancer, corrosive, genetic effects, irritation, etc.), and the exposure scenario (breathing, skin/eye contact, and ingestion).

Each category of modifier or effect was then graded, where a higher number indicates a higher risk or impact of the effect. By default, all modifiers are negative numbers, and all effects are positive. For example, ‘harmful’ could be given a value of 4, ‘toxic’ could be given a value of 8, and ‘fatal’ could be given a value of 12 to reflect the seriousness of the effect.

Modifiers in particular intend to reflect that the risk, while present, might not be so ‘bad’ (in terms of value) because of conditions that *also* need to happen or are not so certain to happen. Therefore, the existence of words like ‘may’ in a hazard statement takes points off the overall grade attributed to the hazard statement. To give an example, compare ‘may be toxic’ with ‘is toxic.’ While there is significant risk in the first example, the risk could be considered lower due to uncertainty in the toxicity of the solvent. To reflect this lower risk, modifiers will count against the total grade of a hazard statement as negatives.

Finally, with the analysis rendering values for the language used, each GHS is then given an overall value depending on the words that make it up. Particularly for the Health Hazard statements, the exposure scenario under which the effect takes place is relevant, as some scenarios might be easier (or more difficult) to encounter due to safeguards that are usually in place to avoid the worker or person encountering the agent in question (e.g., personal protection equipment). 'Ingestion' is considered to be the least likely to happen in a laboratory or an industrial setting and is therefore considered a lesser risk. Alternatively, ‘breathing’ is considered the most likely (and most dangerous) scenario to encounter in these settings. Therefore, ‘breathing’ is penalized with a greater value. Whenever a hazard statement does not specify the scenario of exposure under which the effect occurs, the worst valued (‘breathing’) is considered in the global evaluation.

Let us see an example of GHS statements that do not involve modifiers:

1) Code H310: "Fatal in contact with skin" – ‘fatal’ gives the statement a value of 12 (extent of damage to health category) and ‘in contact with skin’ a value of 2 (exposure scenario). Summed up, code H310 is given an overall hazard value of 14.

2) Code H311: "Toxic in contact with skin" - 'toxic’ gives the statement a value of 8 (extent of damage to health category), and ‘in contact with skin’ a value of 2 (exposure scenario). Summed up, code H311 is given an overall hazard value of 12.

Code H311, while serious, is rendered as less impactful than code H310. Now, let us see an example where the GHS statements do involve modifiers:

1) Code H350: "May cause cancer" – ‘cancer’ is given a value of 10. Nevertheless, the statement indicates that the impact (‘cancer’) is not so certain (modifier ‘may’). This modifier has a value of -2. Finally, the statement does not pinpoint exactly how the effect occurs, so ‘breathing’ is considered, with an additional 3 points. Therefore, the global value given to code H350 is 11.

2) Code H351: "Suspected of causing cancer" – ‘cancer’ is given a value of 10, and similarly the modifier ‘suspected’ has a value of -1. Again, the statement does not identify the scenario of exposure, so ‘breathing’ is considered, for a value of 3. Overall, code H351 is given a value of 12.

As is evident, the penalizations brought through the modifiers do not lessen too significantly the risk/effect value given to the code. The intention is to avoid modifying one statement so much that, as an example, a ‘may cause cancer’ is seen on the same level as a ‘will cause irritation’, while modifying it enough to differentiate between one code and the next one. In the second instance and through its wording, code H351 is seen as more certain than code H350, and the global code values reflect it.

The values provided for each effect element of the health hazard key are attributed based on the perceived standing of the relevant effect against the others. In a first approach, effects are systematically assigned numerical values within their respective categories, facilitating comparative evaluation. Subsequently, the categories are interrelated, ensuring coherence and consistency across all assigned values, thereby enabling meaningful, robust assessments. The full key for evaluating all health hazard statements with the predetermined values for each component can be found in Table 2.1.

It is paramount to state that, even though these proposed preset effect and modifier values are strongly recommended to ensure a well-balanced health hazard evaluation, they can all be modified by the final user or any party, perhaps after a more in-depth analysis. All modifiable values are shown in a blue background in Table 2.1. *Key for health hazard statements.* After any modifications, the solvent tool will automatically fully update to consider the modified values.

Table 2.1. *Key for health hazard statements.*

Key for health hazards (H281, H300s, and relevant EUHs)			
Modifiers		Effects	
-2	May		*Extent of damage to health*
-1	Suspected	12	Fatal
-0.5	Requires contact with another substance	8	Toxic
-0.25	Requires repeated exposure	4	Harmful
			Damage to health
		11	Damaging to organs
		10	Cancer
		9	Corrosive
		8	Genetic effects
		7	Damaging to fertility or unborn child
		6	Damage to breast-fed children
		4	Allergic reaction/allergy
		3	Skin burns/eye damages
		2	Irritation
		1	Drowsiness/dizziness
			Exposure scenario
		3	Breathing
		2	Skin/Eye
		1	Ingested

Regarding specifically the different values awarded to "damaging to organs" and "cancer" as effects of the solvent, it is acknowledged that both share the same hazard classes[8]. Nevertheless, the evaluation was approached differently, reflecting a decision made by the author to consider the possible long-term health impacts, as well as prospects of health improvement. Under these considerations, cancer, while certainly serious and even deadly, can oftentimes be treatable and the afflicted can go into remission. Alternatively, organ damage can frequently have lifelong consequences[9], permanently affecting people's quality of life, with potential to cause severe disabilities, and even lead to further health issues (e.g., cancer or death). Therefore, a greater score is given to "organ damage" vs "cancer". It is also acknowledged that both these considerations depend heavily on the organ targeted. The user is at liberty to modify these values according to their preferences or in case of disagreement with the evaluation scores.

The complete list of all health hazard-related GHS codes and hazard statements with the value assigned to them as a result of this analysis can be found in Annex C: Health hazard-related GHS code and statement evaluations.

Once all health hazard GHS codes had an assigned ‘danger’ value, the overall assessment of the individual solvents could go ahead. In this phase, the additive property of GHS hazard codes comes into play (that is, one solvent could have more than one GHS code). In line with this, the ‘danger’ value given to individual codes are summed up for a “solvent total health hazard value.” However, as the intention was to present the final user with a health hazard value in a 1 to 10 scale, a linear transformation had to take place. To go ahead with a linear transformation, the minimum and maximum of this ‘raw’ “solvent total health hazard value” scale had to be defined. The minimum value is straightforward, understood as the lack of any GHS health hazard codes. Therefore, the minimum will be a zero. The maximum value proved trickier, as theoretically a solvent could be assigned most of the hazard codes at the same time. As an exercise, a hypothetical worst-case solvent was ideated: “fatal when inhaled, toxic if swallowed, inhaled, and/or in contact with skin, will cause severe skin burns/eye damages on contact, will be damaging to organs and have genetic effects when ingested, may cause cancer. Repeated exposure may cause skin dryness or cracking.” This hypothetical worst-case solvent was then

[8] Cancer categories 1A, 1B or 2; organ damage categories 1 or 2 under GHS[8] (United Nations Economic Commission for Europe, 2021, pp. 265-271).

[9] Considering (very generally) different regeneration capabilities or none, depending on the organ.

evaluated as a 64.75 on the untreated scale, which was promptly defined as the maximum for the linear regression. Nevertheless, in the understanding that this worst-case solvent is only hypothetical and there could be worse, a safeguard was built into the linear regression. If the solvent total health hazard value were evaluated over this maximum, the final 'treated' score would show as a 10 on the 1-10 scale.

Through GHS codes-centered analysis, the Health Risk assessment aims to standardize the evaluation process for all solvents, regardless of their chemical families or other characteristics. This approach ensures a unified platform for the assessment, allowing for seamless inclusion of new solvents in the database, if and when it is expanded.

2.4.2. Process Safety

The Process Safety (PS) assessment considers five evaluations:

- T-Rating: referencing the United Kingdom (UK) Electric Equipment Temperature Classification based on the autoignition temperatures in °C for plant accommodation purposes.
- Specific heat capacity (Cp).
- Enthalpy of vaporization (ΔHvap).
- Flammability class: based upon the closed-cup flash points in °C and the US NFPA[10] classification.
- Process hazard-related GHS codes and statements.

For each of the five distinct evaluations, a further analysis was conducted to evaluate the relative significance of any one assessment in relation to another. This examination yielded ponderation scores, which help to effectively allocate varying degrees of importance to specific aspects of the Process Safety assessment under consideration. Furthermore, to ensure equitable evaluation across all fields, the ponderation scores also play a role in aligning the scales of assessment. This harmonization guarantees that all fields are evaluated proportionately to one another, effectively leveling the playing field and maintaining a balanced perspective throughout the assessment. While recommended preset ponderation scores are loaded onto the tool, the user is

[10] National Fire Protection Association.

also able to modify them, with immediate updating of the adjusted assessment across all solvents, lending the tool an extra customizable, versatile feature.

The various smaller evaluations and recommended ponderations can be consulted in Table 2.2. *Process Safety evaluation factors and ponderations.* The modifiable ponderation values are shown in a purple background, along with the recommended preset values. Further explanation on the specific components of the Process Safety assessment will follow.

Table 2.2. *Process Safety evaluation factors and ponderations.*

T-Rating		Ponderation	**4**
	T1 or water		1
	T2		2
	T3		3
	T4		4
	T5		5
	T6		6
	Top risk		7
	Undetermined		8
Cp		Ponderation	**2**
	Cp < 1800		5
	1800 <= Cp <= 3100		3
	Cp > 3100		1
	Missing data		7
ΔHvap		Ponderation	**2**
	ΔHvap < 340		5
	340 <= ΔHvap <= 1050		3
	ΔHvap > 1050		1
	Missing data		7
Flammability class		Ponderation	**4**
	IIIB or water		1
	IIIA		2
	II		3
	IC		4
	IB		5
	IA		6
	Undetermined		7

Table 2.2. *Process Safety evaluation factors and ponderations (continued).*

Relevant GHS hazard codes after transformation	Ponderation **1.5**
1	1
2	2
3	3
4	4
5	5
6	6
7	7
8	7
9	8
10	10

2.4.2.1. T-Rating evaluation

The T-rating evaluation is borrowed from the ACS GCI PR Solvent Tool and references to the UK Electric Equipment Temperature Classification based on each solvent's autoignition temperature in °C as a measure of the safety of working with said solvent in an industrial installation. It is also provided in the database as an information field with color coding of its own, not restricting it only to evaluation purposes.

Solvents are rated in one of 7 main categories, where a higher autoignition temperature reflects greater safety in an industrial context. All categories can be consulted in Table 2.3, where T indicates the autoignition temperature in °C. Please notice that the third column reflects the color code attributed to the T-Rating in the database. Water, considered as safe, will automatically be awarded a T1 rating in the evaluation.

Table 2.3. *PS: T-Rating classification rationale based on autoignition temperatures (°C).*

Condition	T-Rating	Color code in database	Value attributed in assessment
T >= 450	T1		1
450 > T >= 300	T2		2
300 > T >= 200	T3		3
200 > T >= 135	T4		4
135 > T >= 100	T5		5
100 > T >= 85	T6		6
85 > T	Top risk		7
N/A	Undetermined		8

2.4.2.2. Specific heat capacity (Cp)

The Cp intends to measure the amount of heat required to increase the temperature of a substance (in this case a solvent) by 1 degree when heat is applied at a constant pressure, therefore, a lower Cp value will indicate that the solvent will heat more easily (requiring less of an energetic input). When planning an industrial process, solvents with lower Cp values might be preferred in order to minimize the energy requirements of the process itself. On the other hand, in industrial safety a higher Cp value is oftentimes preferred. A solvent with a higher Cp value demonstrates greater resistance to rapid and uncontrollable temperature fluctuations, providing a crucial buffer during emergencies and allowing for a more controlled response, thereby minimizing the risk of escalating the severity of an incident.

For the assessment and due to the nature of the property in consideration, no easy individual values could be decided as a limit to a better or worse classification. Therefore, for the solvent included in the database for which heat capacity values were logged, solvents were divided into three tiers, with the aim to concentrate the 25% lowest (worse) Cp values in one tier, the 15% highest (better) Cp values in another, and lastly leaving a middle tier of approximately 60% of all solvents in the database. The three final tiers were defined as follows:

- Cp < 1800 J/LK, concentrating 22% of solvents.
- 1800 <= Cp <= 3100 J/LK, concentrating 63% of solvents.
- Cp > 3100 J/LK, concentrating the remaining 15% of solvents.

Once the tiers were defined, individual values for the risk associated with each substance's heat capacity were awarded in the evaluation as can be seen in Table 2.4. For solvents for whom no Cp data was available, a cautious approach was adopted by assigning them a conservative estimate, prioritizing safety. Therefore, solvents with unknown Cp were immediately attributed the highest score.

Table 2.4. *PS: Cp classification rationale.*

Condition, where Cp [J/LK]	Value attributed in assessment
Missing data, unknown Cp	7
Cp < 1800	5
1800 <= Cp <= 3100	3
3100 < Cp	1

2.4.2.3. Enthalpy of vaporization (ΔHvap)

Similar to the Cp, it is important to remember that the ΔHvap intends to measure the amount of energy (enthalpy) that must be added to a liquid substance (in this case a solvent) to transform a quantity of said substance into a gas. A lower ΔHvap will indicate that the solvent will vaporize more easily (requiring less of an energetic input). When planning certain processes, such as distillations, solvents with lower ΔHvap values might be preferred in order to minimize the energy requirements of the process itself. On the other hand, in industrial safety a higher ΔHvap value is also oftentimes preferred, as rapid unplanned vaporization of a solvent in face of uncontrolled temperature fluctuations could endanger the safety of the equipment and the workers, even leading to emergency release scenarios.

In this context and as happens with the Cp, due to the nature of the property in consideration, no easy individual values could be decided as a limit to a better or worse classification. Therefore, the same analysis that was done for the Cp was done here, classifying solvents into three tiers, also with the aim to concentrate the 25% lowest (worse) values in one tier, the 15% highest (better) values in another, and lastly leaving a middle tier of approximately 60% of all solvents in the database. The three final tiers were defined as follows:

- ΔHvap < 340 kJ/L, concentrating 23% of solvents.
- 340 <= ΔHvap <= 1050 kJ/L, concentrating 62% of solvents.
- ΔHvap > 1050 kJ/L, concentrating the remaining 15% of solvents.

Once the tiers were defined, individual values for the risk associated with each substance's enthalpy of vaporization were awarded in the evaluation as can be seen in Table 2.5. Once again, for solvents for whom no ΔHvap data was available, a cautious approach was adopted by assigning them a conservative estimate (the highest score), prioritizing safety.

Table 2.5. *PS: ΔHvap classification rationale.*

Condition, where ΔHvap [kJ/L]	Value attributed in assessment
Missing data, unknown ΔHvap	7
ΔHvap < 340	5
340 <= ΔHvap <= 1050	3
1050 < ΔHvap	1

2.4.2.4. Flammability class

The flammability class evaluation is borrowed from the ACS GCI PR Solvent Tool and references the US NFPA based on each solvent's closed-cup flash point in °C as a measure of the safety of working with said solvent in an industrial installation. It is also provided in the database as an information field with color coding of its own, not restricting it only to evaluation purposes. A higher flash point reflects great safety in an industrial context. Additionally, for solvents with particularly low flash points, an additional classification is done based on their boiling point. All categories can be consulted in Table 2.6, where FP indicates the flash point temperature and BP indicates the boiling temperature, both in °C. Please notice that the third column reflects the color code attributed to the flammability class in the database. Water, considered as safe, will automatically be awarded a IIIB rating in the evaluation.

Table 2.6. *PS: Flammability classification rationale based on closed-cup flash points (°C).*

Condition	Flammability class	Color code in database	Value attributed in assessment
FP >= 93.3	IIIB		1
93.3 > FP >= 60	IIIA		2
60 > FP >= 37.8	II		3
37.8 > FP >= 22.8	IC		4
22.8 > FP & 37.8 <= BP	IB		5
22.8 > FP & 37.8 > BP	IA		6
N/A	Undetermined		7

2.4.2.5. Process hazard-related GHS codes

The Process hazard-related GHS code assessment is derived from the GHS codes attributed to each solvent in its Registration Dossier under REACH with ECHA. Process hazard-related GHS codes selected were those identified in earlier chapters (H200s minus H281, plus relevant supplemental hazard information codes EUH014, 019, 044, 209/209A, and 210). A complete list of GHS codes and hazard statements can be found in Annex B: Full list of GHS hazard codes and statements.

As happened in the Health Risk evaluation, for the Process hazard assessment each GHS code was attributed a value as a measurement of the danger associated to the GHS and serving as a comparison with other GHS codes. The lower the value, the less danger the code signifies. The values attributed to the different GHS codes derive from the same type of linguistic and impact analysis of the hazard statement that the Health Risk assessment, but the values attributed to modifiers and effects in Process Safety is completely separate from the earlier assessment. Therefore, no direct comparison between the GHS code values for Health Risk and Process Safety is possible.

Similarly, the effect and modifier values in the Process hazard assessment are once again strongly recommended to ensure a well-balanced process hazard evaluation but can all be modified by the final user or any party, perhaps after a more in-depth analysis. All modifiable values are shown in a yellow background in Table 2.7. After any modifications, the solvent tool will automatically fully update to consider the modified values.

Table 2.7. *Key for process hazard statements.*

Key for process safety hazards (H200s minus H281, and relevant EUHs)			
	Modifiers		Effects
-1	Can become		*Hazard*
-1.5	May	1.5	Flammable
-2.5	Increased risk	3	Explosive
-1	Requires contact with another substance (not air)	4.5	Blast
-0.5	Requires elevated heat and/or pressure conditions	6	Projection
-2	Requires large quantities	6	Violent reaction
		3	Corrosive to metals
		4	Container bursting
			Conditions of flammability and explosiveness hazards
		2	By itself and unless further stated
		4	In mixture with air
		6	Even in absence of air
			Form
		3	Gas
		3	Aerosol
		3	Vapour
		2	Liquid
		1	Solid
		0.5	*if pressurized
			Extra notes
		2	Unstable
		4	Self-heating
		6	Spontaneous effect
			Other actions
		4	Can cause hazardous conditions
		2	Can intensify hazardous conditions
			Intensity of effect
		5	Mass
		4	Extreme
		3	Severe
		2	High
			Intensity of hazard
		1	Extremely
		0.5	Highly

The complete list of all process hazard-related GHS codes and hazard statements with the value assigned to them as a result of this analysis can be found in Annex D: Process hazard-related GHS code and statement evaluations

As with the Health Risk assessment, since any one solvent could be assigned several GHS codes, each solvent had its own ‘untreated’ “solvent total process hazard value.” To proceed with a linear transformation, minimum and maximum attainable values on this ‘untreated’ scale had to be defined. Once again, the minimum value is straightforward, understood as the lack of any GHS process hazard codes. Therefore, the minimum will be zero. For the maximum, a hypothetical worst-case solvent was ideated: “pressurized gas that is corrosive to metals, and (with elevated heat or pressure, aiding it to burst the container) will spontaneously even in absence of air catch fire, explode, and/or cause a mass violent reaction, causing hazardous conditions. May cause explosive peroxides.” This hypothetical worst-case solvent was then evaluated as a forty-three on the untreated scale, which in turn was defined as the maximum for the linear regression. Nevertheless, in the understanding that this worst-case solvent is only hypothetical and there could be worse, a safeguard into the linear regression was built anew. If the solvent total process hazard value were evaluated as being over this maximum, the final ‘treated’ score would show as a 10 on the 1-10 scale.

This final ‘treated’ process hazard value on the 1-10 scale was considered for the evaluation of the Process Safety category, with no further transformation of the value attributed to each solvent.

2.4.3. Environmental Impact

The Environmental Impact (EI) assessment considers four evaluations:

- Ecotoxicity.
- PBT/vPvB: based on if a solvent is considered to be Persistent, Bioaccumulative, and Toxic (PBT) or even very Persistent and very Bioaccumulative (vPvB).
- SVHC: based on if a solvent is deemed to be a Substance of Very High Concern by the ECHA.
- VOC potential: based upon the volatility of an organic solvent, measured through its vapor pressure.

As with the Process Safety assessment, for each evaluation, a further analysis yielded ponderation scores, which once again help to effectively allocate varying degrees of importance to specific aspects of the Environmental Impact assessment while aligning the scales of assessment. Recommended preset ponderation scores are once again loaded onto the tool and shown in a green background, but the user is still able to modify them, with immediate updating of the adjusted assessment across all solvents. The various smaller evaluations and recommended ponderations can be consulted in Table 2.8. Further explanation on the specific components of the Environmental Impact assessment will follow.

Table 2.8. *Environmental Impact evaluation factors and ponderations.*

Ecotoxicity	Ponderation	1
None		0
H400 - Very toxic to aquatic life		4
H410 - Very toxic to aquatic life with long lasting effects		5
H411 - Toxic to aquatic life with long lasting effects		3
H412 - Harmful to aquatic life with long lasting effects		2
H413 - May cause long lasting harmful effects to aquatic life		1
H420 - Harms public health and the environment by destroying ozone in the upper atmosphere.		6
PBT/vPvB	**Ponderation**	**5**
None		0
PBT		3
vPvB		6
SVHC	**Ponderation**	**4**
Yes		4
No		0
VOC	**Ponderation**	**3**
Not a VOC		0
Group 1		2
Group 2		4
Group 3		6

2.4.3.1. Ecotoxicity

The ecotoxicity assessment is derived from the environmental hazard-related GHS codes attributed to each solvent in its Registration Dossier under REACH with ECHA. GHS codes selected were those identified in earlier chapters (H400s, plus supplemental hazard information code EUH401). A complete list of GHS codes and hazard statements can be found in Annex B: Full list of GHS hazard codes and statements

Those GHS codes relevant to this assessment were directly awarded a 'danger' value, such as earlier assessments, in comparison with the other environmental hazard-related GHS codes, as shown in Table 2.9.

Table 2.9. *EI: Ecotoxicity assessment rationale.*

GHS code	GHS hazard statement	Value attributed in assessment
None	-	0
H400	Very toxic to aquatic life.	4
H410	Very toxic to aquatic life with long lasting effects.	5
H411	Toxic to aquatic life with long lasting effects.	3
H412	Harmful to aquatic life with long lasting effects.	2
H413	May cause long lasting harmful effects to aquatic life.	1
H420	Harms public health and the environment by destroying ozone in the upper atmosphere.	6
EUH401	To avoid risks to human health and the environment, comply with the instructions for use.	0

2.4.3.2. Persistent, Bioaccumulative, and Toxic/very Persistent, very Bioaccumulative

This evaluation is derived from the PBT (Persistent, Bioaccumulative, and Toxic) assessment each solvent goes through as part of its registration under REACH with ECHA. These results are easily available in each substance's Registration Dossier, and rank a substance as either PBT, vPvB (very Persistent and very Bioaccumulative) or neither. Values were attributed to each verdict based on impact on the environment, as shown in Table 2.10.

Table 2.10. *EI: PBT assessment rationale.*

Assessment result	Value attributed in assessment
Not a PBT or vPvB	0
PBT	3
vPvB	6

2.4.3.3. Substances of Very High Concern (SVHC)

The Substances of Very High Concern (SVHC) assessment falls back on the registration or lack thereof of each solvent in ECHA's Candidate List for Authorization under Annex XIV of REACH. The aim of the inclusion of this section in the Environmental Impact evaluation relies on the importance of progressively replacing SVHCs by less dangerous substances or technologies where technically and economically feasible alternatives are available, in line with REACH legislation. Therefore, to signal the most problematic solvents, specific values were given to those included in the Candidate List for Authorization under Annex XIV, as shown in Table 2.11.

Table 2.11. *EI: SVHC assessment rationale.*

Classification	Value attributed in assessment
Not an SVHC	0
SVHC	4

2.4.3.4. VOC potential

The VOC (Volatile Organic Compound) potential evaluation is borrowed from the ACS GCI PR Solvent Tool and is intended to act a measure of the potential environmental hazard of each solvent in face of the likeliness or ease of them to evaporate. Solvents are categorized through their vapor pressure (VP) as either a VOC or not a VOC and, in case they are considered a VOC, are then further categorized in one of three groups to reflect those who will more easily evaporate. This assessment is also provided in the database as an information field with color coding of its own, not restricting it only to evaluation purposes. For the VOC evaluation as part of the Environmental Impact assessment, values are provided to each classification, as is shown in Table 2.12. Please notice that the third column reflects the color code attributed to the VOC group in the database.

Table 2.12. *EI: VOC classification rationale based on vapor pressure (mmHg).*

Condition, for VP in mmHg	VOC classification	Color code in database	Value attributed in assessment
VP < 0.075	Not a VOC	N/A	0
0.075 <= VP < 20	Group 1		2
20 <= VP < 150	Group 2		4
150 <= VP	Group 3		6

2.4.4. Sustainability

In the sustainability assessment conducted, a comprehensive evaluation was undertaken, encompassing various key aspects commonly considered across literature as relevant to a sustainability evaluation. The assessment aimed to address mainly three dimensions:

- Environmental impact: The assessment examined the potential environmental repercussions of the evaluated substances, considering factors such as sourcing practices, and ozone depletion potential, among others. The toxicity profile of the solvents is also key when assessing environmental impact but will be included in a dimension of its own.

- Toxicity: Both human health impact and persistence in the environment were carefully assessed separately from general environmental impact to gauge the overall toxicity profile of the solvents at hand.
- Renewability: The evaluation also scrutinized the renewability aspects, encompassing sourcing practices as well as degradability and persistence in the environment.

This evaluation also sought to align itself with Anastas and Warner's 12 Principles of Green Chemistry whenever feasible. Several of the 12 Principles are present in these three main avenues of assessment, resulting in a holistic evaluation of the substances' sustainability profile.

Overall and as with previous assessments, the Sustainability appraisal considers seven evaluations:

- Solvent origin.
- Biodegradation: based on the biodegradation statements following OECD[11] testing guidelines and as registered with ECHA.
- Ecotoxicity.
- PBT/vPvB: based on if a solvent is considered to be Persistent, Bioaccumulative, and Toxic (PBT) or even very Persistent and very Bioaccumulative (vPvB).
- SVHC: based on if a solvent is deemed to be a Substance of Very High Concern by the ECHA.
- VOC potential: based upon the volatility of an organic solvent, measured through its vapor pressure.
- Environmental impact during incineration.

An initial attempt to evaluate the recoverability or ease of purification of solvents was also included in the database development. However, due to the complex nature of solvent purification methods, which vary by solvent, this particular evaluation was ultimately excluded from the overall Sustainability assessment.

As with earlier assessment, a further analysis yielded ponderation scores for each evaluation, which once again help to effectively allocate varying degrees of importance to specific aspects

[11] Organization for Economic Cooperation and Development.

of the Sustainability assessment while aligning the scales of assessment. Recommended preset ponderation scores are loaded onto the tool and shown in a pink background. Once more, the user is able to modify them, with immediate updating of the adjusted assessment across all solvents. The various evaluations and recommended ponderations can be consulted in Table 2.13. Further explanation on each of the specific components of the Sustainability assessment will follow.

Table 2.13. *Sustainability evaluation factors and ponderations.*

Solvent origin	Ponderation	**4**
Bio-based		1
Can be sourced renewably		2
Potential biomass feedstock		3
Not bio-based		4
Biodegradation statement	Ponderation	**3**
Readily biodegradable		1
Inherently biodegradable		2
Not biodegradable but there is no concern for the environment		3
Not biodegradable but inherently biodegradable under specific conditions		4
Not biodegradable but has potential for biodegradation		5
Not biodegradable		6
No information		6
N/A		0
Ecotoxicity	Ponderation	**1**
None		0
H400 - Very toxic to aquatic life		4
H410 - Very toxic to aquatic life with long lasting effects		5
H411 - Toxic to aquatic life with long lasting effects		3
H412 - Harmful to aquatic life with long lasting effects		2
H413 - May cause long lasting harmful effects to aquatic life		1
H420 - Harms public health and the environment by destroying ozone in the upper atmosphere.		6
PBT/vPvB	Ponderation	**3**
None		0
PBT		3
vPvB		6
SVHC	Ponderation	**2**
Yes		4
No		0

Table 2.13. *Sustainability evaluation factors and ponderations (continued).*

VOC	Ponderation **3**
Not a VOC	0
Group 1	2
Group 2	4
Group 3	6

Environmental impact during incineration	Ponderation **1.5**
Water	1
Alcohols	2
Esters	3
Ethers	4
Amines	5
Aldehydes	6
Ketones	7
Nitriles	8
Amides	9
Sulfoxides	10
Urea	11
Sulfones	12
Hydroxyethers	13
Halogenated alcohols	14
Aromatic hydrocarbons	15
Halogenated	16
Aromatic halogenated	17
Hydrocarbons	18

2.4.4.1. Solvent origin

Solvent origin intends to shine a light and give importance to those solvents that can be made from biomass and help make an informed switch from a fossil-fuel-sourced solvent to a biomass-sourced solvent, considering the technological or economic challenges entailed. Solvents are categorized following Byrne's assessment[12] and given values depending on their origin, as shown in Table 2.14:

- Bio-based: solvents produced from biomass on a large scale, if not exclusively.
- Can be sourced renewably: available on the market, but biomass is not the primary feedstock.
- Potential biomass feedstock: solvents with the potential to be produced from biomass because they are derived from bio-methanol (or syngas), bio-ethanol (or bio-ethylene),

[12] (Byrne, et al., 2016)

bio-acetic acid, bio-1-butanol, bio-isobutanol (or bio-isobutene), and bio-acetone (also applicable as a potential precursor to isopropanol).

- Not bio-based.

Water is classified as bio-based for convenience. On the other hand, chlorinated solvents are grouped with those that cannot be made from the suggested bio-based intermediates, not because of technological feasibility (for example, chlorination of bio-methane), but because suppliers have no incentive to produce and distribute these solvents from renewable feedstocks.

Finally, fluorinated solvents are also grouped with solvents that cannot be made from the suggested bio-intermediates. They are not necessarily unrealistic either, but there are points that lower the greenness of these solvents: various fluorinated solvent production processes still rely on chlorinated intermediates and the origin of the fluorine agent can be problematic. Therefore, even though fluorinated solvents offer numerous advantages vs. ozone-depleting and other more dangerous or more unstable chemicals, as of this first edition of the solvent assessment tool they are still considered as 'cannot be made from the suggested bio-based intermediates'.

Table 2.14. *Sustainability: Solvent origin assessment rationale.*

Origin	Value attributed in assessment
Bio-based	1
Can be sourced renewably	2
Potential biomass feedstock	3
Not bio-based	4

2.4.4.2. Biodegradation

The Biodegradation assessment falls back on the assessment each solvent goes through as part of its registration under REACH with ECHA. These results are easily available in each substance's Registration Dossier. Values were attributed to each verdict based on impact on the environment, as shown in Table 2.15. Once again, for solvents whose biodegradability is unknown, the highest (worst) score is attributed out of caution.

Table 2.15. *Sustainability: Biodegradation statement assessment rationale.*

Biodegradation statement	Value attributed in assessment
Readily biodegradable	1
Inherently biodegradable	2
Not biodegradable but there is no concern for the environment	3
Not biodegradable but inherently biodegradable under specific conditions	4
Not biodegradable but has potential for biodegradation	5
Not biodegradable	6
No information	6
N/A	0

2.4.4.3. Ecotoxicity

The ecotoxicity assessment is derived from the environmental hazard-related GHS codes (H400s and EUH401) attributed to each solvent in its Registration Dossier under REACH with ECHA. This Ecotoxicity appraisal is the same evaluation done in chapter 2.4.3.1 Ecotoxicity, as part of the Environmental Impact assessment (Table 2.16).

Table 2.16. *Sustainability: Ecotoxicity assessment rationale.*

GHS code	GHS hazard statement	Value attributed in assessment
None	-	0
H400	Very toxic to aquatic life.	4
H410	Very toxic to aquatic life with long lasting effects.	5
H411	Toxic to aquatic life with long lasting effects.	3
H412	Harmful to aquatic life with long lasting effects.	2
H413	May cause long lasting harmful effects to aquatic life.	1
H420	Harms public health and the environment by destroying ozone in the upper atmosphere.	6
EUH401	To avoid risks to human health and the environment, comply with the instructions for use.	0

2.4.4.1. Persistent, Bioaccumulative, and Toxic/very Persistent, very Bioaccumulative

The PBT/vPvB assessment (Table 2.17) is derived from the PBT (Persistent, Bioaccumulative, and Toxic) assessment each solvent goes through as part of its registration under REACH with ECHA. This PBT/vPvB appraisal is the same evaluation done in chapter 2.4.3.2 Persistent, Bioaccumulative, and Toxic/very Persistent, very B, as part of the Environmental Impact assessment.

Table 2.17. *Sustainability: PBT/vPvB assessment rationale.*

Assessment result	Value attributed in assessment
Not a PBT or vPvB	0
PBT	3
vPvB	6

2.4.4.2. Substances of Very High Concern (SVHC)

The SVHC assessment (Table 2.18) is based on the registration or lack thereof of each solvent in ECHA's Candidate List for Authorization under Annex XIV of REACH. This SVHC appraisal is the same evaluation done in chapter 2.4.3.3 Substances of Very High Concern (SVHC), as part of the Environmental Impact assessment.

Table 2.18. *Sustainability: SVHC assessment rationale.*

Classification	Value attributed in assessment
Not an SVHC	0
SVHC	4

2.4.4.3. VOC potential

The VOC potential assessment (Table 2.19) is borrowed from the ACS GCI PR Solvent Tool and is intended to act a measure of the potential environmental hazard of each solvent in face of the likeliness or ease of them to evaporate, measured through each solvent’s vapor pressure. This VOC potential appraisal is the same evaluation done in chapter 2.4.3.4 VOC potential, as part of the Environmental Impact assessment. Please notice that the third column reflects the color code attributed to the VOC group in the database.

Table 2.19. *Sustainability: VOC classification rationale based on vapor pressure (mmHg).*

Condition, for VP in mmHg	VOC classification	Color code in database	Value attributed in assessment
VP < 0.075	Not a VOC	N/A	0
0.075 <= VP < 20	Group 1		2
20 <= VP < 150	Group 2		4
150 <= VP	Group 3		6

2.4.4.4. Environmental impact during incineration

This section of the Sustainability evaluation aims to assess the potential environmental impact associated with the incineration of solvents, based very generally on the toxicity, persistence, and potential for the formation of harmful byproducts, attributed to the solvent's family. As such, families are assigned values, presented in Table 2.20, based on their anticipated environmental impact from incineration.

In cases where solvents could be categorized into different families (such as halogenated alcohols) or a subset of a family with relevant attributes (such as aromatic hydrocarbons or aromatic halogenates), the creation of an additional "family" became necessary to fully evaluate the environmental impact the solvent could have if incinerated. This additional categorization ensures that the varying environmental concerns are considered in the assessment process.

Table 2.20. *Sustainability: Environmental impact during incineration assessment rationale.*

Family	Value attributed in assessment
Water	1
Alcohols	2
Esters	3
Ethers	4
Amines	5
Aldehydes	6
Ketones	7
Nitriles	8
Amides	9
Sulfoxides	10
Urea	11
Sulfones	12
Hydroxy ethers	13
Halogenated alcohols	14
Aromatic hydrocarbons	15
Halogenated	16
Aromatic halogenated	17
Hydrocarbons	18

A more comprehensive environmental analysis will require the inclusion of many more factors, and it is important to keep in mind that the ranking is a general indication and does not consider specific formulations or the efficiency of combustion technologies, emission control systems, and effluents' pre- or post-treatments.

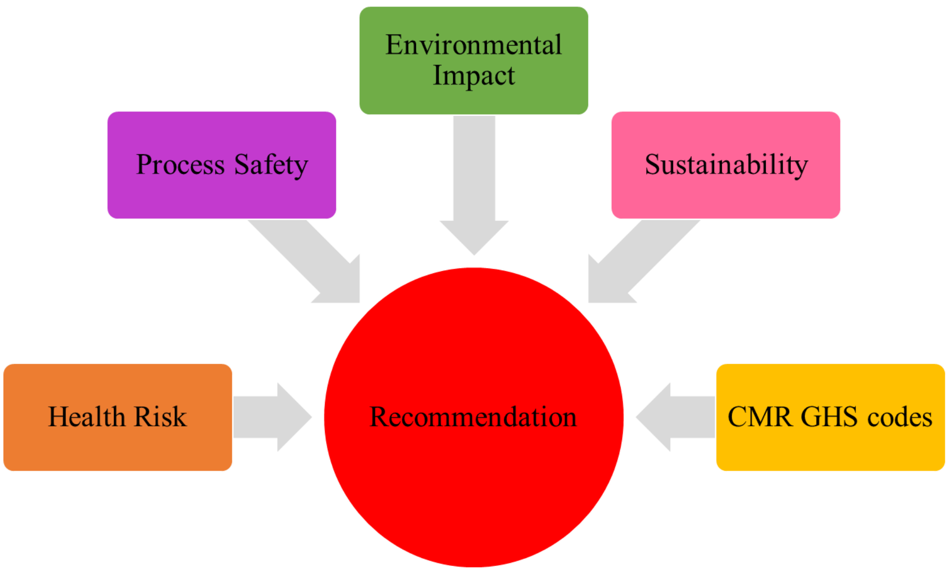
2.4.5. Final recommendation

The final recommendations rely on the four previous evaluations (Health Risk, Process Safety, Environmental Impact, and Sustainability) plus the existence of specific carcinogenic, mutagenic and reprotoxic (CMR) GHS codes deemed to be of special concern:

- H350/H351: May/Suspected of being carcinogenic.
- H360/H361: May/Suspected of damaging fertility or the unborn child.
- H370/H371/H372/H373: May/Suspected of damaging organs.

As shown in Figure 1, all previous evaluations contribute equally into the final recommendation, with no additional supplementary weighting or ponderations. The CMR GHS codes serve as triggers that elevate the severity of the final recommendation, reflecting the increased level of concern associated with the CMR properties and these GHS codes.

Figure 1. *Final assessment strategy.*



Each solvent is assigned to a single classification among four available options: recommended (green), problematic (yellow), hazardous (red), or highly hazardous (dark red), based on a formal framework depending on the color of the individual assessments. Each classification comprises various combinations of assessment results and CMR GHS hazard codes, and a solvent is ranked within that specific recommendation if it satisfies any of the corresponding criteria:

Recommended

- Three or more green evaluations and none of the GHS focus codes
- OR three or more green evaluations plus one GHS code between H360/H361/H370/H371/H372/H373

Problematic

- Three or more green evaluations and the H350/H351 code
- OR two green and two yellow evaluations
- OR two green, one yellow, and one red evaluations
- OR two yellow evaluations, one green, and one red, with or without the H360/H61 GHS codes
- OR three yellows and either no GHS codes or the H360/H361 codes

Hazardous

- Three yellow and one red evaluation
- OR two yellow and two red evaluations
- OR at least two yellow evaluations and one of the GHS code between H350/H351/H370/H371/H372/H373

Highly hazardous

- Three red evaluations or more
- OR two or more of any of the CMR GHS codes
- OR two red evaluations and one GHS code between H350/H351/H370/H371/H372/H373

For the process flow followed for determining the final recommendation in the tool, please refer to Figure 2.

In the uncommon case that one solvent could be classified under two categories, the most hazardous one will be considered for the final recommendation. For other cases not encompassed above, and particularly for newer solvents as they are incorporated into the database, the official recommendation will be for the case to be evaluated separately to determine the most appropriate category for their classification.

Figure 2. *Final recommendation process flow.*

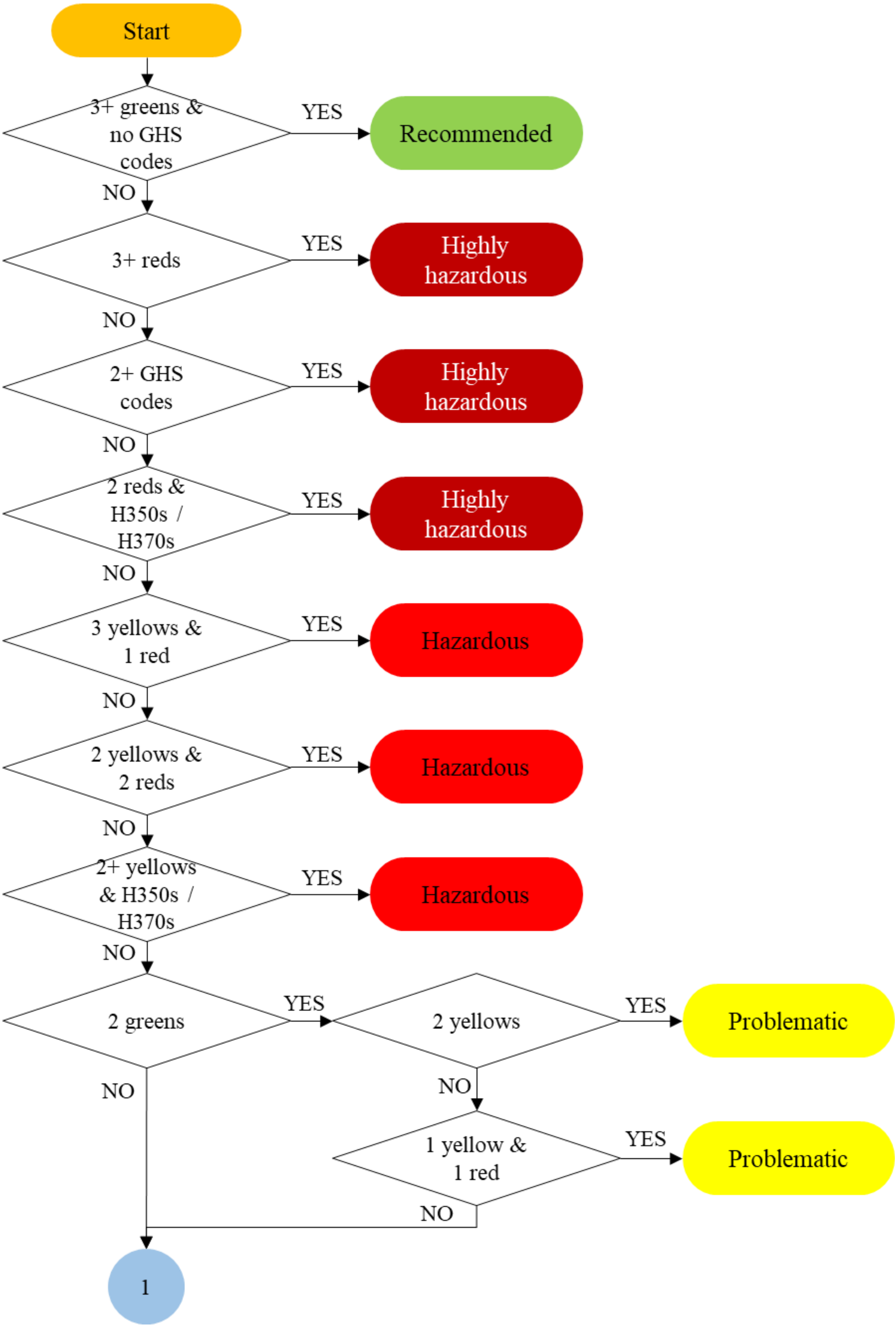
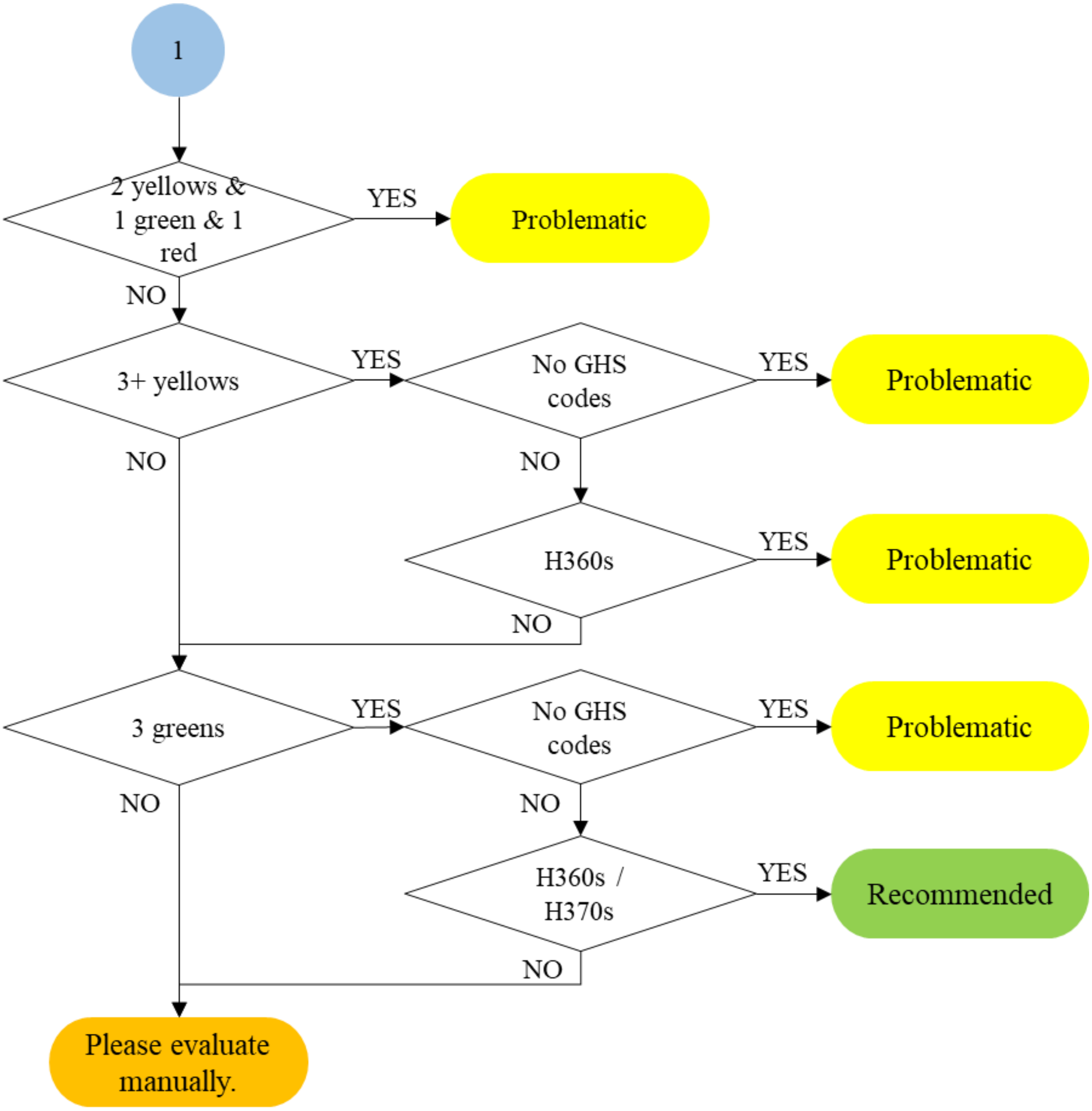


Figure 2. *Final recommendation process flow (continued).*



3. Results and Discussion

Due to the length of the project and the various steps taken, as shown in the previous chapter, the results and discussion will be divided in segments around the 3 main deliverables identified:

1) Priorities, information fields, and delivery method determination.
2) Solvent list.
3) Solvent tool and guide.

An additional note on next steps for this project will be included at the end of the discussion.

3.1 Defining priorities, information fields, and delivery method

The questionnaire sent out to R&D had a total of 58 responses. Two key questions are highlighted in supported by another answer in the poll, regarding which practical considerations (other than technical suitability) are most important to chemists when choosing a solvent (Figure 4). In this case, safety and occupational health concerns are a focus for 66% of respondents.

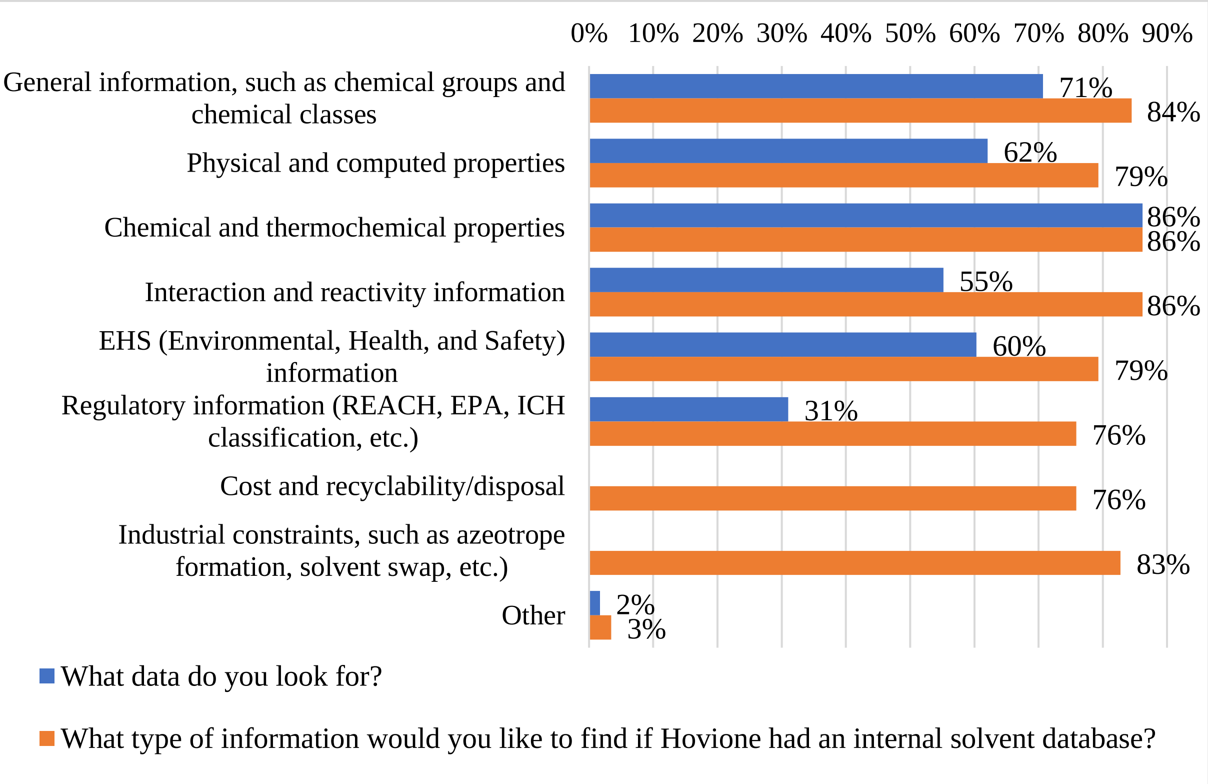
Figure 3: what data scientists look for (in blue) and what type of information they would like to have in this proposed tool (in orange), with results presented in percentage form. In case of the ‘Other’ responses, for the blue question the response was “I just order as requested”. For the orange question, this same message was repeated by the same user, while a new suggestion was also fed: “If an internal database I would like to find SAP[13] solvent density”. This is particularly relevant because, while the intention is undoubtedly for scientists to work with the SAP density from the outset, some concerns were raised regarding the time-consuming nature of accessing SAP to verify each individual density. As a result, some scientists opt to initially use density values from alternative sources for simulations and lab work, and subsequently adjust them when entering the data into the manufacturing sites' systems (who work with the official SAP density). Therefore, incorporating the SAP density directly onto a user-friendly tool will allow its easy accessibility for the scientists, streamlining the process and reducing potential errors or inconsistencies caused by manual adjustments.

[13] System Applications and Products in Data Processing, by it initials in German, is a software used by companies for enterprise resource planning, connecting several key processes and functions in one single system.

The results from the poll show that, in general, scientists would like to have all types of data on the proposed tool. The data they look for and what they would like to find (supported by another answer in the poll, regarding which practical considerations (other than technical suitability) are most important to chemists when choosing a solvent (Figure 4). In this case, safety and occupational health concerns are a focus for 66% of respondents.

Figure 3) exhibit a notable correlation, except for three particular cases where the gap is wider. In one instance, 55% of respondents seek interaction and reactivity data while 86% would like to find it on the tool. In another, 60% research HSE data while 79% would want to find it on the tool. This gap could be interpreted as an indicator of information that, if on hand, could add to the scientists' solvent selection process. This is further supported by another answer in the poll, regarding which practical considerations (other than technical suitability) are most important to chemists when choosing a solvent (Figure 4). In this case, safety and occupational health concerns are a focus for 66% of respondents.

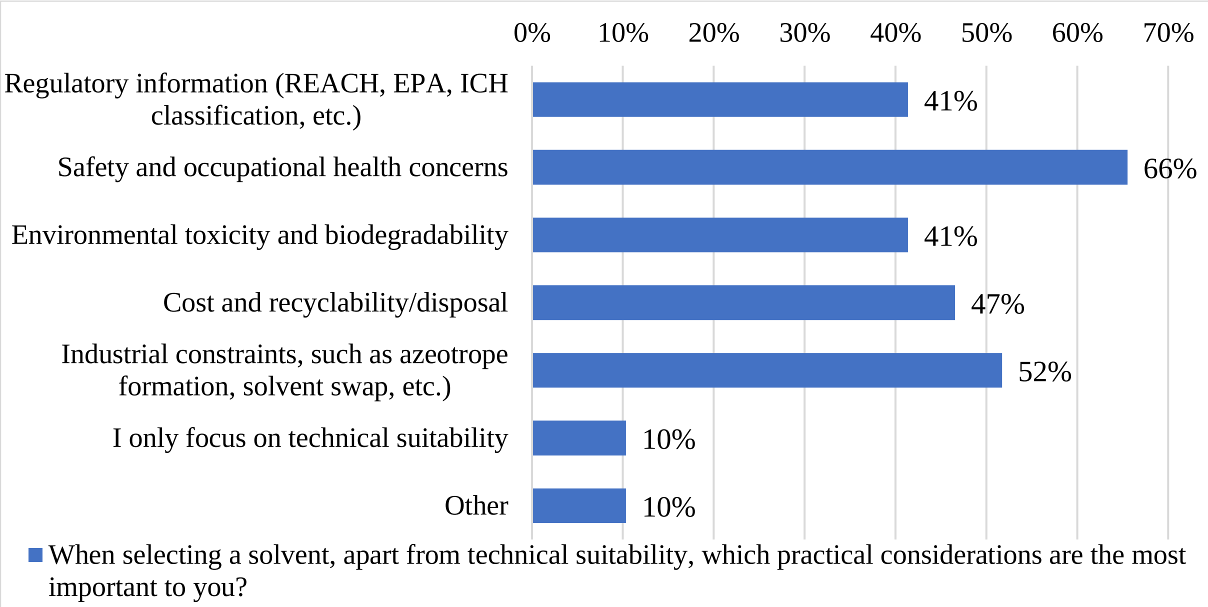
Figure 3. *Key questionnaire answers leading to priority definitions, part 1.*



The third instance of a wide gap in Figure 3 is perhaps the most significant one, regarding regulatory information (REACH, EPA, ICH classification, etc.). While only 31% of respondents look for that information, 76% reported they would like to find it on the tool. The need to include a regulatory framework in the database was also supported by Hovione's regulatory leader, Paulo Baião, in an interview where he compounded the need to reduce the use of SVHC throughout Hovione.

It is also important to remember one additional key finding of the questionnaire previously discussed: every single scientist reported consulting at least two different data sources. Pooling several information fields and data outlets into one in-house tool, such as the proposed solvent assessment database, could also help reduce the time spent scouring individual repositories for information. Additionally, while Hovione has many informatic tools that would allow for easy navigation of a large database, due to time constraints, relative ease of use, and ease of access, Microsoft Excel was chosen for the initial implementation of the project.

Figure 4. *Key questionnaire answers leading to priority definitions, part 2.*



Overall, two main conclusions are highlighted from the questionnaire exercise and the IT tool surveillance:

1) A centralized database that pools information scientists normally look for in several places is key for easy information access.
2) Due to familiarity with the software and time constraints, the database tool will initially be built in Microsoft Excel.
3) While including as much information as possible to build a comprehensive database is understandable, attempting to incorporate all types of data from the start would be impractical and time-consuming. Therefore, the need for prioritization of data fields

(shown in Table 3.1 and fed from the scientists' insights) ensures a guideline both for building this first database, as well as its expansions in the future.

Table 3.1. *Priorities for database fields.*

Higher priorities	Lower priorities
Industrial constraints	HSE information
Chemical and thermochemical properties	Regulatory information
General information	Cost and recyclability/disposal
Physical and computed properties	
Interaction and reactivity information	

Once priorities were established, an initial list of 31 information fields was formulated. As the project progressed, additional fields were incorporated, either to address any oversights from the first list or to allow for a more comprehensive evaluation and overview of the solvents. The final list of information fields numbers 49. Moreover, on order to facilitate user navigation and organized presentation of the information, the data fields were categorized. Table 3.2 showcases both the data fields and their corresponding categories.

Table 3.2. *Information fields for the first iteration of Hovione's database and solvent guide.*

Category	Information field
Basic information	Solvent (main name)
	Other names
	Family
	Grade
	Internal material number
General information	Chemical formula
	CAS Number
	SMILES
	InChI
	InChIKey
General properties	Molecular weight [g/mol]
	Density [g/cm3]
	Boiling Point [°C]
	Melting Point at 1 atm [°C]
	Flash Point [°C]
	Dielectric constant
	Dipole moment [D]
	Miscibility w/water
	log Kow
Engineering properties	Heat capacity (Cp) [J/LK]
	Enthalpy of Evaporation (ΔHvap) [kJ/L]
	T-rating
	Viscosity [cP @25ºC]

Table 3.2. *Information fields for the first iteration of Hovione's database and solvent guide (continued).*

Regulatory	Flags or restrictions
	ICH Q3C class
	ICH Q3C limit [ppm]
	Possible Impurities (per Hovione's specifications)
Health & Safety	OEL [ppm]
	Hovione OHC
	Flammability class
	Autoignition temperature [ºC]
	Properties of concern
	GHS pictogram
	GHS signal word
	GHS hazard statement
	GHS supplemental hazard statement (EUH)
Environmental impact	Ecotoxicity
	PBT/vPvB
	SVHC
	Vapor pressure [mmHg @25°C]
	VOC potential
Sustainability	Biodegradation statement
	Biodegradation code
	Solvent origin
Compatibility	Reactivity
	Materials
Economics	Cost [€]
Final recommendation	Recommendation
	Possible substitutions

3.2 Defining the solvent list

Despite initially identifying over a hundred solvents through an assessment of other published solvent guides, concerns over time constraints led to the compilation of a prioritized list comprising fifty solvents. This curated list specifically focuses on solvents that have been procured by the Purchasing team in recent years and are therefore in use at Hovione. The full list of solvents can be found in Table 3.3.

.

Table 3.3. *Solvent list for the first iteration of Hovione's database and solvent guide.*

Solvent list	
1-bromo-2-chloroethane	Ethylene carbonate
1-Butanol	Ethylene glycol
1-Propanol	Formaldehyde
2-Methoxyethanol	Heptane
2-Methyltetrahydrofuran	Hexane
Acetone	Isopropyl acetate
Acetonitrile	Isopropyl alcohol
Benzene	Isopropyl ether
Benzotrifluoride	MEK
Chlorobenzene	Methanol
Cyclohexane	Methyl isobutyl ketone
Cyclohexanone	MTBE
Cyclopentyl methyl ether	m-Xylene
Dichloromethane	N,N-Dimethylpropylene urea
Dicyclohexylamine	n-Butyl acetate
Diethanolamine	NMP
Diethylamine	Perflubron
Diglyme	Propyl acetate
Diisopropylethyl amine	Sulfolane
Dimethylformamide	t-Butanol
Dioxane	THF
DMAc	Toluene
DMSO	Triethylamine
Ethanol	Trifluoroethanol
Ethyl Acetate	Water

3.3 Solvent tool and guide

3.3.1 Visual representation

Owing to the extensive scale of the database, it was deemed impractical to present all information fields simultaneously due to potential navigational challenges. As a results, the fields, displayed like columns, were minimized per category (refer back to Table 3.2 on page 43), with only the first information field from each category on display. Buttons were added into the worksheet to allow for the full presentation of each category, should the user wish to do so. In total, the full database has 49 columns for information, including the solvents' main name, before the evaluation-related columns. Afterwards, 21 additional columns include all minor[14] and major evaluations, while 2 additional columns include the final recommendations

[14] Referring to all evaluations for each assessment (e.g., the ecotoxicity, PBT/vPvB, SVHC, and VOC potential evaluations for the Environmental Impact assessment).

and possible substitutions per solvent entry. With the categorization strategy, the user is welcomed by 11 initial columns for information (once again including main name), 4 columns corresponding to the main evaluations (Health Risk, Process Safety, Environmental Impact, and Sustainability), and 2 final columns presenting final recommendations and possible substitutions for each solvent entry. It is important to note that these categorizations are simply divisions of the comprehensive database, providing a more manageable representation of the information without compromising the integrity of the data.

In Figure 5, the categorization strategy and minimized look are presented for one solvent entry of the database – in this case dichloromethane (DCM). The reader should consider that, although it may appear as if there are multiple views, each "cut" represents a specific section of one entry, allowing for easier visualization and understanding. They should be interpreted as side-to-side.

Figure 5. *Database entry for dichloromethane with minimized look.*

		General information	General properties	Engineering properties	Regulatory
Solvent	Other names	Chemical formula	Molecular weight [g/mol]	Heat capacity (Cp) [J/LK]	Flags or restrictions
Dichloromethane	DCM, methylene ch	CH2Cl2	84.9305	898	Restricted uses under REACH

Health & Safety	Environmental impact	Sustainability	Compatibility	Economics
OEL [ppm]	Ecotoxicity	Biodegradation statement	Reactivity	Cost [€]
100	-	Readily biodegradable, both under aerobic and anaerobic conditions.	Reacts vigorously with active metals (such as lithium, sodium, and potassium) and with strong bases (such as potassium tert-butoxide). Incompatible with strong oxidizers, strong caustics, and chemically active metals (such as aluminum or magnesium powders). Reacts with sodium-potassium alloy, nitrogen tetraoxide, liquid oxygen, and titanium. Incompatible with alkali metals, amines and zinc. Liable to explode when mixed with dinitrogen pentaoxide or nitric acid. Mixtures of DCM in air with methanol vapor are flammable. Subject to hydrolysis which is accelerated by light.	1.618/KG 0.92/KG 2472/T

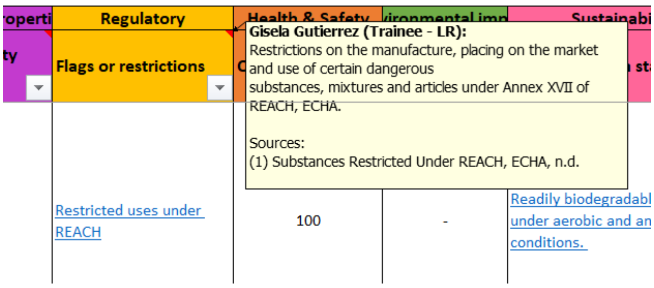
Figure 5. *Database entry for dichloromethane with minimized look (continued).*

Evaluations				Final recommendation	
Health Risk	Process Safety	Environmental Impact	Sustainability	Recommendation	Possible substitutions
3	4	3	6	Hazardous	Application dependant, but some alternatives are: ethyl acetate, MTBE (in chromatography and extractions), toluene, 2-MeTHF, 3:1 ethyl acetate:ethanol (for chromatography), dimethyl carbonate, CPME, supercritical carbon dioxide (scCO2), benzotrifluoride, d-limonene, diacetone alcohol (DAA), methyl soyate (as a cleaning agent), NMP (as a cleaning agent).

As a comparison, the reader should refer to Annex E: Database entry for dichloromethane with unminimized look. Here, the entry for DCM in the solvent database is still presented in the form of distinct "cuts" or sections of the database for easier reading but portrays the way the database would be seen by the user if the relevant sections are put on display via the minimization/maximization buttons. Once again, the reader should consider that, although it may appear as if there are multiple views, each "cut" represents a specific portion of one solvent entry.

Each column header, additionally to indicating the information contained in that column (information field), also contains a comment with additional information on the data field, as well as the sources consulted to populate it (Figure 6).

Figure 6. *Example of additional information comment for one information field.*



Additionally, all fields that show underlined in blue font (Figure 5, Figure 6) contains hyperlinks that allow the user to directly access the source of information. For example, in the case of the “Flags or restrictions” field, the hyperlink connects to the solvent’s Annex XVII document under REACH, regarding the specific conditions of restriction, directly on ECHA’s website.

Finally, in cases where several registrations of the same solvent exist within the company (particularly to signify different material grades), all material numbers, grades, and economic cost are mentioned separately, while properties are considered to be shared across the solvent. Therefore, one solvent might have several associate economic costs, depending on the specific grade needed (as DCM in Figure 5).

3.3.2 Data sources and missing information

The solvent database represents a comprehensive compilation of information gathered from numerous diverse sources, which have previously been briefly discussed in subchapter 2.3. While the database attempted to gather every data point for every solvent proposed, there were some information fields that proved more difficult than others. This resulted in the regrettable following gaps of information:

- Dielectric constant: for diethanolamine, diisopropylethylamine, perflubron, formaldehyde, and N,N-dimethyl propylene urea.
- Dipole moment: for diisopropylethylamine, perflubron, and N,N-dimethyl propylene urea.
- Heat capacity (Cp): for diisopropylethylamine, trifluoroethanol, formaldehyde, and N,N-dimethyl propylene urea.
- Enthalpy of vaporization (ΔHvap): for diisopropylethylamine, formaldehyde, and N,N-dimethyl propylene urea.
- Viscosity: for 1-bromo-2-chloroethane.

The gaps in information are concentrated mainly around three solvents: diisopropylethylamine (4 gaps), formaldehyde (3 gaps), and N,N-Dimethyl propylene urea (4 gaps). As a result, these solvents might evaluated more harshly. In particular, formaldehyde has a final recommendation of “Highly hazardous”, in part due to a score of 9 in Process Safety, as a result of the missing information.

These data gaps will be addressed, and efforts will be made to fill them as part of the ongoing development and refinement of the tool, to be discussed in subchapter 3.4).

Lastly, the full list of sources used for the population of the database, as well as the information snippets, is included as a separate worksheet in the solvent tool. For a total of 46 (final) data points, 55 different sources with 61 documents were considered: 10 ECHA websites or lists, one EMA guideline, 6 external databases, 5 Hovione internal documents or databases, 37 books, articles, and/or reports, and two separate pieces of software. An additional 11 sources were used for the information snippets. The user is also presented with the full list of sources for the data in matrix form. Within this matrix, numbers are used to indicate the prioritization of the sources. A value of one denotes the initial data source used, and subsequent sources were consulted in cascading manner for any missing or unavailable data points. This prioritization approach ensures that the most reliable sources are given precedence in the data compilation process.

A simplified matrix is shown in Figure 7. Please note this matrix only mentions the main source (e.g. ECHA), instead of all the individual documents or websites consulted (e.g. each Occupational Exposures Limit – OELs list). As well, this simplified matrix does not include the sourcing prioritization. The full reference list with source prioritization as is viewable on the tool is available in Annex F: Full list of references used in the data collection process for the database.

Figure 7. *Simplified data sourcing matrix.*

		ECHA	EMA	External databases					
				ACS GCIPR Solvent Tool, 2019	Chemical Compatibility, Fisher Scientific, n.d.	ChemSpider, n.d.	DIPPR Database, Dynochem, 2011	NIST Chemistry WebBook, n.d.	PubChem, n.d.
Basic information	**Solvent**								
	Other names								•
	Grade/more information								
	Material number								
General information	**Chemical formula**								•
	CAS number								•
	SMILES								•
	InChI								•
	InChIKey								•
General properties	**Molecular weight**								•
	Density								
	Boiling Point	•					•	•	
	Melting Point	•				•	•	•	
	Flash Point						•		•
	Dielectric constant						•		
	Dipole moment						•		
	Miscibility w/water			•					•
	log Kow	•		•					•
Engineering properties	**Heat capacity (Cp)**			•				•	
	Enthalpy of Evaporation (ΔHvap)			•				•	
	Viscosity	•							•
Regulatory	**Flags or restrictions**	•							
	ICH Q3C class		•				•		
	ICH Q3C limit		•						
	Possible Impurities (Hovione specification)								
Health & Safety	**OEL**	•							
	Hovione OHC								
	Flammability class								
	Autoignition temperature						•		•
	Properties of concern	•							
	GHS pictogram	•							
	GHS signal word	•							
	GHS hazard statement	•							
	GHS supplemental hazard statement (EUH)	•							
Environmental impact	**Ecotoxicity**	•							
	PBT/vPvB	•							
	SVHC	•							
	Vapor pressure								•
Sustainability	**Biodegradation statement**	•							
	Solvent origin								•
Compatibility	**Reactivity**				•				•
	Materials								
Economics	**Cost**								
Final recommendations	**Possible substitutions**								

Figure 7. *Simplified data sourcing matrix (continued).*

		Hovione internal documentation	External Literature							
			Alfonsi, 2008	Armenta, 2022	Azzena, 2019	Baird, 2019	Byrne, 2017	Canadian Centre for Occupational Health and Safety, 2023	de Gonzalo, 2019	Faveere, 2020
Basic information	**Solvent**	•								
	Other names									
	Grade/more information	•								
	Material number	•								
General information	**Chemical formula**									
	CAS number									
	SMILES									
	InChI									
	InChIKey									
General properties	**Molecular weight**									
	Density	•								
	Boiling Point	•								
	Melting Point	•								
	Flash Point	•								
	Dielectric constant									
	Dipole moment									
	Miscibility w/water									
	log Kow	•								
Engineering properties	**Heat capacity (Cp)**									
	Enthalpy of Evaporation (ΔHvap)					•				
	Viscosity	•								
Regulatory	**Flags or restrictions**									
	ICH Q3C class									
	ICH Q3C limit									
	Possible Impurities (Hovione specification)	•								
Health & Safety	**OEL**									
	Hovione OHC	•								
	Flammability class									
	Autoignition temperature									
	Properties of concern									
	GHS pictogram									
	GHS signal word									
	GHS hazard statement									
	GHS supplemental hazard statement (EUH)									
Environmental impact	**Ecotoxicity**									
	PBT/vPvB									
	SVHC									
	Vapor pressure	•								
Sustainability	**Biodegradation statement**									
	Solvent origin			•	•		•		•	•
Compatibility	**Reactivity**	•						•		
	Materials									
Economics	**Cost**	•								
Final recommendations	**Possible substitutions**		•	•	•		•			

Figure 7. *Simplified data sourcing matrix (continued).*

		External Literature								
		Fisher Science, n.d.	Fisher Scientific, n.d.	Frauenkron, 2000	Future Market Insights, 2023	Great American Insurance Group, 2006	Haynes, 2017	Hopwood, 2009	IFA, n.d.	LOBA Chemie, 2013
Basic information	**Solvent**									
	Other names									
	Grade/more information									
	Material number									
General information	**Chemical formula**									
	CAS number									
	SMILES									
	InChI									
	InChIKey									
General properties	**Molecular weight**									
	Density									
	Boiling Point									
	Melting Point									
	Flash Point									
	Dielectric constant						•			
	Dipole moment						•			
	Miscibility w/water									
	log Kow								•	
Engineering properties	**Heat capacity (Cp)**			•			•			•
	Enthalpy of Evaporation (ΔHvap)						•			
	Viscosity		•				•			
Regulatory	**Flags or restrictions**									
	ICH Q3C class									
	ICH Q3C limit									
	Possible Impurities (Hovione specification)									
Health & Safety	**OEL**									
	Hovione OHC									
	Flammability class					•				
	Autoignition temperature									
	Properties of concern									
	GHS pictogram									
	GHS signal word									
	GHS hazard statement									
	GHS supplemental hazard statement (EUH)									
Environmental impact	**Ecotoxicity**									
	PBT/vPvB									
	SVHC									
	Vapor pressure									
Sustainability	**Biodegradation statement**									
	Solvent origin				•			•		
Compatibility	**Reactivity**									
	Materials									
Economics	**Cost**									
Final recommendations	**Possible substitutions**	•								

Figure 7. *Simplified data sourcing matrix (continued).*

		External Literature									
		Maryott, 1951	Merchant, 2015	Merck, 2020	Merck, n.d.	Ogawa, 1997	Penn Environmental Health & Radiation Safety, 2018	Prat, 2013	Richter, 2018	Riess, 2005	Sat Pad, 2019
Basic information	**Solvent**										
	Other names										
	Grade/more information										
	Material number										
General information	**Chemical formula**										
	CAS number										
	SMILES										
	InChI										
	InChIKey										
General properties	**Molecular weight**										
	Density										
	Boiling Point										
	Melting Point										
	Flash Point										
	Dielectric constant	•									
	Dipole moment										
	Miscibility w/water									•	
	log Kow										
Engineering properties	**Heat capacity (Cp)**										
	Enthalpy of Evaporation (ΔHvap)										
	Viscosity										
Regulatory	**Flags or restrictions**										
	ICH Q3C class										
	ICH Q3C limit										
	Possible Impurities (Hovione specification)										
Health & Safety	**OEL**										
	Hovione OHC										
	Flammability class										
	Autoignition temperature										
	Properties of concern										
	GHS pictogram										
	GHS signal word										
	GHS hazard statement										
	GHS supplemental hazard statement (EUH)										
Environmental impact	**Ecotoxicity**										
	PBT/vPvB										
	SVHC										
	Vapor pressure										
Sustainability	**Biodegradation statement**										
	Solvent origin								•		
Compatibility	**Reactivity**										•
	Materials										
Economics	**Cost**										
Final recommendations	**Possible substitutions**		•	•	•	•	•	•			

Figure 7. *Simplified data sourcing matrix (continued).*

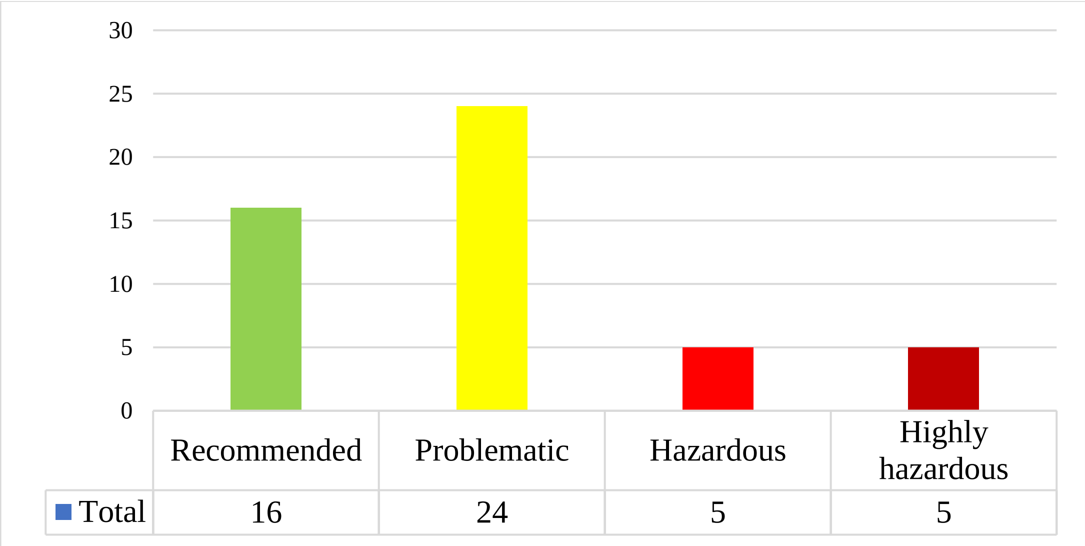
		External literature									Software	
		Sherman, 1998	Sigma Aldrich, 2019	Silver, 2023	Song, 2006	Sorgi, 2001	University of Pittsburgh Department of Chemistry, n.d.	Varushchenko, 1997	Winterton, 2021	Wypych, 2019	CAMEO Chemicals, NOAA	Chemical Reactivity Worksheet (CRW), AIChE
Basic information	Solvent											
	Other names											
	Grade/more information											
	Material number											
General information	Chemical formula											
	CAS number											
	SMILES											
	InChI											
	InChIKey											
General properties	Molecular weight											
	Density											
	Boiling Point											
	Melting Point											
	Flash Point											
	Dielectric constant											
	Dipole moment						•					
	Miscibility w/water					•						
	log Kow											
Engineering properties	Heat capacity (Cp)							•				
	Enthalpy of Evaporation (ΔHvap)										•	
	Viscosity									•		
Regulatory	Flags or restrictions											
	ICH Q3C class											
	ICH Q3C limit											
	Possible Impurities (Hovione specification)											
Health & Safety	OEL											
	Hovione OHC											
	Flammability class											
	Autoignition temperature									•	•	
	Properties of concern											
	GHS pictogram											
	GHS signal word											
	GHS hazard statement											
	GHS supplemental hazard statement (EUH)											
Environmental impact	Ecotoxicity											
	PBT/vPvB											
	SVHC											
	Vapor pressure											
Sustainability	Biodegradation statement											
	Solvent origin											
Compatibility	Reactivity											•
	Materials											•
Economics	Cost											
Final recommendations	Possible substitutions	•	•	•	•				•			

3.3.3 Solvent recommendation results and analysis

Upon the completion of the data input and following this assessment process, a notable number of solvents emerged with a consensus of “recommended” and "problematic" rankings, in line with what was expected. Only a minority of solvents were evaluated as “hazardous” and “highly hazardous” as can be seen in Figure 8.

Particularly for those solvents identified as highly hazardous, all five solvents are confirmed or suspected CMR substances, four of them having two different CMR GHS codes. This outcome underscores the efficacy of the tool in identifying solvents that align with the criteria established and that meet the (un)desired benchmarks.

Figure 8. *Distribution of final recommendations by category.*



The full evaluation scores for each solvent, along with the relevant CMR GHS for determining the final recommendation, are provided in Figure 9. *Hovione solvent tool CMR GHS codes, evaluation scores, and recommendation.*. It is possible to follow the process flow to reach the tool’s final recommendation for each solvent by referring to Figure 2 on page 36.

Figure 9. *Hovione solvent tool CMR GHS codes, evaluation scores, and recommendation.*

Solvent	CMR GHS codes	Evaluations				Recommendation
		Health Risk	Process Safety	Environmental Impact	Sustainability	
Dichloromethane	H351	3	4	3	6	Hazardous
Acetone		2	4	3	4	Problematic
Water		Not classified as hazardous	1	3	2	Recommended
Ethanol		1	4	3	2	Recommended
Methanol	H370	7	3	3	3	Recommended
MEK		2	4	3	4	Problematic
Heptane		3	5	3	6	Problematic
THF	H351	4	5	3	4	Hazardous
Ethyl Acetate		2	4	3	3	Recommended
Acetonitrile		4	4	3	4	Problematic
Isopropyl alcohol		2	3	3	3	Recommended
DMSO		Not classified as hazardous	3	2	3	Recommended
Dimethylformamide	H360	5	3	4	4	Problematic
Benzene	H350 H372	8	4	3	5	Highly hazardous
Hexane	H361 H373	6	4	4	6	Highly hazardous
Chlorobenzene		3	4	2	6	Problematic
Toluene	H361 H373	6	4	3	5	Highly hazardous
2-MeTHF		3	5	3	4	Problematic
DMAc	H360	4	3	4	4	Problematic
NMP	H360	4	3	4	4	Problematic
Dioxane	H350	4	6	5	5	Hazardous
t-Butanol		3	3	3	3	Recommended
Cyclohexane		3	4	3	6	Problematic
Isopropyl ether		2	4	3	4	Problematic
Methyl isobutyl ketone	H351	5	4	2	3	Hazardous
2-Methoxyethanol	H360	5	4	4	5	Problematic
Triethylamine		4	4	3	3	Problematic
Isopropyl acetate		2	4	3	3	Recommended
Benzotrifluoride		1	7	3	7	Problematic
Diglyme	H360	2	5	4	4	Problematic
n-Butyl acetate		2	4	2	3	Recommended
Diethanolamine	H373	5	2	1	2	Recommended
MTBE		2	4	7	6	Problematic
m-Xylene		3	4	2	5	Problematic
Diethylamine		4	4	3	4	Problematic
Cyclopentyl methyl ether		3	6	3	4	Problematic
1-Propanol		2	3	3	3	Recommended
Ethylene carbonate	H373	4	2	1	2	Recommended
1-Butanol		4	4	2	2	Problematic
Ethylene glycol		2	2	1	2	Recommended
Cyclohexanone		2	3	2	4	Recommended
Sulfolane		2	5	1	4	Problematic
Propyl acetate		2	4	3	3	Recommended
Diisopropylethyl amine		4	6	1	4	Problematic
1-bromo-2-chloroethane	H351	7	7	3	7	Hazardous
Dicyclohexylamine		2	4	2	3	Recommended
Trifluoroethanol	H360 H373	6	4	3	6	Highly hazardous
Perflubron		3	7	2	6	Problematic
Formaldehyde	H350	9	9	3	4	Highly hazardous
N,N-Dimethylpropylene urea	H361	4	4	1	5	Problematic

The full list contemplating the final recommendation tallies per solvent is shown in Table 3.4, where R stands for "recommended", P for "problematic", H for "hazardous", and HH for "highly hazardous". Solvents are shown in alphabetical order.

Table 3.4. *Final recommendations per solvent.*

Solvent	Final rec.	Solvent	Final rec.
1-Propanol	R	1-Butanol	P
Cyclohexanone	R	2-Methoxyethanol	P
Dicyclohexylamine	R	2-MeTHF	P
Diethanolamine	R	Acetone	P
DMSO	R	Acetonitrile	P
Ethanol	R	Benzotrifluoride	P
Ethyl acetate	R	Chlorobenzene	P
Ethylene carbonate	R	Cyclohexane	P
Ethylene glycol	R	Cyclopentyl methyl ether	P
Isopropyl acetate	R	Diethylamine	P
Isopropyl alcohol	R	Diglyme	P
Methanol	R	Diisopropylethylamine	P
n-Butyl acetate	R	Dimethylformamide	P
Propyl acetate	R	DMAc	P
t-Butanol	R	Heptane	P
Water	R	Isopropyl ether	P
		MEK	P
1-bromo-2-chloroethane	H	MTBE	P
Dichloromethane	H	m-Xylene	P
Dioxane	H	N,N-Dimethyl propylene urea	P
Methyl isobutyl ketone	H	NMP	P
THF	H	Perflubron	P
		Sulfolane	P
Benzene	HH	Triethylamine	P
Formaldehyde	HH		
Hexane	HH		
Toluene	HH		
Trifluoroethanol	HH		

Comparison of the tool's final recommendations against other published solvent tools (Pfizer, Sanofi, CHEM21, and ACS GCI PR's) and literature reviews (Byrne, et al., 2016), in Table 3.5, also shows good correlation between the various tools. Some solvents present variations with the final recommendations in other guides, but only fourteen, marked with an asterisk, showing differences with the majority of recommendations[15]. All can be explained because of the specific combinations of smaller evaluations, with the exceptions of hexane and toluene.

[15] For those solvents who had been included in at least two other guides.

Table 3.5. *Comparison of the tool's final recommendations against other published solvent tools.*

Solvent	Pfizer	Sanofi	CHEM21	ACS GCI PR	Byrne	Hovione
Dichloromethane	Undesirable	Substitution advisable	Hazardous	Highly Hazardous		Hazardous
Acetone*	Preferred	Recommended	Recommended	Recommended		Problematic
Water	Preferred	Recommended	Recommended	Recommended	Recommended	Recommended
Ethanol	Preferred	Recommended	Recommended	Recommended	Recommended	Recommended
Methanol	Preferred	Recommended	Recommended	Recommended		Recommended
MEK	Preferred	Recommended	Recommended	Recommended		Problematic
Heptane	Usable	Substitution advisable	Problematic	Problematic	Problematic	Problematic
THF*	Usable	Substitution advisable	Problematic	Problematic		Hazardous
Ethyl Acetate	Preferred	Recommended	Recommended	Recommended	Recommended	Recommended
Acetonitrile	Usable	Recommended	Problematic	Problematic	Problematic	Problematic
Isopropyl alcohol		Recommended		Recommended		Recommended
DMSO*	Usable	Substitution advisable	Problematic	Problematic	Problematic	Recommended
Dimethylformamide*	Undesirable	Substitution required	Problematic	Hazardous	Hazardous	Problematic
Benzene	Undesirable	Banned	Highly hazardous	Highly Hazardous	Highly hazardous	Highly hazardous
Hexane*	Undesirable	Substitution required	Hazardous	Hazardous	Hazardous	Highly hazardous
Chlorobenzene		Substitution advisable	Problematic	Problematic	Problematic	Problematic
Toluene*	Usable	Substitution advisable	Problematic	Problematic	Problematic	Highly hazardous
2-MeTHF	Usable	Recommended	Problematic	Problematic	Problematic	Problematic
DMAc*	Undesirable	Substitution required	Hazardous	Hazardous	Hazardous	Problematic
NMP*	Undesirable	Substitution required	Hazardous	Hazardous	Hazardous	Problematic
Dioxane	Undesirable	Substitution required	Hazardous	Hazardous	Hazardous	Hazardous
t-Butanol	Preferred	Substitution advisable	Recommended	Recommended		Recommended
Cyclohexane	Usable	Substitution advisable	Problematic	Problematic		Problematic
Isopropyl ether*	Undesirable	Substitution advisable	Hazardous	Hazardous	Hazardous	Problematic
Methyl isobutyl ketone*		Recommended	Recommended	Recommended		Hazardous
2-Methoxyethanol*		Substitution required	Hazardous	Hazardous	Hazardous	Problematic
Triethylamine*		Substitution requested		Hazardous		Problematic

Table 3.5. *Comparison of the tool's final recommendations against other published solvent tools (continued).*

Solvent	Pfizer	Sanofi	CHEM21	ACS GCI PR	Byrne	Hovione
Isopropyl acetate	Preferred	Recommended	Recommended	Recommended	Recommended	Recommended
Benzotrifluoride				Problematic		Problematic
Diglyme				Hazardous		Problematic
n-Butyl acetate		Recommended	Recommended	Recommended	Recommended	Recommended
Diethanolamine						Recommended
MTBE	Usable	Substitution advisable	Hazardous	Hazardous		Problematic
m-Xylene	Usable	Substitution advisable	Problematic	Problematic	Problematic	Problematic
Diethylamine				Hazardous		Problematic
Cyclopentyl methyl ether		Substitution requested	Problematic	Problematic		Problematic
1-Propanol		Recommended		Problematic		Recommended
Ethylene carbonate			Problematic			Recommended
1-Butanol*	Preferred	Recommended	Recommended	Recommended	Recommended	Problematic
Ethylene glycol	Usable	Substitution advisable	Recommended	Recommended		Recommended
Cyclohexanone*		Substitution advisable	Problematic	Problematic		Recommended
Sulfolane		Substitution advisable	Hazardous	Hazardous	Recommended	Problematic
Propyl acetate		Recommended		Recommended		Recommended
Diisopropylethyl amine				Problematic		Problematic
1-bromo-2-chloroethane						Hazardous
Dicyclohexylamine				Problematic		Recommended
Trifluoroethanol				Hazardous		Highly hazardous
Perflubron						Problematic
Formaldehyde						Highly hazardous
N,N-Dimethylpropylene urea		Substitution advisable	Problematic	Problematic		Problematic

* indicates those solvents whose recommendation under the proposed tool contrasts with the majority of other guides' recommendations, for solvents included in at least two other guides.

For toluene and hexane, even if the individual assessments included no values in the red category (8-10), the ranking provided on the proposed tool was immediately “highly hazardous”, due to having both H361 and H373 CMR GHS codes each.

Therefore, the strong correlation observed between the final recommendations of Hovione’s tool and those of the referenced published solvent tools and literature reviews in Table 3.5 highlights the effectiveness of the proposed assessment strategy in producing consistent outcomes. Additionally, the notable agreement between the internal assessment and these foreign guides suggests that the proposed preset ponderation values employed in each individual assessment hold significant promise. Lastly, the findings provide further validation of the reliability of the proposed tool in identifying solvents that align with the established criteria and meet the (un)desired benchmarks, thus affirming its projected value in supporting informed decision-making processes.

3.3.4 Advantages and shortcomings of the solvent assessment and selection aiding tool

Comparison between Hovione’s proposed tool and other tools out in the market is nothing but inevitable, as earlier guides provided a general framework from which to start working and are a source of reference for many scientists in Hovione. Separate from previous discussions regarding the final recommendation tally and how it compares to other guides and literary reviews, it is important to note some of the advantages and shortcomings that have been identified regarding this solvent assessment and selection aiding tool.

The tool developed in this project showcases several differences and upsides when compared to previous work. One of the key advantages is the adjustable ponderations that allow to personalize or modify the four individual evaluations: Health Risk, Process Safety, Environmental Impact, and Sustainability. While allowing the user to give more weight to or altogether exclude certain aspects of each evaluation carries responsibility and could askew the assessment process, it also provides much flexibility to the tool. Additionally, as the guide is rolled out, management might decide to change the ponderation values and hold back on that adjustability, perhaps designating specific timelines to revise ponderation proposals during the tool’s life. Overall, the personalization and adjustability that the changeable ponderation values provide renders the assessment process very elastic, and is a key feature not discussed in any other solvent guide or assessment tool in literature.

Another factor of the tool's versatility is its platform. By being a simple Excel document, any gadget capable of running the software can be a consultation device, from a phone to a computer. Nevertheless, an identified issue with the platform is also its navigability, due largely to the sheer size of the database. While the category minimization options might make it relatively easier to navigate, it also requires a certain level of familiarity of the user with the file. Ways in which this can be reworked in the future will be further discussed in subchapter 3.4 Next steps.

As the tool was first fully built and then will be presented to the scientists for feedback, it is only to be expected that not all scientists (or any at all) will be comfortable with the navigability and categorizations included in the tool at this stage. One comment regarding the categorization strategy for the information fields (please refer to Table 3.2 in page 43) was already received, putting into question the rationale behind the inclusion of one or another data field in specific categories (and particularly around the existence of an "Engineering properties" classification). While the ACS GCI PR database was taken as a model for this categorization, feedback from the users will define how the tool will evolve in future editions.

While other assessment guides and tools have included an LCA assessment as part of the database, due to time constraints and the difficulties in gathering this type of data, it was not included in this first edition of the Hovione solvent guide. Nevertheless, it is recognized that any conversation regarding sustainability and sustainable solvents necessarily has to involve an assessment of said solvent done, preferably, using LCA methodology (Winterton, 2021). This is one key area of opportunity for further development of the solvent tool.

While the Hovione, Sanofi, CHEM21 and ACS GCI PR solvent guides include a breakdown of the different smaller evaluations that led to the final recommendation, Pfizer's has no such background information for its users. The additional breakdown provides the scientist with more insights on the solvent's assessment for a better evaluation on their part by giving them more tools with which to form an opinion on the advantages and drawbacks of using a specific solvent. With this extra information, scientists will also be able to measure the risks more accurately and can even plan for them (e.g. with personal protective equipment).

Lastly, one other advantage of Hovione's solvent guide and assessment tool is the straightforward and uncomplicated expansion of the database. The addition of new solvents requires few steps, mainly filling in the data and relying on 'dragging down' existing formulas to finalize the evaluations. The ease of incorporating new solvents into the database will be key in the expansion efforts in the future.

3.4 Next steps

Due to time constraints, there are several next steps for the project that will be undertaken in following months. First of all, the dissemination of the tool in the company is of the upmost importance. For the time being, a dashboard for easier user navigation of the database will be built onto the existing Excel file, and a non-editable version of the tool will be shared on an internal SharePoint site accessible to all Hovione collaborators. The aim will be to later develop jointly with the Information Technology (IT) team a more dynamic solution, perhaps mounted on one of Hovione's existing web applications in the company's intranet, rather than a standalone file. This would also allow the tool to connect directly to internal sources of information, which would obviate the need to maintain these parts of the database.

Secondly, it is also necessary to assess the adoption of the tool and evaluate the feedback from users in order to determine possible improvements that can be done in later stages. This will be the main blueprint for how the project will progress past the scope of this thesis.

Thirdly, it is key to expand the existing solvent database. If the purpose is to also lead Hovione's chemists to substitute dangerous solvents with newer, greener ones on the market, then those newer ones must also be available for the chemists to consider and evaluate in the same tool. Therefore, it is a priority for the project to ensure the inclusion and integration of the current as well as the newest environmentally friendly solvents into the expanded database.

Lastly, the database must be kept up to date, as well as the missing data gaps filled in order to ensure continuous validity of the assessments proposed. Options for automating the updating process will be explored with IT, while research will continue to complete the missing information and reinforce current assessment strategies.

4. Conclusions

A new solvent assessment and selection tool was developed for Hovione's unique industrial context, including 50 solvents and 49 data points for each solvent entry. A new strategic assessment proposal across four categories (Health Risk, Process Safety, Environmental Impact, and Sustainability assessments) delivers a final recommendation regarding the solvent's use.

The tool was built into Excel and will be shared internally. Feedback will be gathered in order to determine possible improvements to be done in the future. Efforts will also be focused on expanding the database, filling current data gaps, and developing a more dynamic solution with IT. It is expected that the tool will be gradually adopted as users become familiarized with the information available and its assessments.

Because of the time constraints and the context in which the project was developed, conclusive results regarding adoption of the tool or improvements to processes as a result of the tool were out of the scope of this project. Nevertheless, feedback and more comments will be available in the future.

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Annex A: Questionnaire

1) Before we start, may we ask you which job family do you belong to?
   a. Engineering & Maintenance
   b. HSE
   c. Logistics
   d. Production
   e. Quality
   f. R&D
   g. Other
2) Where do you go for data? Please select all that apply.
   a. Google and other internet sources
   b. Books and literature reviews
   c. Published research articles
   d. Database programs
   e. Data sheets from suppliers
   f. Predictive models
   g. Other
3) What data do you look for?
   a. General information, such as chemical groups and chemical classes
   b. Physical and computed properties
   c. Chemical and thermochemical properties
   d. Interaction and reactivity information
   e. HSE information
   f. Regulatory information (REACH, EPA, ICH classifications, etc.)
   g. Other
4) When selecting/working with[16] a solvent, apart from technical suitability, which practical considerations are the most important for you? Please select all that apply.
   a. Regulatory information (REACH, EPA, ICH classification, etc.)

[16] For users that in the first question reported belonging to R&D, the question reflected as "selecting a solvent". For users who reported belonging to any other part of the Hovione structure, the question reflected as "working with a solvent", in order to accommodate for people in sites that might refer to the database for general information, but do not depend on it for solvent selection.

b. Safety and occupational health concerns
c. Environmental toxicity and biodegradability
d. Cost and recyclability/disposal
e. Industrial constraints, such as azeotrope formation, solvent swap, etc.
f. I only focus on technical suitability.
g. Other

For users that had selected they belonged to the R&D team, the questionnaire continued. For all other users, it automatically jumped to the last question (question 8) and then ended.

5) Do you currently use any tools (internal or external) or methods for solvent selection?
    a. Yes
    b. No
6) Can you share which tools or methods do you use for solvent selection?[17]
7) Can you share why you don’t use any tools or methods for solvent selection?[18]
8) What type of information would you like to find if Hovione had an internal solvent database?
    a. General information, such as chemical groups and chemical classes
    b. Physical and computed properties
    c. Chemical and thermochemical properties
    d. Interaction and reactivity information
    e. HSE information
    f. Regulatory information (REACH, EPA, ICH classifications, etc.)
    g. Cost and recyclability/disposal
    h. Industrial constraints, such as azeotrope formation, solvent swap, etc.
    i. Other

[17] When the user had selected that they do use tools for solvent selection.

[18] When the user had selected that they do not use tools for solvent selection.

Annex B: Full list of GHS hazard codes and statements

In the following list, please consider that physical hazards will be listed with a yellow background, health hazards with a blue background, environmental hazards with a green background, and supplemental hazard information codes with a red background.

Hazard statements	
Code	**Statement**
H200	Unstable explosives.
H201	Explosive; mass explosion hazard.
H202	Explosive; severe projection hazard.
H203	Explosive; fire, blast or projection hazard.
H204	Fire or projection hazard.
H205	May mass explode in fire.
H206	Fire, blast or projection hazard; increased risk of explosion if desensitizing agent is reduced.
H207	Fire or projection hazard; increased risk of explosion if desensitizing agent is reduced.
H208	Fire hazard: increased risk of explosion if desensitizing agent is reduced.
H220	Extremely flammable gas.
H221	Flammable gas.
H222	Extremely flammable aerosol.
H223	Flammable aerosol.
H224	Extremely flammable liquid and vapor.
H225	Highly flammable liquid and vapor.
H226	Flammable liquid and vapour.
H228	Flammable solid.
H229	Pressurized container: May burst if heated.
H230	May react explosively even in the absence of air.
H231	May react explosively even in the absence of air at elevated pressure and/or temperature.
H232	May ignite spontaneously if exposed to air.
H240	Heating may cause an explosion.
H241	Heating may cause a fire or explosion.

H242	Heating may cause a fire.
H250	Catches fire spontaneously if exposed to air.
H251	Self-heating: may catch fire.
H252	Self-heating in large quantities; may catch fire.
H260	In contact with water releases flammable gases which may ignite spontaneously.
H261	In contact with water releases flammable gases.
H270	May cause or intensify fire; oxidizer.
H271	May cause fire or explosion; strong oxidizer.
H272	May intensify fire; oxidiser.
H280	Contains gas under pressure; may explode if heated.
H281	Contains refrigerated gas; may cause cryogenic burns or injury.
H290	May be corrosive to metals.
H300	Fatal if swallowed.
H301	Toxic if swallowed.
H302	Harmful if swallowed.
H304	May be fatal if swallowed and enters airways.
H310	Fatal in contact with skin.
H311	Toxic in contact with skin.
H312	Harmful in contact with skin.
H314	Causes severe skin burns and eye damage.
H315	Causes skin irritation.
H317	May cause an allergic skin reaction.
H318	Causes serious eye damage.
H319	Causes serious eye irritation.
H330	Fatal if inhaled.
H331	Toxic if inhaled.
H332	Harmful if inhaled.
H334	May cause allergy or asthma symptoms or breathing difficulties if inhaled.
H335	May cause respiratory irritation.
H336	May cause drowsiness or dizziness.
H340	May cause genetic defects.
H341	Suspected of causing genetic defects.

H350	May cause cancer.
H351	Suspected of causing cancer.
H360	May damage fertility or the unborn child.
H361	Suspected of damaging fertility or the unborn child.
H362	May cause harm to breast-fed children.
H370	Causes damage to organs.
H371	May cause damage to organs.
H372	Causes damage to organs.
H373	May cause damage to organs.
H300 + H310	Fatal if swallowed or in contact with skin.
H300 + H330	Fatal if swallowed or if inhaled.
H310 + H330	Fatal in contact with skin or if inhaled.
H300 + H310 + H330	Fatal if swallowed, in contact with skin or if inhaled.
H301 + H311	Toxic if swallowed or in contact with skin.
H301 + H331	Toxic if swallowed or if inhaled.
H311 + H331	Toxic in contact with skin or if inhaled.
H301 + H311 + H331	Toxic if swallowed, in contact with skin or if inhaled.
H302 + H312	Harmful if swallowed or in contact with skin.
H302 + H332	Harmful if swallowed or if inhaled.
H312 + H332	Harmful in contact with skin or if inhaled.
H302 + H312 + H332	Harmful if swallowed, in contact with skin or if inhaled.
H400	Very toxic to aquatic life.
H410	Very toxic to aquatic life with long lasting effects.
H411	Toxic to aquatic life with long lasting effects.
H412	Harmful to aquatic life with long lasting effects.
H413	May cause long lasting harmful effects to aquatic life.
H420	Harms public health and the environment by destroying ozone in the upper atmosphere.
EUH014	Reacts violently with water.
EUH018	In use may form flammable/explosive vapor-air mixture.

EUH019	May form explosive peroxides.
EUH044	Risk of explosion if heated under confinement.
EUH029	Contact with water liberates toxic gas.
EUH031	Contact with acids liberates toxic gas.
EUH032	Contact with acids liberates very toxic gas.
EUH066	Repeated exposure may cause skin dryness or cracking.
EUH070	Toxic by eye contact.
EUH071	Corrosive to the respiratory tract.
EUH201/201A	Contains lead. Should not be used on surfaces liable to be chewed or sucked by children. Warning! Contains lead.
EUH202	Cyanoacrylate. Danger. Bonds skin and eyes in seconds. Keep out of the reach of children.
EUH203	Contains chromium (VI). May produce an allergic reaction.
EUH204	Contains isocyanates. May produce an allergic reaction.
EUH205	Contains epoxy constituents. May produce an allergic reaction.
EUH206	Warning! Do not use together with other products. May release dangerous gases (chlorine).
EUH207	Warning! Contains cadmium. Dangerous fumes are formed during use. See information supplied by the manufacturer. Comply with the safety instructions.
EUH208	Contains <name of sensitizing substance>. May produce an allergic reaction.
EUH209/209A	Can become highly flammable in use. Can become flammable in use.
EUH210	Safety data sheet available on request.
EUH211	Warning! H respirable droplets may be formed when sprayed. Do not breathe spray or mist.
EUH212	Warning! H respirable dust may be formed when used. Do not breathe dust.
EUH401	To avoid risks to human health and the environment, comply with the instructions for use.

Annex C: Health hazard-related GHS code and statement evaluations

Health hazard statement evaluations		
Code	**Statement**	**Value**
H281	Contains refrigerated gas; may cause cryogenic burns or injury.	3.00
H300	Fatal if swallowed.	13.00
H301	Toxic if swallowed.	9.00
H302	Harmful if swallowed.	5.00
H304	May be fatal if swallowed and enters airways.	11.00
H310	Fatal in contact with skin.	14.00
H311	Toxic in contact with skin.	10.00
H312	Harmful in contact with skin.	6.00
H314	Causes severe skin burns and eye damage.	5.00
H315	Causes skin irritation.	4.00
H317	May cause an allergic skin reaction.	4.00
H318	Causes serious eye damage.	5.00
H319	Causes serious eye irritation.	4.00
H330	Fatal if inhaled.	15.00
H331	Toxic if inhaled.	11.00
H332	Harmful if inhaled.	7.00
H334	May cause allergy or asthma symptoms or breathing difficulties if inhaled.	5.00
H335	May cause respiratory irritation.	3.00
H336	May cause drowsiness or dizziness.	2.00
H340	May cause genetic defects.	9.00
H341	Suspected of causing genetic defects.	10.00
H350	May cause cancer.	11.00
H351	Suspected of causing cancer.	12.00
H360	May damage fertility or the unborn child.	9.00
H361	Suspected of damaging fertility or the unborn child.	9.00
H362	May cause harm to breast-fed children.	7.00
H370	Causes damage to organs.	14.00
H371	May cause damage to organs.	12.00

H372	Causes damage to organs.	14.00
H373	May cause damage to organs.	12.00
H300 + H310	Fatal if swallowed or in contact with skin.	15.00
H300 + H330	Fatal if swallowed or if inhaled.	16.00
H310 + H330	Fatal in contact with skin or if inhaled.	17.00
H300 + H310 + H330	Fatal if swallowed, in contact with skin or if inhaled.	18.00
H301 + H311	Toxic if swallowed or in contact with skin.	11.00
H301 + H331	Toxic if swallowed or if inhaled.	12.00
H311 + H331	Toxic in contact with skin or if inhaled.	13.00
H301 + H311 + H331	Toxic if swallowed, in contact with skin or if inhaled.	14.00
H302 + H312	Harmful if swallowed or in contact with skin.	7.00
H302 + H332	Harmful if swallowed or if inhaled.	8.00
H312 + H332	Harmful in contact with skin or if inhaled.	9.00
H302 + H312 + H332	Harmful if swallowed, in contact with skin or if inhaled.	10.00
EUH029	Contact with water liberates toxic gas.	10.50
EUH031	Contact with acids liberates toxic gas.	10.50
EUH032	Contact with acids liberates very toxic gas.	10.50
EUH066	Repeated exposure may cause skin dryness or cracking.	3.75
EUH070	Toxic by eye contact.	10.00
EUH071	Corrosive to the respiratory tract.	12.00
EUH201/201A	Contains lead. Should not be used on surfaces liable to be chewed or sucked by children. Warning! Contains lead.	11.00
EUH202	Cyanoacrylate. Danger. Bonds skin and eyes in seconds. Keep out of the reach of children.	6.00
EUH203	Contains chromium (VI). May produce an allergic reaction.	5.00
EUH204	Contains isocyanates. May produce an allergic reaction.	5.00
EUH205	Contains epoxy constituents. May produce an allergic reaction.	5.00
EUH206	Warning! Do not use together with other products. May release dangerous gases (chlorine).	6.50

EUH207	Warning! Contains cadmium. Dangerous fumes are formed during use. See information supplied by the manufacturer. Comply with the safety instructions.	7.00
EUH208	Contains <name of sensitizing substance>. May produce an allergic reaction.	7.00
EUH211	Warning! H respirable droplets may be formed when sprayed. Do not breathe spray or mist.	7.00
EUH212	Warning! H respirable dust may be formed when used. Do not breathe dust.	7.00
EUH401	To avoid risks to human health and the environment, comply with the instructions for use.	0.00

Annex D: Process hazard-related GHS code and statement evaluations

Health hazard statement evaluations		
Code	**Statement**	**Value**
H200	Unstable explosives.	5.00
H201	Explosive; mass explosion hazard.	11.00
H202	Explosive; severe projection hazard.	12.00
H203	Explosive; fire, blast or projection hazard.	15.00
H204	Fire or projection hazard.	7.50
H205	May mass explode in fire.	8.00
H206	Fire, blast or projection hazard; increased risk of explosion if desensitizing agent is reduced.	11.50
H207	Fire or projection hazard; increased risk of explosion if desensitizing agent is reduced.	7.00
H208	Fire hazard: increased risk of explosion if desensitizing agent is reduced.	1.00
H220	Extremely flammable gas.	5.50
H221	Flammable gas.	4.50
H222	Extremely flammable aerosol.	5.50
H223	Flammable aerosol.	4.50
H224	Extremely flammable liquid and vapor.	7.50
H225	Highly flammable liquid and vapor.	7.00
H226	Flammable liquid and vapor.	6.50
H228	Flammable solid.	2.50
H229	Pressurized container: May burst if heated.	4.00
H230	May react explosively even in the absence of air.	7.50
H231	May react explosively even in the absence of air at elevated pressure and/or temperature.	7.00
H232	May ignite spontaneously if exposed to air.	4.00
H240	Heating may cause an explosion.	1.00
H241	Heating may cause a fire or explosion.	2.50
H242	Heating may cause a fire.	-0.50
H250	Catches fire spontaneously if exposed to air.	5.50

H251	Self-heating: may catch fire.	4.00
H252	Self-heating in large quantities; may catch fire.	2.00
H260	In contact with water releases flammable gases which may ignite spontaneously.	8.00
H261	In contact with water releases flammable gases.	3.50
H270	May cause or intensify fire; oxidizer.	2.00
H271	May cause fire or explosion; strong oxidizer.	3.00
H272	May intensify fire; oxidizer.	2.00
H280	Contains gas under pressure; may explode if heated.	1.00
H290	May be corrosive to metals.	1.50
EUH014	Reacts violently with water.	5.00
EUH018	In use may form flammable/explosive vapor-air mixture.	7.00
EUH019	May form explosive peroxides.	3.50
EUH044	Risk of explosion if heated under confinement.	1.00
EUH209/209A	Can become highly flammable in use. Can become flammable in use.	3.00
EUH210	Safety data sheet available on request.	0.00

Annex E: Database entry for dichloromethane with unminimized look

Solvent	Other names	Family	Grade/more information	Material number	General information				
					Chemical formula	CAS Number	SMILES	InChI	InChIKey
Dichloromethane	DCM, methylene ch	Halogenated		100560	CH2Cl2	75-09-2	C(Cl)Cl	1S/CH2Cl2/c2-1-3/	YMWUJEATGCHHI
			E2000	110735					
			Pharma grade	112040					

General properties								
Molecular weight [g/mol]	Density [g/cm3]	Boiling Point [°C]	Melting Point at 1 atm [°C]	Flash Point [°C]	Dielectric constant	Dipole moment [D]	Miscibility w/water	log Kow
84.9305	1.328 (20°C)	39.75	-95.14	-8.15	8.93	1.601	N	1.25

Engineering properties				Regulatory			
Heat capacity (Cp) [J/LK]	Enthalpy of Evaporation (ΔHvap) [kJ/L]	T-rating	Viscosity [cP @25ºC]	Flags or restrictions	ICH Q3C class	ICH Q3C limit [ppm]	Possible Impurities (Hovione specification)
898	205	T1	0.413	Restricted uses under REACH	2	600	Ethanol - NMT 2.0% v/v 2-methylbut-2-ene - NMT 300 ppm Carbon tetrachloride - NMT 10 ppm Chloroform - NMT 50 ppm

Health & Safety										
OEL [ppm]	Hovione OHC	Flammability class	Autoignition temperature [ºC]	Properties of concern	GHS pictogram	GHS signal word	GHS hazard statement		GHS supplemental hazard statement (EUH)	
100	OHC 2a	IB	615	C - Suspected to be Carcinogenic ED - Under assessment as Endocrine Disrupting	GHS08	Warning	H351	Suspected of causing cancer.	-	-

Environmental impact					Sustainability		
Ecotoxicity	PBT/vPvB	SVHC	Vapor pressure [mmHg @25°C]	VOC potential	Biodegradation statement	Biodegradation code	Solvent origin
-	-	-	435	Group 3	Readily biodegradable, both under aerobic and anaerobic conditions.	RB	Not bio-based

Compatibility		Economics
Reactivity	Materials	Cost [€]
Reacts vigorously with active metals (such as lithium, sodium, and potassium) and with strong bases (such as potassium tert-butoxide). Incompatible with strong oxidizers, strong caustics, and chemically active metals (such as aluminum or magnesium powders). Reacts with sodium-potassium alloy, nitrogen tetraoxide, liquid oxygen, and titanium. Incompatible with alkali metals, amines and zinc. Liable to explode when mixed with dinitrogen pentaoxide or nitric acid. Mixtures of DCM in air with methanol vapor are flammable. Subject to hydrolysis which is accelerated by light.	The liquid will attack some forms of plastic, rubber, and coatings. Reacts with titanium. On contact with water corrodes iron, some stainless steels, copper, and nickel. Incompatible with zinc and alloys of aluminum, magnesium, and zinc.	1.618/KG 0.92/KG 2472/T

Evaluations												
Health Risk	T-Rating-Process Safety	Cp- Process Safety	ΔHvap- Process Safety	Flammability class-Process Safety	GHS(raw)- Process Safety	GHS(t)- Process Safety	Process Safety	Ecotoxicity-Environmental I	PBT/vPvB-Environmental I	SHVC-Environmental I	VOC-Environmental I	Environmental Impact
3	1	5	5	5	0	1	4	0	0	0	6	3

Evaluations								Final recommendation	
Biodegradation potential-Sustainability I	Solvent origin-Sustainability I	Ecotoxicity-Sustainability I	PBT/vPvB-Sustainability I	SHVC-Sustainability I	VOC-Sustainability I	Environmental impact during incineration	Sustainability	Recommendation	Possible substitutions
1	4	0	0	0	6	16	6	Hazardous	Application dependant, but some alternatives are: ethyl acetate, MTBE (in chromatography and extractions), toluene, 2-MeTHF, 3:1 ethyl acetate:ethanol (for chromatography), dimethyl carbonate, CPME, supercritical carbon dioxide (scCO2), benzotrifluoride, d-limonene, diacetone alcohol (DAA), methyl soyate (as a cleaning agent), NMP (as a cleaning agent).

Annex F: Full list of references used in the data collection process for the database.

		ECHA					
		Candidate List of Substances of Very High Concern for Authorisation, n.d.	CMD - Carcinogens and Mutagens Directive, Annex III - OELVs, n.d.	Occupational Exposure Limits	PBT Assessment List, n.d.	Registration Dossiers, Registered Substances Factsheets, n.d.	Substances Restricted Under REACH, n.d.
Basic information	**Solvent**						
	Other names						
	Grade/more information						
	Material number						
General information	**Chemical formula**						
	CAS number						
	SMILES						
	InChI						
	InChIKey						
General properties	**Molecular weight**						
	Density						
	Boiling Point					4	
	Melting Point					4	
	Flash Point						
	Dielectric constant						
	Dipole moment						
	Miscibility w/water						
	log Kow					4	
Engineering properties	**Heat capacity (Cp)**						
	Enthalpy of Evaporation (ΔHvap)						
	Viscosity					6	
Regulatory	**Flags or restrictions**						1
	ICH Q3C class						
	ICH Q3C limit						
	Possible Impurities (Hovione specification)						
Health & Safety	**OEL**		2	1		3	
	Hovione OHC						
	Flammability class						
	Autoignition temperature						
	Properties of concern					1	
	GHS pictogram					1	
	GHS signal word					1	
	GHS hazard statement					1	
	GHS supplemental hazard statement (EUH)					1	
Environmental impact	**Ecotoxicity**					1	
	PBT/vPvB				1		
	SVHC	1					
	Vapor pressure						
Sustainability	**Biodegradation statement**					1	
	Solvent origin						
Compatibility	**Reactivity**						
	Materials						
Economics	**Cost**						
Final recommendations	**Possible substitutions**						

		EMA	External databases					
		ICH guideline Q3C (R8) on Impurities, 2022	ACS GCIPR Solvent Tool, 2019	Chemical Compatibility, Fisher Scientific, n.d.	ChemSpider, n.d.	DIPPR Database, Dynochem, 2011	NIST Chemistry WebBook, n.d.	PubChem, n.d.
Basic information	**Solvent**							
	Other names							1
	Grade/more information							
	Material number							
General information	**Chemical formula**							1
	CAS number							1
	SMILES							1
	InChI							1
	InChIKey							1
General properties	**Molecular weight**							1
	Density							
	Boiling Point					1	2	
	Melting Point				5	1	2	
	Flash Point					1		3
	Dielectric constant					1		
	Dipole moment					1		
	Miscibility w/water		1					2
	log Kow		1					2
Engineering properties	**Heat capacity (Cp)**		1				2	
	Enthalpy of Evaporation (ΔHvap)		1				5	
	Viscosity							3
Regulatory	**Flags or restrictions**							
	ICH Q3C class	2				1		
	ICH Q3C limit	1						
	Possible Impurities (Hovione specification)							
Health & Safety	**OEL**							
	Hovione OHC							
	Flammability class							
	Autoignition temperature					1		2
	Properties of concern							
	GHS pictogram							
	GHS signal word							
	GHS hazard statement							
	GHS supplemental hazard statement (EUH)							
Environmental impact	**Ecotoxicity**							
	PBT/vPvB							
	SVHC							
	Vapor pressure							1
Sustainability	**Biodegradation statement**							
	Solvent origin							2
Compatibility	**Reactivity**			2				4
	Materials							
Economics	**Cost**							
Final recommendations	**Possible substitutions**							

		Hovione internal documentation				
		Chemical Profile, NS4, n.d.	CofA Specification C_NORMAL, n.d.	Gestão do risco químico ocupacional, 2021	SDS, NS4 n.d.	Solvents, 2023
Basic information	**Solvent**					1
	Other names					
	Grade/more information					1
	Material number					1
General information	**Chemical formula**					
	CAS number					
	SMILES					
	InChI					
	InChIKey					
General properties	**Molecular weight**					
	Density	1				
	Boiling Point				3	
	Melting Point				3	
	Flash Point				2	
	Dielectric constant					
	Dipole moment					
	Miscibility w/water					
	log Kow				3	
Engineering properties	**Heat capacity (Cp)**					
	Enthalpy of Evaporation (ΔHvap)					
	Viscosity				4	
Regulatory	**Flags or restrictions**					
	ICH Q3C class					
	ICH Q3C limit					
	Possible Impurities (Hovione specification)		1			
Health & Safety	**OEL**					
	Hovione OHC			1		
	Flammability class					
	Autoignition temperature				4	
	Properties of concern					
	GHS pictogram					
	GHS signal word					
	GHS hazard statement					
	GHS supplemental hazard statement (EUH)					
Environmental impact	**Ecotoxicity**					
	PBT/vPvB					
	SVHC					
	Vapor pressure				2	
Sustainability	**Biodegradation statement**					
	Solvent origin					
Compatibility	**Reactivity**	5				
	Materials					
Economics	**Cost**					1
Final recommendations	**Possible substitutions**					

		External Literature						
		Alfonsi, 2008	Armenta, 2022	Azzena, 2019	Baird, 2019	Byrne, 2017	Canadian Centre for Occupational Health and Safety, 2023	de Gonzalo, 2019
Basic information	**Solvent**							
	Other names							
	Grade/more information							
	Material number							
General information	**Chemical formula**							
	CAS number							
	SMILES							
	InChI							
	InChIKey							
General properties	**Molecular weight**							
	Density							
	Boiling Point							
	Melting Point							
	Flash Point							
	Dielectric constant							
	Dipole moment							
	Miscibility w/water							
	log Kow							
Engineering properties	**Heat capacity (Cp)**							
	Enthalpy of Evaporation (ΔHvap)				2			
	Viscosity							
Regulatory	**Flags or restrictions**							
	ICH Q3C class							
	ICH Q3C limit							
	Possible Impurities (Hovione specification)							
Health & Safety	**OEL**							
	Hovione OHC							
	Flammability class							
	Autoignition temperature							
	Properties of concern							
	GHS pictogram							
	GHS signal word							
	GHS hazard statement							
	GHS supplemental hazard statement (EUH)							
Environmental impact	**Ecotoxicity**							
	PBT/vPvB							
	SVHC							
	Vapor pressure							
Sustainability	**Biodegradation statement**							
	Solvent origin		3	7		1		8
Compatibility	**Reactivity**						3	
	Materials							
Economics	**Cost**							
Final recommendations	**Possible substitutions**	1	1	1		1		

		External Literature					
		Faveere, 2020	Fisher Science, n.d.	Fisher Scientific, n.d.	Frauenkron, 2000	Future Market Insights, 2023	Great American Insurance Group, 2006
Basic information	**Solvent**						
	Other names						
	Grade/more information						
	Material number						
General information	**Chemical formula**						
	CAS number						
	SMILES						
	InChI						
	InChIKey						
General properties	**Molecular weight**						
	Density						
	Boiling Point						
	Melting Point						
	Flash Point						
	Dielectric constant						
	Dipole moment						
	Miscibility w/water						
	log Kow						
Engineering properties	**Heat capacity (Cp)**				4		
	Enthalpy of Evaporation (ΔHvap)						
	Viscosity			5			
Regulatory	**Flags or restrictions**						
	ICH Q3C class						
	ICH Q3C limit						
	Possible Impurities (Hovione specification)						
Health & Safety	**OEL**						
	Hovione OHC						
	Flammability class						1
	Autoignition temperature						
	Properties of concern						
	GHS pictogram						
	GHS signal word						
	GHS hazard statement						
	GHS supplemental hazard statement (EUH)						
Environmental impact	**Ecotoxicity**						
	PBT/vPvB						
	SVHC						
	Vapor pressure						
Sustainability	**Biodegradation statement**						
	Solvent origin	5				4	
Compatibility	**Reactivity**						
	Materials						
Economics	**Cost**						
Final recommendations	**Possible substitutions**		1				

		External Literature					
		Haynes, 2017	Hopwood, 2009	IFA, n.d.	LOBA Chemie, 2013	Maryott, 1951	Merchant, 2015
Basic information	**Solvent**						
	Other names						
	Grade/more information						
	Material number						
General information	**Chemical formula**						
	CAS number						
	SMILES						
	InChI						
	InChIKey						
General properties	**Molecular weight**						
	Density						
	Boiling Point						
	Melting Point						
	Flash Point						
	Dielectric constant	2				3	
	Dipole moment	2					
	Miscibility w/water						
	log Kow			5			
Engineering properties	**Heat capacity (Cp)**	3			5		
	Enthalpy of Evaporation (ΔHvap)	3					
	Viscosity	1					
Regulatory	**Flags or restrictions**						
	ICH Q3C class						
	ICH Q3C limit						
	Possible Impurities (Hovione specification)						
Health & Safety	**OEL**						
	Hovione OHC						
	Flammability class						
	Autoignition temperature						
	Properties of concern						
	GHS pictogram						
	GHS signal word						
	GHS hazard statement						
	GHS supplemental hazard statement (EUH)						
Environmental impact	**Ecotoxicity**						
	PBT/vPvB						
	SVHC						
	Vapor pressure						
Sustainability	**Biodegradation statement**						
	Solvent origin		9				
Compatibility	**Reactivity**						
	Materials						
Economics	**Cost**						
Final recommendations	**Possible substitutions**						1

		External Literature					
		Merck, 2020	Merck, n.d.	Ogawa, 1997	Penn Environmental Health & Radiation Safety, 2018	Prat, 2013	Richter, 2018
Basic information	**Solvent**						
	Other names						
	Grade/more information						
	Material number						
General information	**Chemical formula**						
	CAS number						
	SMILES						
	InChI						
	InChIKey						
General properties	**Molecular weight**						
	Density						
	Boiling Point						
	Melting Point						
	Flash Point						
	Dielectric constant						
	Dipole moment						
	Miscibility w/water						
	log Kow						
Engineering properties	**Heat capacity (Cp)**						
	Enthalpy of Evaporation (ΔHvap)						
	Viscosity						
Regulatory	**Flags or restrictions**						
	ICH Q3C class						
	ICH Q3C limit						
	Possible Impurities (Hovione specification)						
Health & Safety	**OEL**						
	Hovione OHC						
	Flammability class						
	Autoignition temperature						
	Properties of concern						
	GHS pictogram						
	GHS signal word						
	GHS hazard statement						
	GHS supplemental hazard statement (EUH)						
Environmental impact	**Ecotoxicity**						
	PBT/vPvB						
	SVHC						
	Vapor pressure						
Sustainability	**Biodegradation statement**						
	Solvent origin						6
Compatibility	**Reactivity**						
	Materials						
Economics	**Cost**						
Final recommendations	**Possible substitutions**	1	1	1	1	1	

		External Literature						
		Riess, 2005	Sat Pad, 2019	Sherman, 1998	Sigma Aldrich, 2019	Silver, 2023	Song, 2006	Sorgi, 2001
Basic information	**Solvent**							
	Other names							
	Grade/more information							
	Material number							
General information	**Chemical formula**							
	CAS number							
	SMILES							
	InChI							
	InChIKey							
General properties	**Molecular weight**							
	Density							
	Boiling Point							
	Melting Point							
	Flash Point							
	Dielectric constant							
	Dipole moment							
	Miscibility w/water	4						3
	log Kow							
Engineering properties	**Heat capacity (Cp)**							
	Enthalpy of Evaporation (ΔHvap)							
	Viscosity							
Regulatory	**Flags or restrictions**							
	ICH Q3C class							
	ICH Q3C limit							
	Possible Impurities (Hovione specification)							
Health & Safety	**OEL**							
	Hovione OHC							
	Flammability class							
	Autoignition temperature							
	Properties of concern							
	GHS pictogram							
	GHS signal word							
	GHS hazard statement							
	GHS supplemental hazard statement (EUH)							
Environmental impact	**Ecotoxicity**							
	PBT/vPvB							
	SVHC							
	Vapor pressure							
Sustainability	**Biodegradation statement**							
	Solvent origin							
Compatibility	**Reactivity**		6					
	Materials							
Economics	**Cost**							
Final recommendations	**Possible substitutions**			1	1	1	1	

		External Literature				Software	
		University of Pittsburgh Department of Chemistry, n.d.	Varushchenko, 1997	Winterton, 2021	Wypych, 2019	CAMEO Chemicals, NOAA	Chemical Reactivity Worksheet (CRW), AIChE
Basic information	**Solvent**						
	Other names						
	Grade/more information						
	Material number						
General information	**Chemical formula**						
	CAS number						
	SMILES						
	InChI						
	InChIKey						
General properties	**Molecular weight**						
	Density						
	Boiling Point						
	Melting Point						
	Flash Point						
	Dielectric constant						
	Dipole moment	3					
	Miscibility w/water						
	log Kow						
Engineering properties	**Heat capacity (Cp)**		6				
	Enthalpy of Evaporation (ΔHvap)					4	
	Viscosity				2		
Regulatory	**Flags or restrictions**						
	ICH Q3C class						
	ICH Q3C limit						
	Possible Impurities (Hovione specification)						
Health & Safety	**OEL**						
	Hovione OHC						
	Flammability class						
	Autoignition temperature				5	3	
	Properties of concern						
	GHS pictogram						
	GHS signal word						
	GHS hazard statement						
	GHS supplemental hazard statement (EUH)						
Environmental impact	**Ecotoxicity**						
	PBT/vPvB						
	SVHC						
	Vapor pressure						
Sustainability	**Biodegradation statement**						
	Solvent origin						
Compatibility	**Reactivity**						1
	Materials						1
Economics	**Cost**						
Final recommendations	**Possible substitutions**			1			