Nordic Council of Ministers

Non-target and suspect screening of articles, chemical products and recycled materials

Contents

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Foreword

This project was initiated by the Nordic Working Group for Chemicals, Environment, and Health (NKE) and funded by the Nordic Council of Ministers for Environment and Climate. The work in the project and preparation of this report were carried out by IVL Swedish Environmental Research Institute.

The IVL project leader for the assignment was Ioannis Liagkouridis, other members of the IVL project implementation team were Maja Edenius, Bahare Esfahani, Gunnar Thorsen, and Ziye Zheng. The project steering group consisted of Kristin Larsson (Swedish Chemicals Agency), Robin Vestergren (Swedish Chemicals Agency), Olof Johansson (Swedish Chemicals Agency), and Sjur Andersen (Norwegian Environmental Agency). The project managers were Kristin Larsson and Robin Vestergren.

Summary

Large and increasing numbers of chemicals are produced and used by modern society. Materials and products we use contain many known and unknown chemicals, some of which can pose hazards to human health and to the environment. Methods capable of mapping all hazardous substances present in materials and products are needed to support proper regulation in order to minimize risks for human and environmental health. There is a need to get an overview describing to which extent these methods have been used, if substances have successfully been identified and whether these identified substances are relevant in a regulatory perspective. This work aims to provide an overview of studies that have been done to date using NTS and SS to identify substances in articles, chemical products, and recycled materials and screen and assess the identified chemicals identified with high confidence (Schymanski levels 1 and 2) for regulatory relevance. This provides a basis for an evaluation of the applicability and efficiency of current NTS and SS methods for identifying substances relevant for regulatory actions.

Overall, 76 documents were initially retrieved and reviewed. Of these, 38 were selected for further review based on relevance and data availability. Identified chemicals and associated information was extracted from each of these studies. Of the final selected studies, 26 directly screened the product, 8 screened for chemical migrants from products, and 4 studies did both. Only 34 out of the 38 studies contained chemicals identified at high confidence level (Schymanski level 1 or 2). Of these, 19 used NTS, 11 SS, and 4 employed both methods. In total, more than 1,500 products were screened covering different product categories such as plastics, elastomers, chemical products/material related, paper/paperboard, textiles and wood. By far most studies looked at plastic products (>900 products), while the second biggest product category was textiles (>200 products). In total, nearly 3000 unique chemical entries were registered at varying confidence levels from which 1,700 were identified at Schymanski level 1 and 2. Of the latter, 28 substances are restricted under REACH, 4 are regulated as POPs with an additional 6 being proposed as POPs. Approximately 200 of the high confidence substances have a harmonized classification (CLH) under the CLP while 50 are included in the SVHC Candidate List. Finally, 62 of the identified chemicals have been prioritized as PMT/vPvM substances. In general, the compounds most frequently detected in each of the high level categories are compounds belonging to relevant types of compounds: antioxidants, plasticizers, pigments, long chain alkanes, etc. The elastomer, paper/paperboard and plastic + wood categories showed large similarities concerning the frequently detected compounds which may be a result of similar surface treatments, additives or modifications in itself or due to a combination of prevalence and bias.

The review highlighted the presence of restricted/hazardous chemicals even among the most frequently detected substances. Key obstacles encountered in this study included time-intensive data curation and lack of standardized workflows for NTS/SS studies making data interpretation/evaluation challenging. Differences in analytical techniques, sample preparation, and database limitations are well known sources of variability in results that can add additional uncertainty to these types of studies. Additionally, both false positives and negatives remain significant concerns, particularly in regulatory applications. Inconsistent usage of chemical identifiers also emerged as a significant challenge.

In summary, NTS and SS have shown potential as tools for identifying regulatory-relevant substances. However, they are currently more suited for early-warning screening due to methodological limitations. The report emphasizes the need for standardized workflows, enhanced QA/QC measures, and collaborative trials to improve comparability and reliability of findings. Future research should focus on integrating computational tools to prioritize chemical hazards and address gaps in regulatory databases. This report serves as a foundational resource for understanding the current capabilities and limitations of NTS and SS methods in regulatory applications, advocating for advancements to realize their full potential in chemical safety and environmental health.

Background and Scope

Large and increasing numbers of chemicals are produced and used by modern society. Many known and unknown chemicals are present in the many materials and products we use, some of which can pose hazards to human health and to the environment. According to a report by the United Nations Environment Programme (UNEP), of the more than 13,000 chemicals associated with plastics and plastic production, only 7,000 have been screened for their hazardous properties (UNEP 2023). Of those, 3,200 chemicals were identified to have hazardous properties of concern with many found across a wide range of sectors and product value chains. The number of chemicals found just in plastics has been recently raised to over 16,000 with at least 4,200 chemicals (26%) presenting high human and environmental hazard (Wagner et al., 2024), Methods capable of mapping all hazardous substances present in materials and products are needed for proper regulation to minimize risks for human and environmental health (i.e. for identification and prioritization of chemicals/chemical groups for regulatory risk management measures under e.g. the REACH and CLP regulations). Most chemical analysis is performed using methods targeting specific compounds with already known structures. This usually provides quantitative data for a relatively small number of compounds; however, advances in technology and data evaluation software now allow broader analyses beyond the target analysis of only a few pre-defined chemicals. Non-target screening (NTS) and suspect screening (SS) methods can theoretically provide a broader screening of potentially hazardous chemicals in materials/products, but whether these methods can in reality and with sufficient reliability identify novel hazardous substances needing regulatory action is unclear and has not been extensively evaluated. This project aims to provide an overview of the extent to which these methods have been used to identify regulatory-relevant substances in articles, chemical products, and recycled materials. Regulatory-relevant substances were, in this context defined, as substances that could be subject for additional risk management measures based on their hazard properties and regulatory status.

NTS is a chemical analytical approach using high-resolution mass spectrometry (HRMS) coupled with liquid or gas chromatography (LC or GC) for identification of organic chemicals not limited to predetermined chemical compounds for which optimized analysis methods have been created. SS is generally considered a subcategory of NTS where a broad list of compounds of concern is screened. Traditional targeted analysis is limited to a much smaller number of pre-selected target compounds, while NTS using HRMS can identify thousands of different mass spectra or chemical fingerprints (USEPA, 2024). Using software these fingerprints can then be compared to catalogued chemical spectra for identification and prioritized by various criteria such as presence or absence in control samples. In SS, molecular features are compared against specific chemical suspect lists or databases to identify potential matches. As NTS aims at generating signals from as many compounds as possible from a given sample matrix, more general sample preparation and chromatographic separation methods are applied.

There are currently methodological issues hampering NTS and SS applicability and efficiency for detecting and identifying new and relevant substances for regulatory purposes. One of the main problems is the often time-consuming task of curating the data and validating the confidence of the identifications. Even though sophisticated digital workflows have been devised by many research groups, much time have to be spent in manually inspecting the output data. A single NTS experiment often gives rise to thousands of "features" in the data set, e.g., regions in the data where a signal increases sufficiently above the background noise and that can be described as being typical for a chromatographic peak. A final quality check by manual inspection is often required, even if most data processing is performed automatically, to ensure that adequate settings have been used in the automatic processing. A single mass spectrum can also have numerous matches or no chemical match, and not every chemical present in a sample will exhibit a spectrum since sample preparation, separation, ionization, and instrument choice will affect the chemical space detectable (USEPA, 2024). Data processing methods and software can also add additional variation. Erroneous assignment of the chemical formula, adduct formation, isotopic patterns or chromatographic peak shapes as well as matching with spectra in databases can all contribute to a false positive or negative identification of compounds in a NTS or SS experiment (Hollender et al., 2023).

As the relationship between the signal intensity and concentration generally is not established in NTS and SS experiments, these techniques are considered as more qualitative than quantitative. Quantification of concentrations is important for risk assessment and improvements in semi-quantification techniques have been made over the recent years (Malm et al., 2021, 2024) but may not provide the level of certainty required by regulators. Absolute confirmation of NTS-identified chemicals still requires comparison to reference standards, which necessitates they are already known and available. Since NTS is still relatively new, methods and reporting are not yet thoroughly standardized even though quality control guidelines and suggested confidence levels have been published with varying levels of uptake (BP4NTA et al., 2023; Schymanski et al., 2014). At the same time, the number of collaborative trials, e.g., studies where several laboratories have used their developed analysis workflows on the same samples, that have been performed is low. This is probably due to the significant effort involved in the evaluation of NTS and SS screening data as compared to the application of traditional target chemical analysis. These studies are discussed in relation to the findings in this literature review in the discussion part of this report.

In this work, Schymanski levels (either provided by the study or assigned within this work) are used to characterize confidence levels of chemical hits. Schymanski levels are a five-tiered classification system used to communicate the level of confidence in compound identification using HRMS in NTS and SS (Schymanski et al., 2014). The levels were first proposed in 2014 and have since been widely adopted by the environmental science community to enhance transparency and comparability of results across different studies (Hollender et al., 2023; Manz et al., 2023; Schulze et al., 2020; Sobus et al., 2018). NTS relies on accurate mass and MS2 fragmentation patterns, along with other evidence, to tentatively identify compounds in complex samples. However, achieving definitive structural confirmation often requires reference standards as mentioned above, which are not always readily available for all compounds, particularly emerging contaminants and transformation products. The Schymanski levels provide a method to communicate the degree of certainty associated with compound identifications given these challenges within NTS and are described in Table 1.

Table 1 Description of Schymanski levels. Information from Schymanski et al 2014.

Level		General Description	Details
1		Confirmed structure by reference standard.	Represents the highest level of confidence and requires matching the compound's MS, MS2, and retention time (RT) to a reference standard. In cases where MS2 data is not available for low-intensity targets, matching MS and RT to a standard is sufficient.
2		Probable structure.	Indicates that enough evidence exists to propose a specific structure, but confirmation with a reference standard is lacking. There are two sublevels:
	A	Probable structure by library spectrum match.	Compound's MS and MS2 spectra match a library or literature spectrum with high confidence. Adequate spectral match scores and sufficient number of matching fragment ions are required for a Level 2a identification.
	B	Probable structure by diagnostic evidence.	No reference standard or library spectrum is available but other diagnostic evidence supports the proposed structure. This may include specific MS2 fragments, ionization behavior, knowledge of potential parent compounds, and the experimental context.
3		Tentative candidate(s).	Evidence from MS2 data suggests possible structures, but a single definitive structure cannot be assigned.
4		Unequivocal molecular formula.	Sufficient evidence supports the assignment of a unique molecular formula to the compound.
5		Exact mass of interest.	An accurate mass has been detected and prioritized for further investigation, but no structural information is available.

To date NTS and SS methods have primarily been applied to analyze environmental matrices and to the best of our knowledge no review of their application to man-made materials/products has been made. Thus, there is a need to get an overview describing to which extent these methods have been used, if substances have successfully been identified and whether these identified substances are relevant in a regulatory perspective for e.g. restriction, harmonized classification, and identification of substances of very high concern (SVHC). In a Swedish government assignment running from 2017 to 2020 to map unrestricted hazardous substances in products/articles, NTS methods were applied to identify hazardous substances in feminine hygiene products, textiles, and paper/paper board food contact materials but relatively few substances (with confirmed identity) for which regulatory risk management measures were needed were identified (KEMI, 2020). The question of whether these methods, in their current state, are suitable for efficient identification of substances of relevance for regulatory actions by national agencies therefore remains. This work aims to provide an overview of studies that have been done to date using NTS and SS to identify substances in articles, chemical products, and recycled materials via literature review and collection of NTS/SS identified chemicals. For substances identified with high confidence (Schymanski levels 1 and 2), the current regulatory status and (potential) intrinsic hazardous properties will be screened and used to identify regulated substances but also indicate potential candidates for risk management measures. This will serve as the basis for an evaluation of the applicability and efficiency of current NTS and SS methods for identifying substances relevant for regulatory actions.

Methodology / Approach

The basis of this project was a literature review of NTS and SS studies of articles, chemical products, and recycled materials and collection of identified substances.

Literature review and data extraction

The literature collected included primary scientific articles and grey literature. The search was performed both via outreach to participant networks for more complete collection of relevant grey literature as well as searches of online databases via Google, Google Scholar, PubMed and Web of Science. Primary search keywords included "non-target screening", "non-target analysis", "suspect screening" and the major product/material categories/subcategories used for the Swedish Chemical Agency's PRIO database (Appendix , spreadsheet "E"). Relevant references within papers were also used. Due to time constraints, the literature search was not exhaustive and ended upon 76 references which might have resulted in some product categories being underrepresented in the collected literature. Besides that, the PRIO categories did not cover every manmade material.

All references were reviewed and assessed for relevance. Relevance entailed true NTS and/or SS methods used on relevant articles, chemical products, or recycled materials. For the references deemed relevant, substances identified were extracted and entered into a master list. If Schymanski levels were provided, these were also entered. If not, Schymanski levels were assigned as described below. For each study the following information was collected: the study aim, a priori information used for study design, type of screening (NTS, SS, or both), PRIO material category/ies, material subcategory/ies (specific material details), instrumentation used, QA/QC performed (described below), and the file location of tentatively identified substances, if available. The relevant study/literature list and associated information is provided in Appendix, spreadsheet "A". For each chemical entry, the following information was collected: chemical name, formula, CAS number, Schymanski level, type of screening (NTS or SS), detection frequency (i.e., the number of product/material samples the substance was found in), sample preparation and chromatographic methods, scanning and ionization modes, PRIO material category, material sub-category (specific material details), study source, and regulatory and hazardous information (described further below). Chemical identifiers (Simplified Molecular Input Line Entry Specification, SMILES) and CAS numbers that were not provided by the literature were collected from the Chemical Identifier Resolver of the U.S. National Cancer institute[1] and PubChem database

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1. https://cactus.nci.nih.gov/chemical/structure

automatically using the Python packages, CirPy and PubChemPy, respectively. Chemicals that still had missing CAS number or SMILES were then manually checked in PubChem and CompTox Chemicals Dashboard[2]. A mixed product category (i.e., plastic + elastomer) was used in cases where multiple product categories were included in the study, but it was not clear which product type each chemical was found in. An additional 'Other' product category was created for product types that didn't clearly fall under any of the PRIO categories. The following additional information was collected if provided by the study: canonical Smiles, InChIkey, molecular weight, mass-to-charge ratio, retention time, and chemical function. For the final version of the chemical list, only chemicals with a Schymanski level of 1 or 2 were kept.

Assignment of missing Schymanski levels

Schymanski levels if not provided by the study were assigned according to the following criteria:

LEVEL 1	Compound is confirmed with MS and MS2 fragments as well as retention time of a reference standard.
LEVEL 2A	Unambiguous and high MS2 fragmentation match with spectral library or database (> 90%) and includes mass of precursor or molecular ion. Requires a good match (+/- 2.5min) with predicted or modeled retention time.
LEVEL 2B	Single match in spectral library or database but with lower confidence (>70%) without using retention time prediction. Might not include mass of precursor or molecular ion.
LEVEL 3	Multiple matches and several tentative candidates for MS2 spectral matches with low confidence (<70%) and without retention time prediction.
LEVEL 4	Unequivocal molecular formula from exact mass and MS isotope data. MS2 data is not available or uninformative.

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[2] https://comptox.epa.gov/dashboard/

Assessment of QA/QC

Quality controls and data processing parameters of each study are described in the QA/QC column in Appendix, spreadsheet "A". Parameters described include: peak filtering cut off values, usage of procedural blanks, application of internal standards, replicates, precursor mass error, retention time difference, library match score limit, spectral databases used and complementary identification through orthogonal methods such as different ionization techniques and inclusion if ion mobility data. The parameters and set cut off limits included in the QA/QC were used for the assessment and assignment of Schymanski levels to data lacking Schymanski scoring.

Chemical regulatory information and hazardous properties

The substances given a Schymanski confidence level of 1 or 2 were then screened through a number of regulatory and hazard information databases using the IVL early warning hazard screening tool to determine if these substances are already regulated, prioritized or under assessment within the EU. Those included the following databases from the European Chemical Agency (ECHA) as accessed in November 2024:

- the List of substances subject to Persistent Organic Pollutants (POPs) Regulation[3],
- the List of substances proposed as POPs[4],
- the Candidate List of substances of very high concern (SVHC) for Authorization[5],
- the Restrictions List in Annex XVII to REACH[6],
- the list of harmonized classifications (CLH) and self-classifications under CLP Annex VI[7],
- the results from PBT/vPvB assessments under the previous EU chemicals legislation[8],
- the new PBT assessment list[9],
- the Endocrine disruptor assessment list[10],

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3. https://echa.europa.eu/list-of-substances-subject-to-pops-regulation
4. https://echa.europa.eu/list-of-substances-proposed-as-pops
5. https://echa.europa.eu/candidate-list-table
6. https://echa.europa.eu/sv/substances-restricted-under-reach
7. https://echa.europa.eu/information-on-chemicals/annex-vi-to-clp and C&L Inventory - ECHA
8. https://echa.europa.eu/information-on-chemicals/pbt-vpvb-assessments-under-the-previous-eu-chemicals-legislation
9. https://echa.europa.eu/pbt
10. https://echa.europa.eu/ed-assessment

as well as:

- The ChemSec Substitute It Now (SIN) list,[11] accessed in November 2023.
- the Prioritized PMT/vPvM substances in REACH registration database as extracted from the German environmental agency (UBA)'s report[12].

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[11] https://sinsearch.chemsec.org/
[12] https://www.umweltbundesamt.de/sites/default/files/medien/11850/publikationen/21_2023_texte_pmt_vpvm_substances_reach_v23032023.pdf

Results

Literature Summary

Overall, 76 documents were initially retrieved and reviewed. Of these, 38 were selected for further review based on SS/NTS relevance and data availability/transparency. Identified chemicals and associated information was extracted from each of these studies. Of the final selected studies, 26 directly screened the product, 8 screened for chemical migrants from products, and 4 studies did both. Over half the studies were published within the last 2 years which further indicates that the application of NTS/SS in product and material analysis is a relatively recent but fast-growing field.

Only 34 out of the 38 studies contained chemicals identified at high confidence level, i.e. Schymanski level 1 or 2. Of these, 19 used NTS, 11 SS, and 4 employed both methods. In total, more than 1,500 products were screened covering different product categories such as plastics, elastomers, chemical products/material related, paper/paperboard, textiles and wood. By far most studies looked at plastic products (>900 products), while the second biggest product category was textiles (>200 products). Although we believe that this is a relevant trend, the literature search was biased due to search terms and time constraints. As seen in Table 2, about 4–8 studies were found for each product category with screening data of high reliability (Schymanski level < 3) with the exception of the plastic material category where 20 studies were found. Many studies screened a broad range of products and therefore contributed with data to multiple product/material categories.

Total number of detected compounds and distribution across material categories

In total, nearly 3,000 unique chemical entries were registered at varying confidence levels from which approximately 1,700 were identified at Schymanski level 1 and 2 (Appendix, spreadsheet "C"). Of the latter, 28 substances are restricted under REACH, 4 are regulated as POPs with an additional 6 being proposed as POPs. Approximately 200 of the high confidence substances have a harmonized classification (CLH) under the CLP while 50 are included in the SVHC Candidate List. Finally, 61 of the identified chemicals have been prioritized as PMT/vPvM substances. Detailed hazard and regulatory information can be found in the Appendix, spreadsheet "D".

The number of unique compounds detected and identified with high confidence in each product category can be seen in Table 2. The highest number (1,014) of unique compounds were detected and identified in the "plastic" material category, and even more compounds were further detected in the mixed product categories, "plastic +/or elastomers " and "plastic + wood". Four hundred unique compounds were identifed in the "other" products category. These categories are very broad and included a range of different products with varying applications. This might partly explain why more compounds were identifed in the "plastic" and "other" material categories in comparison to the material categories "textile", "paper/paperboard" and "elastomers" which included a narrower range of products and applications. For example, the product category "elastomer" included products such as recycled tire products, erasers and crumb rubber, whereas the product category "plastic" included products such as tableware, recycled plastic pellets, water bottles, food contact materials, toys, childrens products, PVC flooring, auto products, plastic electrical waste, single use items, shower curtains and vinyl upholstery. The "other" product category included mostly personal care products, cosmetics, paint and cleaning products.

Table 2 Numbers of unique SI 1 & 2 compounds and studies per material category.

Material category	# unique compounds	# of studies
CHEMICAL PRODUCT / MATERIAL RELATED	117	5
ELASTOMER	167	4
PAPER/PAPERBOARD	276	4
PAPER, PAPERBOARD + WOOD	2	2
PLASTIC	1,014	20
PLASTIC + / OR ELASTOMER	194	2
PLASTIC + WOOD	86	2
TEXTILE	25	8
OTHER	399	6

Overall most frequently detected chemicals

The most frequently detected chemicals at high confidence are presented in Table 3 (see also in Appendix, spreadsheet "C"). These include two widely used phthalate plasticizers that are also ubiquitous environmental pollutants, diethyl phthalate and dibutyl phthalate. Dibutyl phthalate is a known endocrine disruptor and reproductive toxicant and its use is restricted under REACH, while diethyl phthalate is under assessment for endocrine disruption. Benzophenone, a chemical classified as a carcinogen with a wide variety of registered uses for instance in air care/fragrance products, polishes and waxes, personal care products, washing & cleaning products, etc. but also commonly used as a UV stabilizer added to plastic and textile products is also among the most frequently detected. Palmitic acid, a saturated carboxylic acid with 16 carbons in the carbon chain, is the most widely distributed and abundant fatty acid. It has numerous industrial and consumer applications; amongst other things it is commercially used to make lotions. The compound [2,2,4-trimethyl-3-(2-methylpropanoyloxy)pentyl] 2-methylpropanoate is more commonly known as TXIB and is an additive, for instance in PVC, but also in many other consumer products such as adhesives and sealants, cosmetics and personal care products. Tetra-, hexa-, hepta-, octadecane and heptacosane are all saturated linear alkanes, which may be found in fuels or paraffin waxes. With the exception of heptadecane, octadecane and heptacosane all the most frequently detected substances are high production volume chemicals.

Table 3 Overall most frequently detected chemicals identified with high confidence levels (Schymanski level 1 and 2) and related regulatory and hazard information.

Chemical Name	CAS #	Frequency	Regulatory & hazard listing	Hazard property of concern
Diethyl phthalate	84-66-2	316	SIN List	Endocr. Disr.
Benzophenone	119-61-9	307	CLH classified PMT/vPvM list SIN List	Carc. 1B vPvM & PMT Endocr. Disr.
Dibutyl phthalate	84-74-2	301	REACH restricted CLH classified SVHC Candidate List SIN List	Repr. 1B| Aquatic Acute 1| Repr. Tox., Endocr. Disr.
Palmitic acid	57-10-3	299		
2,2,4-Trimethyl-1,3-pentanediol diisobutyrate	6846-50-0	288		
Hexadecane	544-76-3	267		
Tetradecane	629-59-4	258		
Heptadecane	629-78-7	256		
Octadecane	593-45-3	256		
Heptacosane	593-49-7	244		

Most frequently detected compounds using GC versus LC

The most frequently detected compounds (Schymanski level 1 & 2) using GC and LC are presented in Tables 4 and 5 (see also in Appendix, spreadsheet "C"). Compounds frequently detected with GC were mainly aliphatic hydrocarbons and plasticizers, whereas compounds frequently detected with LC techniques mainly included adhesives, copolymers and monomer components, many of which are industrial products and do not have CAS numbers. GC and LC are considered complementary techniques as the methods are applicable to substances of different chemical and physical properties. From the gathered results it was observed that both chromatographic techniques were combined with SS and NTS analysis to the same extent; however, GC techniques were more commonly used in the literature, which resulted in more than twice as many uniquely identifed compounds being detectd with GC techniques compared with LC. The use of these techniques depend on the material category being screened but also on the substances of interest. It was found that GC techniques were the primary chromatographic method used in the detection of compounds in chemical products/ material related, elastomers and textiles while LC techniques were the primary chromatographic method used in the detection of compounds in paper, paperboard and wood. Both GC and LC techniques were used in studies for SS and NTS of plastic although GC was more frequently used. Of the approximately 1700 unique substances identified with high confidence in the different product material categories, 900 (56%) were detected with GC techniques, 600 (38%) with LC techniques and 100 (6%) with both techniques. The reason for the more frequent usage of GC techniques is thought to be due to GC-MS being a more established and standardized technique where large spectral databases such as NIST facilitate and simplify the identification of compounds. This enables for a high confidence level when screening with GC-MS, making it easy to identify peaks with Schymanski level 2b. Advances in ionization techniques and in mass spectrometers have enabled screening to be performed with LC as well where a broad range of compounds can be analyzed and detected. Major challenges with LC screening are that the tehcniqe is not stadardized, spectral databases cover a limited range and high noise levels from interfearing making identification with sufficient reliability more difficult to achieve.

Table 4 Most frequently detected compounds using GC-MS. Chemical names in bold are among the 10 most frequently detected chemicals overall (Table 2)

Name	CAS #	Frequency
Palmitic acid	57-10-3	289
Diethyl phthalate	84-66-2	286
2,2,4-Trimethyl-1,3-pentanediol diisobutyrate	6846-50-0	286
Benzophenone	119-61-9	278
Dibutyl phthalate	84-74-2	275
Hexadecane	544-76-3	267
Tetradecane	629-59-4	258
Heptadecane	629-78-7	256
Octadecane	593-45-3	256
Heptacosane	593-49-7	244

Table 5 Most frequently detected compounds using LC-MS

Name	CAS #	Frequency
Bisphenol A ethoxylate methacrylate (BisEMA-2)	41637-38-1	65
Diethylene glycol adipate	58984-19-3	56
Adipic acid-diethylene glycol-neopentyl glycol-caprolactam	n/a	56
Disperse Red 354	1533-78-4	55
Adipic acid-monoethylene glycol-adipic acid-monoethylene glycol	n/a	55
Monoethylene glycol-adipic acid-neopentyl glycol-phthalic acid	n/a	55
Phthalic acid-diethylene glycol-neopentyl glycol-caprolactam	n/a	52
Azepan-2-one*	105-60-2	49
Neopentyl glycol-adipic acid	103439-11-8/ 27925-07-1	46
Adipic acid-1,4-butanediol-adipic acid-1,4-butanediol	n/a	44
Octadecanamide	124-26-5	

* Substance CLH classified as Acute Tox. 4, STOT SE 3, Skin Irrit. 2, and Eye Irrit. 2

Most frequently detected chemicals across material categories

The most frequently detected compounds in each PRIO category are presented in Table 6 (see also in Appendix, spreadsheet "C"). For the compounds most frequently found in the category 'Chemical product/material related' there were four that can be considered as fuel components, for instance the reproductive toxicant and REACH restricted toluene, 1,3-dimethylbenzene (m-xylene), ethylbenzene and the classified carcinogen cumene. Ethyl butyrate is an ether that is used as a fragrance or fragrance additive, but has also been proposed as a green solvent. Three coloring agents are among the most frequently detected i.e., Disperse Red 354, Red 73 and Blue 291G with the latter identified as a PM substance as well as a plastic monomer classified as carcinogen, styrene, and phenylmethanol (benzylalcohol) which according to ECHA has wide spread use in consumer products.

Table 6 Most frequently detected chemicals per PRIO category. Chemical names in bold are among the 10 most frequently detected chemicals overall (Table 2)

Chemical Name	CAS #	Fre-quency	Regulatory & hazard listing	Hazard property of concern	Study #
CHEMICAL PRODUCT / MATERIAL RELATED					**2**
Toluene	108-88-3	9	REACH restricted		
			CLH classified	Repr. 2|Asp. Tox. 1|STOT SE 3|STOT RE 2|Skin Irrit. 2	
Linalool	78-70-6	9	CLH classified	Skin Sens. 1B	
Ethyl butyrate	105-54-4	8			
Disperse Red 354	1533-78-4	7			
Disperse Red 73	16889-10-4	7			
Disperse Blue 291G	51868-46-3	7	PMT/vPvM list	PM	
Ethyl 2-methylbutyrate	7452-79-1	7			
Styrene	100-42-5	6	CLH classified	Repr. 2|Acute Tox. 4|STOT RE 1|Skin Irrit. 2|Eye Irrit. 2	
			SIN List	Endocr. disr.	
Benzene, 1,3-dimethyl-	108-38-3	6	CLH classified	Acute Tox. 4|Skin Irrit. 2	
Ethylbenzene	100-41-4	5	CLH classified	Acute Tox. 4 |Asp. Tox. 1|STOT RE 2	
Phenylmethanol	100-51-6	5	CLH classified	Acute Tox. 4	
Ethyl Hexanoate	123-66-0	5			
Palmitic acid	57-10-3	5			
E-4-Hexen-1-ol	6126-50-7	5			

Cumene	98-82-8	5	CLH classified	Carc. 1B|Asp. Tox. 1|STOT SE 3|Aquatic Chronic 2
Butyl acrylate	141-32-2	5	CLH classified	STOT SE 3|Skin Irrit. 2|Eye Irrit. 2|Skin Sens. 1
ELASTOMER				**2**
Diphenylamine	122-39-4	35	CLH classified	Acute Tox. 3|STOT RE 2 |Aquatic Acute 1|Aquatic Chronic 1
			PMT/vPvM list	PMT
Butylated Hydroxytoluene	128-37-0	30	SIN List	Endocr. disr.
Palmitic acid	57-10-3	22		
Hexadecane	544-76-3	22		
Tetradecane	629-59-4	22		
Heptadecane	629-78-7	22		
Octadecane	593-45-3	22		
Heptacosane	593-49-7	22		
Eicosane	112-95-8	22		
Heneicosane	629-94-7	22		

PAPER / PAPERBOARD				**2**
Tetradecane	629-59-4	29		
Octadecane	593-45-3	29		
Hexadecane	544-76-3	29		
Benzophenone	119-61-9	29	See Table 3	See Table 3
Octacosane	630-02-4	29		
Pentadecane	629-62-9	29		
Docosane	629-97-0	29		
Tricosane	638-67-5	29		
Palmitic acid	57-10-3	28		
Heptadecane	629-78-7	28		
Nonadecane	629-92-5	28		
Eicosane	112-95-8	28		
Dibutyl phthalate	84-74-2	28	See Table 3	See Table 3
PAPER/PAPERBOARD + WOOD				**1**
Trifluoromethanesulfonic acid	1493-13-6	7	PMT/vPvM list SIN list	vPvM
Trifluoroacetic acid	76-05-1	6	CLH classified PMT/vPvM list	Acute Tox. 4|Skin Corr. 1A|Aquatic Chronic 3 vPvM

PLASTIC				17
Benzophenone	119-61-9	180	See Table 3	See Table 3
2,4-Di-tert-butylphenol	96-76-4	161	PMT/vPvM list	PMT
Diethyl phthalate	84-66-2	160	See Table 3	See Table 3
Dibutyl phthalate	84-74-2	158	See Table 3	See Table 3
Tetrahydrofurfuryl alcohol	97-99-4	152	CLH classified SIN List	Repr. 1B|Eye Irrit. 2
2,2,4-Trimethyl-1,3-pentanediol diisobutyrate	6846-50-0	148		
AT-168	31570-04-4	135		
Butanoic anhydride	106-31-0	129		
Palmitic acid	57-10-3	126		
Bis(2-ethylhexyl) phthalate	117-81-7	113	REACH restricted CLH classified SVHC Candidate List	Repr. 1B Endocr. disr.
PLASTIC + WOOD				1
Tetradecane	629-59-4	45		
Heptadecane	629-78-7	44		
Octadecane	593-45-3	44		
Tridecane	629-50-5	44		
Hexadecane	544-76-3	43		
Eicosane	112-95-8	43		
Heneicosane	629-94-7	43		

Nonadecane	629-92-5	42		
Nonacosane	630-03-5	42		
Diethyl phthalate	84-66-2	41	See Table 3	See Table 3
Heptacosane	593-49-7	41		
PLASTIC + / or ELASTOMER				**1**
Bis(2-ethylhexyl) benzene-1,4-dicarboxylate	6422-86-2	8		
Hexadecane	544-76-3	7		
Erucamide	112-84-5	7		
Dibutyl phthalate	84-74-2	6	See Table 3	See Table 3
2,2,4-Trimethyl-1,3-pentanediol diisobutyrate	6846-50-0	6		
Octacosane	630-02-4	6		
Palmitic acid	57-10-3	6		
2,4,7,9-Tetramethyl-5-decyn-4,7-diol	126-86-3	6	PMT/vPvM list	PM
N-phenyl-4-(2,4,4-trimethylpentan-2-yl)aniline	27177-37-3	6		
Triphenyl phosphate	115-86-6	5	SVHC Candidate List SIN List	Endocr. disr.
Methyl palmitate	112-39-0	5		
Dinonyl phthalate	84-76-4	5		
Dodecanoic acid	143-07-7	5		

TEXTILE				**5**
Disperse Red 354	1533-78-4	55		
Ethanol	64-17-5	42		
Disperse Red 343	68385-96-6	40		
Disperse Red 311	70729-65-6	39		
Disperse Red 153	25150-28-1	38		
Dibutyl phthalate	84-74-2	37	See Table 3	See Table 3
Heptacosane	593-49-7	36		
Hentriacontane	630-04-6	36		
Benzophenone	119-61-9	36	See Table 3	See Table 3
Disperse Red 74	1533-74-0	36		

OTHER				3
Bisphenol A ethoxylate methacrylate (BisEMA-2)	41637-38-1	65		
Palmitic acid	57-10-3	46		
1-Hexadecanol	36653-82-4	38		
Butylated Hydroxytoluene	128-37-0	32	ED assessment list SIN List	Endocr. disr.
1-Dodecanol	112-53-8	32		
Diethyl phthalate	84-66-2	31	See Table 3	See Table 3
Oleic acid	112-80-1	30		
Octadecanoic acid	57-11-4	30		
Cyclopentaneacetic acid, 3-oxo- 2-pentyl-, methyl ester	24851-98-7	30		
Dodecanoic acid	143-07-7	26		
Linalyl acetate	115-95-7	26		
Geranyl acetate	105-87-3	26		

The groups elastomer, paper/paperboard, plastic, and plastic + wood and plastic +/or elastomer all have limited, and quite similar chemicals that are found most frequently. Many compounds are long chain aliphatic hydrocarbons/acids such as tetradecane, hexadecane, heptadecane, octadecane and palmitic (hexadecanoic) acid. For the plastic, plastic +/or elastomer there are also antioxidants, some process chemicals and plasticizers while the elastomer group was dominated by long chain aliphatic hydrocarbons along with a couple of antioxidants such as diphenylamine which is classified as aquatic toxicant and a PMT substance and butylated hydroxytoluene, a potential endocrine disruptor. For the plastic category, benzophenone, diethyl phthalate, dibutyl phthalate along with another restricted phthalate plasticizer, bis(2-ethylhexyl) phthalate are dominant. Tetrahydrofurfuryl alcohol, a reproductive toxic substance that is used as an industrial solvent, a phosphate ether antioxidant, AT-168, and the common additive known as TXIB (2,2,4-trimethyl-1,3-pentanediol diisobutyrate) were also among the most frequently detected. There was also a compound that is used in the production of antioxidants and UV-stabilizers, 2,4-di-tert-butylphenol, which may be present due to degradation of other compounds in the material.

In the plastic + wood category all the frequently detected compounds are long chain aliphatic hydrocarbons exept for the plasticizer diethyl phthalate. The long chain aliphatic compounds also dominate the category of paper/paperboard with the addition of benzophenone and dibutyl phthalate replacing diethyl phthalate. For the category of plastic +/or elastomer another phthalate plasticizer bis(2-ethylhexyl) benzene-1,4-dicarboxylate was frequently detected, along with eurcamide, a chemical commonly used in plastic processing as a slip additive. A surfactant known with the commercial name Surfynol or Surfadol, 2,4,7,9-tetramethyl-5-decyn-4,7-diol (a prioritized PM substance), was also frequently detected. N-phenyl-4-(2,4,4-trimethylpentan-2-yl)aniline, an antioxidant structurally similar to 6PPD and triphenyl phosphate a substance used for is flame retarding and plasticizing properties appeared in the list. Triphenyl phosphate was recently added to the SVHC Candidate List due to its endocrine disruption potential. Interestingly, only two ultra short chain PFAS compounds (both classified as vPvM) are detected frequently in the category paper/paperboard + wood, trifluoromethanesulfonic acid and trifluoroacetic acid.

The textiles category is dominated by color agents, with different dispersive red dyes being most frequently detected, Disperse Red 354, 343, 311, 153 and 74. Other frequently detected compounds are benzophenone, two long chain aliphatic hydrocarbons, dibutyl phthalate and the solvent ethanol. In the last category listed, "other", there is an antioxidant, butylated hydroxytoluene, three long chain aliphatic acids, palmitic acid, octadecanoic acid and oleic acid (an unsaturated octadecanoic acid) as well as a couple of aliphatic alcohols, 1-hexadecanol and 1-dodecanol. Bisphenol A ethoxylate methacrylate (BisEMA-2), which was most frequently identified, is possibly a plastic monomer used together with i.e. bisphenylglycidyl dimethacrylate (BisGMA) in dental composites. One fragrance compound was also identified, cyclopentaneacetic acid, 3-oxo- 2-pentyl-, methyl ester, which is also known as methyl dihydrojasmonate or hedione.

The frequency of detection of alifatic hydrocarbons and plastic or polymer-related compounds such as plastisizers, and antioxidants across several categories may indicate that the categorys themselves may be overlapping in the materials present or that similar additives are used in the different groups. There can also be a bias of which compounds are extracted to a high degree in the extraction methods used and determined with good recovery across the analytical method. It is also possible that a bias pertaining to the analytical method exists as well, with the aliphatic hydrocarbons, acids and alcohols being well suited for GC-MS analysis.

Discussion

In general compound identification via NTS and SS methods can be influenced by i) the availability and reliability of information on compounds, ii) limitations in spectral databases which may result in identification of some compounds more often and iii) the choice of instrument method and sample preparation procedure. Building on the paradigm by Hollender et al., 2023 the final compound identification domain of an NTS/SS method can be conceived as the intersection between the individual method (i.e., sample preparation, chromatographic and mass spectrometry/ionization) and reference data domains (Figure 1).

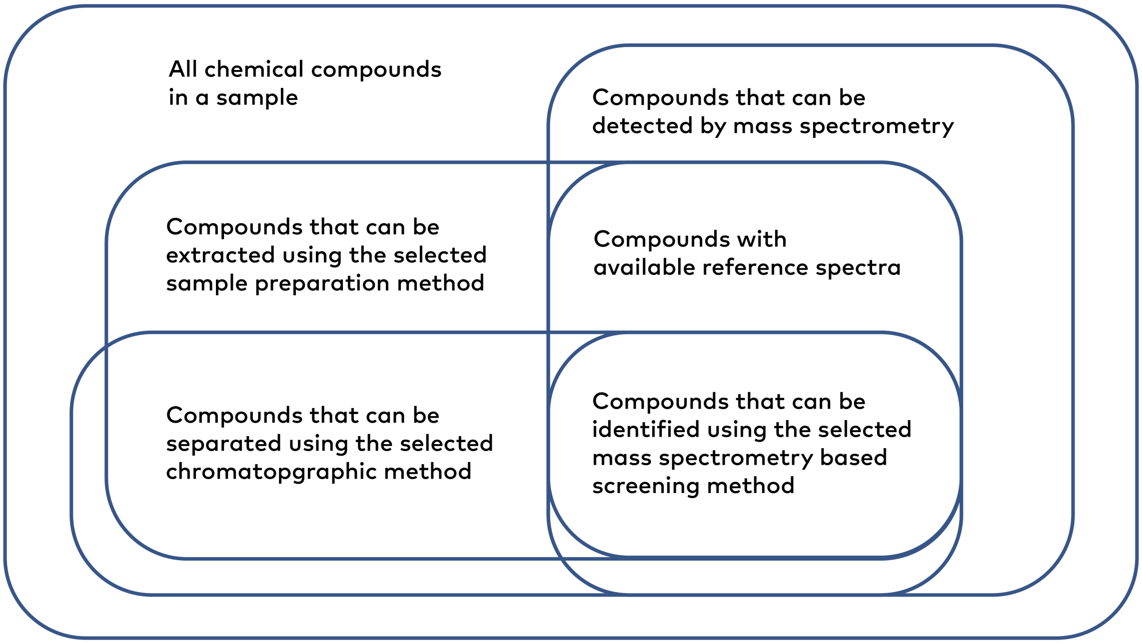

Figure 1 Compound identification domain of an NTS/SS method. Adapted from Hollender et al. 2023

To date no collaborative trials have been performed for NTS on products and materials. However, a collaborative trial on river water in conjunction with the third Joint Danube Survey has been organized by the NORMAN network (Schymanski et al., 2015). There have also been collaborative trials organized on house dust, drinking water in combination with passive sampling, and spiked fish samples within the NORMAN network (Dürig et al., 2023; Haglund et al., 2024; Rostkowski et al., 2019; Schulze et al., 2020). The drinking water study only established a database of the generated data with some fundamental quality assurance (QA) parameters being described. For household dust, two projects have been performed, of which the second is still in the evaluation phase. The US EPA initiated a collaborative trial on synthetic sample mixtures of chemicals included in the

CompTox database through the Nontarget Analysis Collaborative Trial (ENTACT) project (Newton et al., 2020; Sobus et al., 2019; Ulrich et al., 2019). The ENTACT project samples contained different combinations of more than 1,200 chemical compounds.

It is difficult to draw general conclusions based on the collaborative trials since the studies have been made on different types of samples and the evaluations have been performed using different strategies, for instance evaluating the successful identification of spiked compounds or purely unknowns. The differences are very large in the number of compounds identified with proposed structures using LC-MS by the different laboratories in these studies, from 8 to 229 for river water, 12 to 457 for dust and 27 to 185 for fish. Many compounds in these studies are therefore only identified by a single, or a few laboratories. In the urban dust trials about half the identified compounds identified by GC-MS and most of the compounds identified by LC-MS were reported by only one lab for the first trial (Rostkowski et al., 2019) and 70% of all identified compounds were reported by only one lab for the second trial (Haglund et al., 2024). This shows that not sufficient progress has been made concerning this in the last decade. In addition, these studies present that there is little overlap between LC-MS and GC-MS methods, which may be explained by the differences in the chemical space in which the techniques are suitable. This pertains to both the polarity of the compounds and the ionization techniques that are used. The techniques are therefore viewed as complimentary techniques. In the NORMAN fish study, it was shown that the correct assignment of spiked compounds is greatly improved if the presence of the compound in the sample is known beforehand. It was also shown that the percentage of correctly assigned compounds vary greatly between labs, between 6-69% for LC-MS and 20-60% for GC-MS. These results show that harmonization of methodology and implementation of generally accepted quality assurance and quality control (QA/QC) measures is necessary for NTS and SS. The final results of the ENTACT collaborative trials have not been published, but recommendations on performance metrics have been presented (Fisher et al., 2022). The publications from the collaborative trials all contain recommendations concerning improvements that may lead to more reproducible results. Papers have also been published concerning QA/QC measures that are appropriate for NTS and SS (Hollender et al., 2023; Schulze et al., 2020), even though these publications are too recent to have been adopted to any greater degree by the scientific community.

Based on the information provided above it could be challenging to use the most frequently detected compounds from a number of studies as an efficient method to collect hazardous chemicals present in a specific product category or material type, even though it is a logical starting point for a literature study. The fact that different laboratories provide such a range of identified chemicals, from very few to very many, in studies of the same samples either requires that many studies are performed on the same products or materials before any consensus list starts to materialize or that more rigorus standardization must be applied to harmonize the methods between the laboratories. Similarly to what was observed here, it has been shown that GC-MS and LC-MS methods are mostly to be considered as complementary methods (Rostkowski et al., 2019) and that both the polarity and type of ionization method in LC-MS, electrospray ionization and atmospheric pressure chemical ionization, provide different results (Singh et al., 2020). For more specific product categories the studies are not extensive and may have been performed over a wider period of time, resulting in differences in the number of identified compounds arising from improvements in instrumentation or methodology. Finding a balance between i) a relatively small number of compounds detected as a result of false negative reporting from laboratories having, for instance, insufficient detection levels and ii) false positive reportings from laboratories that have implemented insufficient quality control measures is therefore difficult. An alternative approach could be to use the entire data set, and apply computational (in-silico) tools to prioritize which chemicals to lift for further investigation based on potential hazard profiles. This, however, is only possible if the structure of the compound is known (and not ambigous). The addition of retention time index standards and calculations to reduce false positives or increase the certainty of identifications are valuable (Aalizadeh et al., 2019; Hollender et al., 2023). Within the EU partnership for the assessment of risks from chemicals (PARC) programme work is being performed to test new standard mixtures that can provide information on the chemical space covered by an NTS or SS analysis. This would thereby provide useful information on false negatives.

In general, the compounds most frequently detected in each of the high level categories are compounds belonging to relevant types of compounds: antioxidants, plasticizers, pigments, long chain alkanes, etc. The similarity of the detected compounds in the categories elastomer, paper/paperboard and plastic + wood may arise from similar surface treatments, additives or modifications in itself or through a combination of prevalence and bias. To achieve a more detailed understanding, narrower categories would need to be investigated, but this would also lead to fewer publications per category. Interestingly, restricted substances were found in products and materials even among the most frequently detected ones but this may be partly due to older products being tested (i.e., before the regulation entried into force) or the specific use not being covered or being exempted from the restriction. It is also likely that despite having been restricted these substances are still used or result as contamination during the production process e.g., by the introduction of recycled materials in the manufacturing process. Even though the most frequently detected compounds in the high Schymanski level categories contain a number of chemicals with hazard properties, to identify in more detail hazardous chemicals in relevant product categories there may be a need to accept a risk for more false positive findings due to smaller data sets.

Conclusions

The application of NTS and SS methods for article, chemical product and recycled material screening is a relatively new but presumably fast-growing field as suggested by the majority of studies reviewed here being published in the last couple of years. Most of these studies have focused on screening different types of products aiming to identify hazardous (or not) chemicals in these products, often by developing and applying new improved workflows. Some studies have also looked at which chemicals can migrate from the products under exposure-relevant scenarios as well as their transformation products. Besides identifying chemical substances with a well characterized hazard profile that may also be regulated, prioritized or under assessment, there are few studies that have also investigated potential hazard properties of the identified chemicals using in silico approaches or tested their cocktail effect under experimental conditions.

To use NTS and SS data for identifying compounds of regulatory concern, the data needs to be searched through regulatory and hazard information databases or applied to in silico prediction tools. This type of processing is highly dependent on chemical identifiers such as CAS-numbers, SMIILES, InChI keys, chemical names, and molecular formulas. Thus, ambiguities in these may lead to inconsistent or incorrect conclusions about hazardous properties and chemical risks. Challenges observed in this study regarding data from NTS and SS studies included the lack or inconsistent usage of chemical identifiers. The challenge becomes more complex as regulatory and hazard information databases often utilize a single CAS-number as a chemical identifier for a compound which may have many CAS-numbers assigned. A sufficient data curation process is therefore required to assign unique and comprehensive chemicals identifiers in order to minimize the risk of failing to assign hazardous properties to chemicals identified with NTS and SS methods.

Our evaluation of the data has shown that a focus on the most frequently detected compounds in a specific product or material category might result in a rather low number of compounds, and that these compounds may be influenced by different types of bias. This is supported by the interlaboratory comparisons presented in the discussion. Future work, building on the gathered data from this study could include in silico hazard assessment of compounds which were detected frequently with sufficient reliability but were not found in the regulatory and hazard information databases, to further investigate the extent of which NTS and SS techniques are capable of detecting compounds of emerging concern and potential regulatory relevance.

Non-target and suspect screening approaches have the potential for being suitable and effective for identifying regulatory-relevant substances in products and materials, but they are probably better suited for early warning screening purposes at this stage given their current limitations especially with the identification uncertainty/confidence. Positive identifications may require large efforts for verification, especially since not all chemicals on the market are available for purchase as reference standards that could facilitate a confirmation of the identity. As long as a compound has not been positively identified using a reference standard the risk that it may constitute a false positive identification will exist and therefore also requires preparedness from regulators that this may be the case. False negative identification of hazardous compounds presents an additional challenge as there is a hazardous substance that remains undetected. However, multiple developments could reduce such risks. The introduction of more standardized workflows, with well-defined QA/QC criteria, are needed to increase the overall screening method robustness and the comparability between results from different labs. This may involve introduction of QC-samples to verify the performance of the method within the desired chemical space or providing information on, for instance, false negative results.

Appendix

Excel file containing spreadsheets A–E:

- **A - Study** contains the final literature list from which chemical data was extracted;
- **B – Chemicals SI 1+2 per study** contains all chemicals extracted per study from studies in spreadsheet A assigned Schymanski Levels 1 or 2;
- **C – Unique compounds SI 1+2_DF** contains all unique chemicals with Schymanski Levels 1 or 2 including detection frequencies;
- **C – Hazard & regulatory info** contains the hazard and regulatory information for all unique chemicals with Schymanski Levels 1 or 2;
- **E - PRIO categories** contains descriptions of the PRIO categories. Additional information as described in the methodology section is also included in this file.

Download Excel file

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Nordic co-operation has firm traditions in politics, economics and culture and plays an important role in European and international forums. The Nordic community strives for a strong Nordic Region in a strong Europe.

Nordic co-operation promotes regional interests and values in a global world. The values shared by the Nordic countries help make the region one of the most innovative and competitive in the world.

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